TEACHING COURSE I

Behavioural aspects of headache management – State of the art and science

TI-1

Limbically augmented pain syndrome: kindling and corticolimbic sensitization

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Patients with chronic pain typically obtain only limited relief from antinociceptive therapies. They also commonly experience a myriad of associated affective and behavioural symptoms, including dysphoria, anxiousness/irritability, insomnia, fatigue, impaired performance in social/occupational roles, and sensitivity to stress. The association between chronic pain, emotional distress, and behavioural dysfunction has garnered much attention from clinicians, researchers and psychosomatic theorists. Although this association has long been recognized phenomenologically and epidemiologically, it has not been well described at the neurobiological level. Prevailing theories have primarily addressed short-term/state-related considerations or have focused on ‘psychogenic’ aetiologies for obscure pain complaints. The complex processes of neuroplasticity are key to developing a scientifically based, unified approach to individuals engulfed in the experience of chronic pain. The heuristic construct of a Limbically Augmented Pain Syndrome (LAPS) is introduced to describe chronic pain syndromes which are the result of kindling-induced sensitization in corticolimbic structures that subserve both nociception and emotion. The hallmark features of LAPS include pain that is chronic and resistant to analgesic treatments, in association with disturbances of mood, affect regulation, sleep, energy, libido, and memory/concentration. Behavioural dysfunction, along with generalized intolerance of stressful life events, are also features of the complex chronic pain disorders which are labelled LAPS. LAPS is proposed as a biopsychosocial model for chronic pain disorders which incorporates the cumulative effects of physically noxious and psychologically adverse stimuli on corticolimbic structures that orchestrate the experience of pain. The neuroanatomic substrate for pain can be divided into two distinct processing networks: the lateral pain system (involved in localization and sensory discrimination of painful stimuli) and the medial pain system (involved in affective-motivational responses to painful stimuli). The LAPS hypothesis states that kindling-induced changes in the medial and lateral pain systems, produced by specific patterns of noxious/adverse stimuli, result in a state of corticolimbic sensitization which is responsible for the clinical features of complex chronic pain disorders. Kindling (in this use to include long-term potentiation, long-term depression, behavioural sensitization, and related neuroplastic processes) is a mechanism through which life experiences can sensitize corticolimbic structures which mediate both the somatic and psychological aspects of pain. The kindling properties of amplification, spontaneity, neuroanatomic spreading, and cross-sensitization can account for the multifaceted symptomatology of LAPS.

TI-2

Chronic pain and headache: a biobehavioural perspective

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We have recently shown that states of chronic pain are accompanied by plastic changes in primary somatosensory cortex indicating that the representation of the affected body part is enlarged. This cortical reorganization is positively correlated with chronicity. We have proposed that such plastic alterations of primary somatosensory cortex are an important factor in the development and maintenance of chronic pain problems. Learning processes such as operant and classical conditioning of pain behaviours and pain-related physiological responses can also alter the cortical map and contribute to chronicity. We will present several examples on the effects of learning on plasticity and pain. In addition, we will discuss both behavioural and pharmacological treatment implications of these findings.

TI-3

Born to be wild or learned? A new biobehavioural hypothesis of the etio-pathogenesis of migraine

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Abnormal behavioural patterns like perfectionism, hypersensitivity, and others often have been described to be specific psychological characteristics in migraine patients which possibly seems to be acquired in consequence of the migraine disease. The main question is whether these behavioural patterns may be the result of a learning processes. Or, on the opposite side, that these patterns may be associated with or caused by genetic determined cortical hypersensitivitiy. Many studies based on neuro(psycho)physiological data confirmed the notion that migraine is a brain stem information processing dysfunction that is characterized by cortical hypersensitivitiy and reduced habituation to stimuli. The cortical activity reflects a (time) periodicity and may be
related to endogenous or exogenous factors. Based on the current understanding of behavioural and neurophysiological aspects of migraine, we assume a two-process model of migraine aetiology: (1) a genetically determined hyperactivity of the central monoaminergic (catecholaminergic) system which could be possibly modulated by learning processes and (2) a homeostatic (counter) regulation and mobilization of reduced (mitochondrial) energy reserve. We further hypothesize that the catechol-aminergic hyperactivity represents a possibly learned Self-Reinforcement-System (SRS). The chronicity of migraine could be the result of operant conditioning processes which are related to both, biological and behavioural patterns. These hypothesis are examined by several studies with migraine families and twins. The results of some new data will be presented during the conference. These findings indicate to new behavioural procedures in the treatment of migraine especially the ‘Sensoric Coping Training’.

TI-4

Behavioural medicine for headache: review of the evidence

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This presentation provides an overview of recent developments in the non-pharmacological management of headache. Behavioural therapies may be particularly well suited for patients with a preference for minimizing medication use, poor tolerance of or medical contraindications for specific medications, an inadequate response to drug treatment, a history of long-term, frequent, or excessive use of some types of medications, and those who are pregnant, planning pregnancy, or nursing. Behavioural headache therapies have a well-established track record, and they may be helpful when applied as a sole treatment or combined with medications. With a focus on headache prevention, these therapies can help reduce the frequency and severity of headaches, headache-related disability, and reliance on medications. Relaxation training, biofeedback, and stress-management have been studied extensively, and they have proven effective for migraine and tension-type headache in both the laboratory and clinical practice (avg. 35–50% headache reduction). The best of the behavioural treatments yield improvements similar to drugs commonly prescribed to prevent migraine and tension-type headache and approximately three times as large as improvements reported with placebo. In addition, initial reductions in headache activity achieved with behavioural therapies appear to endure well after treatment is completed. There is considerable evidence from both meta-analytic and narrative reviews of an extensive research literature that these behavioural therapies can produce meaningful reductions in headache activity. The findings of two separate and exhaustive meta-analytic reviews (funded by the US Agency for Health Care Research and Quality) addressing behavioural management of migraine and tension-type headache will be presented. In addition, the integration of these findings into the multidisciplinary US Headache Consortium’s recently released evidence-based guideline for diagnosis and treatment of migraine in primary care settings will be reviewed.

TI-5

Headache in children and adolescents

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Headache is a common problem in childhood and adolescence. Left untreated, it can have a significant negative impact on functioning and may even continue into adulthood. Increasing recognition of the prevalence, intensity, and chronicity of headaches in children and adolescents has heightened interest in both pharmacological and non-pharmacological treatment approaches. This presentation will review the most common non-pharmacological or biobehavioural approaches—electromyographic and thermal/autogenic biofeedback; progressive muscle relaxation training and related procedures; and cognitive stress coping training—and summarize efficacy data for each single approach, as well as data comparing biobehavioural approaches to one another and to some medications. Treatments meeting established efficacy criteria will be identified and concerns regarding application of such criteria discussed. Factors associated with improved outcomes and possible mechanisms of therapeutic change will be reviewed, as will research that has examined alternative delivery approaches (reduced/minimal therapist contact and group administration) and implementation in non-traditional settings (at school vs clinic). Advantages from augmenting biobehavioural treatment with parent-mediated pain behaviour management strategies and from adding a developmental perspective (that addresses cognitive, self-regulation, and psychosocial factors that arise at various stages of development) to evaluation and treatment will be discussed. The talk will conclude with suggestions for assessment and treatment, as well as for the conduct of future research (investigation of patient–treatment interactions, the role of comorbid conditions, varied modes of administration, and setting effects).

TI-6

New results in neurofeedback training in children suffering from migraine

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Objective The aim of present study is the investigation of the following questions: (1) to what extent the regulation of excitability in cortical networks, as indicated by surface-negative slow cortical potentials ( SCPs), is impaired in...
migraine patients and (2) to what extent training of SCP self-regulation by means of biofeedback and instrumental learning procedures could influence attack frequency and severity.

**Subjects and methods** Ten children suffering from migraine without aura (age – 10.7 ± 1.56) and 10 healthy children (age – 10.1 ± 0.63) participated in 5 sessions of biofeedback and instrumental conditioning of their SCPs. The migraine children were than treated during the 3 additional sessions. EEG was recorded from Cz with a time constant of 5 s and high pass filter of 35 Hz. DC shifts towards increased or suppressed negativity relative to the 2 s prettrial baseline were demonstrated by delayed visual feedback. Self-regulation of SCPs was carried out during 3 s interval between two acoustic stimuli (S1 and S2). The children had to react on S2 with pressing a button and received feedback in 3 s after a trial has been finished. The amplitude of SCP (total CNV) was presented as stripe moving to the right or to the left according to changes in brain activity. Each session contained the following phases: 60 trials feedback and 30 trials voluntary control (increase and suppression of negativity).

**Results** All subjects (migraine and healthy children) regulated their SCPs successfully, especially in the last sessions. Migraine children were characterized by difficulties in suppression of cortical negativity compared with healthy controls. This may explain the increased amplitudes and reduced habituation of event-related potentials in migraine. Before an attack the self-regulation of SCPs was more impaired than after an attack. The SCPs-feedback training resulted in significant reduction of attack frequency and severity in children suffering from migraine (70% responders after 3 months follow-up) compared with wait-list group (10 age-matched children). After the training a significant reduction of increased SCPs amplitudes and normalization of abnormal SCPs habituation were observed. Family environment seems to be the important predictor of clinical efficacy of the feedback training. The results show that neurofeedback of SCPs may be used as an alternative non-pharmacological prophylactic treatment for juvenile migraine.

**TI-7**

**Combining behavioural treatment and medication**

K. A. Holroyd

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Behavioural interventions may be used to enhance the effectiveness of drug therapy, as an alternative to drug therapy (e.g. in the pregnant or nursing woman), or to produce improvements in areas not readily improved with drug therapy (e.g. modification of stresses that trigger or exacerbate headaches). This presentation will summarize available data on the relative effectiveness and combined effects of drug and behavioural therapies as well as information on the variables that predict treatment response. Meta-analyses of trials that have evaluated preventive drug and behavioural therapies, and trials that have evaluated the benefits of combined drug and behavioural therapies will be summarized. Innovative methods of delivering behavioural interventions and the incorporation of interventions that teach decision making skills for effectively using acute therapies into behavioural treatment also will be noted.

**TI-8**

**Behavioural issues in the management of chronic daily headache**

A. E. Lake

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Chronic daily headache (CDH) is associated with more behavioural disturbance than intermittent migraine, and poses special problems in behavioural treatment. CDH can be defined as >15 days of headache/month, although only 37% may actually have daily headache, and some have continuous head-pain. In clinical settings, most patients with CDH also have frequent episodes of severe migraine. Controlled studies of cognitive-behavioural therapies for migraine, such as biofeedback and relaxation therapy, have a prophylactic efficacy of about 50%, roughly equivalent to propranolol. Patients with chronic daily headache (CDH) are more likely to overuse symptomatic medication (and in some cases abuse analgesics), have more psychiatric comorbidity, more functional impairment and disability, and are at least as likely to experience stress-related intensification of headache as those whose episodic headaches occurring <15 days/month. Despite the significance of these behavioural factors, patients with CDH (particularly those with migrainous features) are less likely to benefit from behavioural treatment as a sole modality without concomitant prophylactic medication than is the case for episodic tension-type headache and migraine sufferers. The combination of behavioural therapies with prophylactic medication creates a synergistic effect, increasing efficacy beyond either type of treatment alone. Compliance-enhancement techniques, including behavioural contracts for patients with severe personality disorders, can increase adherence to behavioural recommendations. This talk will present a multiaxial approach to assessment of the headache patient as a simple but comprehensive means of identifying appropriate targets for behavioural treatment, using the following axes: I – Headache diagnosis, frequency, severity; II – Analgesic/abortive use, overuse, and misuse; III – Cognitive-behavioural analysis of stress-related risk factors, reactivity to pain, and possible reinforcement of dysfunctional pain behaviour; IV – Comorbid psychiatric disorders; and V – Functional impact of headache and disability. The evidence supporting the importance of these dimensions in CDH will be reviewed, including a discussion of evidence for significant differences in treatment response for migraine vs those with >15 headaches/month, true daily headaches, and continuous head-pain. Pathophysiological aspects of CDH will be
addressed, followed by a discussion of cognitive-behavioural methods of addressing these issues.

TI-9

Biofeedback and behavioural therapy: ‘hands-on’ introduction for the primary care provider

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Although many behavioural applications for chronic headache require therapists who possess specialized skills and training, frequent office visits, and sometimes special equipment (e.g. biofeedback), there remains much that the primary care provider and allied care providers can do that is brief, time efficient, and likely to be of value to patients in managing their pain levels and reactions. The following topics will be reviewed, along with audience discussion, brief demonstrations, and role play exercises as appropriate: meeting patient needs at the first consultation, patient education and self-help approaches, self-monitoring to facilitate awareness of headache antecedents and consequences, practical considerations for biofeedback and related approaches, implementation strategies for simplified relaxation treatments, use of reinforcement contingencies to decrease pain behaviour and to increase well behaviour, impact of recurrent pain on significant others and the family unit, and guidelines for selecting therapists when lesser efforts have met with minimal success and more intensive treatment is warranted.

TI-10

Stages of change: enhancing adherence to behavioural treatment recommendations

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It has been said that the Achilles’ heel of behavioural interventions is adherence – patients like health care professionals, even with the best of intentions, find it difficult to change behaviour, particularly longstanding patterns of behaviour. In this session techniques for identifying and addressing obstacles to adherence prior to making specific behavioural recommendations, for tailoring recommendations to patients, and for enhancing adherence with resultant behavioural recommendations will be addressed. The Behavioural Migraine Management program which employs a workbook and 10 audiotapes to enhance adherence with a range of behavioural recommendations will be used to illustrate these techniques. Behavioural activities in the program include headache monitoring, learning and application of relaxation skills to headache management, identification of triggers and prodromal (‘early warning’) signs, effective use of migraine medications, and acquisition of stress-management and self-regulation (biofeedback) skills for managing headaches.

TI-11

Maintaining focus, measuring change, and increasing the efficiency of behavioural treatment

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This section of the ‘Behavioural Aspects of Headache Management Course’ will provide an opportunity for interaction and discussion of behavioural strategies for assessing the course of therapy, enhancing and measuring outcomes, and containing costs of non-pharmacological therapies. Techniques for identifying patients who are candidates for behavioural interventions will be discussed. Likewise, strategies for shaping appropriate patient expectations and motivating patients for participation in behavioural therapies will be reviewed. For many patients, behavioural therapies can be administered effectively in limited-contact or group treatment formats. In limited-contact or ‘home-based’ treatment, behavioural therapies are introduced in 3–4 monthly clinic sessions, and written materials and audiotapes are provided to assist patients in acquiring self-regulation skills at home. For both adolescents and adults, limited-contact behavioural therapies have proven as effective as therapist-administered clinic-based treatment and are much more cost-effective. Likewise, available evidence indicates group treatment also can be an effective strategy for providing headache therapy in a cost-conscious fashion. Dr Penzien has extensive experience in directing a multi-specialty head pain treatment programme. He will describe the structure of his programme and will focus specifically upon the application of home-based behavioural headache treatment strategies (to include discussion of recommended treatment inclusion/exclusion criteria, headache assessment and compliance interviews, outcomes assessment, strategies for treatment refractory patients, etc.). Discussion and interaction among the attendees will be encouraged.

TI-12

Managing the difficult patient: analgesic misuse and abuse; personality disorders

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Headache specialists will encounter patients with patterns of analgesic misuse and abuse, and personality disorders. However, few guidelines exist for the management of the headache patients who present with these difficulties. The overuse of analgesics and abortives can be resistant to change, and patients often relapse. As many as 60% of CDH patients may return to analgesic overuse when preventative medication is withdrawn, despite experiencing a period of significant improvement after detoxification, explanation of the analgesic rebound problem, and an effective prophylactic medication programme. CDH patients who fail to improve are
significantly more likely to persist in the abuse of symptomatic drugs despite medical efforts to limit their use. And, analgesic overuse has been shown to be a significant predictor of poor outcome 2–4 years later. Personality disorders may be present in 10–13% of the general population. Borderline personality disorder (BPD) has a prevalence of about 1.8% of the general population, with prevalence rates increasing in patients with comorbid psychopathology and substance abuse. The prevalence of severe headaches in the borderline patient is as high as 60%, and between 24% of men and 52% of women with BPD have comorbid migraine. Reported histories of abuse are common in BPD, but must be interpreted with caution. Recent research has shown reduced hippocampal volume; hypometabolism in the premotor, prefrontal and anterior cingulate cortex, as well as the thalamic, caudate and lenticular nuclei; serotonergic dysfunction, and abnormal responses to opioid antagonists. Opioid medications may be toxic in some patients with BPD. Treatment should combine appropriate pharmacotherapy with ongoing psychotherapy. Early identification of analgesic abuse and personality disorders improves the course of treatment. Patients can benefit from learning methods of emotional self-regulation, including biofeedback. However, treatment often requires explicit contracts, consistent limit-setting, compassionate confrontation, and clear communication among different treatment providers to counteract the BPD patient’s tendency to split, and play one treatment provider against another. Treatment providers must learn to recognize and manage countertransference reactions. The use of explicit treatment contracts can help sustain patients in treatment, reduce the risk of substance abuse, and minimize distress in the treatment provider. Headaches and other symptoms in the analgesic abusing and BPD patient can improve over the course of a long-term relationship, with clearly defined limits. Non-compliant patients may need to be terminated from treatment.
Animal models of migraine

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Migraine is quintessentially a disease of humans so that modeling migraine in the laboratory is a significant challenge (1). Thus far, migraine models have been restricted to those which study the acute attack process, with models for prevention lagging behind in development. Acute attack models have studied the cranial circulation, its peripheral innervation by the first (ophthalmic) division of the trigeminal nerve and the central projections of that nerve to the trigemino-cervical complex. The study of the cranial circulation using the arteriovenous (AV) shunt model (2), and pharmacological studies in other vessels that were triggered by observations of the clinical effect of serotonin were important in the development of sumatriptan (3). The development of the plasma protein extravasation model with a sterile inflammatory response in the dura mater allowed study of the peripheral trigeminal terminals (4), while the intravital microscopic study of meningeal vascular diameter (5) has permitted study of the peripheral trigeminal synapse. Studies of the central trigeminovascular synapse have presented a further target, which may have the advantage of not involving peripheral vascular mechanisms (6). Measurements of neuropeptide markers of trigeminal activation have allowed comparisons between trigeminovascular activation in humans and experimental animals providing an important link from bench to bedside (7). The future is bright for headache in general and migraine in particular as we explore further the systems that have been studied and open up new avenues to develop medicines to treat migraine and other primary headache syndromes.

References


Receptor pharmacology in migraine treatment

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The serotonin receptor family is currently grouped into seven subfamilies (5-HT1 to 5-HT7) and 14 receptor subtypes that have different anatomical locations. All the receptors, apart from the 5-HT3 receptor which is a ligand gated ion channel, belong to the superfamily of seven transmembrane domain G-protein coupled receptors. Receptors within each subfamily share high amino acid identity and couple to the same second messenger system but each has a unique pharmacological profile that can be delineated using selective drugs. Research and drug development aimed towards modulation of central and peripheral 5-HT systems and targeting of specific 5-HT receptors has produced a wealth of clinically proven therapeutic agents and valuable research tools. Triptan 5-HT1B/1D receptor agonists inhibit the trigemino-vascular system that becomes activated in migraine and so are highly effective acute antimigraine agents. There is also now some proof of concept with 5-HT1F receptor agonists that lack the vasoconstrictor effects of the Triptan class. 5-HT1A receptor activation may be involved in the pro-nauseant effects of some antimigraine agents. 5-HT2B receptor antagonism has been suggested as a putative mechanism for migraine prophylaxis. 5-HT3 receptor antagonists alone have little efficacy as antimigraine agents but may have some utility in the prevention of nausea and emesis – their main utility is during cancer chemotherapy. 5-HT4 receptor antagonists have been used for gastric motility disorders and may play a role in the efficacy of some gastroprokinetic agents. Drugs such as metoclopramide act broadly as an antagonist at 5-HT3 receptors and an agonist at 5-HT4 receptors (as well as the dopamine D2 receptor subtype) and has proven useful in treating the gastrointestinal stasis and nausea associated with a migraine attack perhaps also improving the efficacy of antimigraine agents that are affected by the disease related g.i. stasis. Most recently, agonists acting at 5-HT7 receptors have been shown to be vasodilator in the meningeal vasculature giving rise to the suggestion that 5-HT7 receptor antagonists may be suitable as migraine prophylaxis agents. Given the wide success of serotonergic drugs in the treatment of migraine and the large number of 5-HT receptor subtypes and their isoforms which have yet to be fully investigated it is not surprising that efforts to discover new drug therapies are
considerable in this area. Other novel approaches to anti-migraine treatments are targeted at specific sites in the intracranial vasculature to reverse migraine-triggered vaso-dilation and sites on the peripheral central sensory neurones that could modulate of transmission within the trigemino-vascular nociceptive pathways and prevent the central trigeminal sensitization 'wind-up' phenomenon that appears to accompany an attack.

TII-3
How pharmacology translates into efficacy and side effects in the treatment of migraine
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The development of a new highly specific serotonin (5-HT) agonist in the early nineties improved antimigraine therapy and achieved both higher efficacy and fewer side effects. The key to achieving both was the development of drugs which bind highly specifically only to those receptors involved in the pathophysiology of migraine pain. Since the early 20th century, ergot derivatives were the classical anti-migraine compounds. Unlike modern antimigraine drugs, ergots exhibit affinities to various receptor families such as adrenergic receptors, dopaminergic receptors and – more important for anti-migraine efficacy – serotoninergic receptors. Clinically, the typical side effects of ergots reflect these affinities: (a) ergots cause an increase in blood pressure by the activation of α- and β-adrenergic receptors (with high affinity to α2A and α2C and moderate affinity to β3 receptors) through vasoconstriction; (b) most patients describe an increase of nausea following ergot administration which is caused by activation of central dopaminergic receptors (high affinity to D2, moderate to high to D3 and D4 receptors) and (c) resolves migraine pain by activating 5-HT1B/D receptors in cerebral vessel and brain stem. Within the serotoninergic system, ergots possess high affinities to 5-HT1A and moderate affinities to 5-HT2A and 5-HT2C receptors as well. The latter affinities might be of special importance since 5-HT2 receptors are expressed in coronary vessels and mediate vasoconstriction as well. The family of 5-HT1B/D agonists (shortly triptans) has grown within the last 3 years and in most countries 4–5 triptans are now available. Compared to ergots, all triptans share similar receptor characteristics: high affinities to 5-HT1B/D receptors, some possess high affinities to 5-HT1F and 5-HT7 receptors (the relevance of these receptors remains to be determined), but only low affinity to 5-HT2 receptors and no affinity to adrenergic or dopaminergic receptors. These characteristics are reflected in the improved profile of side effects: triptans hardly affect blood pressure and do not increase but rather reduce nausea. Despite these similarities in their pharmacological profile, triptans can vary significantly with regard to their pharmacokinetic characteristics. An important aspect is the time in which peak plasma levels are reached (tmax). This parameter varies between 50 min and 3 h and corresponds clinically with the time of relief onset. Another important parameter is the oral bioavailability, which ranges between 14 and 70%. Although it has been suggested that bioavailability may reflect a more consistent efficacy over multiple attacks, this is less clear and still needs to be confirmed. In all clinical trials recurrence rates of up to 40% have been reported. Initially this was thought to be the result of a short half life (2 h for, e.g. sumatriptan), but since recurrence rates do not decrease significantly in triptans with half lives 6–10 times as long (e.g. 12–25 h for frovatriptan) other properties appear to determine the recurrence rate.

TII-4
Can headache be shown by imaging?
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New functional imaging techniques including SPECT, PET and fMRI are increasingly being focused on the investigation of primary headache disorders. This lecture will review the information relating to headache gleaned thus far using these new imaging techniques.

TII-5
The pathophysiology of aura
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Spreading cortical depression of Leao (SCD) may be the underlying mechanism of migraine aura. Investigation of this concept in humans, however, remains far from complete. During experimental SCD, excitable neurons in the cortical surface fires synchronously and become electrically silent for up to 30 min. This neuron depolarization propagates across the cortical surface at a rate of 3–7 mm/min. The early depolarization phase of SCD is accompanied by redundant flow and oxygen delivery to the tissue. Most clinical studies linking SCD to the neurological features of migraine aura have been indirect, using measurement of blood flow. Magnetoencephalography (MEG), a non-invasive technique may be used for mapping magnetic fields arising from cortical electrical activity. DC MEG shifts are a direct measurement of neuronal excitation. DC MEG field shifts occurred during spontaneous and visually induced migraine aura resembling those arising from SCD crossing a sulcus in animal models. Multi-phasic forms of the MEG waves during aura were typical of an extended propagating wave of excitation. Functional MRI-BOLD studies confirmed transient hyperaemia and hyperoxia during the early stage of the migraine attack. The mechanisms whereby SCD is triggered in vivo may be fundamental to migraine susceptibility. Transcranial magnetic stimulation has confirmed that the excitability threshold of the occipital cortex in migraine sufferers is low, compared to normal. The concept of hyper-excitability is entirely compatible with a heightened susceptibility to spontaneous or triggered synchronous depolarization of occipital cortex neurons that initiates a
spreading depression-like event. Based on these findings, a model of visually induced migraine aura and headache has been established and refined in our laboratory. First, using fMRI-BOLD for assessing neuronal function and a checkerboard-patterned visual stimulus delivered at a rate of 8 Hz, visual stimulation was associated with immediate neuronal activation in occipital cortex, though not confined to primary visual cortex. This visual stress initiated spreading suppression of the initial activation at rates compatible with SCD. Multiple events were evoked from different regions of the occipital cortex bilaterally. MEG measurements using a different visual stimulus designed to activate primary visual cortex alone, by their more direct nature confirmed the multifocality of neuronal excitation and DC MEG shifts. Spontaneous auras, however, were associated with DC MEG shifts that emanated from less widespread regions of occipital cortex, although still from regions beyond the primary visual cortex. Thus hyperexcitability of widespread regions throughout occipital cortex provide the susceptibility for triggering SCD and aura in migraine sufferers.

TII-6

The scientific basis of cluster headache and other short-lived headaches

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Although treatment is still empirical, much recent thinking about trigemino-autonomic headache has been devoted to the pathophysiology of these syndromes. Cluster headache has been attributed to an inflammatory process in the cavernous sinus and tributary veins. However, given the circadian rhythmicity and unilaterality of the symptoms, a purely vasogenic cause cannot explain the entire picture of cluster headache. There does seem to be a genetic component, although this is limited to a small number of observations. Recent electrophysiological and NMR-spectroscopic data are promising and strongly support the increasingly accepted concept of a central origin for initiation of cluster headache. Positron Emission Tomography (PET), as one of the most refined techniques in visualizing in vivo changes in neuronal activity, has provided unambiguous information regarding the area concerned with the source of cluster headache attacks. Using PET, for the first time a possible site of the central origin of cluster headache has been visualised in the hypothalamic grey matter. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is among the rarest idiopathic headache syndromes. Even though there are marked differences in the clinical pictures, such as the frequency and duration of attacks and the different approach to treatment, many of the basic features of SUNCT, such as episodicity, autonomic symptoms and unilaterality, are shared by other headache types, such as cluster headache and CPH. This suggests a pathophysiological similarity to these syndromes and prompted the suggestion to unify them on clinical grounds as trigeminal-autonomic cephalgias (TACs). Using functional magnetic resonance imaging (fMRI) in SUNCT syndrome, activation was seen in the ipsilateral inferior posterior hypothalamic grey when comparing the pain attacks with the resting state. The similar activation pattern in functional imaging studies suggests considerable commonalities between SUNCT and cluster headache. Indeed, the data may explain the episodic nature of the pain. If this biological model is correct, the underlying cause for trigeminal autonomic cephalgias may be similar and the variation in duration and frequency might be generally dependant on a different disorder of the inferior posterior hypothalamic neurons, perhaps a modulation of neuronal activity or a different involvement of the trigeminovascular system. This might explain the relatively different phenotypes of these related syndromes. There is a strong need to investigate other related idiopathic headache syndromes such as chronic paroxysmal hemicrania and hemiocrania continua to discover the anatomical or functional basis for the variation in trigeminal autonomic cephalgias.

TII-7

Placebo

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The use of placebo is recommended by the Drugs Trial Committee of the IHS. In migraine studies with analgesics or triptans, the placebo effect for the improvement of headache from severe or moderate to mild or no headache after 2 h is between 20 and 30%. For the end point pain free, the placebo effect is between 6 and 12%. Subcutaneous placebo has higher efficacy (34%) than oral application (26%). The placebo effect is identical treating migraine attacks at home or in the hospital. Children and adolescents have higher placebo rates than adults. Placebo rates are higher in the USA than in the rest of the world. In migraine prevention trials, placebo responses are more variable than in trials investigating the treatment of acute attacks. Information about possible side effects may lead to these side effects (e.g. weight gain) with placebo treatment. Patients with anxiety disorders report more often headache as side effect of placebo treatment than patients with diabetes mellitus or angina pectoris. The new Declaration of Helsinki restricts the use of placebo in cases where an effective treatment is available. The use of placebo, however, is the only way to detect whether the study sample of patients is representative of the general population and whether the side effect profile deviates from the expected pattern.

TII-8

Pathophysiology of daily headache

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Chronic daily headache (CDH) generally refers to the occurrence of headache on more than 15 days per month ...
or 180 days per year, in the absence of an underlying structural or systemic disease. Primary chronic daily headache disorders of long-duration (headache duration >4 h) include chronic tension-type headache (CTTH), chronic ('transformed') migraine (CM), new daily persistent headache (NDPH), and hemicrania continua (HC). Population-based studies in the USA, Europe, and Asia, have consistently demonstrated an overall prevalence of CDH between 4 and 5%. In the USA, CDH accounts for the majority of patients seen in subspecialty practice, with 70–90% of patients having evolved from an intermittent to a chronic pattern of headache. The majority of patients with CDH have chronic migraine (70%) while up to 20% have CTTH. Chronic daily headache may be associated with the overuse of symptomatic (immediate-relief) medications. Analgesic overuse ranges from 50 to 82% in clinic-based samples of CDH, while community based surveys have shown analgesic overuse in 30% of CDH patients compared to 10–12% of patients with episodic headache. Although the pathophysiology of CDH is not exactly known, the prevailing theories include central neuronal sensitization, dysfunction of the central antinociceptive network, and enhanced nociceptive transmission from the effects of excessive analgesics on serotonin metabolism and critical brainstem nociceptive circuits. This lecture will review these prevailing hypotheses in light of recent biochemical, neurophysiological, neuroimaging findings.
Migraine is common, disabling and important to neurologists. Migraine and headache are the leading reasons for visits to neurologists in the USA, accounting for about 20% of all outpatient appointments. By far, the most common headache disorder in the general population is episodic tension-type headache, which affects 40% of the population. Migraine is also a very common primary headache disorder affecting 18% of women and 6% of men. Though migraine can begin at any age, about 50% of all cases begin before the age of 20. As a consequence, diagnosis during childhood and adolescence is especially important. The prevalence of migraine rises through early adult life, peaks around age 40 and then declines. Prevalence is highest between the ages of 25 and 55. Part of the reason the condition has such a big impact in the workplace is that it affects people during their peak productive years. Race influences migraine prevalence in the USA. Migraine prevalence both for females and males is highest in Caucasians, intermediate in African-Americans and lowest in Asian Americans. Migraine prevalence is inversely related to income and education. The burden of migraine is considerable and greatest for the most severely affected sufferers. The individual burden is determined by symptoms during attacks, anticipation of symptoms between attacks, by the decrease in quality of life compared with the general population, and by the lost economic opportunity. Societal burdens include direct costs such as the cost of medical care and indirect costs which refer to the impact the illness has on work and other endeavours. The burden of the disease is the target for effective therapy. Despite improvement, migraine remains under diagnosed and under-treated. Of the migraine sufferers who consult a doctor, about two-thirds consult PCPs, while 16% consult neurologists or headache specialists. Only 48% of migraine sufferers identified by direct questionnaires have received a medical diagnosis. The proportion of patients using prescription drugs is increasing but most migraineurs still treat with over-the-counter products. Resolving barriers to care requires improvement in consultation, diagnosis, initial treatment and ongoing monitoring.

References
Headache diagnosis and testing

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Headache is, without question, one of the most common symptoms that neurologists evaluate. Not unexpectedly, the differential diagnosis of this highly prevalent symptom is vast, with over 300 different headache types and aetiologies. Understanding headache classification and diagnosis is therefore a clinical imperative and a requisite for diagnostic testing and treatment. The cause or type of most headaches can be determined by a careful history and physical examination. The clinical imperative is to recognize the warning signals, which should raise red flags and prompt further diagnostic testing. In the absence of worrisome features in the history or examination, the task is then to diagnose the primary syndrome based on the clinical features. If there are atypical features or a lack of response to conventional therapy, the diagnosis should be questioned and the possibility of a secondary headache disorder revisited. Laboratory testing is not routinely performed in the evaluation of a headache patient. The necessity for and extent to which laboratory tests are obtained should be determined by the clinical suspicion of a secondary headache disorder. Occasionally, depending on the medications prescribed, a pertinent screening baseline laboratory assessment may be necessary. The American Academy of Neurology (AAN) concluded that EEG lacks both sensitivity and specificity and should not be considered useful in the routine evaluation of patients with headache or to exclude a structural cause. The AAN has also concluded that CT and MRI are not likely to significantly increase diagnostic yield or uncover pathological entities therefore use is not warranted in patients whose headaches fit a broad definition of recurrent migraine and who have had no recent change in headache pattern, no history of seizures and no focal neurological findings. No formal guidelines exist on the use of lumbar puncture (LP) as a diagnostic test in headache. However, LP is critical in situations such as a first unusually severe headache or thundertcap headache, patients with a subacute and progressive headache syndrome, and those suspected of having an acute intracranial infection or raised or low intracranial pressure. MR angiography and venography are safe, useful screening procedures for a suspected aneurysm or AVM in patients who have not had a subarachnoid haemorrhage (SAH) and for those suspected of having a carotid or vertebral dissection. It is also the preferred imaging modality for the detection of a thrombosed cerebral venous sinus. Otherwise, there is no reason to perform angiography in a patient with headache who has a normal neurological examination and normal brain MRI.

Acute treatment of migraine

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Pharmacological treatment of migraine can involve both acute and preventive interventions. Patients with frequent headaches may require both approaches. Acute treatment is aimed at aborting the headache, while preventive treatment is geared toward reducing the frequency and severity of anticipated attacks. Acute migraine medications include non-specific and specific treatments. Non-specific agents are those effective for any pain disorder and include NSAIDS, combination analgesics, opioids, neuroleptics/antiemetics and corticosteroids. Specific therapies, such as ergotamine-containing compounds, DHE, and triptans, are effective only for the treatment of migraine and related disorders. A recent government-funded meta-analysis of acute migraine therapies classified treatments into several groups ranging from most to least effective. Group I demonstrated the best evidence for efficacy-consistent statistical significance and pronounced clinical benefit. Included in group I are aspirin/acetaminophen/caffeine, aspirin, naproxen sodium, ibuprofen, DHE, all of the available triptans and butorphanol. Group II demonstrated less significant clinical effect and includes a number of narcotics, several non-steroidal agents, prochlorperazine and intranasal lidocaine. Group III drugs, which showed either mixed results in studies or small effect sizes, include butalbital/aspirin/caffeine, ergotamine ± caffeine and metoclopramide. Group IV includes those deemed ineffective including acetaminophen, chlorpromazine IM, and lidocaine IV. Group V agents are those for which benefits are unknown, i.e. dexamethasone IV and hydrocortisone IV. When choosing acute therapy several factors need to be considered. Time to onset of headache, associated symptoms, frequency of headache, and the patient’s past therapeutic experience including successes and failures as well as preferences are important considerations. The formulation selected depends on the desired time to onset of action. Oral preparations are generally the least rapidly acting medications. Additionally, onset of some oral preparations may be delayed by migraine-associated gastroparesis. Among the non-oral formulations, suppositories have the slowest and intravenous drugs the fastest onset of action. When choosing an agent for initial acute therapy, the intensity of the treatment should match the severity of the attack. It is important to try to get the treatment right the first time for effective reduction in pain and disability, enhanced patient satisfaction, reduced drop-out rates, and more cost-effective care.
TIII-5
Preventive management of migraine
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Preventive therapy is recommended for recurring migraines that significantly interfere with the patient’s routine despite acute treatment; frequent headaches, when acute therapy is ineffective or associated with adverse effects; and when acute treatment is used more than twice per week. Goals of preventive therapy are to decrease headache frequency, improve responsiveness to acute therapy, and improve function. The major classes of preventive agents include β-adrenergic blockers, antidepressants, calcium channel antagonists, serotonin antagonists, anticonvulsants and NSAIDS. For initiation of preventive treatment coexistent or comorbid diseases should be considered. For example, when treating migraine and hypertension or angina, β-blockers or calcium channel blockers may be effective for all conditions. However, in the asthmatic or depressed patient or insulin-dependent diabetic, β-blockers should be used with caution. Patients treated with preventive medication may continue to have attacks of episodic migraine necessitating use of preventive and acute medication together. Under these circumstances, the amount of acute medication must be limited to prevent the development of drug-induced daily rebound headache and loss of efficacy of the preventive medication, which is one of the causes of secondary failure of preventive medication. Non-pharmacological treatment measures are an adjunct to preventive therapies but they can also be effective alone. They are particularly beneficial for patients who are intolerant of medication and for those in whom abortive and preventive agents are contraindicated or ineffective. Pregnant women and analgesic overusers are also prime candidates for non-pharmacological management.

TIII-6
Chronic daily headache
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The term chronic daily headache (CDH) has not been formally accepted worldwide and continues to generate scholarly debate as to its validity and precise criteria. The term is best considered an ‘umbrella’ concept under which several related or unrelated headache disorders may reside. Chronic daily headache includes the following primary headache disorders: transformed migraine, chronic tension-type headache, new daily, persistent headache, and hemiconia continua. CDH generally occurs more than 15 days per month with a duration of longer than 4 h per day. Study populations show that 30% to 80% of patients report daily pain, but in practice, this is actually closer to 80% to 90%. The source of pain in CDH is unknown, however, there are a number of theories. Diagnostic studies do not establish the diagnosis but rule out accompanying and mimicking organic diseases. It is particularly important to rule out intracranial disease, occipitocervical disorders, sinusitis, systemic conditions and alterations of CSF pressure. Acute treatment for CDH is directed at the acute migraine or migraine-like events and includes standard abortive medications for migraine. Medication should not be used for more than two headaches per week and not more than two doses per headache. Non-medical treatment, as well as aggressive preventative and acute pharmacotherapy are required. Often critical to outcome is the treatment of neuropsychiatric, comorbid and behavioural disturbances. These conditions often interfere with headache treatment, frustrating both physician and patient. If the patient is rebounding, it is necessary to substitute acute medications that do not cause rebound for the offending regimen. A respectable percentage of patients with intractable chronic headache will not respond to outpatient management and require aggressive treatment in a hospital setting. Principles of treatment include: detoxification (if necessary); aggressive attempts to terminate the intractable painful cycle using individual or cotherapeutic regimens from an expanding list of parenteral therapies and protocols; and strategic confrontation of behavioural and psychological factors that frequently serve to confound the ongoing painful process. Rehabilitational concepts for recovery are implemented during this time in the most effective programmes. Thoughtful reconsideration of organic possibilities must likewise occur. Development of an effective abortive and preventive program so as to allay fear and reduce the likelihood of recidivism and headache recurrence represents an important element in the hospitalization process.

TIII-7
Cluster headache and other short-lasting headaches
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Two major temporal patterns of cluster headache (CH) have been identified by the International Headache Society. The episodic type (ECH) is the most common and is characterized by discrete attack and remission phases, while the chronic type (CCH) is defined by attacks that occur daily for more than one year without remission periods or with remission periods that last less than 14 days. Cluster headache is not common. In the general population, the prevalence is approximately 0.4%. However, this condition may encompass 10% of the patients seen in a headache clinic. Cluster headache occurs predominantly in males and can occur at any age including childhood. It usually begins in the third or fourth decade in males with an average age of onset at 28 years. When compared to the prevalence of CH in the general population, first-degree relatives have about a 14-fold increased risk of developing CH. The most striking feature of CH, and from which its name is derived, is the unmistakable stereotyped periodicity. Individual cluster attacks occur during attack phases known as cluster periods.

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Most patients have one to two annual cluster periods, each lasting between 1 and 3 months. Cluster periods interrupt longer-lasting remission periods that usually last 6 months to 2 years. Cluster headache also has a striking circadian periodicity, with most individuals having one to three attacks per day although some may have as many as eight attacks per day. Cluster attacks are almost exclusively unilateral. The pain is excruciatingly severe and is located around the orbit and temporal region. Cranial autonomic symptoms occur in the vast majority of patients and are integral to the diagnosis. Treatment includes both acute therapy designed to abort individual attacks as well as prophylactic therapy to prevent recurrent attacks that occur daily during a cluster period. In a small number of patients who are resistant to aggressive medical therapy, or when there are contraindications or intolerable side effects, surgery may be a viable option.
Epidemiology of headache

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Headache and migraine occur at all ages from the newborn period to late adulthood. The incidence only varies by age and other variables. However, in unselected child populations, headache is rare during the first years of life. In Finnish studies, headache occurred in 2%, 3% and 4% up to ages 2, 3 and 4 years, respectively. In an extensive population-based study of approx. 5500 children at age 5 years, headache occurred in 20%, but was frequent or fairly frequent in less than one percent only. At the start of school, which takes place at the age of 7 in the Nordic countries, one third experienced disturbing headache and 3–4% migraine. In the beginning of school attendance, an occasional headache significantly increases but returns to the preschool level within one year. At the same time, the prevalence of migraine and other recurrent headaches remains unchanged. During school years, there is a continuing increase in the prevalence of both migraine and other headaches. At age 15, approximately two-thirds of children have disturbing headache and 8% migraine. Few secular trend studies show a remarkable increase in headache and migraine in children, which is in agreement with observations made from adult populations. In a Finnish study, the prevalence of overall present headache had increased from 14% in 1974 to 52% in 1992. Similarly, the increase in the prevalence of migraine was from 1.9% in 1974 to 5.7% in 1992. In a prospective population-based study, 1205 children were followed from the age of 7 years to 22 years. The rise was found in all frequency categories of more than once a month. A similar increase was shown in migraine: from 2.7% to 10.6%. The prevalence rate rose more significantly in girls than in boys. Migraine disappeared during follow-up totally in every fourth child. The discontinuation of migraine attacks was more probable if the onset had been before the age of 7 years. At the final follow-up, 7% suffered from migraine. Of children who had migraine at age 7, 11.5% continued to suffer from attacks, but 5% of children who had had no attacks at age 7 had migraine at age 22. A current question for study is why headache is increasing, and probably worldwide. Many suggestions have been made – e.g. changes in psychosocial environment, family structure, nutrition, and life-style. Whatever the causes are, it is obvious that our children are not doing well.

Paediatric headache classification update: 2001

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The objective is to review the classification systems for paediatric headache. Over the past 50 years, there has been a significant effort to define the clinical features which best characterize paediatric headache syndromes. The most carefully studied is paediatric migraine. Valquist was the first to venture into the development of diagnostic criteria for paediatric migraine in 1955. For the next 30 years, modifications were made in attempt to make these criteria more specific and sensitive by authors such as Bille, Prensky and others. In 1988, the IHS published its landmark classification system, reshaping the classification system and markedly enhancing the specificity of diagnostic criteria. However, is it useful in children? For the past decade, research has been conducted in an effort to validate the IHS criteria for paediatric patients. It became apparent early that these criteria were exceedingly specific, but lacked sensitivity for paediatric patients. Focus then turned to developing modifications to the IHS criteria, which would be more developmentally sensitive. Authors such as Rossi, Mortimer, Raieli, Wober-Bingol, Seshia, and Winner have vigorously investigated this topic. The purpose of this session is to review the results of the recent body of literature as we work toward a consensus in the clinical definition of paediatric migraine.

Childhood abdominal migraine

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It has long been recognised that migraine is not merely a headache, but a syndrome where headache is associated with other symptoms. In children the associated symptoms may be more prominent than the headache and in many cases may occur in the absence of headache. These associated abdominal symptoms form recognised syndromes such as abdominal migraine and cyclical vomiting, although it is not unusual to see a degree of overlap clinically between the syndromes and they may collectively be referred to as ‘the periodic syndrome’. Recurrent episodes of abdominal pain are a common problem in childhood. About 8% of school children report two or more episodes in the past year. The most frequent cause identified is constipation, but in many children no organic cause is found. From clinical observation it has been possible to identify a small number of children with
TIV-4

Chronic daily headache in childhood update

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Chronic daily headache (CDH) is a debilitating and painful condition. In this update, we will review the diagnostic criteria employed in adults and discuss their applicability in childhood CDH patients. We will present an approach to the youngster suffering with CDH, including diagnosis, work-up and treatment considerations. Finally, we will discuss the findings of a multicentre study of CDH in childhood, performed by members of the Pediatric Subcommittee of AHS.

TIV-5

Changing acute migraine treatment

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The greater understanding of paediatric migraine demographics and the increased attention to the disability associated with acute attacks will help guide your management. Migraine often results in school absences as well as restricting sports, recreational and family activities. Rapid and effective relief without added disability is needed. Presently, none of the triptan class specifically designed for acute migraine treatment, have been approved by the FDA for use in the paediatric population. Are triptans as effective in the paediatric population as they are in adults? Recent sumatriptan nasal spray study in adolescents demonstrated pain relief rates of 66%, 64%, 63%, for 5 mg, 10 mg, 20 mg dosages at 2 h. Pain-free response for sumatriptan nasal spray 20 mg at 2 h was statistically significant over placebo. A long-term safety and tolerability study of sumatriptan nasal spray involving 431 adolescents, treating 3272 migraine attacks demonstrated pain relief at 2 h of 76% and 72% for 10–20 mg dosages. Pain-free rates at 2 h were 43% and 40% for 10 and 20 mg dosages, with lower occurrence rates 12 and 15%, respectively. Recent rizatriptan 5 mg evaluation in adolescent migraineurs revealed a 66% pain relief rate at 2 h, which is similar to the response rate seen in adults. Pain-free 2 h response was 37% also similar to adult data. Statistical significance was obtained in a subset of adolescents treating a weekend migraine with pain relief at 2 h of 65% over placebo rate of 36%. The long-term tolerability of sumatriptan nasal spray, rizatriptan and zolmitriptan has been studied across multiple attacks, drug-related adverse events were similar to those reported in the adult studies. The triptans are clearly effective in the adolescent population. The pain relief and pain free response rates in adolescent triptan studies have been similar to that of adults. Changing acute migraine management in the paediatric population will require new study designs and ongoing research to further clarify the proper usage of triptans and other acute treatment strategies.
approach, and do not wish further management. (2) Avoidance of triggers: Many children are aware of factors that trigger their attacks of abdominal pain. These are many and varied, and include the following: stress related to school and family activities; travel; prolonged fasting; alterations of sleep patterns; exposure to flickering or glaring lights; exercise. The insight provided by an appreciation of the migrainous nature of the attacks provides a background against which to modify life-style factors, and occasionally to invoke the help of clinical psychologists. (3) Simple dietary management: In many cases, a diet low in amines results in marked reduction in both the frequency and severity of attacks. (4) Few foods diet: This is a difficult process, and is reserved for children with frequent headaches – my own practice is to use it in children with two or more episodes per week. In such children, it is highly successful. (5) Acute management: Acute management must be explored, as satisfactory management of attacks will often obviate the need for prophylactic drugs. None of the triptans is licensed for paediatric use, nor are they available in child-sized doses, but on occasion in older children I have used nasal sumatriptan with success. Effective acute management can relieve the anxiety and stress associated with frequent, unpredictable and incapacitating headaches, thereby serving as an effective preventative. (6) Drug prophylaxis: This is reserved for the minority of patients whose symptoms are severe enough, and frequent enough, to be interfering significantly with their everyday activities. I find that a satisfactory result can be usually be obtained with one of the following three drugs: propanolol, pizotifen (not available in USA) and cyproheptadine. On occasion I have used clonidine or sodium valproate with apparent success. It is most important that a logical sequence is followed, not necessarily that outlined above, but one that can be explained to the family and to which all members of the clinic staff are signed up.

TIV-7

Behavioural treatment

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The increasing recognition of the prevalence, intensity, and chronicity of headaches in children and adolescents has heightened interest in both pharmacological and non-pharmacological treatment approaches. This presentation will review the most common non-pharmacological or biobehavioural approaches – electromyographic, thermal/autogenic, vasomotor, Doppler, and electroencephalographic biofeedback; progressive muscle relaxation training and related procedures; and cognitive stress coping training – and summarize efficacy data for each single approach, as well as data comparing biobehavioural approaches to one another and to select medications. Treatments meeting established efficacy criteria will be identified and concerns regarding application of such criteria discussed. Factors associated with improved outcomes and possible mechanisms of therapeutic change will be reviewed, as will research that has examined alternative delivery approaches (reduced/minimal therapist contact and group administration) and implementation in non-traditional settings (at school vs clinic). Advantages from augmenting biobehavioural treatment with parent-mediated pain behaviour management strategies and from adding a developmental perspective (that addresses cognitive, self-regulation, and psychosocial factors that arise at various stages of development) to evaluation and treatment will be discussed. The talk will conclude with suggestions for assessment and treatment, as well as for the conduct of future research (investigation of patient–treatment interactions, the role of comorbid conditions, varied modes of administration, and setting effects).

TIV-8

The relevance of psychiatric comorbidity in childhood and adolescence headache

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Research and clinical findings strongly support the importance of psychiatric comorbidity (P-Co) in headache (h) management. P-Co concerns the co-occurrence of one or more psychiatric disorders in patients with an index disease (h). Aetiology, diagnosis, therapy and prognosis of headache may be influenced by P-Co. H clinical features and psychiatric disorders have age-related phenomenology to be considered. Several points need closer examinations. (1) The ‘time’ factor: We need to differentiate current (copresence of disorders in the same time span), lifetime, or successive (the disorders not overlapping in time) P-Co. Specifying the timing is important to avoid confounding the time trend of age-related characteristics with the phenomenology of disorders. Dealing with P-Co allows describing clinical situations without inevitably embracing causal explanations, even if a better specification of the temporal interval may give a valid aid in the systematization of the subject. Therapeutic implications relate both to the negative prognostic weight of presenting P-Co and to the need for tailoring treatment. (2) ‘Which’ psychiatric categories? Whether the diverse psychiatric categories are specifically related to different h subtypes is not well acknowledged. In general, psychopathological disorders present age-related manifestations, not yet well recognized and systematized by paediatric research. The concepts of ‘homotypic’ (continuity of disease phenomenology without strong changes over time) or ‘heterotypic’ (a continuous process assuming different forms over time) comorbidity must deal with biological and psychological developmental changes, and age-related phenomenology of psychiatric disorders. For example, the boundaries between school phobia and separation anxiety disorder (SAD), social phobia or depression, sleep disorders as ‘main’ disorder or expression of the ‘main anxiety disorder’ are not well recognized. Whether child psychiatric disorders are ‘equivalent’ or
predisposing to adult ones (e.g. SAD and panic disorder) is not understood. Whether P-Co is specifically related to h, or other pains (e.g. low back pain, abdominal pain) is a matter of debate. (3) The use of population or clinical study in research on P-Co pros and cons. (4) The likely mechanisms of comorbidity have related implications for the comprehension of h aetiology. The role of the neurotransmitters (serotonin, dopamine) involved both in P-Co (anxiety, mood, sleep disorders) and h needs further attention. The four points highlighted will be treated in detail, giving the theoretic frames and practical suggestions in treating young h sufferers presenting P-Co.

TIV-9

Determinants of pain and quality of life in juvenile headache patients

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Introduction Health status (HS) or quality of life (QOL) are outcome measures that are now generally included in the description of patient groups and treatment-effects, apart from pain parameters. However, the introduction of ‘pain behaviour’ by Loeser as part of the pain concept has blurred the distinction of pain and the quality of life of the patient. Following the IASP definition, pain has to be considered as a sensory and emotionally phenomenon.

Objective To understand the factors which explain the variance between juvenile headache patients in pain and QOL.

Methods Studies on the relationship of potential determinants of pain and QOL will be reviewed, and fresh data from our own research line will be interpreted.

Materials Data are collected by questionnaire, dairy and interview.

Results The QOL of juvenile patients with chronic headache from the general population is moderately afflicted in comparison with that of healthy persons. More salient than the differences in QOL between juvenile headache patients and other patient groups, are the within-group differences. More than half of the variance in QOL has to be explained by other factors than pain. As psychological determinants of both pain and pain-related QOL, the following were proposed: the presence of pain-models in the family, parental rewarding of pain behaviour, life stress of the young patient, pain coping and the personality trait ‘vulnerability’ (the tendency to become easily depressed and anxious).

Conclusions When we, in line with the IASP definition, operationalize (juvenile) head pain by the parameters ‘intensity’, ‘frequency’, ‘duration’ and ‘unpleasantness’ of the pain, factors derived from emotional theories seem to have a better predictive value than those derived from behavioural theories. For the explanation of differences between youngsters in the more encompassing concept of (pain-related) quality of life, more theories are relevant. The choice of headache or QOL as the focus of psychological treatment, implies a choice of different treatment strategies.

TIV-10

Post-traumatic headaches

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Post-traumatic headaches (PTH) can be seen following trivial as well as moderate and severe head injury. The headache can be associated with symptoms of vertigo, dizziness, and difficulties with concentration and memory, with subsequent difficulties in school. In addition, sleep disturbances, personality changes and depression may also be present. Some patients may also have autonomic instability such as orthostatic hypotension. This constellation of symptoms has been called postconcussional syndrome (PCS). The pathophysiology of this syndrome is not well understood. The headaches can be similar to migraine and tension headaches or a combination of the two and often fall into the category of chronic daily headache (CDH). Even though these headaches are similar to migraine, they often do not respond to routine migraine medications. Severe incapacitating headaches may be treated with standard triptan drugs and if necessary, dihydroergotamine. It is equally important to treat comorbid problems such as depression and anxiety. Symptoms such as vertigo and orthostatic hypotension may be more difficult to treat. Often the symptoms appear much more severe than the injury itself. Patients whose symptoms persist should have an MRI of the brain looking for treatable lesions as well as shear injuries, which if present, are seen in the white matter. Most children have recovery within several weeks; however, it can take several months. Unfortunately, a certain group never recovers. The percentage of patients who do not recover is not known at this time. There is no good way to determine which patients fall into this category. Management starts with a discussion of PTH and PCS with the family and patient. A comprehensive headache examination is necessary to formulate a pharmacological as well as non-pharmacological approach for these patients’ headaches. While the headaches are being treated, a plan to deal with other comorbid problems should be outlined. With children it is imperative to have the school involved because children who have done very well in the past might now have difficulties. A child psychiatric evaluation is an integral part of a multidisciplinary approach.
the Hospital das Clínicas de Ribeirão Preto (EUHCRP), Brazil, in 1996, the following objectives were established for my presentation: (a) to revise the epidemiological and aetiological aspects of acute headaches in children; (b) to analyse the most common clinical patterns of acute headache at these ages; (c) to summarize the most important topics in the physical examination of children complaining of acute headache in the emergency room; (d) to summarize the red flags of secondary headaches in children.

**Materials and methods** The EUHCRP is a secondary hospital in which 133,356 patients from the area of Ribeirão Preto were seen in 1996. Among all these patients, only those children suffering from acute headaches were selected. The etiological diagnosis was made using the IHS diagnostic criteria (1988). In addition, a study of the direct cost of these patients was carried out.

**Results** In 1996, 14,760 children were seen at the EUHCRP, 1% of them (148) because of acute headache. Out of these 148 children, 14 of them (9.4%) were hospitalized: 11 of them had secondary headache and 3 of them primary headache. Out of the 113 children who were not hospitalized, 85% of them were suffering from primary headaches. The most important causes of secondary headache were: non-cephalic infection, acute sinusitis, otitis, acute post-traumatic headache, postlumbar puncture headache, meningitis and subdural haematoma. A direct cost of US$91.49 for those children who were not hospitalized and US$125.86 for those who were hospitalized was calculated.

**Conclusion** The study above and the related literature will give the support to the author to develop and present clearly and objectively the theme, making the presentation didatic and interesting.
**PS-1**

**Migraine: a multifactorial episodic neurovascular channelopathy**

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Clinical and genetic heterogeneity as well as the influence of environmental factors have hampered the identification of the genetic factors that are involved in episodic diseases such as migraine, episodic ataxia, and epilepsy. The study of rare, but clearly genetically determined subtypes may help to unravel the pathogenesis of the more common forms. Recently, different types of mutations in the brain specific P/Q-type calcium channel \( \alpha_{1A} \) subunit gene (CACNA1A) on chromosome 19p13 were shown to be involved in three human disorders: (I) familial hemiplegic migraine (FHM); (II) episodic ataxia type 2 (EA-2); and (III) chronic spinocerebellar ataxia type 6 (SCA6). In addition, evidence is accumulating that the same gene is also involved in the common forms of migraine with and without aura. In the tottering and leaner mouse, which is characterized by epilepsy and ataxia, similar mutations were identified in the mouse homologue of the calcium channel \( \alpha_{1A} \) subunit gene. These findings add to the growing list of episodic (and now also chronic) neurological disorders, which are caused by inherited abnormalities of voltage-dependent ion channels. The findings in migraine illustrate that rare, but monogenic variants of a disorder, may be successfully used to identify candidate genes for the more common, but genetically more complex, forms.

**PS-2**

**Functional properties of normal and mutated calcium channels**

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Calcium influx through voltage-gated calcium channels mediates an extensive array of neuronal processes, including neurotransmitter release, neuronal excitability, signal transduction via second-messenger systems and gene expression. A diversity of calcium channels has been described in both excitable and non-excitable tissue, and extensive characterization studies have revealed the existence of five high- (L, N, excitable and non-excitable tissue, and extensive characterization studies have revealed the existence of five high- (L, N, Q, R, and P) and three low (T) voltage-activated calcium channel types. The high voltage-activated calcium channels are hetero-multimer proteins, consisting of the pore-forming \( \alpha_1 \) subunit, and the auxiliary subunits \( \beta, \gamma, \delta \), and \( \gamma \). To date, molecular cloning has revealed the existence of at least nine genes encoding the \( \alpha_1 \), three that encode the \( \gamma, \delta \), four that encode the \( \beta \), and five that encode the \( \gamma \) subunit. Important understanding of calcium channel function has emerged from structure-function studies using various recombinant \( \alpha_1 \) and auxiliary calcium channel subunits. Functional domains within the \( \alpha_1 \) subunit have been identified that determine, e.g. ion selectivity, the voltage dependence of channel gating, kinetics, and pharmacological properties. Alternative splicing within these sites can have drastic effects on the functional properties of the channel and represents a powerful mechanism to adapt the various calcium channel subtypes to their different physiological roles. The structure and diversity of the individual subunit families will be introduced, and their roles in determining some of the functional properties of the calcium channels will be discussed.

The brain-specific P/Q-type calcium channel \( \alpha_{1A} \)-subunit gene CACNA1A on chromosome 19p13 has been implicated recently in a wide range of disease phenotypes with a tendency for missense mutations within familial hemiplegic migraine (FHM), truncating mutations within episodic ataxia type-2 (EA-2), and CAG repeat expansions within spinocerebellar ataxia 6 (SCA-6). In addition, the effectiveness of acetazolamide treatment recognized in EA2 was also reported in a patient with FHM and ataxia associated with a new CACNA1A gene mutation. Therefore, the present objective is to understand the mechanisms leading the gene mutations to the different phenotypes. Besides the direct alteration of neurotransmission, the dysfunction of the P/Q-type channel may lead to a misregulation of intracellular calcium concentration which plays a major role in cell metabolism. Magnetic resonance spectroscopy (MRS) can detect the proton signal arising from four metabolites: N-acetyl-aspartate, choline, creatine and lactate, the phosphorus signal arising from ATP, phosphocreatine, inorganic phosphate and phospholipids compounds, and can measure the intracellular pH. Decreases in high-energy phosphates were demonstrated both in FHM and migraine with or without aura. Increased lactate and low brain magnesium were observed in patients who had experienced migraine attack. In EA2 patients, intracellular alkalosis was detected in association with or without lactate increase. These findings indicate that a dysfunction of the calcium channel function will be discussed.
P/Q-type channel induces a metabolic cascade resulting from a possible increase in intracellular Ca\textsuperscript{2+} concentration. The necessary Ca\textsuperscript{2+} extrusion needs the activation of several mechanisms such as ion exchangers and pumps, increasing energy consumption, altering the homeostasis and leading to intracellular alkalosis. The observation of a reversible reduction in water mobility measured by diffusion-MRI during a prolonged attack of FHM is according to the well-known role of the calcium channel in exocytotic release. These modifications of ionic and water balance may be enhanced by the release of excitatory amino acids also mediated by the calcium channel and thereby, prolonging the swelling of brain cells. Finally, these biochemical events could lead to cell damage as shown by the severe atrophy of the cerebellar vermis, and to a less extent of the cerebellum and brain hemispheres. In conclusion, further investigations of the metabolism consequences of these mutations as well as the mechanism of acetazolamide action may help to better understand the physiopathology of these disorders and develop a rational pharmacologic treatment.

**PS-4**

**What are possible functional consequences of calcium-channel abnormalities in the common forms of migraine?**

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Mutations in CACNA1A gene are found in most cases of familial hemiplegic migraine (FHM). Sib-pair and linkage analyses have provided indirect evidence that CACNA1A may also be involved in the more prevalent forms of migraine, especially in migraine with aura. A dysfunction of P/Q Ca\textsuperscript{2+} channels may be responsible for certain forms of migraine, but also for subclinical symptoms or functional disturbances some of which may be detectable with appropriate sensitive methods. As the highest density of P/Q Ca\textsuperscript{2+} channels is found in the cerebellum and FHM can be associated with cerebellar ataxia, we sought for subcortical cerebellar signs in migraine patients (16 without [MO] and 19 with aura [MA]) by studying pointing movements using an infra-red opto-electronic tracking system (ELITE\textsuperscript{39}) and found a significant hypermetria aggravated by increasing armload. P/Q Ca\textsuperscript{2+} channels on motor axons are responsible for stimulation-induced acetylcholine release. We used therefore single fibre EMG (SFEMG) to detect abnormalities of neuromuscular transmission. Such abnormalities were found in 17 out of 36 patients and were significantly correlated with the occurrence of complex aura features ($P=0.013$) and with a diagnosis of migraine with prolonged aura ($P=0.012$).

After acetazolamide treatment (250 mg b.i.d.) in 2 patients, SFEMG normalized. A significant correlation between cerebellar and SFEMG abnormalities was found in the subgroup of migraine with complex and/or prolonged aura. Sensitive neurophysiological are thus able to detect in certain migraineurs subclinical abnormalities of neuronal functions that are controlled by P/Q Ca\textsuperscript{2+} channels and may contribute to better phenotyping. Genetic analyses are clearly necessary to determine whether this might be due to abnormalities in the CACNA1A gene. As the detected functional abnormalities are subtle, genetic changes less dramatic than mutations, such as polymorphisms, could be responsible.

**PS-5**

**Ion channels as potential targets for antimigraine drugs**

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Ion channels by virtue of their prominent involvement in many pathological disturbances in the excitability of the nervous system, are key molecular targets for the development of new drugs for a diverse range of neurological disorders. However, these molecules also play a fundamental role in the normal functioning of neurons and a balance needs to be struck therefore between attempting to reduce abnormal function without interfering with normal function. This presentation will examine those families of neuronal ion channels that may contribute to migraine. These include transducer proteins, specialized ion channels that transduce an external stimulus such as a mechanical force or an inflammatory mediator, into an inward current at the peripheral ends of primary sensory neurons, voltage-gated ion channels involved in conduction and transmitter release, and glutamate-gated ion channels that modulate the excitability of the neuronal membrane altering the responsiveness and output of the neurons and ligand-gated ion channels that contribute pre- and postsynaptically to synaptic transmission. The suitability of a given ion channel as a potential target for the development of antimigraine drugs depends on its functional properties, cellular localization, and its transcriptional and post-translational regulation. Ideal targets would be those that are expressed only in those neurons involved in sensory transmission and are not essential for normal function. New molecular screening techniques are making the detection of such channels and their single nucleotide polymorphisms easier, however, screening for drugs that specifically activate or inhibit only a single homo- or heteromeric channel remains prodigiously difficult.
SCIENTIFIC SESSION I

Epidemiology and diagnosis

OR1

Revision of the International Headache Classification. An interim report

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The International Headache Classification published in 1988 has perhaps been the most successful disease classification ever to appear. Nevertheless, 12 years of rapid progress in our knowledge about headache have made a revision necessary. The new headache classification committee started its work in December 1999 and has so far had 4 meetings. The general format of the classification and the operational diagnostic criteria will remain largely unchanged. However, a number of important changes have already been agreed. While preserving the hierarchical classification system, numbering will be done according to WHO’s ICD10 NA code numbers. A number of conditions have been switched from one major diagnostic group to another and infections have been brought together in one group while previously separated into intracranial infections and extracranial infections. A new group deals with headaches due to metabolic and other systemic disorders. Chronic migraine has been identified as a condition that fulfills criteria for migraine more than 15 days a month. Major changes may also take place in the classification of migraine aura related syndromes, while changes in the tension-type headache group are likely to be small. Episodic paroxysmal hemicrania, SUNCT, hypnic headache and idiopathic thunderclap headache are among new entities included in the classification while others have been moved from the main classification into an appendix. The latter is intended for syndromes on the way out or syndromes on the way into the classification and will provide criteria in order to facilitate research. The second edition of the International Headache Classification is expected to be published in 2003, 15 years after the appearance of the first edition.

OR2

Structural brain change in migraine: a population-based MRI study, the camera-project

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Objectives Case-control studies indicate that migraine is a risk factor for stroke in young women; there are no studies on silent infarcts. Small MRI-studies suggest an increased prevalence of white matter lesions (WML) in migraineurs. However, results are inconsistent across studies and are based on convenience samples. We conducted the a population-based MRI study to examine the association of structural brain lesions and migraine.

Methods The sample is from the GEM study, which is based on a cohort of 6039 Dutch adults, including 863 migraineurs, who participated in a population-based study of cardiovascular risk factors. Migraine diagnosis was assessed according to IHS-criteria in a multistage procedure including a semistructured clinical interview by telephone. From the cohort aged 30–60 year, we randomly selected for MRI of the brain, 134 migraineurs without aura (MO), 161 migraineurs with aura (MA) and 140 controls who were matched to the cases. One neuroradiologist, blinded to clinical status, read MR images to identify infarcts and to assess subcortical WML [using a semiquantitative scale that takes into account a fixed volume of small (≤3 mm), medium (4–10 mm) and large (>10 mm) WML]. Total WML volume was dichotomized into the upper 20% vs the rest. We separately estimated the risk (Odds Ratio; OR) for any infarct and high WML load, respectively, in migraineurs vs controls, using logistic regression, controlling for demographic and cardiovascular risk factors.

Results Sixty infarcts in 31 subjects (free of neurological signs and history of stroke/TIA) were identified. There was no statistically significant association between presence of any infarct and type of migraine [OR=1.2 (P=0.7) for MO and OR=1.8 (P=0.2) for MA]. However, 55% of infarcts were located in the cerebellum. Proportions of controls, MO and MA with one or more cerebellar infarcts were 0.7%, 2.2% and 8.1%, respectively. This corresponded to a significantly increased risk for infarct in the cerebellum, varying by migraine type [OR=2.3 (P=0.5) for MO and OR=13.7 (P=0.015) for MA], compared to controls. These effects did not vary by sex. Overall prevalence of any subcortical WML was 59% in both groups. Among women, migraineurs were at significantly increased risk for high WML load, regardless of subtype [OR=2.0 (P=0.05) for MO and OR=1.8 (P=0.1) for MA]. No association of high WML load to migraine was found in men [OR=0.6 (P=0.3)].

Conclusion Migraineurs, notably those with MA, are at high risk for cerebellar infarcts. Female, but not male migraineurs are at increased risk for WML.
OR3

Primary headache as a spectrum disorder
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Objectives The null hypothesis is proposed that the primary headache syndromes (1 HAS) of migraine with aura (M-A), migraine without aura (M-O) and tension type headache (TTH) can be differentiated or defined statistically from analysis of two large databases of primary headache patients (1 HP) without making a priori rules defining the syndromes.

Background The 1 HAS of M-A, M-O and TTH have been defined by clinical observation but the composition is still empirical, i.e. the syndrome exists because it is defined in that manner. The criteria for these entities, while clinically sensible, are based on clinical judgement but not on statistical likelihood of occurrence. In this study, two statistical analyses were applied to two large databases of 1 HP to determine (1) if the syndromes of M-A, M-O and TTH could be replicated without making a priori assumptions on syndrome composition and (2) if the composition of syndromes created by this method from each database agreed with each other.

Methods Subjects were obtained from two databases of 1 HP seen in clinic by JRC at: (1) SIU, from 1980 to 92 (N=808) and (2) OU, from 1992 to 2001 (N=852). Presence or absence of 20 symptoms and family history were collected from each subject. Each database was analysed individually using (1) principal component analysis and (2) rotated factor analysis.

Results The principal component analysis identified 8 factors with an Eigen (E') value of >1. These 8 factors, the E' value, and the percent variance (var) accounted for by the factor are in the table. Note that the general migraine features photophobia and phonophobia appear as factor 1 in both databases. Otherwise, neither the principal component analysis nor rotated factor analysis identified any other factors of note. The analyses did not identify subgroups compatible with M-A, M-O, or TTH.

Discussion These analyses do not support the null hypothesis that syndromes M-A, M-O, or TTH can be created from a database of 1 HP without defining the above syndromes a priori. The results of the analyses suggest that the primary headache syndromes of M-A, M-O, and TTH are not clearly differentiated and may represent a continuous spectrum of primary headache.

OR4

Relationships of daily stress, sleep, and headache: a time-series analysis
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Introduction Stress and sleep disruptions are frequently cited precipitants of migraine and tension-type headache. Evidence for these precipitants derives principally from retrospective surveys or cross-sectional designs that preclude conclusions regarding causality and obscure individual variability. Thus, the strength and direction of these associations remain unclear. This prospective longitudinal study examined temporal relationships between daily stress, sleep and headache using time-series analysis with lagged correlations.

Method Migraine (MH; n=25) and tension-type (TTH; n=24) headache patients recorded stress (Daily Stress Inventory, DSI), sleep (hours sleep per night) and headache activity daily for 28 days. Peak daily headache rating (HP) was the dependent variable. Four lags of both independent variables (DSI Impact scores [sum of stress ratings] and sleep) were tested as predictors of HP within each subject. To compare the headache groups on the temporal patterning of stress-headache and sleep–headache associations, patients were classified into two groups based on the lag that produced the ‘most characteristic’ correlation: (1) lag = 0; if the correlation was lag 0; (2) lag > 0, if the correlation was lag 1, 2 or 3, or (3) no correlation. Patients were classified in this manner for both the Stress-HP, and the Sleep-HP correlations.

Results Large individual differences were observed in the stress-headache correlations (r = -0.49 to 0.63). Stress accounted for significant variance in headache over time for

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<table>
<thead>
<tr>
<th>Factor</th>
<th>Correlation w/factor</th>
<th>Eigen/Var</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Photo, Phono, Age</td>
<td>0.8, 0.8, 0.4</td>
<td>2.09/10.5%</td>
</tr>
<tr>
<td>(2) Hemisensory Loss, Hemiparesis</td>
<td>0.8, 0.8</td>
<td>1.67/8.4%</td>
</tr>
<tr>
<td>(3) Osmophob, Aphasia, Confusion</td>
<td>0.5, 0.7, 0.7</td>
<td>1.31/6.6%</td>
</tr>
<tr>
<td>(4) Female, Anorexia, Nausea</td>
<td>0.59, 0.54, 0.65</td>
<td>1.24/6.2%</td>
</tr>
<tr>
<td>(5) Unilat., – Visual</td>
<td>0.7, –0.64</td>
<td>1.18/5.9%</td>
</tr>
<tr>
<td>(6) Giddy, Fam.Hx, Age</td>
<td>0.7, –0.53, –0.4</td>
<td>1.12/5.6%</td>
</tr>
<tr>
<td>(7) Blurring, Vertigo</td>
<td>0.64, 0.74</td>
<td>1.02/5.1%</td>
</tr>
<tr>
<td>(8) + Visual</td>
<td>0.75</td>
<td>1.00/5.0%</td>
</tr>
<tr>
<td>OU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1) Photo, Phono</td>
<td>0.8, 0.8</td>
<td>2.77/13.2%</td>
</tr>
<tr>
<td>(2) Unilat., Bilat.</td>
<td>0.77, 0.72</td>
<td>1.52/7.2%</td>
</tr>
<tr>
<td>(3) Diarrhea, Vomiting</td>
<td>0.56, 0.76</td>
<td>1.31/6.2%</td>
</tr>
<tr>
<td>(4) Vertigo, LOC, HP, Blurring, HSL</td>
<td>0.59, 0.59, 0.48, 0.42</td>
<td>1.21/5.8%</td>
</tr>
<tr>
<td>(5) Aphasia, Confusion, HSL</td>
<td>0.69, 0.68, 0.42</td>
<td>1.17/5.6%</td>
</tr>
<tr>
<td>(6) Female, Osmophob</td>
<td>0.65, 0.68</td>
<td>1.11/5.3%</td>
</tr>
<tr>
<td>(7) Anorexia, Giddy</td>
<td>0.64, 0.62</td>
<td>1.06/5.1%</td>
</tr>
<tr>
<td>(8) – Visual, + Visual</td>
<td>0.73, –0.62</td>
<td>1.02/4.9%</td>
</tr>
</tbody>
</table>
These findings suggest minor stressful life events and sleep patterns play an important role in precipitating or exacerbating recurrent headache. These prospective data support anecdotal observations regarding the temporal patterning of the stress-headache and sleep–headache associations.

OR5

Sumatriptan exposure during pregnancy and risk of birth defects: what have we learned?

S. A. Ephross & the Sumatriptan Pregnancy Registry Advisory Committee

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Objectives When a drug is approved, little information is available about use during pregnancy, particularly effects on the fetus. To date, sumatriptan is the only triptan with published postmarketing pregnancy data. Results from the GlaxoSmithKline Sumatriptan Pregnancy Registry (SPR) and other sources are presented.

Materials and methods The SPR, established in 1996, is an ongoing, international exposure-registration and follow-up registry monitoring outcomes of voluntarily reported prenatal sumatriptan exposure. Studies in women voluntarily contacting Teratogen Information Services (Shuhaiber et al., 1998), an open-label prospective study (O’Quinn et al., 1999) and the Danish Medical Birth Registry (Olesen et al., 2000) are published. Results from the Swedish Medical Birth Registry are in press (Källén).

Results Through October 2000, the SPR prospectively obtained 289 pregnancy outcomes. The 264 involving first trimester sumatriptan exposure include 226 infants without birth defects; 15 spontaneous pregnancy losses, 3 stillbirths, and 10 induced abortions, all without birth defects; 8 infants with birth defects; 1 stillbirth and induced abortion, each with birth defects. The proportion with birth defects (10/236, excluding spontaneous pregnancy losses and voluntary terminations without birth defects) is 4.2% (95% confidence interval 2.2–7.9%), which is not significantly different from the expected proportion in the general population. There is no consistent pattern among reported birth defects. Shuhaiber compared sumatriptan users to migraineurs without sumatriptan and women taking non-teratogenic drugs (each n = 96), finding no significant difference in major birth defect rates (RR = 1.05 and 1.06). O’Quinn found no birth defects in 76 first trimester sumatriptan exposures. Olesen linked birth registry and prescription data and found no birth defects in 34 women dispensed sumatriptan in pregnancy. Källén compared 658 sumatriptan exposures with 254 exposures to other migraine drugs, finding no significant difference in congenital malformation rates (1.3% vs 2.8%, respectively).

Conclusions Sumatriptan is the only triptan with available pregnancy information. While the sample sizes of individual studies remain too small to draw definitive conclusions about the safety of sumatriptan use in pregnancy, five studies using different methodologies suggest no increased frequency of birth defects following prenatal exposure. Although use during pregnancy still cannot be encouraged, the data overall are reassuring regarding individual inadvertent exposure. Registration of new exposures in the Sumatriptan Pregnancy Registry continues and is encouraged as early in pregnancy as possible.

OR6

Characteristics of menstrual and non-menstrual attacks in women with menstrually related migraine

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Objectives This study was set out to compare the clinical features and response to symptomatic treatment of menstrual and non-menstrual attacks in women with menstrually related migraine attending tertiary care centers.

Methods 100 women in fertile age with migraine without aura (MO) and at least 1 perimenstrual MO attack (i.e. an attack beginning on days −2 to +2 in respect to the first day of menses) in at least 5 of the previous 6 months were enrolled in a 2-month prospective diary study. Women on prophylactic therapy were excluded. Chi-square test and Student’s t-test were applied, when appropriate.

Results 82 women completed the 2-month diary. Eighteen women were subsequently excluded for various reasons (no menstrual attacks, more than 6 attacks per month, deficient diary compilation, etc.). Sixty-four women (mean age 34.7 ± 6.3 years) had a total of 459 attacks (136 perimenstrual, 323 non-menstrual). We separated menstrual attacks (MA, occurring on days 1–2; no. = 78) from premenstrual attacks (PMA, occurring on days 1–2; no. = 58) and compared both to non-menstrual attacks (NMA; no. = 323). Mean duration of
Migraine attacks occurring on the first 2 days of the cycle are longer, more severe and less responsive to analgesics, without significant differences among groups) was 2.5 ± 1.8 per attack in MA, 2.0 ± 1.4 in PMA and 1.7 ± 1.2 in NMA (MA vs NMA: P = 0.001). Two hours after first analgesic administration, patients were pain-free in 13.5% of MA and NMA.

Conclusions Migraine attacks occurring on the first 2 days of the cycle are more severe than those occurring on other days. The characteristics of premenstrual attacks lie between those of MA and NMA.

Acknowledgement This study was supported by a grant from the Ministry of Public Health – RC2000.

OR7

Visual aura rating scale (VARS) – a tool for diagnosing visual symptoms

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Objective Diagnosing the visual migraine aura remains difficult even with the IHS classification. To ensure a valid diagnosis of migraine aura, we have developed a Visual Aura Rating Scale that further operationalizes the classification of definite aura and patients with visual disturbances not judged to be visual aura.

Materials and methods The patients were recruited from research projects of the Copenhagen Headache Research Group. Patients and affected relatives with visual symptoms participated in a semi-structured telephone interview by a trained physician. A total of 337 patients were included. The patients were separated into two subsamples: A training sample used to generate the model and a validation sample for validating the model. The training sample comprised 141 patients with MA (migraine with typical aura, prolonged aura, or migraine aura without headache, IHS criteria) and 59 patients with reversible visual disturbances related to headache. The validation sample comprised 137 patients with an IHS diagnosis of MA. The score of the Visual Aura Rating Scale is based on the characteristics of the visual symptoms recorded in the semi-structured interview. Using logistic regression we selected the explanatory variables/characteristics of definite aura. The score is the weighted sum of the number of characteristics present. By statistical modelling we then defined the score which separated the training sample into patients with definite aura and patients with visual disturbances not judged to be visual aura.

Results Visual symptom characteristics correlated to definite aura were: duration 5–60 min (3 points), develops gradually >4 min (2 points), scotoma (2 points), zig-zag lines (2 points), flickering light (1 point), and headache follows aura with a free interval of less than 60 min (1 point). Thus, the maximum score is 11 points. In the training sample a score of at least 5 separated the patients with visual migraine aura from patients with other reversible visual disturbances. The sensitivity of the score is (136/141) 96% (95% CI 94–99%) and the specificity is (54/59) 92% (95% CI 88–95%). The positive predictive value is 96% and the negative predictive value is 92%. Validating the score on the validation sample the sensitivity is 95%.

Conclusion The Visual Aura Rating Scale is a simple, sensitive, and specific tool for diagnosing the visual migraine aura. It seems eminently suited for drug trials, epidemiological, and genetic studies. It will also be useful in making clinical diagnoses more comparable between centres and nations.

OR8

Are migraine sufferers treated according to published guidelines?


University of Toronto, Toronto, ON, Canada, University of Calgary, Calgary, AB, Canada, Dalhousie University, Halifax, ON, Canada, Clinique de la Migraine, Charlesbourg, PQ, Canada, Ipsos-Reid, Toronto, ON, Canada, Pfizer Inc., Kirkland, PQ, Canada

Objective Guidelines for the diagnosis and management of migraine were published in 1997 by the Canadian Headache Society. This paper examines the degree to which Canadian migraine sufferers who consult doctors are treated in accordance with these guidelines.

Materials and methods Telephone interviews were conducted in June 2000 with 1004 self-identified migraine sufferers drawn from the randomly recruited Ipsos-Reid panel. Potential respondents were screened using an adaptation of the IHS criteria for migraine.

Results Half (54%) of the migraineurs surveyed are currently consulting a physician about their headaches and 92% of these have been diagnosed as suffering migraines. The guidelines’ recommendations for treatment of acute attacks vary according to the severity of the attack. Among the current consulted, 83% experience attacks which are severe (requiring bed rest), 86% have attacks which are moderate (limited function but not requiring bed rest) and 69% have mild/somewhat limiting attacks (able to function at reduced capacity). Most consulters experience attacks of different severity on a regular basis. For example, among those 54% of consulters who suffer severely, moderately and...
somewhat limiting attacks, 3.7 of their last 10 attacks were severely limiting, 3.5 were moderately limiting and 2.8 were somewhat limiting. Analysis of medication usage vs the guidelines reveals that the more severe a migraine is, the less likely it is to be treated according to the guidelines. 59% of consultants who experience mild attacks treat them with medications recommended by the guidelines. 45% of those who experience moderately limiting attacks use the recommended medications. However, 55% also suboptimally treat moderate attacks with medications recommended for mild attacks. Only 28% of consultants treat severely limiting attacks with medications recommended for severe/ultra-severe attacks. Many attempt to manage severe attacks with medications recommended for moderate (70%) and mild (39%) attacks.

Conclusions Most consultants experience attacks of variable severity but many do not manage all of their migraines in accordance with the guidelines, especially their more severe attacks. It appears there is a need to encourage greater utilisation of the guidelines among both primary care physicians and migraine sufferers. These findings have implications for CME and those implementing guidelines elsewhere in the world.

OR9
Comparison of different methods of patient education for migraine: a headache clinic study of 1000 patients
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Objectives Proper patient education forms one of the cornerstones in the management of patients with migraine. This aspect of the treatment plan, however, is often neglected in routine practice. The aim of this study was to compare the results of two different methods of explaining migraine and the treatment plan to patients. The standard verbal method of patient education was compared with a pictorial method in 1000 migraine patients who attended our headache clinic. This pictorial migraine patient education protocol utilized flip-charts, slides and humorous cartoons. This method can be employed more usefully in developing countries where literacy levels vary. It was found to improve compliance and set the right expectation levels in migraine patients.

OR10
Prodromal symptoms and aura in cluster headache patients: a nation-wide study in 1844 Dutch patients
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1Neurology, Atrium Medical Centre, Heerlen, The Netherlands,
2Neurology, Leiden University Medical Centre, Leiden, The Netherlands, 3Neurology, Rijnland Ziekenhuis, Leiderdorp, The Netherlands

Background Prodromal symptoms and aura have been studied extensively in migraine patients but only a few studies have focused on these symptoms in cluster headache (CH).

Objectives In order to assess prodromal and aura symptoms in CH attacks and periods, we conducted a questionnaire-study in a large Dutch population of CH patients.

Methods Patients with CH or CH-like syndromes were identified by means of public announcements and by direct mailings to all neurologists (n = 580) and general practitioners (n = 5800) in The Netherlands. All patients were sent two questionnaires, which included the IHS criteria.

Results From 04-01-1998 until 01-03-2001, 1844 patients returned the screening questionnaire. The second, more extensive questionnaire was returned by 1406 patients. Of these, 1076 (77%) were IHS-CH and 289 (21%) were non-IHS-CH patients. Of these 1076 IHS-CH patients, the prodromal symptoms and aura will be reported. This study included 844 male (78%) and 232 female (22%) IHS-CH patients (M/F ratio 3.6:1). (1) Three classes of prodromal symptoms, preceding the cluster period, were reported by 611 patients (57%): sensory, mood and autonomic prodromata. Two-hundred-and-four patients (33%) reported strange, tingling sensations...
in the area of the eye, 130 (21%) in the area of the nose and 206 (34%) in the area of the neck. Mood prodromata, such as restlessness and depression, were reported by 409 patients (67%). Autonomic prodromata, including nasal congestion, conjunctival injection and lacrimation, were reported by 385 patients (63%). The prodromata preceded the cluster period by 1 day to over 2 months (median, 7 days). (2) Prodromal symptoms preceded the actual attack by minutes to hours in 844 patients (78%): 497 (59%) reported a tingling, irritating feeling in the area of the eye, 318 (38%) in the area of the nose; 332 (39%) in the area of the neck. Some 233 patients (28%) had mood prodromata and 188 (22%) autonomic phenomena. (3) Aura symptoms were reported by 280 patients (26%). None of these patients had migraine with aura in addition to CH. The aura symptoms were divided into visual (n = 17), sensory (n = 14), aphasia (n = 13), dysarthria (n = 3), or motor (n = 2).

Conclusion Prodromal symptoms occur more frequently in cluster headache than previously assumed. This may have therapeutic implications, such as, for example, earlier treatment. Aura in cluster headache is as yet unexplained. An association with migraine seems unlikely, as these patients did not have concomittant migraine attacks.

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Novel targets for migraine therapy

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The 1990s might usefully be thought of as the decade of the triptans. The isolation of a serotonin, 5-HT1-like receptor in the cranial circulation by Humphrey and collaborators and its specificity in closing arterio-venous shunts, heralded a major advance in migraine therapy. The development of the triptans brought substantial benefits to many very disabled patients, and pointed to neuroanatomical and pathophysiological substrates for further developments. Some of these targets have been tested and found wanting, while others show great promise. Many will be tested over the next 5 years and hopefully new, particularly non-vascular targets will be found. Novel targets that do not have antimigraine effects: a number of targets for acute antimigraine compounds have been suggested by the model of neurogenic plasma protein extravasation (PPE) in the rat. Some have been tested and failed, notably substance P (neurokinin-1) antagonists, endothelin antagonists and specific potent PPE blockers, CP122 288 and 4991w93. Novel targets explored and as yet unclear: Sumatriptan is a serotonin 5-HT1B/1D/1F agonist, so two possibilities have been tested. Initial studies with 5-HT1F receptor agonists suggested that they worked as antimigraine agents but toxicity problems stopped that compound. Initial studies with a 5-HT1D agonist were not successful but this compound may not have been optimal. Nitric oxide (NO) synthase inhibitors have been studied and worked in one placebo-controlled trial. This observation bears repetition and exploration with NO being a major possible target. Novel targets to be explored: A number of targets can be adduced from trigeminovascular anatomy and physiology; these include calcitonin gene-related peptide (CGRP) antagonists, which have the best rationale, excitatory amino acid receptor antagonists, adenosine A1 receptor agonists and channel modulators. The future is bright with a number of possible targets that may deliver more effective, or safer options to the many patients who seek adequate care of acute migraine.

IV LY293558, an AMPA/KA receptor antagonist, is effective in migraine

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Background Glutamate hyperactivity is implicated in migraine. LY293558 is an AMPA/KA receptor antagonist with proven efficacy in preclinical models of migraine, and is inactive in the rabbit saphenous vein model up to 10–4M.

Objective To test the efficacy and tolerability of LY293558 during migraine.

Methods Randomized, placebo-controlled, double-blind, double-dummy, multicentre study of 1.2 mg/kg iv LY293558 (LY), 6 mg sc sumatriptan (S) or placebo (Pl) to treat an IHS-diagnosed moderate or severe migraine ± aura. Severity of headache or associated symptoms (AS) was scored as 0 = no symptom, 1 = mild, 2 = moderate, 3 = severe. Efficacy measures were: response (R = % with headache mild or no pain 2 h postdosing), pain free (PF = % without headache at 2 h), sustained response (SR = % with response at 2 h and no rescue/recurrence from 2–24 h), sustained pain free (SPF = % pain free at 2 h and no rescue/recurrence from 2–24 h), recurrence (RR = % responders/pain free with 2/3 headache from 2–24 h), relief of AS (% with no symptom at 2 h, from a 2/3 baseline score). Adverse events (AEs) were recorded for 24 h. The study was conducted in accordance with IHC Guidelines.

Results 44 patients (M:F = 20:24; age [mean ± SD] = 40 ± 9 years) completed the study. Efficacy results are in the table (*P = 0.017 LY293558 vs placebo, **P < 0.01 LY293558 or sumatriptan vs placebo; P > 0.1 sumatriptan vs LY293558 for all comparisons (chi-square test)). Two (15% of patients on LY), eight (53% on S) and five (31% on Pl) reported AEs (P = 0.037 LY vs S), which included chest/throat symptoms (0% LY, 13% S, 0% Pl), disorientation (8% LY, 27% S, 6% Pl), dizziness (15% LY, 27% S, 13% Pl), extremity heaviness/tingling (0% LY, 33% S, 0% Pl), nervousness (0% LY, 7% S, 0% Pl), sedation/drowsiness (15% LY, 33% S, 25% Pl), warm feeling (8% LY, 33% S, 6% Pl), and visual symptoms (8% LY, 27% S, 6% Pl).
GLUR5 antagonists as novel migraine therapies

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Background L-glutamate activates neurons in the trigeminal nucleus caudalis (TNC). Furthermore, non-NMDA ionotropic glutamate receptors such as GluR5 are expressed in rat trigeminal ganglion (TG), and GluR5 receptors play an important role in central sensitization (CS). CS is implicated in, and the trigeminal system is at the core of, migraine. Therefore, we hypothesized that GluR5 receptor antagonists would be effective in preclinical models of migraine.

Objectives (1) To test the potency and efficacy of GluR5 antagonists with varying degrees of affinity and selectivity for the GluR5/kainate receptor in the dural plasma protein extravasation (PPE) and the c-fos models of migraine. (2) To test these GluR5 receptor antagonists for their ability to contract the rabbit saphenous vein (RSV) in vitro.

Methods GluR5 antagonists were synthesized in the Lilly Research Laboratories. Ligand binding studies using recombiant human non-NMDA receptors expressed in HEK293 cell membranes were used to determine compound affinity. We evaluated parenterally administered compounds in the PPE and the c-fos models induced by electrical stimulation of male rats’ TG. Fos protein in the TNC was measured in the c-fos experiment. Ring preparations of RSV were suspended in tissue baths and isometric contractions were recorded following incremental increases in the concentration of the test compound. Sumatriptan was used as a positive control for the RSV studies.

Results LY293558, LY382884 and LY435735 dose-dependently blocked protein extravasation in the PPE model. The rank order of potency correlated with affinity for GluR5. In contrast, LY300168, a potent and selective AMPA antagonist, did not block protein extravasation, even at relatively high doses. LY293558 and LY435735 also blocked c-fos expression in the TNC. LY293558 and LY382884 did not contract the tissue in the RSV assay at concentrations up to 100 μM.

Conclusions The inhibitory effects of GluR5 antagonists in the PPE and c-fos preclinical models of migraine suggest a novel role for GluR5 antagonism in migraine therapy. The lack of efficacy of the selective AMPA antagonist LY300168 in PPE does not support a role for this mechanism in migraine. The lack of activity of these compounds in the RSV provides a therapeutic advantage of GluR5 antagonists over current vasoactive migraine therapies. These pharmacological properties of GluR5 antagonists suggest that they could be used in the treatment of acute migraine without a cardiovascular liability.

OR14

Inhibition of trigeminal nociceptive afferents by adenosine A1 receptor activation: a novel approach towards the design of new anti-migraine compounds

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Introduction The discovery and development of sumatriptan has revolutionized the acute treatment of migraine. The antimigraine effects of sumatriptan are mediated via 5-HT1B and 5-HT1D receptors. These receptors transduce their effects via G proteins of the G1 type, and hence we have examined the effects of agonists at other G1 protein-coupled receptor types for their trigeminovascular actions. One such receptor is the adenosine A1 receptor at which GR 79236 is a highly selective agonist (1).

Methods The release of CGRP was measured by an ELISA from rat trigeminal neurones cultured as described by Eckert and colleagues (2). The effects of GR79236 on neurogenic vasodilatation of meningeal arteries were measured in the anaesthetized rat using intravital microscopy (3). The central effects of GR 79236 were examined onnoxious inputs from the dura to the trigeminal nucleus caudalis (TNC) using an in vivo electrophysiological model and protocol like that reported by Cumberbatch and colleagues (4).

Results We have shown that A1 receptors are located on human trigeminal neurones (5) and that GR79236 (10 nM–1 μM) inhibited CGRP release from rat trigeminal neurones in culture by about 70%. In in vivo studies, GR79236 (1–10 μg/kg) inhibited neurogenically mediated vasodilatation, which results from CGRP release from perivascular trigeminal nerve terminals innervating the meningeal vasculature. In separate experiments involving electrical stimulation of the meninges, GR 79236 (10 and 30 μg/kg) also...
markedly inhibited transmission centrally within the TNC. All these effects were attributable to A₁ receptor activation.

**Conclusion** We have shown that activation of A₁ receptors leads to inhibition of trigeminal neurones and their release of CGRP both in vitro and in vivo. This suggests that agonists at A₁ receptors may be useful in the acute treatment of migraine. Early indications from pilot clinical studies suggest that GR 79236 does have an antinociceptive action, which probably results from an inhibitory effect on nociceptive trigeminal neurones. The implications and insights gained from pursuing this novel integrated approach to finding new antinociceptive drugs will be discussed.

**References**


**OR15**

**Effect of adenosine (A₁) receptor agonist GR79236 on trigeminal nociception by blink reflex recordings in healthy human subjects**

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**Introduction** There are no good migraine models in humans, although established models of trigeminovascular nociception in animals exist. The recent development of a low-current intensity trigeminally mediated blink reflex (BR) allows the study of nociception specific transmission in the trigeminal nucleus caudalis, believed to be pivotal in trigeminovascular activation in migraine. Adenosine and its analogues are antinociceptive in humans and animals. GR79236 is a highly potent and selective adenosine A₁-receptor agonist that has been shown to have analgesic and anti-inflammatory actions at doses with no cardiovascular effect and may have therapeutic potential in migraine. We investigated the effect of GR79236 on the nociceptive BR.

**Methods** 12 female healthy volunteers (20–36 years) were randomized in a placebo-controlled double-blind crossover study. **Measurements**: BRs were elicited by supraorbital nerve stimulation with standard or nociception-specific electrodes. **Stimulation parameters**: Monopolar square pulses, 300 µs, 10–15 mA for standard or 1.5–2× pain sensation threshold (1.43 ± 0.06 mA) for nociceptive reflexes at random intervals of 12–18 s. BR responses were recorded bilaterally from infraorbital muscles (sampling frequency 2.5 kHz, 300 ms sweeps and analysed offline. Each measurement was based on 25 sweeps. Areas under the curve (AUCs) of the R2 component of the BR were calculated from the rectified EMG, before and 30 min after drug administration. **Drugs**: GR79236 (10 µg/kg) or placebo was administered IV over 15 min. **Primary end points**: Median AUC at 30 min, modelled using analysis of covariance with subject, period, treatment and baseline AUC as terms in the model.

**Results** Comparison of the two groups showed a non-significant reduction of the ipsilateral nociceptive R2 after GR79236 vs placebo of 17% (−567 [95% CI −1260–125.8] µVms). However, there was a significant reduction of the contralateral nociceptive R2 (P < 0.05) of 20% (−473 [95% CI −786.6, −138.7] µVms). There were no significant adverse events attributable to GR79236.

**Conclusion** The contralateral BR is mediated via polysynaptic trigeminal connections. Although this pathway is less well understood than the ipsilateral reflex, the results suggest an inhibitory effect of the A₁-receptor agonist GR79236 on trigeminal nociceptive pathways. The nociception-specific electrode directly depolarises cutaneous fibres and GR79236 may therefore act at second order trigeminal neurons in the nucleus caudalis, or more rostrally, and thus crosses the blood–brain barrier. This suggests that it may be effective in primary headache disorders.

**OR16**

**Characterization of the prostanoid receptor types involved in mediating CGRP release from trigeminal neurones**

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**Objectives** The neuropeptide, CGRP, is a potent vasodilator that has been implicated in migraine. It is released into the cephalic venous blood of migraineurs during attacks and levels are normalised by the clinically effective antimigraine agent, sumatriptan. The cyclooxygenase inhibitor, aspirin, is also effective in treating acute migraine, particularly when administered intravenously. This evidence, coupled with the observation that prostaglandins can cause migraine-like symptoms when injected into volunteers, suggests a role for prostaglandins in migraine pathophysiology. In this study, we have investigated the effects of prostaglandins on CGRP release from cultured trigeminal neurones.

**Materials and methods** Primary cultures were derived from adult rat trigeminal ganglia as previously described (1). Neurones were grown for 4–6 days in the presence of nerve growth factor (50 ng/mL) and cytosine-β-D-arabinofuranoside (Ara-C; 20 µM). CGRP levels were measured after 30 min using an enzyme immunometric assay (SPIbio, Massy, France) and quantified in pg/mL. To account for differences in neuronal numbers between preparations, CGRP levels following exposure to drug or vehicle (DMSO, 0.01%) were compared to the baseline value obtained immediately before stimulation in the same test well. All values are shown as mean ± SE mean of at least 3 experiments, and drug concentrations were all 1 µM. Statistical comparison was by one-way analysis of variance followed by the Tukey test with
Results
The average baseline CGRP concentration obtained over 30 min was 106 ± 17 pg/mL that varied between 23 and 231 pg/mL (n = 11 individual preparations) and no increase in CGRP levels occurred in vehicle control wells (6.7 ± 8%). Exposure to 1 μM PGE₂, carbaprostacyclin (cPGI₂) or PGD₂ resulted in a significant increase in CGRP levels of 199 ± 23%, 306 ± 41% and 150 ± 16%, respectively. In contrast, no CGRP release was observed when cells were stimulated with PGE₂α (29 ± 24%), the thromboxane receptor agonist, U46619 (32 ± 26%), the EP₃ receptor agonist, GR63799 (25 ± 5%), or the EP₃ > EP₁ receptor agonist, sulprostone (−6 ± 11%). However, a significant increase was observed in response to the EP₂ receptor agonist, butaprost (244 ± 23%), and the EP₃ > EP₂ receptor agonist, misoprostol (123 ± 14%).

Conclusion
These data suggest that CGRP release from trigeminal neurones can be stimulated by the activation of either EP, IP or DP receptors, but not by FP or TP receptors. Furthermore, the use of EP subtype specific agonists suggests that the EP subtype involved may be the EP₂ receptor.

Reference

OR17
Characterization of the effects of the CGRP receptor antagonist BIBN4096BS in SK-N-MC cells and isolated human cerebral, meningeal and coronary arteries
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Intracranial and coronary blood vessels are innervated by calcitonin gene-related peptide (CGRP) containing fibres originating in the sensory ganglion. During migraine attacks, circulating levels of CGRP are elevated and administration of the antimigraine drug sumatriptan has been shown to normalize CGRP levels concomitant with headache relief. A CGRP antagonist therefore may serve as a novel abortive migraine treatment. Here we present data on a human cell line and isolated human vessels for such an antagonist, BIBN4096BS (1). On SK-N-MC membranes, radiolabelled CGRP was displaced by both CGRP8-37 and BIBN4096BS, yielding pKi values of 8.5 and 11.4, respectively. Functional studies with SK-N-MC cells showed a CGRP-induced cAMP production which was antagonised by both CGRP8-37 and BIBN4096BS with pA2 values of 7.8 and 11.2, respectively. Isolated human cerebral, meningeal and coronary arteries were studied with a sensitive myograph technique. CGRP induced a concentration-dependent relaxation which was antagonized by both CGRP8-37 and BIBN4096BS in a competitive manner. In the coronary arteries CGRP was less potent as compared to the intracranial arteries; BIBN4096BS was an effective antagonist also in this tissue. In human omental arteries CGRP did not produce relaxation. When compared to another CGRP antagonist, Compound 1 (2) BIBN4096BS was significantly more potent. The clinical effect on acute migraine attacks of the CGRP antagonists is awaited with great interest.

Acknowledgement
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References

OR18
Intranasal sumatriptan is effective in the treatment of acute cluster headache – a double-blind placebo-controlled crossover study
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Cluster headache attacks reach a peak of pain intensity quickly, and are short-lasting; therefore acute treatments need to be fast acting. This study sought to determine if intranasal sumatriptan is an effective treatment of acute cluster headache. Patients with episodic and chronic cluster headache, by IHS criteria, were recruited and after explanation and obtaining informed consent were randomized to a double-blind placebo-controlled two-period crossover study. Patients were instructed to treat two attacks of at least moderate pain severity, with at least a 12-h break, using intranasal sumatriptan 20 mg or matching placebo. Patients recorded the time of onset of the attack, time of treatment, headache severity on a five point scale (0-nil, 1-mild, 2-moderate, 3-severe, 4-very severe) at 5, 10, 15, 20 and 30 min after treatment. The primary endpoint was the headache response defined as: very severe, severe or moderate pain becomes mild or nil, at 30 min. Secondary measures included pain free rates, treatment of associated symptoms and adverse events. The primary endpoint was analysed using a Multilevel Analysis (1) approach with MLwiN (http://www.ioe.ac.uk/ml) with P < 0.05 as the level of significance for testing. In total, 118 patients were recruited; 97 males and 21 females.
Of these, 87 provided efficacy data on attack one and 81 on attack two. Twenty-five provided no efficacy data because their bout ended, and six were lost to follow-up. Six cycled out of a cluster period between attack one and attack two. Modelling the treatment outcome as a binomial where response was determined by treatment, using the patient as the level 2 variable, and considering period effect, sex, site and cluster headache type as other variables of interest, the effect of intranasal sumatriptan 20 mg was superior to placebo at 30 min on the headache response endpoint (P = 0.01). For the first attack the placebo response rate was 11/37 (30%) and the sumatriptan 20 mg rate 29/50 (58%); for the second attack the rates were 15/45 (33%) and 18/36 (50%), respectively. There were no serious adverse events. It can be concluded that intranasal sumatriptan 20 mg is effective in the acute treatment of cluster headache when compared to placebo. For cluster headache patients, these data add a further evidence-based treatment to the management portfolio of this disabling primary headache.

Reference

OR19
Zolmitriptan nasal spray is effective, fast-acting and well tolerated during both short- and long-term treatment
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Objectives Zolmitriptan nasal spray offers an alternative formulation that may be advantageous for patients in terms of rapid onset and convenience. The results of the first clinical study involving the nasal spray are presented, along with results from a 1-year follow-up study. The objectives were to determine the efficacy of zolmitriptan nasal spray compared with zolmitriptan 2.5 mg oral tablet and placebo, and to assess the long-term efficacy and tolerability of the zolmitriptan 5 mg nasal spray.

Methods In the first study, 1547 patients were randomized to zolmitriptan nasal spray 0.5, 1.0, 2.5 or 5 mg, oral zolmitriptan tablet 2.5 mg or placebo in a double-blind, double-dummy manner for the treatment of 3 moderate or severe migraine attacks. The primary end point was 2-h headache response (reduction from moderate/severe pain at baseline to mild/no pain). In the long term study, patients were initially randomized to zolmitriptan nasal spray 0.5, 1.0, 2.5 or 5 mg. Once the optimal dose had been determined from the dose-finding study, patients were switched to the optimal 5 mg dose for the rest of the 1-year period.

Results 1371 patients were included in the ITT population of the dose-ranging study. Each dose of zolmitriptan nasal spray gave a significantly greater 2-h headache response rate than placebo. Response rates at 2-h for the 0.5, 1, 2.5 and 5 mg doses were 41%, 55%, 59% and 70%, respectively, compared with 30% for placebo (all P < 0.001) and 61% for the 2.5 mg tablet. The speed of onset following treatment with the nasal spray was rapid. Within 15 min, a significantly greater headache response rate was seen with zolmitriptan 5 mg nasal spray compared with placebo (11% vs 5% of attacks; P < 0.01). The efficacy of the nasal spray was examined in a subgroup of patients with pretreatment nausea, i.e. those for whom oral medication may not be optimal. In these patients, 42%, 49%, 58% and 68% of patients receiving nasal spray doses of 0.5, 1, 2.5 and 5 mg, respectively, achieved a 2-h headache response rate of 31% for placebo and 57% for the tablet. In the long term study, 783 patients took at least one dose of zolmitriptan 5 mg nasal spray and treated a total of 10505 attacks. The nasal spray was consistently effective over time, with 2-h headache response rates of 73%, 75%, 75% and 75% for the periods 0–3, 4–6, 7–9 and 10–12 months, respectively. Long-term use was well tolerated, with a low incidence of adverse events that remained stable over the 12-month period (24%, 20%, 23% and 22% of attacks for months 0–3, 4–6, 7–9 and 10–12, respectively).

Conclusions Zolmitriptan nasal spray has a rapid onset of action and is highly effective in the treatment of migraine. The nasal spray produces a consistent response and is well tolerated with long-term use.

OR20
Efficacy of intramuscular droperidol for migraine treatment: a dose-response study
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Objective To evaluate the efficacy and tolerability of 4 different doses of IM droperidol vs placebo for the acute treatment of migraine with or without aura.

Background Droperidol, an adjunct during general anesthesia, has been used to treat agitation, surgical pain in combination with an opiate analgesic, and nausea and vomiting. Two recent reports suggest that droperidol is effective in selected migraine patients (1,2).

Design and methods Double-blind, placebo-controlled, randomized, parallel group, 22-centre study. Patients had an IHS migraine diagnosis and were randomized to one of four doses of droperidol (0.1, 2.75, 5.5 or 8.25 mg) or placebo at clinic visit 1. At migraine onset, patients returned to the clinic (visit 2) for treatment of a single moderate or severe attack via intramuscular injection in the deltoid, thigh, or buttock delivered as a 1-mL volume.

Results Of 537 screened patients, 305 patients received treatment. Compared with placebo (57%), more patients in the droperidol 2.75, 5.5 and 8.25 mg treatment groups experienced a significant reduction in headache by 2 h (moderate or severe to none or mild; 87%, 81%, and 84%, respectively).
respectively; primary outcome; $P = 0.0002$). Onset of response was assessed at multiple time points (secondary end point) and was significantly improved at 1 and 1.5 h with the 2.75- and 5.5-mg doses. The 8.25-mg group was statistically superior to placebo at 0.5 h. Pain-free response rates were significantly greater than placebo at 1 h in the 2.75-mg treatment group and more than 60% of patients receiving droperidol were pain free at 2 h (placebo 30%). Headache improvement $>2$ grade levels, fewer headache recurrences, less use of rescue medications, and fewer non-headache-associated symptoms were significantly associated with droperidol doses $>2.75$ mg. AEs occurring in greater than 5% of patients receiving droperidol included asthenia, anxiety, akathisia, somnolence, and injection site reactions. Most AEs were mild to moderate. Anxiety, akathisia, and somnolence were present in 15–30% of patients with a dose $>2.75$ mg (approximately 30% of these were of severe intensity). There was no effect on standard clinical chemistry, hematology, urinalysis, vital signs or ECG, or evidence of adverse cardiovascular effects.

**Conclusions** Droperidol 2.75 IM is effective in treating acute migraine headache with a 2-h headache response of over 80% in patients with moderate to severe migraine. Higher doses were no more effective, but produced more AEs.

**References**

Mechanisms of headache: lessons from neuroimaging

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Migraine and other primary headache disorders must ultimately be studied in the human. For half a century, this fact imposed numerous logistical and technical limitations on attempts to understand the pathophysiology of headache syndromes. Fortunately, the appearance of non-invasive functional imaging techniques has allowed us to make the first steps in what will undoubtedly be a long but fascinating journey in our quest to understand how and why primary headache disorders occur humans. This lecture will serve as an overview of functional imaging as applied to headache thus far, and will provide a context in which to understand the newest neuroimaging data.

Refining the localization of the brainstem dysfunction in migraine: a PET study

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Introduction Primary headache, such as migraine and cluster headache, has classically been diagnosed and characterized on the basis of a careful history and physical examination. Migraine and cluster headache are recognized as distinct clinical entities despite sharing some associated features and treatment options. Recently, positron emission tomography (PET) has been used to study both migraine (1) and cluster headache (2). The results suggest that there is a differential activation pattern in the brain, which may have fundamental implications for the pathophysiology of these disorders. We report PET scan findings in a patient with both migraine and cluster headache who experienced a migraine attack while in an active cluster period.

Methods Using a slow bolus injection of H215O-water PET was used to examine changes in regional cerebral blood flow, as an index of synaptic activity, during an acute attack of migraine headache triggered with nitroglycerine. The data were analysed using Statistical Parametric Mapping as has been previously reported (2).

Results The patient experienced migraine headache typical of his previous attacks and fulfilling IHS criteria for migraine, although he was in an active cluster headache period. PET activations were observed in three broad regions of interest during the acute migraine headache. First, there was activation of structures generally reported in functional brain imaging studies of pain: the cingulate, prefrontal, posterior insular and cerebellar cortices, the thalamus and basal ganglia. Secondly, there was strong bilateral activation of structures outside the brain corresponding to the region of the large intracranial vessels. The vessel activation was strongly correlated to a visual-analogue score of the pain and resolved with successful treatment of the headache with sumatriptan. Thirdly, there was activation of the rostral brainstem in the pons, slightly lateralized to the left, which persisted following treatment with sumatriptan, and headache resolution. There was no activation in the region of the hypothalamus as has been reported for acute cluster headache imaged with PET.

Conclusion These data demonstrate the fundamentally neurovascular nature of migraine. Moreover, using functional brain imaging the clinical syndromes are, for the first time, distinguishable by objective means suggesting the real possibility of the eventual development of investigative strategies for biological markers of primary headaches.

CDNA array analysis of gene expression following cortical spreading depression (CSD)

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Objectives The goals of the study were to examine changes in gene expression following cortical spreading depression (CSD) using cDNA array technology.

Materials and methods Male C57Bl6X129 mice (10–11 weeks old) were anesthetized with Avertin and four episodes of CSD were induced by application of 300 mM KCl on the left hemisphere. No CSDs were observed in control mice where NaCl was applied to the cortex. Other control groups included anesthesia only and electrode implantation only. The mice were sacrificed 2 h after the last episode of CSD, after NaCl application, anesthesia or electrode placement. The left cerebral cortex plus thalamus were flash frozen in liquid
Conclusions
Cytokines and chemokines are induced following CSD. Genes differentially induced by CSD include major prion proteins involved in signal transduction, nitric oxide signalling, and atrial natriuretic peptide (ANP). Neuropeptide Y (NPY). Growth factor and monocyte chemoattractant protein-1. Genes differentially induced by CSD include major prion protein precursor (PRP), protein inhibitor of neuronal nitric oxide (mPIN), guanine nucleotide releasing protein (GNRP) and atrial natriuretic peptide (ANP). Neuropeptide Y (NPY) was down-regulated following CSD.

Conclusions
Cytokines and chemokines are induced following surgery. Genes specifically altered following CSD include proteins involved in signal transduction (GNRP), nitric oxide signalling (mPIN) as well as vasoactive peptides (ANP and NPY).

Acknowledgement
Supported by P50NS32399.

OR25
Cortical spreading depression increases vascular permeability in the cerebral microcirculation via reactive oxidant generation and leukocyte-endothelial adherence
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Objective
The significance of microvascular alterations to migraine aura, inflammatory-trigeminal-vascular changes, and head pain remains to be determined. Recent evidence has shown that cortical spreading depression (CSD) promotes reactive oxidant species (ROS) generation and leukocyte-endothelial adherence in the pial microcirculation. These events could contribute to increased vascular permeability during migraine. Our goal was to evaluate: (1) whether CSD increases vascular permeability in the pial microcirculation, (2) the role of ROS in this response by measuring ROS generation and assessing the effects of antioxidants, and (3) the role of leukocytes in this response by examining leukocyte adherence and the effect of neutropenia.

Materials and methods
Intravital microscopy was used to examine the pial microcirculation in rats. After a control period, CSD was produced by application of KCl to the cortex. Vascular permeability was assessed as the ratio of extravascular to intravascular fluorescence intensity of fluorescein isothiocyanate (FITC). ROS generation was measured using the fluorescent probe dihydrorhodamine123 (DHR). Leukocytes were labelled with rhodamine-6G. Adherent leukocytes were defined as cells remaining stationary in pial venules for greater than 30 s. Animals received saline or lipoic acid (an antioxidant) iv prior to observation. Since neutrophils are the predominant leukocyte involved in rapid adhesive interactions, neutropenia was produced in rats by ip injections of an antineutrophil antibody prior to experiments.

Results
CSD increased vascular permeability as indicated by extravascular accumulation of FITC over time. ROS generation and leukocyte adherence within pial venules increased after CSD. There were no changes in these parameters in animals in which CSD was not produced. Lipoic acid reduced CSD-induced increases in vascular permeability as well as ROS generation and the number of adherent leukocytes. The CSD-induced increase in vascular permeability was attenuated in neutropenic rats.

Conclusions
Our results demonstrate an increase in cerebral vascular permeability during CSD. The mechanism of this response involves ROS generation since the antioxidant lipoic acid reduced FITC extravasation. Finally, adherent leukocytes appear to contribute to CSD-induced changes in vascular permeability based on results obtained in neutropenic animals. These microvascular changes may have relevance to neurogenic inflammation associated with headache and migraine aura.

Acknowledgement
Supported by NIH grant P50NS32399 (KMAW).

OR26
Sumatriptan inhibits propagation of cortical spreading depression (SD), as well as cerebrovascular responses, detected with MRI
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Background and objectives
The evidence that SD underlies the aura of migraine remains debated, perhaps because SD is transient and technically difficult to detect clinically, using MRI or other imaging paradigms. Here we determined the effects of sumatriptan on SD and the cerebrovascular responses using MRI in the gyrencephalic cat brain. The complex gyrencephalic brain has properties that limit the extent of SD, a functional property likely to occur also in man.

Methods
Experiments were ethically approved. Animals were anaesthetized (a-chloralose) without recovery and were continuously monitored to ensure physiological and anaesthetic stability. After craniotomy and duroectomy sumatriptan (SUMA, 0.3 mg/kg, n = 4) or saline (SAL, 1 mL/kg, n = 5) was administered iv. 15 min before SD induction, evoked with KCl for 10 min MRI at 2T used intercalated echo planar pulse sequences sensitive to water diffusion (DWI) and blood oxygenation (BOLD). Horizontal images through the cortical surface were acquired for 25 min before and 76 min after SD induction, in total 181–226 frames. DWI was used to measure SD characteristics. Independent component analysis (ICA) of the BOLD signal detected biphasic
(negative/positive) waveforms, indicating cortical hypo/hyper-perfusion changes. Waveforms (z-score > 5) were localized to map their source.

**Results** After SAL 24 SD events (range 4–7 per animal) were observed on the hemisphere ipsilateral to SD induction. The first event was hemispheric in extent, but 50% of secondary SD events failed to cross the suprasylvian sulcus. SUMA halved the area affected by the first SD event (P < 0.05), but increased event propagation across the suprasylvian sulcus. SUMA had no effect on total event number (range 4–8 in increased event propagation across the suprasylvian sulcus. SUMA had no effect on total event number (range 4–8 in 40 ± 4.4 min, mean ± SEM) or velocity (2.2 ± 0.4 mm/min). ICA detected prolonged localised biphasic BOLD responses after SD induction only in the ipsilateral cortex in 3/4 SAL animals. The two phases lasted? 10 min each. After SUMA such waveforms were not observed, in line with the known inhibitory effects of SUMA on cerebrovascular alterations during the migraine attack.

**Conclusions** The results indicate SUMA may directly modulate the spatial distribution of SD activity and eliminate the later biphasic waveforms. The biphasic BOLD response detected with ICA may therefore represent the 'headache' phase of migraine. We conclude the combination of intercalated MRI and ICA should improve the chances of detecting SD and its sequelae in the human brain.

**OR27**

Nitroglycerin infusion causes a delayed inflammatory response in rat dura mater

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Nitroglycerin infusion (GTN) can induce a delayed migraine attack (4–6 h) in migraineurs, and nitric oxide has been implicated in migraine pathophysiology. We therefore examined the pathophysiological mechanisms underlying this relationship. GTN, which has a relatively short half-life of 1–4 min, was infused in pentobarbital anaesthetized male rats for 30 min Inducible nitric oxide synthase was dose dependently increased in dura mater on Western blots after SD induction only in the ipsilateral cortex in 3/4 SAL animals. The two phases lasted?10 min each. After SUMA such waveforms were not observed, in line with the known inhibitory effects of SUMA on cerebrovascular alterations during the migraine attack.

**Results** After SAL 24 SD events (range 4–7 per animal) were observed on the hemisphere ipsilateral to SD induction. The first event was hemispheric in extent, but 50% of secondary SD events failed to cross the suprasylvian sulcus. SUMA halved the area affected by the first SD event (P < 0.05), but increased event propagation across the suprasylvian sulcus. SUMA had no effect on total event number (range 4–8 in 40 ± 4.4 min, mean ± SEM) or velocity (2.2 ± 0.4 mm/min). ICA detected prolonged localised biphasic BOLD responses after SD induction only in the ipsilateral cortex in 3/4 SAL animals. The two phases lasted?10 min each. After SUMA such waveforms were not observed, in line with the known inhibitory effects of SUMA on cerebrovascular alterations during the migraine attack.

**Conclusions** The results indicate SUMA may directly modulate the spatial distribution of SD activity and eliminate the later biphasic waveforms. The biphasic BOLD response detected with ICA may therefore represent the 'headache' phase of migraine. We conclude the combination of intercalated MRI and ICA should improve the chances of detecting SD and its sequelae in the human brain.

**OR28**

The effect of nitric oxide and nitric oxide synthase inhibitors on rat dural meningeal vessels

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**Background and objectives** Nitric oxide (NO) donors can produce headache in healthy subjects, but frequently trigger migraine in patients with the disorder. NO-induced headache is accompanied by dilation of large intra and extracranial vessels. Sumatriptan has been shown to alleviate these NO-induced headaches in migraine patients. One controlled trial has shown efficacy for NO synthase inhibitors in the acute treatment of migraine. Histamine triggers migraine headache in patients probably by activating the synthesis of NO via nitric oxide synthase (NOS). This study has used the intravital microscopy technique to measure dural meningeal vessels after NO donor infusion and the effect of two antimigraine compounds and histamine receptor antagonists, and the effect of NOS inhibitors on neurogenic stimulation of dural vessels.

**Methods** Rats were anaesthetised with 60 mg/kg i.p. sodium pentobarbitone and cannulated for measurement of blood pressure and intravenous administration of experimental drugs and supplementary anaesthesia. The parietal bone was thinned to form a cranial window through which the diameter of the middle meningeal artery or one of its branches was measured with a video dimension analyser.

**Results** Infusion of sodium nitroprusside (NO donor) at 0.5–2.0 µg/kg/min for 15 min caused an immediate and reproducible dilation of the dural vessels for the time of the infusion. Neither sumatriptan (10 mg/kg) nor flunarizine (5 mg/kg) inhibited this dilation. It was also not inhibited by the histamine receptor antagonists mepyramine (H1-receptor) 1, 2, and 10 mg/kg and famotidine (H2-receptor) (0.1, 0.3, 1.0 and 3.0 mg/kg). The NOS inhibitor L-NAME at 40 mg/kg had a small inhibitory effect of neurogenic vasodilation.

**Discussion** The NO-induced meningeal dilation followed a similar time course to NO-induced headache in patients. Sumatriptan could not inhibit this dilation. This may be accounted for by species differences, because the affinity of sumatriptan to human 5-HT1B/1D receptors is much greater than in the rat, or because sumatriptan affects other vessels or following GTN infusion exhibits features overlapping with that of neurogenic inflammation within meninges. Our present data indicate that GTN causes delayed onset of dural inflammation in dura mater, which is mediated by NO mostly derived from iNOS expression in macrophages. A similar mechanism may promote the development of a migraine headache after GTN in susceptible humans.

**Acknowledgement** This study was supported by the NIH grant 1P01NS25611 (MAM and CW). UK is supported by the IHS-Research Fellowship 1999 and the Deutsche Forschungsgemeinschaft (Re-1316/1–1).
indeed neurons to ameliorate NO-induced headache. The response of L-NAME is consistent with the view that NO synthase inhibitors may have some therapeutic value in migraine. Histamine antagonists could not block the NO-induced dilation because their role in the system would be to block the histamine that activates NO synthase and not to block exogenously introduced NO. The small inhibitory effect of L-NAME to neurogenic stimulation suggests that NO can directly cause the dilation of the meningeal vessels, probably working in parallel with calcitonin gene-related peptide.
OR30
Clinical features of withdrawal headache and long-term follow up after withdrawal from triptans in comparison to other antimigraine drugs
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Objective Medication overuse headache (MOH) is caused by overuse of analgesics, ergots and/or triptans. There are no prospective studies evaluating the clinical features of withdrawal of or data concerning the relapse rate with regard to different classes of antimigraine drugs. In a prospective study in 94 patients with MOH, we investigated duration and severity of withdrawal headache as well as the relapse rate one year after withdrawal.

Design and methods 94 patients suffering from MOH according to the IHS criteria were included and underwent inpatient withdrawal. During withdrawal the following features were assessed: (A) duration of withdrawal (number of headache days), (B) intensity of withdrawal headache (4-step scale), (C) number of requests for rescue medication. The follow-up 1 year after withdrawal was conducted by structured interviews, which enclosed characteristics of current headache and currently used medication.

Results Features of withdrawal headache. (A) Duration of withdrawal headache was shorter in migraine patients (MH, 5.7 days) than in patients with tension-type headache (TTH, 8.6 days) or combined headache (CH, 7.5 days, P < 0.05). Duration was significantly shorter in patients overusing triptans (2.9 days), when compared to ergots (5.7 days) or analgesics (8.2 days; P < 0.001). (B) The mean headache intensity on the first day of withdrawal did not differ between the drug groups. At the 14th day (last day of observation) of withdrawal, however, the mean intensity was significantly lower in patients overusing triptans (0.08) when compared to ergots (0.4) or analgesics (0.9, P < 0.001). (C) Rescue medication was significantly less often requested by patients undergoing triptan withdrawal (mean: 0.25 requests), when compared to ergots (1.25) or analgesics (1.85, P < 0.001). Relapse rate: Complete sets of data from 80 patients were available after one year. Overall, 31 patients (39%) developed the features of MOH again. While only 25% of patients with MH (14/56) suffered from MOH again, this was observed in 73% (8/11) and 69% (9/13) in patients with TTH and CH, respectively (P < 0.001). Sub-analysis regarding the drugs primarily overused revealed a relapse rate of 20% in patients who overused triptans or ergots and a relapse rate of 58% in patients who overused analgesics (P < 0.005).

Conclusions The study indicates, that only two factors (type of primary headache and type of overused medication) significantly influenced duration and severity of withdrawal headache as well as the long-term success after withdrawal therapy. Patients with MH as the primary headache and the patients who overused triptans had a shorter and less severe withdrawal as well as a significantly lower relapse rate.
The varieties of CDH with analgesic overuse were classified according to Silberstein et al.'s criteria (1).

**Results** The questionnaire was returned by 4578 subjects (46%). 73 (1.6%, 95% CI 1.3–2.1%) fulfilled criteria for CDH with analgesic overuse: 69 (95%) were women. Mean age was 56 years (range 19–82 years). Transformed migraine was diagnosed in 35 (75%), chronic tension-type headache in 13 (18%), and 5 subjects (7%) met new daily persistent headache criteria. Analgesic overuse pattern was as follows: simple analgesics (40%) > ergotamine (+ caffeine) (22%) > opioids (mainly codeine) (10%) > triptans (3%). The remaining patients (26%) were abusing different combinations of analgesics.

**Conclusions** Between 1 and 2% of the general population (3% of women) suffers from CDH with analgesic overuse; one-fourth are fulfilling transformed migraine with analgesic overuse criteria. Analgesics, alone or in combination, and ergotamine (plus caffeine) account for two-thirds of these cases.

**Acknowledgement** Supported by a research grant from MSD Spain.

**OR32**

**Stressful life events and risk of chronic daily headache: results from the frequent headache epidemiology study (FRHE)**

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**Objective** To assess the role of stressful life events as risk factors for chronic daily headache (CDH) in a community sample.

**Background** Anecdotal evidence suggests that stressful life events may increase the risk of CDH.

**Methods** CDH cases (> 180 HA days per year) and controls (2–104 HA days per year) were identified from a community sample participating in a telephone interview on general health topics. Follow-up interviews were completed with cases (n = 206) and controls (n = 507) on risk factors for the development of CDH, including the occurrence of stressful life events (work changes, relationship changes, changes with children, moves, deaths in the family or of close friends, and ongoing extremely stressful situations). An affirmative response to a question about each type of stressful life event was followed by questions on the year of occurrence and level of stress associated with the event (i.e. on an anchored 0–10 scale). Events that occurred during the year of or year before frequent headache onset in cases or in an equivalent time period in controls were considered in the analysis as potential precipitating events.

**Results** In the year before or same year as onset of CDH, cases were more likely than controls to move (33% vs. 26%, P = 0.06), to have a change in relationship (18% vs. 15%), to have a major problem with children (16% vs 10%, P = 0.04), and to have an extremely stressful ongoing situation (42% vs. 21%, P < 0.001). Cases were more likely than controls to have experienced a change in relationships that involved a breakup (e.g. widowhood, divorce, separation, break-up) (18% vs 11%, P < 0.012). In contrast, controls were more likely than cases to have married. The total number of precipitating stressful life events was significantly higher in cases than in controls (2.7 vs. 2.0, P < 0.0001). No differences between cases and controls were observed in subsequent years. The average level of stress reported for each type of event was higher in cases than in controls.

**Discussion** This is the first study to show that stressful life events are a risk factor for CDH in a population sample. The dominant risk factors involved an extremely stressful ongoing situation and challenges with significant relationships (i.e. children and significant other). The association between stressful life events and CDH is limited to the year of and the year before CDH onset, supporting a causal association. Management of stressful life events in patients with episodic headache may reduce the risk of CDH.

**OR33**

**Association between migraine and endothelin type A receptor (ETA-231 A/G) gene polymorphism**

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**Background** Previous studies have described an association between migraine and endothelin, a potent vasoconstrictor. The aim of the present study was to investigate whether there was an association between polymorphisms in genes encoding ET-1 and its receptors and the common forms of migraine, in a population-based setting.

**Methods** A population-based study of elderly individuals (n = 1179) in Nantes (Western France). Lifetime migraine was defined according to the International Headache Society criteria through a two-phase procedure. Participants were first systematically asked about attacks of severe headaches during their life as part of the general questionnaire during a face-to-face interview with lay interviewers. Those who answered yes to the screening question were then asked to participate in a telephone interview with a headache specialist using a structured questionnaire. Five polymorphisms in genes encoding endothelin 1, endothelin type A (ETA) and type B receptors were determined in more than 90% of the sample.

**Results** Migraine was diagnosed in 140 participants (11.9%). The ETA (−231 A/G) polymorphism was the only one
Gene modulates the risk for migraine. These results offer new insights into the pathophysiology of the vascular component of migraine.

Conclusions We found that a variant of the ETA receptor gene modulates the risk for migraine. These results offer new insights into the pathophysiology of the vascular component of migraine.

OR34

Single nucleotide polymorphism (SNP) alleles in the insulin receptor (INSR) gene are associated with migraine

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A migraine locus was identified on chromosome 19p13.3/2 using linkage analysis in 16 migraine pedigrees. Fifty-three single nucleotide polymorphisms (SNPs) were isolated across the locus, of which 24 were genotyped in 1000 unrelated migraine cases and 1000 controls. Five SNPs within the Insulin Receptor (INSR) gene showed significant association with migraine. This association was independently replicated in a separately ascertained case/control population. The association between INS R and migraine suggests that INS R may play a role in migraine pathogenesis, although the possibility that the migraine-associated SNPs in INS R may be in linkage disequilibrium with a nearby migraine susceptibility gene cannot yet be excluded. Experiments with INS R RNA and protein were performed to investigate functionality for the migraine-associated SNPs. We suggest possible roles for INS R in migraine pathogenesis.

OR35

Genetic analysis of the X chromosome in migraine families

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Objective Investigate 80 families with migraine and possible X dominant inheritance for evidence of allele sharing and linkage to Chromosome X.

Background Familial clustering of migraine is long known, although the disease does not consistently follow Mendelian inheritance patterns and is thought to be genetically complex. We recognized a maternal bias for transmission of migraine to daughters based on limited segregation analysis in the collection of families described below. Others have proposed that female: male predominance for migraine cannot be entirely attributed to hormonal factors. One potential explanation is an X linked dominant component to disease. A familial migraine locus has been previously suggested at Xq24–28.

Methods We screened the entire X chromosome in 80 families diagnosed with familial migraine or hemiplegic migraine according to IHS criteria. Families with possible male to male transmission were excluded (five). Eighteen markers (ABI PRISM Linkage Mapping Set, Panel 28) spanning the entire X chromosome and spaced 10 cm apart were genotyped using a 3700 ABI PRISM DNA Analyser. Alleles were assigned using the GeneScan Analysis software. Analysis for allele sharing and linkage was performed using GENEHUNTER-X, VITESSE 1.1 programs and the maximized maximum LOD score (MMLS) method.

Results Sixty-six multigenerational families and 14 sibships were ascertained from Spain (27), Germany (18) and USA (35) among 478 total samples. Of these, 155 had migraine without aura, 101 migraine with aura, 32 hemiplegic migraine, and 44 were of uncertain type (IHS 1.7). Preliminary results on the genotyping of 40 families and 300 samples without stratification shows combined LOD 0.91, theta 0 at marker DXS8043 using MMLS.

Conclusion Preliminary results suggest further analysis of Chromosome X is warranted. The complete analysis of the total sample with stratification by ethnic groups and migraine type will be described.

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Periaqueductal grey matter dysfunction in migraine: cause or the burden of illness?

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Objective The periaqueductal grey matter (PAG) is at the center of a powerful descending antinociceptive neuronal network. As an indicator of function we studied iron homeostasis in the PAG in episodic migraine patients between attacks and chronic daily headache patients during headache. We used high-resolution MR techniques to map the transverse relaxation rates $R_2$, $R_2^*$ and $R_2'$ in the PAG, red nucleus (RN) and substantia nigra (SN). $R_2'$ is a measure of non-heme iron in tissues.

Methods Seventeen patients diagnosed with episodic migraine with and without aura (EM), 17 with chronic daily headache (CDH) and medication overuse, and 17 normal adults (N) were imaged with a 3 Tesla MRI system. Relaxation rates, $R_2 (1/T_2)$, $R_2^* (1/T_2^*)$ and $R_2' (R_2^* – R_2)$ were obtained for the PAG, RN and SN. $R_2$, $R_2^*$ and $R_2'$ values of the EM, CDH, and N groups were compared using analysis of variance (ANOVA), Student’s t-test, and correlation analysis.

Results In the PAG, there was a significant increase in mean $R_2$ and $R_2^*$ values in the EM and CDH groups ($P<0.05$) compared to normal, but no significant difference between the EM and CDH groups, or between migraine with or without aura. Positive correlations were found for duration of illness with $R_2'$ in the EM ($r=0.65$, $P=0.0052$) and CDH ($r=0.71$, $P=0.0014$) groups. Decrease in mean $R_2'$ and $R_2^*$ values was observed in the RN and SN of the CDH compared to N and EM groups ($P<0.05$), explained best by flow activation due to head pain.

Conclusions Iron homeostasis in the PAG was selectively, persistently and progressively impaired in the EM and CDH groups, possibly caused by the burden of repeated migraine attacks and putatively implicating cumulative iron catalysed free radical damage. These results also emphasize the PAG as a possible ‘generator’ of migraine attacks, potentially by dysfunctional control of the trigeminovascular nociceptive system.

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Very frequent primary headaches, non-pharmacological mechanisms and outcomes

OR37
Possible contributions of peripheral and central sensitization to chronic daily headache
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We recently showed that a few minutes after the initiation of a migraine headache primary afferent neurons that innervate the meninges become hypersensitive and we proposed that this sensitization mediates the symptoms of intracranial hypersensitivity. We also showed that the barrage of impulses that come from the meningeal nociceptors sensitize second-order trigeminovascular neurons that receive convergent input from the dura and facial skin, and proposed that this sensitization can mediate the cutaneous allodynia on the ipsilateral head. These findings raised the question of whether a similar sequence of events occurs in chronic daily headache. Based on anatomical and physiological differences between muscular and cutaneous nociceptors, an hypothesis will be presented regarding the constant muscle ache that accompanies chronic daily headache and the possible contribution of peripheral and central sensitization to this neurological disorder.

Since the sensitized second-order neurons in the medullary dorsal horn project to multiple brainstem, thalamic and hypothalamic areas, it is reasonable to hypothesize that the barrage of impulses that come from the sensitized second-order neurons alters the response properties of neurons in these brainstem and diencephalic areas. Based on our clinical and scientific data we proposed that sensitization of thalamic neurons can mediate the development of cutaneous allodynia all over the body, and that altered responses of hypothalamic neurons can mediate changes in integrated behaviours such as appetite, sleep, and anxiety. The discussion will reexamine the question of whether the activation of hypothalamic and brainstem neurons 'generate' the headache or is 'secondary' to the pain.

OR38
In vivo evidence of altered skeletal muscle blood flow in chronic tension-type headache
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Background Painful impulses from tender pericranial muscles may play a major role in the pathophysiology of chronic tension-type headache. Firm evidence for peripheral muscle pathology as a cause of muscle pain and chronic headache is still lacking.

Objectives Using microdialysis technique, we aimed to estimate in vivo blood flow and interstitial lactate concentrations in the trapezius muscle at rest and during static exercise in patients with chronic tension-type headache and in healthy subjects.

Methods We recruited 16 patients with chronic tension-type headache and 17 healthy control subjects. Two microdialysis catheters were inserted into the trapezius muscle (on the non-dominant side) of subjects and dialysates were collected at rest, 15 and 30 min after start of static exercise (10% of maximal force) and 15 and 30 min after stop of exercise. All samples were coded and analysed blindly. The primary end points were to detect a difference between patients and controls in changes of muscle blood flow and the interstitial lactate concentration from baseline to exercise and postexercise periods.

Findings The increase in muscle blood flow from baseline to exercise and postexercise periods was significantly lower in patients than controls (P=0.02). There was no difference in resting blood flow between patients and controls (P=0.43). Resting interstitial concentration of lactate did not differ between patients, 2.51±0.17 mM, and controls, 2.35±0.23 mM (P=0.57). There was no difference in change in interstitial lactate from baseline to exercise and postexercise periods between patients and controls (P=0.38).

Interpretation The present study provides in vivo evidence of decreased blood flow in response to static exercise in a tender muscle in patients with chronic tension-type headache. We suggest that because of increased excitability of neurons in the CNS the central interpretation and response to normal sensory input are altered in patients with chronic tension-type headache. This may lead to enhanced sympathetically mediated vasoconstriction and thereby a decreased blood flow in response to static exercise.
Efficacy of behavioural and physical treatments for tension-type headache and cervicogenic headache: meta-analysis of controlled trials

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Objective and method This study was undertaken to identify and summarize evidence from controlled trials examining the efficacy of behavioural and physical treatments for tension-type and cervicogenic headache. We identified English-language reports from databases (Medline and others; 1966–99), experts, and prior reviews. We calculated standardized mean differences (effect sizes) for treatment comparisons and percentage improvement for treatment arms based on headache index or frequency. Where similar trials provided data, a multivariable, random effects model meta-analysis of efficacy measures was performed. The number of patients obtaining at least a 50% reduction in headache was recorded and used to calculate odds ratios.

Results Summary effect sizes from a meta-analysis of 23 trials suggest that relaxation training, cognitive-behavioural therapy, electromyographic (EMG) biofeedback combined with relaxation training, and EMG biofeedback without relaxation training were all effective in treating tension-type headache (TTH) when compared to a wait-list control. In addition, these behavioural treatments were similar in effectiveness to drug treatment with amitriptyline. Physical treatments have been less often studied. Six small trials of acupuncture yielded inconsistent results. Cervical spinal manipulation effectively relieved headaches compared with control treatments in two studies of patients with cervicogenic headache, but there were no wait list or placebo controlled studies for patients with TTH. Other physical treatments for which controlled trials have been reported include cranial electrical stimulation, aerobic exercise, and therapeutic touch.

Conclusions Each of the behavioural therapies considered appear to be an effective treatment for TTH. There is little information about which patients will benefit from particular behavioural approaches; the choice among them may, for the present, depend more on availability and acceptability than on data about relative efficacy. Manipulation is effective in patients with cervicogenic headache, but its efficacy in patients with TTH is unproven. There are insufficient data about any of the other physical treatments to draw conclusions about their efficacy.

OR39

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OR40

Patient characteristics predict response to antidepressant medication and to stress management therapy for chronic tension-type headache

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Objective Tricyclic antidepressant therapy (AMT) and stress-management therapy (SMT) are each moderately effective in managing chronic tension-type headaches (CTTH). However, little information is available about patient characteristics that predict response to treatment or identify patients most likely to benefit from either SMT or AMT. Investigators have hypothesized that patients with more severe or complex problems (more frequent headaches or comorbid psychiatric disorders) would be both more and less responsive to one of these treatments. This paper provides the first systematic empirical examination of this question.

Methods 169 patients (125 females; mean age 38) with an International Headache Society diagnosis of CTTH (mean 26 headache days per month) were randomized to one of four treatments [Placebo (PL), AMT, SMT + PL, SMT + AMT] and evaluated by clinical assessments, daily headache diary, and psychosocial testing for 8 months. Primary outcome measures were the Headache Index (HI; average daily pain rating taken 4 times per day) and the Headache Disability Inventory (HDI), a measure of the impact of headaches on psychosocial and affective functioning. Co-morbid psychiatric disorders were assessed with the Prime MD Structured
Interview supplemented by self-report psychological tests of anxiety and depression.

**Results** Hierarchical linear modeling with best fitting AR(1) error structure was used to examine the patient characteristics that predicted response to AMT or to SMT. AMT showed the greatest advantage over PL when headache activity ($P = 0.001$ HI) and disability ($P < 0.001$ HDI) were high, and when a comorbid mood ($P = 0.047$ HI; $P < 0.001$ HDI) or anxiety disorder ($P = 0.027$ HDI) was present (HICOMPLX patients). In fact, in HICOMPLX patients either failed to improve or deteriorated with PL, but showed substantial improvements with AMT. In contrast, when headache activity levels were lower and comorbid mood and anxiety disorders were absent (LO/MODCOMPLEX patients) AMT yielded small improvements or no improvement beyond that observed with PL. The same pattern of results was observed with SMT, with SMT showing the greatest advantage over PL when headache activity ($P = 0.003$ HI) and disability ($P < 0.001$ HDI) were high, and when a comorbid anxiety disorder ($P = 0.009$ HDI) was present. However, robust predictors of differential response to the unimodal treatments (AMT or SMT) vs combination therapy (AMT+SMT) were not evident.

**Conclusion** Both AMT and SMT showed clear benefit with HICOMPLX patients, but small benefit or no benefit (beyond PL) with LO/MODCOMPLEX patients.

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**OR41**

**Lifestyle and migraine**

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**Objectives** To compare quality of life and lifestyle characteristics such as physical activity, sleeping, smoking and consumption of alcohol, caffeine and chocolate in migraine patients and migraine-free controls.

**Patients and methods** Sixty-six consecutive patients suffering from migraine with and/or without aura and 45 migraine-free controls completed a semistructured interview covering demographic data, headache characteristics, quality of life, physical activity, quality of sleep, smoking, consumption of alcohol, caffeine and chocolate and experience with potential headache triggers. Patients with overuse of analgesics, ergotamines and/or triptans as well as patients with relevant organic and/or psychiatric disorders were excluded. All interviews were performed by one and the same person (JH) either personally or by telephone. For statistical analysis SPSS-WIN 10.0 was used.

**Results** Patients and controls were comparable regarding age, sex, educational level and profession. Migraine patients rated their productivity and quality of life more often severely impaired than controls ($47.0\%$ vs $6.7\%$, $P < 0.001$; $37.9\%$ vs $8.9\%$, $P < 0.001$). Nevertheless, migraineurs more often reported leisure time physical activities than controls ($83.3\%$ vs $64.4\%$, $P < 0.05$). Physical activity at work, quality of sleep and consumption of caffeine and chocolate did not differ in the two study groups, whereas drinking alcohol was less common ($34.8\%$ vs $44.4\%$, $P < 0.05$) and smoking was more common ($33.3\%$ vs $15.6\%$, $P < 0.05$) in migraineurs. Asking whether the patients were used to consuming more alcohol, caffeine, or chocolate or whether they increased smoking in certain situations (stress, fatigue, menstruation, days at work, days off, onset of headache) we found only few statistically significant differences: migraineurs less often consumed chocolate in stressful situations, alcohol less often during days off and caffeine less often when tired. Interestingly, only 4.5% of the migraine patients and none of the controls increased their consumption of caffeine during headache and 17% of the female subjects in both groups consumed more chocolate during menstruation. Surprisingly, the number of patients drinking alcohol did not depend upon the patients’ experience with headache precipitated by alcohol. The same was true for physical activity, caffeine and smoking, whereas patients relating (some of) their headaches to chocolate actually less often consumed chocolate with AMT.

**Conclusions** Comparing migraine patients and migraine-free controls, the marked impairment of productivity and quality of life in migraineurs contrasts with minor differences in lifestyle. Headache related by the patients themselves to a certain precipitating factor is not necessarily associated with avoidance of this factor.

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**OR42**

**Oral dual-release ketoprofen safe and effective in the acute treatment of migraine attacks: a double blind placebo-controlled crossover trial**

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**Background** The non-steroidal anti-inflammatory drug ketoprofen has been found more effective than placebo, ergotamine and paracetamol in the acute treatment of migraine attacks at a dose of 100 mg intrarectal or intramuscular (1,2). The aim of the present study is to evaluate the efficacy of an oral dual-release formulation of ketoprofen (Bi-profenid®) in the treatment of migraine attacks. This formulation contains an equal proportion of immediate and slow release ketoprofen.

**Methods** We performed a double-blind cross-over trial on 4 consecutive attacks with moderate or severe headache. Four treatments were studied: dual-release ketoprofen 75 mg (drK75) and 150 mg (drK150), placebo (P), and zolmitriptan (2.5 mg) (Z). They were compared using a generalized linear model. The primary outcome was headache relief: from severe (3) or moderate (2) to mild (1) or absent (0) at 2 h.

**Results** Among 257 patients included, 235 (females $83.4\%$; mean age: 38.1 years) treated at least one attack and 838 attacks were evaluable (1/3 with a severe headache, 2/3 with a moderate headache, 8.4% with a previous aura). Headache relief was significantly ($P < 0.05$) more frequent with drK75 ($62.6\%$), drK150 ($61.6\%$) and Z ($66.8\%$) than...
with P (27.8%). Headache disappearance at 2 h was also significantly (P <0.05) more frequent with drK75 (26.6%), drK150 (31.3%) and Z (36.1%) than with P (12.2%). A test of non-inferiority with a —10% clinical equivalence limit showed no inferiority of drK vs Z for these two outcomes. The tolerance of K was good: the number of patients presenting showed no inferiority of drK vs Z for these two outcomes. The tolerance of K was good: the number of patients presenting vs

**Conclusion**

Non-superiority with a —10% clinical equivalence limit showed no inferiority of drK vs Z for these two outcomes. The tolerance of K was good: the number of patients presenting with P (27.8%). Headache disappearance at 2 h was also significantly (P <0.05) more frequent with drK75 (26.6%), drK150 (31.3%) and Z (36.1%) than with P (12.2%). A test of non-inferiority with a —10% clinical equivalence limit showed no inferiority of drK vs Z for these two outcomes. The tolerance of K was good: the number of patients presenting.

**Objectives**

In this study we sought to investigate the possible involvement in the disorder.

**imaging studies in migraine and is a key candidate for**

**is included in the region identified in human functional responses associated with adjustment of pain thresholds. It nociception and integrates behavioural and autonomic region of the brainstem is a modulator of craniovascular**

A calcium channelopathy. The periaqueductal grey (PAG) of chromosome 19 in normal migraineurs, and the clinical plegic migraineurs, genetic linkage studies to the same region is within the central nervous system. In preclinical models it has been shown that triptans act on cranial vessels and on peripheral prejunctional trigeminal nerves (1). The question then arises as to whether the central nervous system effects of triptans are pre or postsynaptic.

**Methods**

Cats were anaesthetized (a-chloralose 60 mg/kg, intraperitoneally and, in addition, halothane for all surgical procedures), and prepared for physiological monitoring. The superior sagittal sinus (SSS) was isolated and electrically stimulated with a tungsten microelectrode, located centrally in a 7-barrelled glass micropipette, in the most caudal part of the trigeminal nucleus, in the region of the dorsal horn of the spinal cord at the level of C2. Signals from the neurons were amplified, filtered and passed to a microcomputer for analysis and storage. Neurons that responded to stimulation of the SSS were identified (2).

**Results**

Ejection of DL-homocysteate (DL-H) increased the baseline firing rate of these neurons from 13.6 ± 1.4 to 50.2 ± 5.6 Hz (n = 10 units). Microiontophoresis of L-glutamate increased firing of neurons linked to SSS from a baseline of 0.48 ± 0.06 to 27.9 ± 2.4 Hz (n = 5 units). Iontophoresis of sumatriptan during continued ejection of DL-H resulted in a reduction in firing rate from 54.3 ± 2.9 to 29.8 ± 4.2 Hz (n = 5 units). Co-ejection of either ergometrine or 4991W93, a 5-HT1B/1D agonist, also resulted in substantial reductions in the evoked firing rates of trigeminal neurons.

**Conclusions**

These data establish the existence of triptan-sensitive receptors on postsynaptic trigeminal neurons since neuronal activation associated with local ejection of the glutamate receptor agonists, DL-H or L-glutamate, is blocked by iontophoresis of 5-HT1B/1D/1F receptor voltage-gated calcium channel in familial hemiplegic migraine. If migraine is a calcium channelopathy, its episodic recurrent headache and triggerable nature might, in part, be explained by the presence of mutated P/Q-type calcium channels in the PAG.

**References**


**OR43**

The effect on trigeminal firing of P/Q-type calcium channel blockade in the periaqueductal grey

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**Introduction**

Mis-sense mutations in the α1A subunit of the P/Q-type voltage-gated calcium channel in familial hemiplegic migraineurs, genetic linkage studies to the same region of chromosome 19 in normal migraineurs, and the clinical features of migraine, indicate that migraine may derive from a calcium channelopathy. The periaqueductal grey (PAG) region of the brainstem is a modulator of craniovascular nociception and integrates behavioural and autonomic responses associated with adjustment of pain thresholds. It is included in the region identified in human functional imaging studies in migraine and is a key candidate for involvement in the disorder.

**Objectives**

In this study we sought to investigate the possible link between the genetic mutations found in the calcium channels of migraineurs and the PAG as a modulator of craniovascular nociception.

**Methods**

An intracranial vessel, namely superior sagittal sinus (SSS) in cat and middle meningeal artery (MMA) in rat, was exposed and electrically stimulated. Cells evoked by SSS or MMA stimulation were recorded in the caudal trigeminal nucleus caudalis (TNC) using a tungsten electrode. Post-stimulus histograms were made of the cells’ firing profile. Cells inhibited by electrical or chemical stimulation of the ventrolateral (vl)PAG were then recorded in response to injection of the P/Q-type calcium channel blocker, ω-agatoxin-IVA, into the vlPAG.

**Results**

Wide dynamic range and noxious-specific cells with ophthalmic division receptive fields and linked to vessel stimulation were recorded from the TNC. Administration of 90–400 nL of ω-agatoxin IVA into the PAG facilitated SSS-linked TNC neurons. Facilitation ranged from 122% to 178%, mean 144 ± 14%. This effect may result from either blockade of the tonic descending inhibitory input from the PAG to the TNC, or from direct activation of descending facilitatory input to the TNC, or by another mechanism.

**Conclusion**

Blockade of P/Q-type calcium channels in the vlPAG produces facilitation of trigeminal firing. These results suggest a possible site for the dysfunctional P/Q-type calcium channels in migraine and familial hemiplegic migraine. If migraine is a calcium channelopathy, its episodic recurrent headache and triggerable nature might, in part, be explained by the presence of mutated P/Q-type calcium channels in the PAG.

**OR44**

Triptans can act post-synaptically in the trigeminal nucleus: a microiontophoretic study

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**Introduction**

The mechanism of action of specific acute migraine treatments, notably triptans – the serotonin 5-HT1B/1D receptor agonists, is an important question in clinical neuroscience. One putative site of action for triptans is within the central nervous system. In preclinical models it has been shown that triptans act on cranial vessels and on peripheral prejunctional trigeminal nerves (1). The question then arises as to whether the central nervous system effects of triptans are pre or postsynaptic.

**Methods**

Cats were anaesthetized (a-chloralose 60 mg/kg, intraperitoneally and, in addition, halothane for all surgical procedures), and prepared for physiological monitoring. The superior sagittal sinus (SSS) was isolated and electrically stimulated with a tungsten microelectrode, located centrally in a 7-barrelled glass micropipette, in the most caudal part of the trigeminal nucleus, in the region of the dorsal horn of the spinal cord at the level of C2. Signals from the neurons were amplified, filtered and passed to a microcomputer for analysis and storage. Neurons that responded to stimulation of the SSS were identified (2).

**Results**

Ejection of DL-homocysteate (DL-H) increased the baseline firing rate of these neurons from 13.6 ± 1.4 to 50.2 ± 5.6 Hz (n = 10 units). Microiontophoresis of L-glutamate increased firing of neurons linked to SSS from a baseline of 0.48 ± 0.06 to 27.9 ± 2.4 Hz (n = 5 units). Iontophoresis of sumatriptan during continued ejection of DL-H resulted in a reduction in firing rate from 54.3 ± 2.9 to 29.8 ± 4.2 Hz (n = 5 units). Co-ejection of either ergometrine or 4991W93, a 5-HT1B/1D agonist, also resulted in substantial reductions in the evoked firing rates of trigeminal neurons.

**Conclusions**

These data establish the existence of triptan-sensitive receptors on postsynaptic trigeminal neurons since neuronal activation associated with local ejection of the glutamate receptor agonists, DL-H or L-glutamate, is blocked by iontophoresis of 5-HT1B/1D/1F receptor...
agonists, sumatriptan, ergometrine and 4991W93. These receptors may be located on either second order neurons, or on neurons modulating the second order synapse. The existence of modulation of the trigeminocervical synapse, other than presynaptic effects, adds a further target for the action of current and future antimigraine drugs.

References
2 Storer RJ, Goadsby PJ. Direct evidence using microiontophoresis that neurons of the caudal trigeminal nucleus contain 5HT1B/1D receptors. Cephalalgia 1997; 17:241.
POSTER SESSION I

A: Diagnosis and clinical features

P1-A1
A model for studying headache diagnostic data in family practice
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Objectives To propose a method for quantifying headache symptoms and other headache features in Family Practice charts for patients diagnosed with Headache 'NOS' (Not Otherwise Specified, ICD-9[784]), and to identify those with clinical data strongly suggesting migraine or migrainous headache.

Material and methods Data on headache symptoms and other headache features were obtained retrospectively from charts (n = 1623), recorded at headache visits (n = 3434) to 30 Family Physicians in group practice from 7/1/95 through 12/31/99. 69% (1112/1623) of these patients were diagnosed as having Headache 'NOS.' A random sample of these (n = 201), who made 289 visits, was selected for examination by the proposed method as follows. A Template was constructed containing 20 headache items combining IHS diagnostic criteria and additional headache features. This enabling conversion of clinical data into quantifiable categories including: physical examination, personal headache history and description, (e.g. duration, severity, throbbing, unilaterality), nausea, vomiting, effect of movement, photo/phonophobia, and aura. An open-ended category was also used and contained information relating to stress, menses, pregnancy, diet, and behavioural and neurological findings. Consistency among the 4 chart reviewers in data interpretation and template recording was maintained by adherence to a practical set of Decision Rules concerning the words, phrases, abbreviations and language recorded in the charts, e.g. pain scaled 1–3 = mild; 4–7 = moderate; 8–10 = severe; headache relieved by OTC = mild; requiring narcotic = severe. Reclassification as possible migraine or migrainous headache was considered only when physical exam, (including neurological findings), was recorded with no evidence of secondary headache. Data excluding secondary headache were found at 70% of visits.

Results With this method we found 1 in every 3 Headache 'NOS' patients may have had migraine (13%) or migrainous headache (21%). Consistency in the application of our guidelines is very strong; migraine averaged 6.1 symptoms and migrainous headache 4.5. Our regression model is predictive of 86% of variation in our reclassification and the percentage of discordant pairs of model-predicted and observed headaches is 1.1%.

Conclusions More headache diagnostic research is clearly needed. A method is described for such research, which showed how much migraine and migrainous headache may be being missed. This research needs large numbers of patients studied over long periods of time and requires rigorous investigational methods done in clinical settings. We suggest others consider using our procedures in this needed area of diagnostic research.

P1-A2
Migraine: are Latin American physicians trained to diagnose?
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Introduction Migraine is a highly prevalent disease that has a negative impact on patients' QOL. Diagnosis and proper treatment are crucial for the optimal outcome of migraine patients.

Methods A survey among 100 non-neurologist physicians was done during the 1999 Peruvian College of Physicians board elections. Physicians interviewed were randomly selected by the Elections Board to help at elections desks. A questionnaire dealing with diagnostic criteria, epidemiology, knowledge of drug treatments, treatment choice and impact of the disease was used.

Results Tables are to be presented comparing the knowledge of GPs, surgeons, OBGYN and paediatricians on headaches. Time taken during medical school training in Latin American countries on headache topics is compared.

Conclusion Knowledge about diagnosis and therapy for migraine headaches is poor among non-neurology physicians. Physician education on migraine headache is extremely important to improve QOL of patients from this part of the world.

P1-A3
Extent of migraine and migrainous headache in headache NOS patients in family practice
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Objectives To estimate the proportions of patients with migraine and migrainous headaches in Family Practice diagnosed as Headache 'NOS' (Not Otherwise Specified; ICD-9: 784).

Materials and methods Headache visits data from chart records of 30 Family Practitioners were gathered retrospectively from 7/1/95 to 12/31/99. Practice population
was 23,470 patients, of whom 1,623 (7%) were headache patients. A headache patient was defined as making at least one visit for headache during the study period. Of these headache patients, 1,112 (69%) were diagnosed as Headache ‘NOS.’ A random sample of 201 Headache ‘NOS’ patients, who made a total of 289 headache visits, was studied. A template was created, using Microsoft Access Software, comprising 20 headache symptoms and other headache features, based on IHS migraine diagnostic criteria. An ‘a priori’ set of decision rules was developed to maintain consistency of data collection in identifying words, abbreviations, phrases and language used in recording headache features and symptoms in the chart at the visit. After recording the data using the decision rules, headache symptoms, symptom pattern, symptom value (e.g. headache severity), and other headache features, weighted by IHS standards for diagnostic significance, were used to classify the presenting headache as referencing migraine, migrainous, or other types of headache.

**Results** 13% of Headache ‘NOS’ patients, at a single visit, had multiple IHS migraine symptoms, symptom pattern and other headache features that strongly suggested migraine. An additional 21% had fewer IHS migraine symptoms, less definite symptom pattern, and fewer other headache features but still strongly suggested migrainous headaches. Physical examination, including neurological data, was recorded in 70% of visits; chronicity, 64%; frequency, 57%; duration, 31%; severity, 29%; unilaterality, 27%; nausea, 18%; throbbing, 10%; photophobia, 9%; phonophobia, 4%; effect of movement, 4%; disability, 4%; aura, 3%. Headaches reclassified to migraine averaged 6.1 migraine symptoms and to migrainous headache 4.5 migraine symptoms.

**Conclusions** In this sample of Family Practice headache patients, the majority (69%) are diagnosed as Headache ‘NOS.’ At a single headache visit, one-third of these patients present with symptoms strongly suggesting migraine or migrainous headaches. This number is likely to increase when headache symptoms across all visits, recorded as Headache ‘NOS’ as well as for other diagnoses, are reviewed (study now in progress). So far, these data suggest that more attention paid during a headache visit to eliminate a secondary headache than in making a specific headache diagnosis.

**References**
the first or second year. Case Western Reserve University (CWRU) School of Medicine’s second year curriculum includes one hour on headache, which is taught in a large lecture setting. However, all third and fourth year students complete a month-long core clerkship in the neurosciences in which a small group session devotes one and a half hours to the teaching of headache. The faculty are rotating neurology attendings. The session consists of seven case vignettes: a young woman with migraine without aura, a middle-aged nurse with tension-type headache, an elderly man with temporal arteritis, a patient with trigeminal neuralgia, a patient with a first and worst headache due to subarachnoid bleed, a child with a pontine glioma, and an alcoholic with a subdural haematoma. Questions follow each vignette guide the student to an accurate diagnosis and treatment plan. Trigeminal pathways in the brain, neuropeptides, and serotonin receptors influential in headache pathogenesis are also reviewed.

Objectives We designed a Headache Assessment Examination taken by all students before and after their clerkship. We wanted to determine if students’ initial knowledge base would expand following the focused teaching session during the clerkship and after outpatient exposure to headache patients seen in the clinics.

Methods All 290 medical students participating in the neuroscience clerkship from July 2000 through June 2001 were given the same standardized Headache Assessment Examination at the start and completion of their clerkship. We compared these scores as well as the scores of students who had completed the required core clerkships in medicine and family medicine prior to taking neurology and those who had not. The examination was written by the director of the neuroscience clerkship, the chairman of the Department of Anatomy, and the director of Curricular Evaluation at the CWRU. Multiple choice questions cover the clinical characteristics, epidemiology, pathophysiology, and management of primary and secondary headache syndromes.

Conclusions At the time of submission of the abstract, data compilation is at its midpoint. 73% of students improved following the clerkship, 9% did worse, and 18% were unchanged. Analysis of the differences between third and fourth year student scores (pre- and post-medicine clerkships) and percentage improvement ratios will be discussed at the Liberty 2001 meeting.

Note A complete copy of the 40-question Headache Assessment Examination will be available at the meeting.

P1-A6

Migraine in female neurologists

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Objectives To assess the prevalence, features, and self-treatment patterns of migraine (M) in female neurologists.

A high prevalence of migraine among male neurologists was present in this physician sample.

Materials and methods A survey was administered to a convenience sample of neurologists and other physicians attending regional continuing medical education courses on headache from 6/3/00 through 11/18/00. These programmes (‘The Neurology Ambassador Program’) were sponsored by the American Academy of Neurology and the American Headache Society with an educational grant from Glaxo-Wellcome. Physicians were asked to self-diagnose using IHS criteria attached to the survey. 79.4% of all attendees completed the survey.

Results The lifetime prevalences of M in various groups of females were: neurologists (N), 67% (n=43); neurologist headache specialists (those who spend more than 50% of their time in the area of headache, N-HA), 81% (n=27); and non-neurologist physicians (9 different specialists but predominately internists and family physicians), 50.4% (n=119). Because of the higher prevalence of M in N-HA, the results are presented separately from N. Mean age of N was 42.9 and of N-HA, 39.4 years. (1) The one-year period prevalence of migraine was 63% for N and 81% for N-HA. The mean frequency of M in the last year was N, 1.4/month and N-HA, 0.98/month. (2) The most common triggers for both groups, in order of decreasing frequency, were: stress, lack of sleep, missing a meal, menses, alcoholic beverages, after stress, oversleeping, and certain foods. The mean number of triggers was 5.4. (3) 77% of both groups has not received M advice from other physicians and 56% of N and 81% of N-HA self-prescribe for M. 22% of both groups has taken preventative medication in the last year. (4) Acute medications taken in the last year by N and N-HA (percentages, respectively) include: over the counter, 82.6, 35; NSAIDs, 78.3, 85; triptans, 47.8, 50; Midrin, 13, 10; opioids, 4.3, 10; and combination with butalbital, 4.3, 5.

Conclusion There is a much greater prevalence of M among female neurologists than in the general female population. One reason may be selection bias (e.g. attending a headache course or completing the survey). Alternatively, M may be more prevalent in neurologists if having M stimulates interest in neurology, if being a neurologist causes M (stress?) or if the states have shared environmental or genetic risk factors. Features of treatment of M in female neurologists are also provided for the first time.

Acknowledgement This study was supported by an educational grant from Merck Pharmaceuticals.

P1-A7

The effect of optokinetic stimulation on sensitivity to pain in migraine

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Objectives Migraine sufferers appear to have a heightened susceptibility to motion sickness, a disorder that is mediated by brain stem nuclei. Apart from nausea, motion sickness is associated with upper abdominal sensations, sleepiness,
apy, dizziness and headache. Thus, similar disturbances may be involved in migraine and motion sickness. The aim of this study was to determine whether motion sickness would increase sensitivity to pain in migraine sufferers, particularly within the trigeminal nerve distribution.

**Methods** Symptoms of motion sickness were provoked by 15 minutes of optokinetic stimulation in 32 migraine sufferers and 17 headache-free controls. Pain ratings to four levels of mechanical stimulation to the forehead and fingertips were obtained before and after optokinetic stimulation.

**Results** Migraine sufferers reported greater nausea than controls. Pain ratings to mechanical stimulation of the forehead increased in both groups after optokinetic stimulation but returned toward baseline 20 min later. Pain ratings to mechanical stimulation of the fingertips increased after optokinetic stimulation in migraine sufferers but not in controls.

**Conclusions** These findings indicate that migraine sufferers are more susceptible than normal to the brainstem disturbance induced by optokinetic stimulation. The disturbance appears to heighten scalp tenderness both in migraine sufferers and controls, and also increases nausea and general sensitivity to pain in migraine sufferers. The findings suggest that motion sickness may provoke symptoms of migraine by disrupting general inhibitory mechanisms that normally suppress unpleasant sensations such as nausea and pain.

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**P1-A8**

**Subclinical glaucomatous alterations in migraine: a study by the frequency-doubling technology perimetry**


**Background** A higher than expected prevalence of migraine has been described in retrospective studies on glaucomatous patients. Recent studies have reported a high diagnostic accuracy of the Frequency-doubling technology (FDT) perimetry in the identification of glaucomatous optic nerve damage. This technique is intended to isolate a subset of mechanisms usually attributed to retinal magnocellular ganglion cells, which may be preferentially affected in glaucoma. We studied glaucomatous visual field loss in migraine patients.

**Methods** According to the IHS criteria we enrolled 35 primary headache patients: 25 with migraine and 10 with tension-type headache (TTH). Patients underwent clinical examination of the optic disk, optic nerve head and nerve fibre layer, tonometry and FDT perimetry. If the presence of glaucoma-like changes was different in the 2 eyes, the worse eye was selected for data analysis. We used the counting method for analysing FDT results by summing the number of defective field regions (range 0–17) regardless of the qualitative loss gradation. Visual field damage was compatible with early glaucoma when the mean deviation (MD) index was between –2 and –10 dB.

**Results** No differences were found as regards age, sex, age of headache onset and disease duration between migraineurs and TTH patients. In all patients intraocular pressure was normal at rest (<21 mmHg). Signs of glaucomatous optic neuropathy were detected in none of the TTH patients and 11 (44%) of the migraineurs ($P=0.01$). FDT perimetry detected at least 2 abnormal points in the visual field in 13 (52%) migraineurs and only 1 TTH patient ($P=0.04$). MANOVA showed: higher number of defective fields in migraineurs than TTH patients ($4.3\pm5.2$ and $0.6\pm0.5$, respectively; $P=0.04$); the mean value for mean deviation (MD) was lower in migraineurs than TTH patients ($–2.8\pm3.7$ and $0.5\pm1.4$, respectively; $P=0.01$). Post-hoc analysis evidenced that low MD values correlated with a high frequency of migraine attacks ($P=0.01$).

**Conclusions** The present study shows that asymptomatic optic disk changes and visual field losses can be detected in a significant proportion of migraine patients. These alterations are similar to those described in glaucomatous patients with the FDT perimetry and are associated with high frequency of migraine attacks. These findings support the hypothesis that migraine and glaucoma may share some common pathophysiological mechanisms which remain to be elucidated. In order to avoid a possible silent worsening of glaucomatous disturbances, FDT perimetry should be taken into account to further address migraine acute and preventive treatment.

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**P1-A9**

**A prospective study of the headache phase in 26 migraine with aura patients**

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Very few reports have been published so far on the clinical features of the headache phase of migraine with aura (MA) attacks. The diagnostic criteria for MA listed in the 1988 International Headache Society (IHS) classification do not mention any such features, either. The only reference that can be found on this subject regards migraine with acute onset aura (1.2.6), to which headache phase the IHS classification applies the same criteria used for migraine without aura (MO). Therefore, for an accurate description of the clinical features of the headache phase in MA, we thought it useful to conduct a prospective study on a consecutive series of first referrals with MA seeking treatment at the Headache Centre of the University of Parma Institute of Neurology. The case series included 32 patients (22 women and 10 men). Mean age at the time of the first visit was 30.3 years (range 12–61) and mean age at onset of MA was 22 years (range 6–48). At the time of the first visit, each patient was given a specially designed, previously validated questionnaire to be filled in with the clinical features of the headache phase at the next MA attack. The interval of time between the date when the questionnaire was handed to the patient and his/her next MA attack. The interval of time between the date when the questionnaire was handed to the patient and his/her next MA

attack was on average 2.9 months. For the purpose of our study, we had to exclude 6 patients (4 women and 2 men), who had an attack of migraine aura without headache (12.5%). Among the remaining 26 patients (18 women and 8 men), the duration of the headache phase was less than 24 h in 23 (88.5%); pain location was bilateral in 14 (53.8%) and only in one patient of 12 with unilateral pain occurring on the opposite side to aura; pain intensity was severe in 13 (50.0%). A comparison of the clinical features of the headache phase using the IHS diagnostic criteria for MO vs those for episodic tension-type headache (TTH) shows that headache phase was consistent with the IHS diagnostic criteria for MO in seven patients (26.9%), including six women (33.3%) and one man (12.5%); for migrainous disorder not fulfilling above criteria (coded as 1.7 in the IHS classification) in three (11.5%), all of them female; for TTH in six (23.1%), all of them female; for tension-type disorder not fulfilling above criteria (coded as 2.3 in the IHS classification) in four (15.4%), including three women (16.7%) and one man (12.5%); both for the 1.7 and 2.3 conditions in six (23.1%), including four women (22.2%) and two men (25.0%). The results of our study demonstrate that the headache phase of MA has clinical features that may differ widely from patient to patient and only in half the cases does it fulfill the IHS diagnostic criteria for MO.

P1-A10

Neurovascular symptoms during migraine attacks
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Background and objectives Some migraineurs refer the presence of unilateral neurovascular symptoms (NVs: lacrimation, eye redness, ptosis, eyelid oedema, nasal congestion, rhinorrhea) during the attacks. The aim of this study was to assess the percentage of migraineurs with NVs and their clinical characteristics in a migraine outpatient population.

Patients and methods We studied 148 patients affected by migraine with or without aura consecutively seen at our headache centre from 1 April 2000. Each patient underwent a complete medical and neurological examination. Personal and family history and clinical features of migraine were carefully investigated. The presence of NVs in migraineurs was screened at the interview by the following question: During the migraine attack do you also have unilateral conjunctival injection and/or lacrimation and/or ptosis and/or eyelid oedema and/or nasal congestion/rhinorrhea? We compared clinical and epidemiological characteristics of migraine patients with NVs with those of migraineurs without NV.

Results Sixty-seven (45.2%) of 148 migraineurs studied referred the presence of at least one NVs during the attacks. Of these, 14 patients had nasal symptoms (congestion and/or rhinorrhea), 23 had ocular symptoms (conjunctival injection and/or lacrimation and/or ptosis and/or eyelid oedema), whereas 30 had both ocular and nasal symptoms. Headache pain was more severe and more frequently unilateral in migraineurs with NVs than in those without NVs (P < 0.05), whereas the other clinical (type of migraine, quality and duration of pain, attack frequency) and epidemiological characteristics (sex, age, age at onset) did not differ in the 2 groups of migraineurs.

Conclusions Our study suggests that a considerable percentage of migraineurs show NVs during the attacks, probably reflecting a more marked neurovascular activation. Headache pain is more severe and more frequently unilateral in these patients than in migraineurs without NVs. It will be of interest to assess if the presence of NVs might be predictive of a better response to triptans than in the general migraine population.

P1-A11

Migraine with autonomic symptoms
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Introduction Migraine and cluster headaches can coexist in the same patient but occur independently. Migraine can also have the seasonal variation seen in cluster headache (cyclic migraine), and episodic migraine can be associated with autonomic symptoms typical of cluster headache. The term cluster-migraine has been utilized for this dependent association, but it lacks definition. We present a group of patients with episodic migraine associated with autonomic symptoms and proposed new nomenclature.

Case 1 28-year-old woman had a four year history of pulsating pain, located in the right orbital/frontal, radiating to the temporal and occipital region. Headaches were associated with nausea, photophobia and phonophobia. Autonomic symptoms present included tearing, conjunctival injection, eyelid oedema and rhinorrhea. The pain lasted 24 hours and occurred three times a month. Neurological examination and neuroimaging (MRI, MRA) were normal.

Case 2 28-year-old woman had a two year history of throbbing, unilateral right sided temporo/orbital headache. Accompanying symptoms included nausea, vomiting, phonophobia, photophobia, and osmophobia. The attacks were always associated with ipsilateral ptosis and conjunctival injection. Pain was moderate in intensity, lasted 24 hours, and occurred one to three times a month. Neurological examination and neuroimaging were normal.

Case 3 52-year-old woman had a 25 year history of moderate-severe right sided headaches, which lasted 6–12 hours, occurred once a month. Headaches were associated with nausea, photophobia, phonophobia. They were accompanied by ipsilateral tearing and nasal congestion. Neurological examination and neuroimaging were normal.

We suggest the term migraine with autonomic symptoms for patients who have episodic migraine associated with the typical cluster headache autonomic symptoms. Migraine with autonomic symptoms may be a different migraine subtype, not currently included in the IHS classification.
**P1-A12**

Migraine and gastric pathologies

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**Objective** The relationship between food consumption and migraine during migraine attacks has been widely reported by the literature. The predominance of gastrointestinal symptoms such as nausea, vomiting, diarrhea, etc. underlines involvement of the gastroenteric apparatus in migraine. Our study is finalized to evaluate the clinical alterations of digestive apparatus in migraineurs.

**Materials and methods** The research was conducted on 150 patients (108 women) with a mean age of 34.6 (SD 13.6) years, who were suffering from migraine with or without aura (IHS 1988 criteria) and who were observed during March–December 2000. During the first visit, a detailed clinical computerized schedule was adopted involving all data with special regard to clinical signs of nutrient deficiency related to erratic food habits.

**Results** Data obtained showed altered breath 36%; dry mouth 54%; inflammation of the oral cavity 36.6%; nausea 60.6%; vomiting 48%; pyrosis 56%; slow digestion 56%; gastralgia 60.6%; meteorism 54%; constipation 62%; cold feet 48%; limb cyanosis 12.6%; cold hands 36%; cramps 48%; paraesthesiais at the upper and lower limbs 44%–42%; diarrhoea 56%; unpleasant odour of faeces 48%; photophobia 70.6%; and nyctalopia 48.6%.

**Conclusions** By analysing the results, it has been demonstrated that in patients with migraine there is a predominance of functional and organic gastric affections, especially gastritis. The gastric mucous impairment damaged the intrinsic factor production and reduced the activation of B12 vitamin and its coenzyme and their important functions. These data stress the role of gastroenteric dysfunction in migraine.

**P1-A13**

A prospective study of the heterogeneity of the migraine attack

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**Introduction** Migraine is a complex disease whose clinical features show a wide variability.

**Objectives** Evaluation of migraine symptoms, including its premonitory and post-dromic disturbances, in a representative sample of migraine sufferers with (MA) and without (MO) aura in order to quantify and qualitatively describe the occurrence of different clinical presentations.

**Materials and methods** MA and MO sufferers were instructed to record hourly and prospectively on an ad hoc diary all of the symptoms experienced before, during and after a migraine attack.

**Results** A total of 151 migraine attacks (130 MO, 21 MA) were evaluated. Premonitory symptoms were referred to by 46% of patients, with a higher incidence in MO than in MA (50% vs 14%; P = 0.004). They mainly consisted of tiredness, irritability, mindfulness, nausea, craving for sweet foods, yawning, drowsiness, euphoria, and body pain. Premonitory symptoms preceded the onset of the painful phase by variable periods of time which ranged from minutes up to 24 h. In the MA group, visual aura represented the most frequently reported symptom, but we found 15 possible types of visual symptoms or combinations with other sensory and/or motor disturbances. Duration of attacks and accompanying symptoms proved to be the most variable parameters, particularly in MO. The mean duration of attacks was of 13.8 ± 12.4 h, with an extreme variability which oscillated between a minimum of 60 minutes and a maximum of 79 hours. The triad nausea–phonophobia–photophobia represented the most frequent combination of accompanying symptoms (39% of patients), although almost 30 other combinations were described. A lower variability was observed in terms of impairment of daily activities, which was partial in most of the patients, and as regards the timing of maximal disability, which was reached by 80% of patients within 4 hours from the pain onset. Severe attacks were more frequent in MO than in MA (68.5% vs 23.8%; P = 0.001). Post-dromes were reported in 20.5% of the total number of attacks, with no significant differences between MO and MA.

**Conclusions** The present findings confirm the extreme clinical variability of migraine attacks between subjects. The described wide range of clinical expression of the disease probably results from the interaction of genetic determinants with different environmental conditions. The proper identification of clinical sub-types of migraine and of their relative occurrence may be important in guiding the therapeutic approach to the disease.

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**P1-A14**

Cervicalgia in migraine: prevalence, clinical characteristics, and response to treatment

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**Objective** To document the clinical features of neck pain as a component of migraine.

**Background** Migraine patients often complain of neck pain which may precede, accompany, or follow their attacks. Migraine is commonly misdiagnosed as tension-type headache in clinical settings, perhaps partly secondary to this
clinical characteristic. The features of cervicalgia in migraine have not been extensively studied to date.

**Methods** Single-centre retrospective chart analysis and interview of migraine (IHS 1.1 or 1.2) patients, followed by prospective open-label treatment phase. Patients who met criteria for another IHS diagnostic category, or those whose migraines were provoked or exacerbated by head or neck trauma, were excluded. Response to treatment was defined as complete eradication of cervical pain.

**Results** A total of 144 patients met criteria and were interviewed. One hundred and eight (75%) reported neck pain associated with migraine attacks, with 46 patients (43%) describing bilateral pain and 62 patients (57%) unilateral pain. Of those with unilateral pain, 61/62 (98%) reported pain ipsilateral to the headache discomfort. The most common descriptions were ‘tightness’ and ‘stiffness.’ The neck pain was associated with the phases of migraine in the following fashion: 7 patients (7%) prodrome only; 23 patients (21%) prodrome and headache; 33 patients (31%) headache only; 8 patients (7%) headache and postdrome; 1 patient (1%) postdrome only; and 36 patients (33%) all three phases. Overall, 71 patients (66%) reported resolution of neck pain with their acute migraine therapy. Response rates for the different phase categories were: 5/7 (71%) prodrome only; 18/23 (78%) prodrome and headache; 25/33 (76%) headache only; 3/8 (38%) headache and postdrome; 1/11 postdrome only; and 19/36 (53%) all three phases. A total of 42 patients reporting neck pain with their migraine attacks were prospectively identified. Of this group, 36 patients agreed to track their symptoms of neck pain as they were treated with triptan therapy. A total of 30 patients were treated with triptans and completed their diaries. Two hundred seventy-eight attacks were treated, with neck pain identified in 231 (83%) of these episodes. The rates of resolution of headache (189 of 278 or 68%) and neck pain (165 of 231 or 73%) were not significantly different.

**Conclusions** Cervicalgia commonly accompanies migraine headache. Although it may occasionally be seen isolated to the prodrome or postdrome, the majority of patients describe association with the headache phase. Tightness bilaterally or ipsilateral to the headache pain were frequently reported. Response to acute migraine treatment (specifically to triptan therapy) parallels the response of the headache, suggesting a shared pathophysiology.

**P1-A15**

**Cardiac migraine – a discrete entity?**

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**Objective** To evaluate frequencies of chest pain consistent with angina at time of predefined migraine headache and correlation with subtypes in a large cohort of migraine patients.

**Background** A speculative relationship between migraine, coronary spasm and myocardial infarction has been previously reported but remains rare in clinical practice. The registry antedated extensive triptan therapy for migraine.

**Methods** Migraine registry Patients were derived from the Durban Migraine Data Base (DMDB). Patients were categorized in accordance with the International Headache Association for migraine classification. Pain characteristics suggestive of cardiac origin during an acute migraine episode were specifically sought, prospectively, during the clinical interview and examination; if present, electrocardiographic and cardiac evaluation followed.

**Results** There were 6 (0.9%) patients in the DMDB (n=832) with reported chest pain during an acute migraine episode. The case series included 5 women and one man (mean age 32.8 years, range 14–48), 4 presenting with migraine without aura, one with complicated migraine and one with migraine with aura. No cardiotropic, tricyclic antidepressant medication or sumatriptan had been administered during or prior to the episodes in these patients. One young woman showed reversible ST segment depression and T wave inversion in the inferolateral leads and subsequent coronary angiography revealed normal, non-atheromatous coronary arteries. A cardiological diagnosis of variant angina due to spasm during migraine attack was made.

**Conclusions** (1) Cardiac migraine may be a discrete, albeit rare entity. (2) Chest pain may be due to the migrainous process per se, requiring delineation from triptan-induced chest pain. (3) Cardiac migraine may reflect a more generalized vasospastic component of migraine and management needs to be directed at the variant angina as well as the migraine syndrome.

**P1-A16**

**Electrogastrography in migraine**

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**Background and objectives** Migraine attacks are associated with gastrointestinal stasis and reduced rate of gastric emptying, as has been shown by gastric emptying and absorption measurements. Autonomic system abnormalities have been documented in migraineurs between attacks. Electrogastrography (EGG) is a non-invasive test measuring gastric electrical activity. It does not measure gastric emptying or contraction directly, but can detect a disturbance in the physiological mechanism responsible for gastric contraction.

**Aim** Investigating gastric electrical activity in migraine patients between attacks, as part of a generalized autonomic dysfunction.

**Method** An EGG was performed in 29 female migraineurs aged 18–60 and in 9 healthy female volunteers. All EGGs were performed between attacks. Patients with any chronic
Poster Session 1

P1-A17

Subjects with self-described ‘sinus’ headache meet IHS diagnostic criteria for migraine

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Objective To assess headache symptoms, satisfaction with treatment, and disability (via Headache Impact Test-6 [HIT-6]) reported by subjects with self-described ‘sinus’ headache.

Methods Subjects with self-described ‘sinus’ headache (n=24) were recruited from the general community and were interviewed about their ‘sinus’ headaches. No subject had acute sinusitis and all were triptan naive.

Results 23/24 (96%) subjects’ descriptions of their ‘sinus’ headaches met IHS criteria for migraine (1.1, 1.2 or 1.7). 20/24 (83%) reported congestion and/or rhinitis. Only 1/24 (4%) subjects reported aura, which was distinguished from photophobia. All subjects previously treated their ‘sinus’ headaches with OTCs and 12/24 (50%) reported that they were dissatisfied with treatment. The average HIT-6 score was 60, indicating very severe impact with respect to disability associated with ‘sinus’ headaches. 17/34 (50%) ‘sinus’ headaches were pain free at approximately 2 hours following oral sumatriptan 50 mg.

Conclusions Many subjects with self-described ‘sinus’ headache meet IHS diagnostic criteria for migraine. Oral sumatriptan 50 mg appears to provide relief for self-described ‘sinus’ headache.

P1-A18

Oral sumatriptan for self-described ‘sinus’ headache

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Objective To determine if oral sumatriptan 50 mg is effective for self-described ‘sinus’ headache in subjects who have never had a diagnosis of migraine.

Methods Subjects were recruited from family practice clinics. Subjects with self-described ‘sinus’ headache who had no evidence of acute sinusitis and who were triptan naive were enrolled. Subjects were queried regarding sinus symptoms, treatment, and disability (via Headache Impact Test-6 [HIT-6]). Subjects were asked to treat two ‘sinus’ headaches with sumatriptan 50 mg tablets. Subjects recorded symptoms and use of rescue for either persistence or recurrence on diaries. Afterwards, subjects recorded preference for sumatriptan vs previous treatment.

Results Seventeen adults treated a total of 34 ‘sinus’ headaches. Although never diagnosed with migraine, at baseline 16/17 (94%) subjects described headache features that met IHS criteria for migraine (migraine without aura, n=8; migrainous, n=8). Additionally, 15/17 (88%) reported congestion and/or runny nose. 12/17 (71%) subjects reported that ‘sinus’ headaches were triggered by weather. At baseline, the average HIT-6 score was 60, indicating very severe impact with respect to disability associated with ‘sinus’ headaches. 17/34 (50%) ‘sinus’ headaches were pain free at approximately 2 hours following oral sumatriptan 50 mg. (These results are consistent with what is seen in clinical trials following treatment with sumatriptan in migraineurs meeting IHS criteria.) Of these 17 headaches, 3 (18%) had recurrence. 10/16 (63%) subjects preferred sumatriptan to previous treatment.

Conclusions Many subjects with self-described ‘sinus’ headache meet IHS diagnostic criteria for migraine. Oral sumatriptan 50 mg appears to provide relief for self-described ‘sinus’ headache.

P1-A19

The effect of weather on migraine headache

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Headache patients, especially migraineurs, often note several factors which trigger their headaches. Most patients believe that weather is a trigger. This study investigates the relationship between weather and headache. Seventy-seven patients at The New England Center for Headache in Stamford, Connecticut, provided daily headache calendars for a period ranging from 2 to 24 months from February 1997
to January 1999. Seventy-three of the 77 patients had a diagnosis of migraine only or migraine in combination with tension-type headache. The remaining four patients had a diagnosis of chronic tension-type headache only. Weather data were collected from the National Weather Service throughout this time from three stations central to the residences of the study participants. In order to minimize the complication of co-linearity of multiple weather variables, analysis was performed on the raw weather data to generate three independent variables termed ‘factors.’ These three factors each represented a compilation of individual measures of weather, and accounted for the necessary relationship that exists between such measures. The factors were then used in linear regression analysis to examine the relationship between headache and weather in our study population, including analysis for each individual patient and patient subgroups. Thirty-nine of 77, or 50.6%, of headache patients studied for the presence or absence of weather triggers were statistically significantly sensitive to various weather conditions. Thirty patients were sensitive to one of the three weather factors generated in the analysis, and nine patients were sensitive to two of the three factors. Twenty-six patients were sensitive to factor 1, absolute temperature and humidity. Eleven patients were sensitive to factor 2, a changing weather pattern including change in barometric pressure, temperature, and humidity. Ten patients were sensitive to factor 3, absolute barometric pressure and change in pressure from 2 days prior to the start of the headache. Subgroup analysis showed no effect on susceptibility to weather based on gender, age, diagnosis, frequency of headache, or self-report of weather sensitivity.

P1-A20
Precipitating factors of migraine: experience and theories of the patients

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Objectives To compare the actual experience with various precipitating factors of headache and the theoretical knowledge about such factors in migraine patients and migraine-free controls.

Patients and methods Sixty-six consecutive patients suffering from migraine with and/or without aura and 45 migraine-free controls completed a semi-structured interview covering demographic data, headache characteristics, own experience with potential headache triggers and theoretical knowledge about such triggers. Patients with overuse of analgesics, ergotamines and/or triptans as well as patients with relevant organic and/or psychiatric disorders were excluded. The subjects included gave an informed consent. All interviews were performed by one and the same person (JH) either personally or by telephone. For statistical analysis SPSS-WIN 10.0 was used.

Results Patients and controls were comparable regarding age, sex, educational level and profession. Among a total of 34 potential precipitating factors, migraine patients experienced most often stress (74.2%), menstruation (66.7%), weekend (63.7%), alcohol in general (50.8%) and red wine in particular (45.5%). Controls experienced most often stress (46.7%), missing a meal (44.5%), exhaustion (37.8%), alcohol (35.5%) and menstruation (33.4%). Statistically significant differences (migraine > controls) were found in stress, menstruation, weekend and red wine, whereas all other triggers did not differ in the two study groups. The theoretical knowledge of the patients concerning headache triggers was in general more extensive in migraineurs, but the differences were statistically significant for red wine, cheese, chocolate and oral contraceptives only. Against the general trend, noise was suspected of being a headache trigger significantly more often by controls than by migraineurs. Comparing the actually experienced with the theoretically suspected headache triggers did not reveal major discrepancies (i.e. frequently experienced precipitating factors were well known, less frequently experienced factors were less well known). Cheese and chocolate, however, were grossly overrated by patients as well as by controls. Only 4.4–15.1% of the subjects experienced one of these triggers, whereas up to 80% suspected that cheese or chocolate might cause headache or migraine.

Conclusions Migraine patients experience more often headache precipitated by stress, menstruation, weekend and red wine. All other precipitating factors investigated are not specific for migraine. The level of theoretical knowledge about precipitating factors is usually related to their occurrence as experienced by the patients. The importance of cheese and chocolate, however, is grossly overestimated.

P1-A21
Migraine with aura triggered by orgasmic phase of sexual intercourse – case report

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Introduction Migraine with aura (MA) is a condition in which attacks are rarely provoked by trigger factors. However, at times, stress and mental tension, bright light, red wine and physical activity can provoke MA attacks. We describe the first case, as far as we know, of MA triggered exclusively by the orgasmic phase of sexual intercourse.

Case report A 36-year-old woman presented a 3-year history of MA attacks starting soon after sexual intercourse. 5 min after the orgasm, she suddenly began to complain of blurred vision in the left or right side of the visual field, developing into a flickering zigzag line together with pinpoint circles of red and blue light. Around these fortification spectra, hemianopsia developed. These positive and negative signs lasted 20–30 min and were immediately followed by a mild to moderate, throbbing pain in the frontal-temporal region contralateral to the side of aura. Pain was accompanied by photophobia and phonophobia. The headache duration was
4–12 h. She had tried several prophylactic treatments (flunarizine, beta-blockers, benzodiazepines, valproate and carbamazepine) without any improvement. The aura symptomatology was perceived with a great feeling of anxiety and fear, so much so that, after a few months, she lessened the activity of sexual intercourses and, during them, she behaved in a way to avoid orgasm. In 1996, 3 years after the beginning of the attacks, she came to our observation. The history was unremarkable. Physical and neurological examinations were normal, as well as EEG and a brain MRI. Routine blood analyses were normal too. We treated the patient with lamotrigine, at the dosage of 100 mg daily (after a period of titration), obtaining the complete disappearance of MA attacks related to orgasm. After 3 months of treatment, the drug was stopped and MA attacks promptly recurred. Treatment with lamotrigine was restarted, with complete success. The patient withdrew treatment after 2 years, without any recurrence in a 30-month follow-up.

**Conclusions** Our case suggests that orgasm may constitute a trigger factor for MA. Lamotrigine was the only drug effective in abolishing the attacks.

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**P1-A22**

**Noise exposure and headache**

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Migraine is a common illness characterized by severe headache, which may be accompanied by sensitivity to light or particularly noise. Headache and migraine are common also in childhood and may be influenced by social, familial, environmental and psychological factors. Noise is the dominant element among the whole complex of adverse professional factors. Loud noise is a potent sensorial stimulation by which migraine episodes are frequently triggered. Noise due to the activities and overcrowding of schools is the main source of teachers’ discomfort. The higher the noise level, the higher the number of teachers assessing negatively the acoustic climate of school and the intensity of discomfort. Teachers working under more adverse acoustic conditions experience a higher incidence of irritation states: headaches, sleepiness, tiredness and depression. Teachers in noisy schools also report greater difficulty in motivating children in their school work. The prevention and treatment of snoring are important issues for couples, because women living with heavy snorers were more frequently affected by symptoms of insomnia, morning headache, daytime sleepiness, and fatigue than those living with a non-snoring spouse. Experienced headaches are frequently attributed to insufficient sleep, mental stress, stress, alcohol, excess heat, reading, excess noise or light and sleeping too long. Exposure to continuous noise over 90 dBA has showed that 70% of those workers exposed had headache symptoms. A close association of headache and discomfort due to noise has been noted. Heart rate, systolic blood pressure and cerebral blood flow have shown increases at a noise level of over 90 dBA. Jet noise, ranging up to 150 dBA, induces dysfunction of the autonomic nervous system and various kinds of psychosomatic diseases. It can also significantly affect the health of children. The characteristics and causes of headache differ across individuals and between groups. Such differences are of interest from an epidemiological point of view. Emotional, dietary, physical, environmental, and hormonal factors are all reported to be equally likely to precipitate a headache episode regardless of headache diagnosis. There are, however, differences in specific behavioural responses to headache episodes depending upon headache diagnosis. Migraine patients are significantly more likely to avoid light, social activity, physical activity and particularly noise, compared with tension-type and combined headache patients, because noise is one of the common aggravating factors of chronic daily headache.

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**P1-A23**

The misdiagnosis of disabling episodic headache: results from the spectrum study

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**Background** Patients with disabling episodic headache may be diagnosed with migraine, migrainous, or tension-type headache (TTH). The accuracy of these clinical diagnoses is unknown.

**Objective** To examine the accuracy of initial clinical diagnoses for patients with disabling episodic headache using a neurologist’s diagnosis, based on review of the medical record and diary data as the gold standard.

**Design and methods** We conducted a post hoc analysis of adults (18–65 years) with disabling episodic headache (Headache Impact Score >250) from The Spectrum Study. At screening, patients were initially diagnosed by a clinician as having migraine with or without aura (IHS 1.2, 1.1), migrainous headache (IHS 1.7), or TTH (IHS 2.1). Patients then treated up to 10 headaches over 6 months with sumatriptan 50 mg tablets or placebo (4:1). Prior to each treatment, patients recorded headache characteristics in diaries. An independent neurologist retrospectively applied IHS criteria to the medical record and the diary data to determine a final headache diagnosis. The neurologist did not know the treatment response or initial diagnosis. A comparison of the initial clinical diagnoses and the final IHS-based diagnoses are presented.

**Results** 432 patients treated at least one headache. Of the 249 patients initially diagnosed with migraine, 249 (100%) had a final diagnosis of migraine. Of the 108 patients initially diagnosed with migrainous headache, 49 (45%) patients had a final diagnosis of migraine and 59 (5%) patients had a final diagnosis of migrainous headache. Of the 75 patients...
initially diagnosed with TTH, 24 (32%) patients had a final diagnosis of migraine, 4 (5%) patients had a final diagnosis of migrainous headache, and 47 (63%) patients had a final diagnosis of pure TTH. Sumatriptan effectively treated migraine, migrainous headache, and TTH in migraineurs, but not TTH in patients with pure TTH.

Conclusion Patients with disabling episodic headache on initial clinical exam, usually have migraine. The diagnosis of migraine in these patients was accurate. Diaries reveal that nearly one-half of patients thought to have disabling migrainous headache meet IHS criteria for migraine. Sumatriptan was virtually always associated with other aura symptoms in 73%, came prior to the visual aura in 17%, while both occurred simultaneously in 10%. Only 9% reported head traumas as a precipitating factor.

Conclusion FHM was not seen with motor aura alone and was virtually always associated with other aura symptoms and headache.

P1-A24
Clinical characteristics of Danish families with familial hemiplegic migraine
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Objectives To describe the characteristics of aura symptoms and headache in 147 Danish familial hemiplegic migraine (FHM) patients.

Materials and methods The patients were recruited from the Nationwide Patient Registry comprising all patients, admitted or outpatient treated in a Danish hospital from 1994 to 1997 and discharged with migraine with aura (MA). In addition, more than 27 000 files from Danish headache clinics and neurologists were screened for patients with MA with motor symptoms. All Danish private specialists in Neurology or Paediatrics and all departments of Neurology and Paediatrics were asked to report patients with MA with motor symptoms. Furthermore, a review article and an advertisement were placed in a major Danish medical journal. A total of 1881 patients (28% M; 72% F) were included for analysis program was used. Body symptoms were as follows descriptive statistics and Sign test. SPSS 10.0 statistical analysis (non-parametric, ordinal) included descriptive statistics and Sign test. SPSS 10.0 statistical analysis program was used. Body symptoms were as follows (see table).

Results The composition of the aura symptoms were visual, sensory, motor and aphasic aura in 70%; visual, sensory and motor aura in 17%; sensory, motor and aphasic aura in 7%; sensory and motor aura in 4%; visual and motor aura in 1% and visual, motor and aphasic aura in 1%. The median time (min) of gradual progression and the median aura duration (min) were 10 (range 1–180)/45 (range 1–1440) for visual aura; 15 (range 1–720)/90 (range 10–2880) for sensory aura; 15 (range 1–720)/120 (range 10–4320) for motor aura. Median duration for aphasic aura was 60 min (range 5–1440). The most frequent succession of the aura symptoms was visual, sensory, motor and aphasic aura (63%). During FHM-attacks, 95% of the patients always experienced a headache, 4% experienced headache in some attacks and 1% never experienced headache. The duration of the headache was 30 min – 4 h in 7%, 4 h – 1 day in 65%, 1–3 days in 26%, >3 days in 2%. The pain characteristics were 53% unilateral, 81% pulsating, 96% moderate/severe intensity and 97% aggravation by physical activity. The accompanying symptoms were 84% nausea, 61% vomiting, 87% photophobia and 86% phonophobia. Headache followed the visual aura in 73%, came prior to the visual aura in 17%, while both occurred simultaneously in 10%. Only 9% reported head traumas as a precipitating factor.

Conclusions FHM was not seen with motor aura alone and was virtually always associated with other aura symptoms and headache.

P1-A25
One year follow-up of headache and body symptoms in Lebanese dental students
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A prospective body pain symptoms study in dental student was initiated in January 2001. The aim of the study is to follow-up body pain symptoms every single year for dental students. All 38 first-year dental students (26 males/12 females – average age in first year: 18.5 years) at Saint Joseph University, Lebanon, answered a 0–3 Numeric Visual Analogue Scale. They were asked to score their recent symptoms using: ‘0’ for no pain, ‘1’ for mild pain, ‘2’ for moderate and ‘3’ for intolerable pain. Questions were about: earache, ear stuffiness, temporomandibular joint (TMJ) pain, TMJ sounds, headache, face pain, arm symptoms, neck symptoms (pain/numbness/burning), upper back symptoms, lower back symptoms, toothache. One year later, the same group of students was asked to fill in the same questionnaire (January 2001). After the first year, 3 male students left school, which brought the total to 35 students. Statistical analysis (non-parametric, ordinal) included descriptive statistics and Sign test. SPSS 10.0 statistical analysis program was used. Body symptoms were as follows (see table).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>First year</th>
<th>Second year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earache</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Ear stuffiness</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>TMJ pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>TMJ click</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Face pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Arm</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Neck</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Upper back</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Lower back</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Tooth pain</td>
<td>7</td>
<td>3</td>
</tr>
</tbody>
</table>

N = 35.
Sign test did not show any significant statistical difference in symptoms between the first and second year. The most prevalent symptom in both consecutive years was headache: 63% in the first year and 57% in the second. This study will be repeated every year at the same date for the same group of students to follow the evolution of symptoms during five dental consecutive years. Controls will be used in the future in order to assess the impact of dental environment on body symptoms.

P1-A26

Headache, the most prevalent pain symptom in Lebanese dental students

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Dental students often complain of body fatigue and discomfort, especially at the end of their work. Stressful working posture is thought to be a major contributing factor. The goal of this study was to determine the prevalence of body symptoms in dental students. All 178 dental students (117 males/61 females, average age: 20.7 years) at Saint Joseph University, Lebanon, answered a 0–3 Numeric Visual Analogue Scale. They were asked to score their recent symptoms using: ‘0’ for no pain, ‘1’ for mild pain, ‘2’ for moderate and ‘3’ for intolerable pain. The students represented all five academic dental years. Questions were about: earache, ear stuffiness, temporomandibular joint (TMJ) pain, TMJ sounds, headache, face pain, arm symptoms, neck symptoms (pain/numbness/burning), upper back symptoms, lower back symptoms, toothache. SPSS 10.0 program was used for statistical analysis. The most prevalent symptom was headache (101 students; 57%), followed by: neck symptoms (80; 45%), lower back symptoms (66; 37%), upper back symptoms (52; 29%), TMJ sounds (48; 27%), arm symptoms (45; 25%), ear stuffiness (40; 22%), toothache (38; 21%), TMJ pain (25; 14%), earache (18; 10%) and face pain (7; 4%). Correlation (Pearson correlation, p < 0.01, 2-tailed) was found between the following symptoms: upper back and neck symptoms (r = 0.41), upper back and arm symptoms (r = 0.42), lower back and arm symptoms (r = 0.42), ear stuffiness and earache (r = 0.38), earache and TMJ pain (0.36), TMJ sound and TMJ pain (r = 0.31), neck symptoms and headaches (r = 0.37), neck and arm symptoms (r = 0.38), lower back symptoms and ear stuffiness (r = 0.33), lower back and upper back symptoms (r = 0.31), lower back symptoms and toothache (r = 0.33), TMJ sound and earache (r = 0.25), face pain and ear stuffiness (r = 0.22), face pain and TMJ pain (r = 0.21), arm symptoms and earache (r = 0.22), arm symptoms and TMJ pain (r = 0.27), arm symptoms and headache (r = 0.21), arm symptoms and face pain (r = 0.26), upper back and age (r = 0.21), upper back and earache (r = 0.20), upper back and headache (r = 0.24), upper back and face pain (r = 0.20), lower back and earache (r = 0.27), lower back and TMJ pain (r = 0.24), lower back and headache (r = 0.20), lower back and face pain (r = 0.23), lower back and neck symptoms (r = 0.28), toothache and earache (r = 0.27), toothache and ear stuffiness (r = 0.27), toothache and TMJ pain (r = 0.22), toothache and headache (r = 0.24), toothache and arm symptoms (r = 0.23), toothache and neck symptoms (r = 0.23). Headache being the most prevalent symptom in dental students, further investigation is needed to uncover predisposing, precipitating and perpetuating factors.

Tension-type headache and migraine. A discriminative analysis using the McGill Pain Questionnaire

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Objectives The McGill Pain Questionnaire (MPQ) is, by far, the best known and most widely employed verbal methodology for pain assessment. Descriptors may be examined individually, a pain rating index (PRI) may be calculated cumulatively and for each pain dimension (sensory, affective, evaluative and mixed). The discriminative capacity of this instrument has been evaluated in different headache and facial pain syndromes. Since, to date, no study has been conducted to compare data from the MPQ in patients with headache of tension type (TTH) and migraine (M), our purpose was to assess the discriminative capacity of the MPQ when applied to these two groups of patients.

Methods 134 patients consecutively referred were considered, with TTH (n = 49, 1 male, 48 females) or M with aura or without aura (n = 85, 9 males, 76 females). The MPQ was administered to all patients, and they were also asked to assess the level of pain using the Visual Analogue Scale (VAS). Weighted MPQ item scores were calculated by dividing the rank order weight of the pain descriptors chosen by the total number of descriptors in that item. Subscale Pain Rating Indexes (PRI) were calculated by summing weighted item scores within each subscale: sensory, affective, evaluative, mixed sensory, mixed affective-evaluative. A Total Pain Rating Index was also calculated by summing all subscale scores. Mean item scores, subscale scores, Total Pain Rating Index and VAS scores were tested for significant differences between M and TTH patients using the Student’s t test. In addition, the frequency values with which each descriptor was chosen by the two groups were calculated and the differences in choice frequency between the two groups were assessed for each descriptor.

Results All mean MPQ subscales scores, the total PRI and VAS score were higher for M patients: this was significant in all cases except for evaluative and mixed-sensory PRI. Moreover, M patients had significantly higher item scores on three items of the sensory subscale and on all but one item of the affective subscale. There was a consistent difference in descriptor selection between the two groups. The following items were chosen at least 20% more frequently by M patients: gnawing, stinging, tender, exhausting, sickening, blinding and intense. The TTH group chose at least 20% more frequently the followings: pressing, hurting, sore, and punishing. It is notable that the item pulsing was chosen by about 50% of the patients in both groups.

Conclusions It is concluded that the MPQ has a relevant discriminative capacity between M and TTH patients.

Validation of a simple questionnaire for migraine diagnosis for use in epidemiological research

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Background The gathering of research data based on questionnaires applied by non-medically trained personnel is very common in Europe and the United States. However, in Brazil there is no strong tradition of using such questionnaires. Our team previously validated a questionnaire based on International Headache Society (IHS) criteria for research purposes (Arq Neuro Psiq 1997; 55:364–9). Now, we are testing a simpler and more practical questionnaire, also following IHS criteria, to be applied to field research. We are using the principle of ‘minimizing questions for maximizing answers’.

Objectives To validate a simple questionnaire in Portuguese, for primary migraine diagnosis in epidemiological research.

Methods We included 90 randomly selected individuals at an outpatient care unit, who were seeking medical services with diverse complaints that did not necessarily include headache. The questionnaire consisted of only 12 questions, which asked about the lifetime number of headaches, duration of a typical episode, frequency of headache, type of pain, laterality and severity of pain, influence of physical activities and presence of nausea, vomiting, photophobia and phonophobia, according to IHS criteria. Medical residents applied the questionnaire to the patients, and after the regular medical interview, patients were invited to participate in a special medical interview with a headache specialist. The diagnosis from this interview was considered as the gold standard. For statistical analysis, calculations were made of sensitivity, specificity, positive and negative predictive values, positive and negative likelihood values and chance agreement (k value).

Results In comparison with the headache specialist’s consultation, the short questionnaire showed a sensitivity of 78.3%, a specificity of 83.3%, a positive predictive value of 90.4% and a negative predictive value of 65.8%. The positive likelihood ratio was 4.7 and the negative likelihood ratio was 3.8. The agreement beyond chance (k value) was 0.58. The accuracy rate for the short questionnaire (80%) was greater than obtained previously for the complete questionnaire (72.5%).

Conclusions This uncomplicated questionnaire can allow us to identify migraine headaches in epidemiological research.
with only 12 questions. It has an acceptable comparison with a more complete questionnaire previously validated by us and used by other Brazilian researchers. This questionnaire using IHS criteria will be very useful for future use in epidemiological research.

P1-B3
The internet headache questionnaire: 1500 test report
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Background The Headache Test has been on the Web site of the San Francisco Clinical Research Center and the San Francisco Headache Clinic since 1998. Over 1500 persons have completed the questionnaire and over 900 have received responses to the test. Previous presentations of the Headache Test have included agreement between the clinical diagnosis of headache and an automated analysis using IHS criteria. A second presentation included the demographics of the Internet Migraineur. The final analysis was on the degree of disability. The current analysis centres on the validity of the migraine diagnosis as well as an assessment of accessing medical care and utilization of appropriate medications and other therapies.

Materials and methods 1500 questionnaires were analysed for the validity of the migraine diagnosis separating tension headache, common migraine headache, classic migraine headache, chronic daily headache, and cluster headache. Questionnaires were further analysed for physician consultation, testing, and medication usage. These results were further correlated with personal, environmental and work-related factors affecting the headaches.

Results As in previous presentations, there was a high correlation of the automated responses with the clinical diagnosis and degree of disability. The more recent analyses have indicated a very low physician or consultation rate (<10%), an even lower testing rate (<5%), and an even lower utility of newer triptan-type medications.

Conclusion In a defined and self-selected Internet migraine population, it is clear that over 90% of the respondents have diagnosable migraine headache. It is also clear that very few of these respondents access medical care, have had an evaluation for their headaches, or have utilized triptan drugs. These findings exist despite large educational efforts made over the past 10–15 years on migraine headache. These results may be somewhat confirmatory of previous random digit dialling efforts at assessing the prevalence of migraine headache in the United States, considering that a self-selected group of migraineurs who fulfil all IHS criteria for the diagnosis do not access the medical system and are unaware of current treatment options.

P1-B4
Examining the validity of IHS migraine criteria using the pathfinder algorithm
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Objective To evaluate the validity of migraine criteria in the IHS system using a structural knowledge assessment technique. The technique, the Pathfinder network scaling algorithm, generates an empirically derived representation of knowledge structure. In this case, the knowledge structure derived was headache experts’ conceptualizations of migraine diagnostic criteria.

Background Establishing a valid classification system for headache is challenging because headache is a disease entity that lacks objective defining markers. Lacking defining markers, the IHS classification committee relied on expert consensus to develop the 1988 classification system. Expert consensus is also relied upon to evaluate the validity of the IHS classification system. For example, some studies have compared the IHS diagnoses with the diagnoses of expert clinicians. Further studies using varied methods are needed to evaluate the validity of diagnostic criteria.

Methods In this study, 26 headache experts representing the Executive Committee of IHS and the Board of Directors of AHS were asked to rate the relatedness of 14 criteria (7 IHS and 7 non-IHS) considered relevant in diagnosing migraine. Twelve (n = 12) were returned; 11 were completed (42% response rate). Each participant made 91 pairwise ratings of relatedness (e.g. unilateral–hormonal relationship) using a 1 (unrelated) to 9 (highly related) scale. From these ratings, distance estimates were calculated and used as the input. The output generated using the Pathfinder algorithm was a network structure representing experts’ conceptualizations of migraine diagnostic criteria.

Results The expert network had three groupings, termed (a) headache characteristics (photophobia, phonophobia, unilateral, throbbing, moderate/severe, nausea, and activity), (b) biological contributing factors (family, sleep, hormone, female), and (c) triggers (smells, stress, food). In the expert network, graph theory indices were calculated revealing that the most central criteria were unilateral, moderate/severe intensity, and nausea. The IHS criteria were clustered together in the center portion of the network. An analysis of distances followed by a t-test showed that each IHS criterion was closer conceptually to other IHS criteria than to non-IHS criteria ([t(6) = −6.0, P = 0.001].

Conclusions The findings suggest that headache experts conceptualize migraine diagnostic criteria in a manner consistent with the IHS classification system. Thus, the expert consensus observed in this study is further support for the validity of migraine criteria in the IHS system.
P1-B5

Migraine quick screen in clinical practice

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Objective The Migraine Quick Screen (MQS) has been developed to quickly and accurately identify those patients with migraine for further evaluation who might otherwise go undiagnosed.

Background It has been estimated that nearly half of the patients with migraine in the USA remain undiagnosed.

Methods A questionnaire containing the Migraine Quick Screen (MQS) and International Headache Society (IHS) criteria for Migraine with and without aura was administered to 108 consecutive adult patients and reviewed by a physician. The MQS can be administered in under one minute. A positive MQS results from a yes to the following questions: 1. Do your headaches come and go? (Episodic Headache); 2. Do you get sick to your stomach? (Nausea); 3. Are you sensitive to light or sound? 4. Do your headaches interfere with your daily activities? (Disability).

Results Eighty-two patients meet the IHS criteria for migraine with and without aura; 27 patients had migraine with aura. Forty seven patients meet Migraine Quick Screen criteria. The sensitivity of MQS as compared to IHS criteria was 57%; specificity was 100 and positive predictive value was 100%. All the patients who meet MQS meet the IHS criteria.

Conclusions The Migraine Quick Screen (MQS) may prove to be a helpful tool in decreasing the number of undiagnosed migraine patients. The MQS is under further study and modification to increase sensitivity without sacrificing specificity and to keep it under one minute to administer to help identify those patients who need further headache evaluation.

P1-B6

Migraine in France in 2000: epidemiological data

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Objective A French national epidemiological study on migraine was presented 10 years ago at the Migraine Trust. It was the first study to cover an entire country (1). This study has provided also data on the burden of migraine in terms of its economic and social impact. We would like today to update the data.

Methods 1486 persons, aged over 15 and suffering from headaches, were randomly selected from a large representative sample of the French population. They were asked to complete a questionnaire, which categorized sufferers of migraine according to IHS criteria.

Results Among the 1486 headache sufferers, we find 880 migrainous people (1–1, 1–2 and 1–7 IHS criteria), 454 without migrainous headache and 152 with chronic daily headache. If we compare the results of the certain migraine group (1–1 and 1–2 IHS) we find that they are identical (8.1% [1989] vs. 8.2% [1999]). However, if we include the migrainous disorder group fulfilling all criteria but one (1–7 IHS), the prevalence rate for migraine headache in France between 1989 and 1999 seems to show a clear increase, rising from 12.1% to 17.3% because of less restrictive criteria than those applied ten years ago. Regarding the prevalence in general population for chronic daily headache, the rate is around 5% with 1.8% for men and 3.9% for women in 1999.

Reference

P1-B7

Prevalence and clinical features of migraine in a population of visually impaired subjects at Curitiba, Brazil

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Objective To evaluate the prevalence and clinical features of a population of blind subjects, aiming to determine the relevance of lacking or diminished visual afferences on the expression of migraine.

Background Although there are several studies on the relationships of the visual system, visual stimuli and migraine, the effects of diminished light afferences on migraine had never before been studied.

Design and methods Between the months of September 1999 and April 2000, 203 visually impaired subjects were submitted to an inventory for the detection of headache. Those with headache were further evaluated with an IHS-based protocol for the occurrence of migraine in the last six months. Those with confirmed migraine and who were able to read Braille signs were asked fullfill a headache diary, with a tactile analogic pain scale (TAS) specially designed for the study.

Results Of the 104 subjects presenting some type of headache in the last six months, 29 had migraine (14.2%). Migraine rate
A prevalence study of headache in Florianopolis, Brazil

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Objective To estimate the lifetime prevalence of headache, and the 1-year and point prevalence of headache, migraine and tension-type headache (TTH), according to the International Headache Society criteria, in a representative sample of the adult population of Florianopolis, Brazil.

Participants and methods This is a cross-sectional, door-to-door, population-based study. The survey was done in the central area of Florianopolis, including downtown and 23 suburbs, which represents 58.5% of the whole population. Three hundred households were randomly selected, stratified by energy consumption, expecting to select subjects of different socio-economic levels. From 719 eligible subjects, aged 15–64 years, 625 (337 females and 288 males) responded to a questionnaire about headache. The participation rate was 87%. Medical students conducted the direct structured interview. To avoid recall bias, the whole questionnaire was completed only with subjects with headache within the last year; with the others, sociodemographic data were taken.

Results Headache: The lifetime prevalence of headache was 94.6%, the 1-year prevalence 80.8%, and the point prevalence 13.3%. The 1-year prevalence in female subjects was 88.7% and in male 71.5%. In both sexes the rates were higher at ages 15–64 years (95.3% in women and 79.5% in men). Migraine: Prevalence of migraine in the last year was 22.1% (28.8% in women and 14.2% in men), with a female: male ratio of 2:1. Prevalence in migraine without aura was 10.9% and in with aura 11.2%. Migraine was more prevalent in females than in males at all ages. In women, the prevalence was higher at ages 15–24 (30.7%); in men, at 25–34 (34.1%). If we included headache of the tension type not fulfilling all criteria, the 1-year prevalence of the tensional group was 33.0%. The point prevalence of TTH was 2.9%.

Conclusions This is the first population-based study of headache in Brazil. The 1-year prevalence of migraine was close to the higher rates of European and North American studies, and higher than the previous estimated prevalences from Latin American, African and Asian populations. Prevalences of TTH were similar to the described in some other surveys. There was a preponderance of headache of the migrainous group over the tensional group.

Migraine and quality of life: utilization of SF-36 in an employee population of a hospital in Brazil


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Objectives Evaluate the quality of life using the SF-36 questionnaire in persons with migraine, comparing with those without headache, in a population that is not attended by a specialized medical service.

Material and methods 310 employees of the Municipal Hospital Mario Gatti, in Campinas, SP, selected at random from among the 1540 employees of that institution, were interviewed applying the version of SF-36 which was previously translated and validated to our idiom. The employees who reported headache in the last 6 months answered another questionnaire with the IHS diagnosis criteria for headache and were evaluated by one of the authors (HMSJ). The SF-36 questionnaire was analysed blindly by another author (RPG), who did not conduct the interviews or have knowledge about the presence or not of the headache complaint.

Results Of the 310 interviewed, 143 (average age of 38.1; 87 women and 56 men) didn’t report headache in the last 6 months; 62 (average age of 36.4; 54 women and 8 men) had headache with migraine diagnosis according to the IHS criteria and 105 (average age of 36.6; 131 women and 36 men) complained of other type of headache. The scores to the various capacities evaluated by the SF-36 (physical function, role physical, bodily pain, general health, vitality, social function, role emotional and mental health) in the control group were as follows, respectively: 87.5; 80.5; 72.6; 78.3; 64; 78.6; 81.2; 69.6. In the migraine group the results were as follows: 81.3; 72.6; 58.5; 73.6; 53; 75.6; 74.7 and 65. Using the Mann–Whitney test with IC of 95% and P < 0.05 the differences among the two groups were significant for physical function (P < 0.0013), vitality (P < 0.0001), mental health (P < 0.0123) and bodily pain (P < 0.0001).

Conclusions The SF-36 showed itself a useful instrument in the evaluation of quality of life, distinguishing the employees group with headache in the last 6 months from the control group. There is no previous experience in evaluate the quality...
of life using the SF-36 questionnaire in Brazil. Our results in the migraine group are consistent with the findings in previous publications, with the lowest scores in physical function, vitality and bodily pain.

P1-B10

The prevalence of migraine and tension-type headaches among adolescents in Norway: the Nord-Trøndelag Health Study (Head-Hunt-Youth), a large population based epidemiological study

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Objectives To examine the prevalence of migraine and tension-type headaches among adolescents and explore the differences in prevalence by gender and age.

Methods This cross-sectional study conducted in Nord-Trøndelag County, Norway, 1995–1997, included 91% of all students aged 13–19 years. In total 8984 students completed a comprehensive questionnaire, whereof 5995 were interviewed about their headache complaints.

Results The overall 1-year prevalence of migraine was 7.1% (9.1% in girls and 4.9% in boys), and for tension-type headache 18.4% (23.8% in girls and 12.6% in boys). Higher prevalence rates for girls were found in all age groups for both migraine and tension-type headache. The prevalence of migraine among girls increased gradually from the age of 13, while the opposite trend was found for boys.

Conclusions Migraine and tension-type headaches are prevalent among Norwegian adolescents, especially among girls.

P1-B11

The first prospective longitudinal study of headaches: do migraine and tension-type headaches change over time?

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Objective To investigate the degree to which migraine and tension-type headaches change over time.

Background A number of different terms and definitions have been used to describe headaches that change over time. ‘Transformed migraine’ is one of the more commonly used terms which refers to a theory originally positing that migraine ‘transforms’ into chronic tension-type headache. This theory has not been empirically substantiated in a prospective, longitudinal manner. Studies done to date have been retrospective and thus suffer from inherent weaknesses due to limitations in this design.

Materials and methods Participants were given a structured diagnostic headache interview in 1997 (Time I) and again approximately three years later (Time II). Complete data were obtained from 88 participants reporting 102 headaches classified at Time I as migraine (n = 60) and tension-type (n = 42). At Time II, a total of 70 (migraine = 44; tension-type = 26) follow-up diagnostic interviews were completed. The Kappa test statistic was used to measure the level of diagnostic agreement between Time I and Time II.

Results More than half (52%; 23 of 44) of the headaches originally diagnosed as migraine received different diagnoses at Time II, indicating only a fair level of diagnostic agreement (κ = 0.23). Over one third (38%; 10 of 26) of headaches originally diagnosed as tension-type headaches were classified differently at Time II, indicating a moderate level of diagnostic agreement (κ = 0.46). A total of six headaches diagnosed as migraine at Time I met criteria for tension-type headache at Time II and two headaches classified as tension-type at Time I met criteria for migraine at Time II. Furthermore, 19% of the headaches reassessed no longer met full criteria for diagnoses of either migraine or tension-type headache.

Conclusions The results of this study show a wide variation in the presentation of migraine and tension-type symptomatology over time. In the case of migraine, more than half of the participants had headaches that no longer met criteria for migraine headache. However, only 6 of 23 (26%) changed in the manner posited by the ‘transformed migraine’ theory, while 17 of 23 (74%) changed in other ways. Similar variation among tension-type headache sufferers supports the notion that clinical practice should incorporate frequent re-evaluations of the patient’s headache type to ensure that an accurate headache diagnosis is the focus of ongoing treatment.

P1-B12

A longitudinal study of two neglected primary headache types: ‘non-specific’ migraine (1.7) and ‘non-specific’ tension-type headache (2.3)

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Objective To examine the stability over time of headaches diagnosed as not meeting full criteria for migraine and tension-type headache at three-year follow-up.

Background The study of ‘non-specific’ headaches has been neglected. A recent community-based study showed that nearly 1/3 of headache sufferers did not meet full criteria for primary headache disorders. The few studies conducted to date have focused on identifying subgroups in each category (e.g. chronic-daily migraine). Additionally, research has shown that nearly 25% of ‘non-specific’ headaches diagnosed...
in children or adolescence disappear and approximately
1/3 meet full criteria, at 2–5 year follow-up. Thus, ‘non-
specific’ headaches were shown to be possible predictors of
full criteria headaches for children and adolescence. The
degree to which ‘non-specific’ headaches change in the adult
population has not been explored.

Materials and methods Participants took part in a structured
diagnostic headache interview in 1997 (Time I) and again
three years later (Time II). Follow-up information was
gathered from 30 adults originally classified with ‘non-
specific’ migraine (n = 8), ‘non-specific’ tension-type (n = 8)
and ‘non-specific’ combined migraine and tension-type
(n = 14).

Results The diagnostic agreement between Time I and Time
II was no better than chance (κ = 0.03). For example, only
21% of the diagnoses were consistent between Time I and
Time II (4/19). The majority (68%) of ‘non-specific’ head-
aches at Time I met full diagnostic criteria for either migraine
(9/13) or tension-type (4/13).

Conclusions The results of this study indicate that ‘non-
specific’ headaches vary widely over time in the adult
population. Clearly, ‘non-specific’ headaches warrant further
investigation, as they have been found to change across
time in the child, adolescent, and now the adult population.
The ‘non-specific’ diagnosis may represent an intermittent
phase of headache development, a predictor of subsequent
headache diagnosis, or perhaps reflects a stage of headache
change.

P1-B13

Daily, episodic, and paroxysmal headaches in
a headache-practice population

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The purpose of the study was to categorize the headache-
practice population of the second author in terms of daily,
episodic, and paroxysmal headaches and to describe some of
the features of the first two groups in particular. The first
author, a family physician and epidemiologist, analysed the
initial evaluation reports of 1452 patients with headache,
seen personally by the second author, a neurologist with
specialty training in headache management. Of the 1452
patients, 55.7% had daily headaches (headaches <5 days/
week), 38.9% episodic headaches (headaches <5 days/week),
and 5.4% paroxysmal headaches (cluster headache, parox-
symal hemicrania, or jabs & jolts syndrome). The patients
with the daily headaches, in comparison with those with the
episodic headaches, were more likely to have an onset of
any headache in adulthood (51.0% vs. 45.4% before age 20;
P < 0.041). They were older at the time of initial evaluation
(41.0 vs. 38.3 years; P < 0.001), were more likely to have a
history of other headaches (61.9% vs. 35.4%; P < 0.001), and
were less likely to report nausea or vomiting with their
headaches (64.2% vs. 73.8%; P < 0.001). With the approach
taken, all headaches could be categorized with a minimum of
assumptions. On the basis of the observed differences, it is
suggested that the patients with daily headaches do represent
a different population than those with episodic headaches.

P1-B14

Influence of putative risk factors for migraine with
aura, analysed by discordant twin-pairs from
the general population

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Objectives Recent studies of families, siblings and twins
have established that migraine with aura (MA) is due to
an interaction of multiple additively genetic factors, and
influence of the environment. We wanted to detect possible
risk factors involving the environment by analysing twin
pairs discordant of MA.

Materials A cohort of 5360 twin pairs born in the period
1953–1960, recruited from the New Danish Twin Register,
was screened by questionnaire for migraine. All twins with
possible migraine were telephone interviewed by a physician.
For the present study, all twin pairs discordant for MA were
included. The analyses included variables related to lifestyle
and living conditions. Other headache types, that is, migraine
without aura (MO) and tension-type headache (TH) were also
included as variables.

Methods A matched case-control study was performed to
evaluate the association between MA and the risk factors. The
cases were the individuals with MA and the controls were the
individuals who had never had MA. The relative risk of MA
was given by the odds ratio, analysing pairs with cases and
controls being discordant for the exposure. The significance of
the odds ratio was found by means of the McNemars test. The
95% confidence intervals for the odds ratios were calculated
using methods for confidence intervals for proportions. A
total of 87% of the twins replied to the questionnaire. The
participation rate of twins in the interview was 90%, and the
sensitivity of ascertainment of twins with migraine was 85%.

Results The lifetime prevalence of MA in the twin sample
was 7% with a male-to-female ratio of 1: 1.1. In total, 169 pairs
discordant for MA were identified. The distribution of
zygosity was 51 monozygotic and 118 same-gender dizygotic
pairs. The odds ratios were as follows: schooling more
than 9 years 0.77 (0.30–1.90), education more than 3 years
1.19 (0.40–1.73), married vs. non-married 1.75 (0.69–4.81),
smoker vs. non-smoker 0.63 (0.25–1.47), drinking more than
7 drinks of alcohol a week 0.92 (0.37–2.27), MO vs. no MO
1.26 (0.66–2.44), TH vs. no TH 1.46 (0.98–2.89). None of the
odd ratios reached significance. No variation of odds ratios
was found concerning zygosity.

Conclusions Several putative risk factors – schooling,
marital status, smoking status, and alcohol consumption –
showed no association with MA. The presence of other
headache types than MA did not increase the risk of MA.
P1-B15

Headache and video display terminal use: myth or reality
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Background and objectives In several occupational health and ophthalmology publications the symptom most described by video display terminal (VDT) operators after visual disturbances is headache. In specific literature there is no study on the prevalence, features and diagnostic profile, of these headaches according to the IHS 1988 criteria. Our aim is to assess the real magnitude of the problem.

Methods In our country a medical examination is done on all video operators exposed more than 4 h a day. A total of 1314 of these clerical workers (male 707, female 607, mean 39±9), from public corporations, were asked to fill out a questionnaire specifically concerning headache, to undergo medical and eye examinations, ergonomic and psychometric tests, combined with investigations of the features of working environment, type and years of work and amount of daily exposure to VDT. The 380 subjects who responded positively for headache were assessed by a group of specialists according to the IHS 1988 diagnostic criteria.

Results Of the 380 only 166 subjects (male 48, female 118, mean 38±8) suffered from real headaches: 107 cases of migraine without aura, 47 of episodic tension-type headache, 12 of migraine and tension-type headache, 2 of unclassified headache. Over half of the subjects, 214 (male 80, female 134, mean 38±9), complained of vague and ill-defined symptoms (dizziness, confusion, heaviness, gogginess and fogginess) not properly painful syndromes and thus not diagnosable as headaches but as a generic ‘head discomfort.’ The possible role of VDT use in inducing the symptoms appeared highest in migraines, followed by head discomfort and tension-type headaches. No association was found between presence or type of headaches with work station and work environment, because on average they were rated as comfortable.

Conclusions The presence of headache in VDT operators appears to be overestimated in non-specialist literature. In our sample 13% suffered from primary headaches and 8% from migraine without aura. This prevalence is no higher than in the general population and below that in other categories of workers, as reported. On the other hand subjective symptoms, which we define as ‘head discomfort’, do not fall within the IHS 1988 criteria, were frequent. The real role of VDT in inducing headache attacks and other disturbances requires further investigation, particularly considering that VDT use is constantly rising.

P1-B16

Symptom expectation after minor head injury: a comparative study between Lithuania and Canada
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Objectives The purpose of the present study is to compare the frequency and nature of expected symptoms in Lithuania (a country where the chronic post-concussive syndrome is little known) with that in Canada.

Materials and methods A symptom checklist was administered to 2 subject groups selected from local companies in Kaunas, Lithuania, and Edmonton, Canada, respectively (171 vs. 179). Subjects were asked to imagine having suffered head trauma with loss of consciousness in a motor vehicle accident, and to check off symptoms they expected might arise from the injury. For symptoms they anticipated, they were asked to select the period of time they expected those symptoms to persist. Considering that Lithuanian subjects may simply be naive to any chronic problems, the subjects were also asked to fill out a symptom checklist of rheumatoid arthritis.

Results In both the Lithuanian and Edmontonian groups, the pattern of symptoms anticipated closely resembled the acute symptoms commonly reported by accident victims with minor head injury. Yet, while many Edmontonians also anticipated symptoms to last months or years, very few Lithuanian subjects selected any symptoms as being likely to persist in a chronic manner. The Edmontonian and Lithuanian subjects’ expectations of disability from rheumatoid arthritis are equivalent.

Conclusions In Lithuania, despite the frequent experience of minor head injury in motor vehicle accidents, there is a very low rate of expectation of any chronic sequels from such an injury, contrasting greatly with the response shown in Canada, where the prevalence of the chronic post-concussive syndrome is higher. Symptom expectation in some countries may be an important factor in the development of the chronic post-concussive syndrome.

P1-B17

Headache in the elderly: an evaluation of common causes of headache in late life
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Background Even though headache prevalence is reduced in elderly, it is still frequently within the range of 11% for female and 5% for male population, in accordance with available data from previous studies. The objective of this study is to define the most frequent causes of headache within the population of our patients over 60 years old.
Methods and results Within our out-patient clinic, investigations were performed within the group of 76 patients over 60 years old (60–86), (average of 68), with headache as a basic or marginal symptom. To define such diagnosis and treatment of different entities of headache we were using the recommendations of the International Headache Society. 6.5% (n = 5) of patients had drug induced headache (rebound: n = 4; acute induced: n = 1); 7.9% had systemic disease cause (hypoglycaemia: n = 1; dialysed: n = 1; hypertension n =4); 9.2% with cervical headache; 7.9% with cranial neuralgia (trigeminal neuralgia: n =4; occipital neuralgia: n =2); 1.3% intracranial mass lesion (metastatic tumour: n =1); 2.6% with cerebrovascular disease (cerebral infarct in the area of MCA: n =1; gigantocellular arteritis: n =1); 23.6% migraine headache (migraine without aura: n =7; migraine with aura: n =11); 38.1% tension headache (episodic tension type: n = 23; chronic tension type: n =6). Prevalence of tension and dominant migraine headaches is significantly increased in comparison to other study results. Also there is a significant increase in frequency of episodic tension headaches with patients associated with migraine history. 61% of patients with existing migraine headache in late life have migraine with aura.

Conclusions In accordance with this study, we have noticed the significant high prevalence of primary headache as well as migraine and tension headache within the population of examinees. Selective sensitivity of those entities to quality of life is the most probable cause of this disorder.

P1-B18

Age related changes in the symptoms of the spectrum of primary headache

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Objective To evaluate changes in the spectrum of primary headache disorder (1 HAD) at different ages.

Background Migraine and other 1 HAD may be seen at any age but is most prevalent in the age range from 30 to 49 years. This study examines 1660 subjects with 1 HAD to determine the features of the spectrum of 1 HAD at different ages.

Methods The data was drawn from two databases of 1 headache patients subjects seen in clinic by JRC at 1. SIU from 1980 to 1992, n =808 and 2. OU from 1992 to 2001, n =852. A group of 16 symptoms and family history were taken from each patient at an initial interview. Patients with secondary headache were excluded. The subjects were divided into groups by age as: <30, 30–49, and >50 years. The groups were compared with 3×2 χ2 analysis to determine differences in symptom occurrence.

Results The 3×2 analysis summarizes the findings and is presented in the table. The asterisk indicates that differences in occurrence were sig. at P < 0.01 level. Note the symptoms of nausea, vomiting, diarrhoea, hemiparesis (HP), hemisensory loss (HSL), phonophobia and aphasia are more prevalent in the 30–49 group while vertigo, and LOC were more prevalent in the <30 and unilateral/more prevalent in the after 50 group. Overall the differences, while statistically significant, were modest is size. Note that in older subjects aphasia, HP, HSL, and LOC occurred less often by at least 33% in comparison to the 30–49 year groups.

<table>
<thead>
<tr>
<th>% Yes</th>
<th>≤29 years</th>
<th>30–49 years</th>
<th>&gt;50 years</th>
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</thead>
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<tr>
<td>Middle life peak</td>
<td>Aphasia</td>
<td>12.34</td>
<td>18.07</td>
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<tr>
<td></td>
<td>Diarrhoea</td>
<td>14.91</td>
<td>25.45</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>83.55</td>
<td>90.37</td>
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<tr>
<td></td>
<td>Vomiting</td>
<td>52.44</td>
<td>59.57</td>
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<tr>
<td></td>
<td>Phonophobia</td>
<td>73.52</td>
<td>77.17</td>
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<tr>
<td></td>
<td>Hemiparesis</td>
<td>7.71</td>
<td>12.13</td>
</tr>
<tr>
<td></td>
<td>Hemisensory loss</td>
<td>16.71</td>
<td>21.40</td>
</tr>
<tr>
<td></td>
<td>Lights/geom design</td>
<td>30.85</td>
<td>36.39</td>
</tr>
<tr>
<td></td>
<td>Osmophobia</td>
<td>19.79</td>
<td>23.19</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>6.94</td>
<td>10.82</td>
</tr>
<tr>
<td>Less than 30 peak</td>
<td>LOC</td>
<td>12.60</td>
<td>21.40</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
<td>85.60</td>
<td>83.95</td>
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<tr>
<td></td>
<td>Vertigo</td>
<td>15.42</td>
<td>13.20</td>
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<tr>
<td>Older group peak</td>
<td>Unilateral location</td>
<td>43.44</td>
<td>52.79</td>
</tr>
<tr>
<td>Level occurrence</td>
<td>Blurring</td>
<td>28.28</td>
<td>28.89</td>
</tr>
<tr>
<td></td>
<td>Spots</td>
<td>19.54</td>
<td>20.33</td>
</tr>
</tbody>
</table>

Discussion In these 1 headache patients, migraine associated symptoms were fairly uniform across the age span. Vomiting, HP, HSL, and aphasia occurred more often in middle life but major features of the migraine syndrome were present over the age span covered.

P1-B19

Headache in the elderly

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Objectives Despite the frequency of headache in the elderly, the clinical and epidemiological studies of headache patients aged 65 and older are scant. Our study seeks to define the types of headache and the sex and age distribution of this population.

Materials and methods We reviewed the clinical records of 3143 headache patients consecutively referred to our headache centre from 1995 to 2000. Data were collected for diagnoses given, sex and age. We studied the population of patients aged 65 and older.
Results The patients over 65 years of age were 214, constituting 6.8% of the total headache population evaluated. The median age of the elderly headache sufferers was 69.4 years. There were 178 female patients (83.2%) and 36 male patients (16.8%). Patients aged 65–74 years represented the great majority of the study group (81.3%); the prevalence rates were significantly lower in the patients over 75 years of age (18.7%). Primary headaches accounted for 81.3% of our cases, while the prevalence of secondary and unclassified headaches was respectively 14.5% and 4.2%. The mean age of primary headache patients (68.5 years) was lower when compared with the other two groups (respectively 72.5 years for secondary headache and 76.8 years for unclassified headache patients). Among the 174 primary headache cases, the following diagnoses regarding the headache subtypes were made: migraine without aura 29.3%, chronic daily headache (transformed migraine) 27.5%, chronic tension-type headache 25.9%, mixed headache (migraine + tension-type headache) 8.6%, migraine with aura 3.4%, episodic cluster headache 2.3%, episodic tension-type headache 1.2%, hypnic headache 1.2%, chronic cluster headache 0.6%. The 31 cases of secondary headache were: trigeminal neuralgia 29.1%, cervicogenic headache 22.7%, headache associated with disorder of cervical spine 19.4%, giant cell arteritis 6.4%, chronic post-traumatic headache 6.4%, intracranial neoplasm 3.2%, chronic post-herpetic neuralgia 3.2%, headache associated with dialysis 3.2%, acute sinus headache 3.2%, sleep apnoea headache 3.2%. Conclusions Headache still affects a high percentage of elderly subjects and causes significant morbidity. Additional epidemiological studies are warranted to further evaluate the prevalence of this disorder in the elderly and to improve the care of these patients.

P1-B21

The prevalence of familial hemiplegic migraine
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Objectives Approximately 100 families with familial hemiplegic migraine (FHM) are reported in the literature. The objective of the present study was to identify all Danish families with FHM in order to estimate the prevalence.

Materials and methods The patients were recruited from the Nation-wide Person Registry comprising all patients, admitted or outpatient treated on a Danish hospital from 1994 to 1997 and discharged with migraine with aura (MA). In addition, more than 27 000 files from Danish headache clinics and neurologists were screened for patients with MA with motor symptoms. All Danish private specialists in Neurology or Paediatrics and all departments of Neurology and Paediatrics were asked to report patients with MA with motor symptoms. Furthermore, a review article and an advertisement were placed in a major Danish medical journal. A total of 1881 patients (28%M: 72%F) were included for admission or outpatient treated on a Danish hospital from January 1997 to December 2000.

Results Forty-four families, consisting of 147 affected individuals with FHM, were identified. The median age was 37 years (range 9–82) and the male: female ratio was 1:2.5. The number of affected individuals per FHM-family ranged from 2 to 11 (median 3). The median age of onset was 13 years (range 1–45). Lifetime number of FHM attacks was >100 in 37%, 50–100 in 18%, 10–50 in 24%, 5–9 in 5% and 2–4 in 16%. The majority (73%) had had FHM-attacks within the last 2 years. The number of attacks within the last year was 0 in 39%, 1–6 in 46%, 7–12 in 8%, 13–24 in 3%, 25–36 in 1% and >36 attacks in 3%. Of the 27% with no FHM-attacks within the last 2 years, 87% no longer had attacks after the age of 50 years.

Conclusions In our study, the most common type of headache was chronic daily headache with overused analgesics (48.1%). The prevalence of headache sufferers was significantly greater in older men than in women. Thus, it seems that sex is an age-related factor.
Conclusions FHM is not as rare as previously thought, as a total of 44 families were identified among 5,200,000 Danish inhabitants. Other differential diagnosis should be considered if onset of isolated motor symptoms occurs after age 45 years.

P1-B22

Long-term outcome and predictive factors in the prognosis of migraine with aura

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Objectives Identifying predictive factors in the prognosis of migraine with aura (MA) is essential to guide patients and to identify subgroups of MA. A 16-year follow-up study of 53 patients assessed the long-term outcome and possible predictive factors in the prognosis of MA.

Materials and methods The patients were recruited from the headache clinic at the Danish National Hospital or from Professor Jes Olesen, Glostrup Hospital. Case records from 1977 to 1984 were examined. Sixty patients had a diagnosis of MA according to the IHS criteria. The participation rate was 88% (53/60). The 53 patients (11M, 42F) had a semistructured telephone interview by a trained medical student (MKE).

Results The mean follow-up period was 16 years (14–21). The median age at follow-up was 52 years (27–80). At follow-up, attacks had ceased in 36% of patients. Cessation of attacks was defined as no MA for at least 2 years. The median age at cessation of attacks was 40 years (20–70). Attacks had ceased in 55% of males and 31% of females ($P = 0.17$). Attacks had ceased in 41% of patients with visual aura without other aura symptoms and in 25% of those with sensory or aphasic aura besides their visual aura ($P = 0.36$). The median age at onset of MA was 26 years in patients with cessation of attacks and 17 years in patients still having attacks ($P = 0.08$). The median length of time having MA was 11 years in patients with cessation of attacks and 28 years in patients still having attacks. An improvement was noted in the majority of patients still having attacks, i.e. 44% had less frequent and 41% had less severe attacks. However, some patients had more frequent (20%) or more severe (22%) attacks.

Conclusions MA has a favourable evolution over time. Attacks had ceased in 36% of patients at follow-up. Being male, having visual aura without other aura symptoms, or having onset of migraine with aura late in life showed a positive relation to cessation of attacks.
POSTER SESSION I

C: Comorbidity of headache

P1-C1
Raynaud’s phenomenon in migraine patients: a population-based study, the camera-project
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Background and objectives Dysregulation of vascular tone may play a role in both migraine and Raynaud’s phenomenon. We investigated the prevalence of Raynaud’s phenomenon (RP) in a population-based sample of migraine patients.

Materials and methods The sample is from the GEM study, which is based on a cohort of 6039 Dutch adults aged 20–60 years, including 863 migraineurs, who participated in a population-based study of cardiovascular risk factors. Migraine was assessed according to IHS criteria in a multistage procedure that included a semistructured clinical interview by telephone. From this cohort aged 30–60 years, we randomly selected 134 migraineurs without aura (MO) (27.8% of all identified MO), 161 migraineurs with aura (MA) (70% of all identified MA) and 140 controls who were frequency matched to the cases by sex, 5 years of age strata and region of residence. History of Raynaud’s phenomenon was assessed according to a validated, standardized questionnaire (1). We used chi-squared tests for comparisons of proportions.

Results Overall prevalence of Raynaud’s phenomenon tended to be higher in migraineurs than in controls (19.7% vs 12.9%, P = 0.08). The difference was significant for female migraineurs < 55 years (23.4% vs 11.5%, P = 0.03) but not for males (12.0% vs 4.3%, P = 0.22). The prevalence of RP did not differ between MA or MO (20.6% vs 18.7%, P = 0.32).

Conclusions Female migraineurs have an increased prevalence of Raynaud’s phenomenon.

Reference

P1-C2
Association between TMJ dysfunction, headaches and malocclusion
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Objective Since TMJ dysfunction frequently involves headaches and headaches are associated with malocclusion, we investigated the relationship between these.

Methods We examined patients who currently suffer from TMJ dysfunction and experienced headaches within the previous year from among 1,593 patients who had received treatment at the Department of Dentistry. Malocclusions were classified as normal, maxillary protrusion and mandibular protrusion anteroposteriorly and normal, deep bite and open bite vertically. The diagnosis of headaches was performed by a neurologist according to the criteria of ISH.

Results (1) TMJ dysfunction was seen in 28.2% (449 patients) of the 1,593 subjects surveyed and headaches were seen in 47.0% (748 patients). (2) Headaches were seen in 65.0% of the patients suffering from TMJ dysfunction and TMJ dysfunction was seen in 39.0% of patients who experienced headaches. Both TMJ dysfunction and headaches were seen in 18.3%. (3) Anteroposterior malocclusion: TMJ dysfunction was seen in 29.5% of patients with normal occlusion, 31.3% with maxillary protrusion and 34.6% with mandibular protrusion. Vertical malocclusion: TMJ dysfunction was seen in 27.8% of patients with normal tegmentum, 31.1% with deep bite and 52.3% with open bite. (4) The incidence of malocclusive patients with TMJ dysfunction and headaches was high, and among such patients many tension-type headaches were seen in patients with deep bite and maxillary protrusion.

Conclusions Many patients suffering from TMJ dysfunction experienced headaches and an association with malocclusion was observed.

P1-C3
Family history of migraine and epilepsy: clinical study on possible common genetic determinants
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Background and purpose The prevalence of epilepsy on migraine sufferers is on average 5.9% and the prevalence of migraine on epilepsy patients ranges from 8% to 24%. One possible explanation is a genetic factor that they hold in common. We present a case-control study to test that hypothesis.

Methods Using clinical interview, migraine and epilepsy patients were questioned about family background on both diseases. Headache- and epilepsy-free subjects were selected from a healthy, non-hospital-based population, to act as controls. An unmatched case-control analysis was performed and risk estimates were calculated.

Results 53 migraine sufferers and 25 epilepsy patients formed two groups of cases and were confronted with information from 60 controls. Controls were on average younger (P < 0.001) and had a higher proportion of male

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subjects \((P=0.013)\) than the two groups of cases. Migraine patients had more frequently a migraine family history than controls \((OR=4.8; 95\% CI, 2.1–10.9)\) or epilepsy patients \((OR=6.1; 95\% CI, 2.2–17.2)\) but the existence of relatives with epilepsy in this group was not different from controls \((OR=1.7; 95\% CI, 0.5–5.6)\). We detected no difference between somnambulism and the migraine. A history of somnambulism is statistically more frequent in the migrainous group, as in previous epidemiological studies of migraine in the family was similar to controls \((OR=0.8; 95\% CI, 0.3–2.1)\) and lower than in migraine patients \((OR=0.2; 95\% CI, 0.06–0.5)\). The number of relatives with epilepsy was higher than in migraine sufferers or controls \((P<0.001)\).

**Conclusions** In spite of an obvious occurrence of more relatives with migraine on migraine sufferers and a clear family history of epilepsy on epileptic patients, each one of those groups did not emerge as having an increased frequency of the opposite disease in their family. This argues against a common genetic determinant.

### P1-C4

**Migraine and somnambulism: a prospective study**

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Since 1983 (Barabas et al.), somnambulism has been suspected to be more frequent in migraineous patients than in others. To explore this association, we systematically studied a somnambulism history in cephalalgic patients (migraine headache and non-migraine headache). Over 9 months, we included prospectively 75 patients. 48 (64%) were migrainous (73% without manifestation of aura, 23% with visual aura and 5% with another type). 40 (52%) were females. The mean age at the beginning of headaches was 18.4 years. 18 (37%) of these patients had two or more somnambulism occurrences during infancy (between 6.2 and 9.1 years old). The other 27 (37%) patients suffered from tension-type headache, post-traumatic headache (22%), cluster headache (7.4%), neuralgia (3.7%), and other types (especially iatrogenic headache) (29.6%). 14 (52%) were female. Mean age when headaches began was 33.8 years old. 2 of these patients (7.4%) had two or more somnambulism occurrences during infancy (between 7.5 and 9 years old). Our two populations were statistically different because of a female predominance \((83\% \text{ vs } 52\%: P<0.05)\) and a younger mean age \((18.4 \text{ vs } 33.8 \text{ years old})\). The beginning of headaches in the migrainous group, as in previous epidemiological studies of migraine. A history of somnambulism is statistically more frequent in the migrainous group \((37\% \text{ vs } 7.4\%: P<0.05)\).

We detected no difference between somnambulism and the subtype migrainous group, nor with the mean age occurring in either. We excluded the sex difference between migrainous and non-migrainous group as an explanation because there is usually no such a sex predominance in somnambulism. Thus, we suggest that migraine and somnambulism could have the same predispositions factors or identical physiopathological mechanisms.

### P1-C5

**Headache and psychiatric comorbidity in Sao Paulo, Brazil**

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**Background** Headache is one of the most prevalent physical symptoms in the general population. There has been discussion about a possible relationship between psychological factors and headache for a very long time. However, most of studies were performed in hospitals and/or psychiatric clinics.

**Objective** To determine the frequency with which people complain of a ‘lot of problems with’ any kind of headache, and relating this to socio-demographic characteristics and the co-occurrence of psychiatric disorders in a population-based study.

**Methods** A representative sample of the population (3-level: census district, house, person) living in the catchment area of the University of Sao Paulo Medical Center, in Sao Paulo, Brazil, was interviewed using the Brazilian version of the ‘Composite International Diagnostic Interview (CIDI 1.1). Questions were asked regarding the occurrence of ‘a lot of problems with’ headache during the patient’s lifetime and the frequent use of any medication for headache. Answers to these questions permitted us to classify headaches as primary or secondary. Logistic regression analysis was used to examine the association between headache types and psychiatric disorders.

**Results** The lifetime prevalence of ‘a lot of problems with’ headache of any type for the total sample was 37.4%, of which 28.3% were secondary headache and 8.8% primary headache. The odds ratio (OR) for ‘a lot of problems with’ primary headaches was increased for depression as a whole \((OR, 2.1; 95\% CI, 1.3–3.4)\), depressive episodes \((OR, 2.1; 95\% CI, 1.4–3.4)\) and dysthymia \((OR, 3.4; 95\% CI, 1.6–7.4)\); anxiety as a whole \((OR, 3.0; 95\% CI, 1.9–4.7)\); panic disorder \((OR, 1.9; 95\% CI, 0.9–3.9)\) and generalized anxiety disorder (GAD) \((OR, 4.3; 95\% CI, 2.1–8.6)\). For a ‘lot of problems with’ secondary headaches, the risk of psychiatric comorbidity was not increased except for dysthymia \((OR, 2.2; 95\% CI, 1.1–4.3)\) and GAD \((OR, 3.2; 95\% CI, 1.5–6.9)\).

**Conclusions** These data show that headache and psychiatric comorbidity are very common in a Brazilian population sample of adults living in a large city. These conditions are especially associated with chronic anxiety and depression disorders.

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Alexithymia in migraine: aminergic tone correlates
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Objectives Alexithymia is a personality trait characterized by difficulty in verbal expression of emotions. This temperament is associated with chronic somatoform pain and essential hypertension and a high sympathetic arousal. Psychosomatic disorder with information-processing dysfunction probably linked to high noradrenergic activity has also been hypothesized in migraine pathophysiology (Gerber and Schoenen, 1998). The aim of our study was to investigate the relationships between migraine, alexithymia, and the aminergic neurotransmitter systems by means of the Tri-dimensional Personality Questionnaire (TPQ) (Cloninger, 1987).

Materials and methods We selected migraine patients first-attending our headache clinic according to the IHS criteria (1988). We excluded patients with psychiatric disorders or under migraine prophylactic treatment during the last three months prior to enrolment. A healthy control group was also recruited among patients relatives. All subjects studied submitted to the following psychometric tests: Rome Depression Inventory (RDI), Toronto Alexithymia Scale 20 (TAS-20), and TPQ. RDI is a 25-item self-rating scale constructed and validated directly on an Italian population (Pancheri et al. 1987). TPQ is a self-report inventory consisting of 100 true/false items which describes four dimensions of personality: Novelty Seeking (NS: dopaminergic tone), Harm Avoidance (HA: serotonergic tone), Reward Dependence (RD: noradrenergic tone) and Persistence (P: glutaminergic tone). TAS-20 is a self-report 20-item inventory for the evaluation of alexithymic trait (Todarello et al. 1995).

Results We consecutively recruited 66 patients presenting with migraine and 21 healthy controls. Out of 66 migraineurs, 23 patients met criteria for migraine with aura. No significant differences were observed in age, gender and education between patients and controls. By ANOVA, migraine patients showed higher score in RDI (P < 0.0001), the HA dimension (serotonergic tone) of TPQ (P < 0.001), and TAS-20 (P < 0.001) than healthy controls. In addition, a higher occurrence of alexithymic trait was found in migraine patients than healthy controls (P < 0.03). When we considered only migraine patients, we found that alexithymic group presented lower score on RD dimension (high noradrenergic tone) than the group without alexithymia (P < 0.04).

Conclusions These data suggest a role of serotonin in the pathophysiology of migraine and confirm its association with depressive state. The high score in TAS-20 and the low score in RD dimension observed in alexithymic migraine patients might represent a psychometric marker of high noradrenergic tone and might be a useful tool in the choice of migraine prophylactic treatment in this particular group of patients.

Causality of migraine in stroke – does it exist?
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Background Migraine stroke is a controversial entity. Few young stroke registries have addressed this topic systematically with modern neuroinvestigative protocols.

Aim Determine in the young stroke (15–49 years) population, relatively devoid of comorbid neurodegenerative disease the frequency and extent of migraine stroke.

Methods Patients were evaluated in a prospective stroke registry with quantitative stroke scales including neurological deficit, etiological scales, disability scales, migraine International headache classification and migraine stroke according to Welch’s classification. All had confirmatory MRI brain scans.

Results In young stroke patients (n = 349/1316; 26.5%), migraine-associated stroke was detected in 11/349 (3.2%) of alert (n = 307) patients. These included Welch category I (n = 1), category II (n = 5), category III (n = 3) and category IV (n = 2). Partial anterior (n = 8) circulation lesions predominated compared to posterior circulation (n = 3) lesions (P = 0.14). Aetiological assessment revealed comorbidity in all 5 TOAST categories as being a more plausible cause (patent foramen ovale [n = 1], cardiac valvular disease [n = 1], anticardiolipin antibody [n = 1], dissection [n = 1], intracerebral haemorrhage [n = 1], drug induced [n = 2], small and large vessel disease [n = 3] with only 1 patient having no other identifiable cause other than migraine). Atheromatous disease was the most common aetiology of stroke as compared with other aetiologies.

Conclusions (1) Migraine at time of stroke is rare. (2) Migraine was more common with anterior circulation events. (3) Aetiology of competing stroke causation was heterogeneous, typical of young stroke populations with only one patient not classifiable other than with stroke caused by migraine.

Association between migraine and personality changes. A long term study
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Objectives The association between migraine and personality changes is still disputed. In particular, the question is raised whether this association is unidirectional (that is, migraine causing personality changes) or bidirectional. Purpose of this work was to study this issue in a group of patients with migraine with or without aura.

Methods 92 patients consecutively sent (10 men and 82 women) with migraine with aura (n = 16) or migraine without...
aura \( (n=76) \) were enrolled (Time 0). They were given a diary in which they were to record for one month, on a daily basis, occurrence, severity (score 1–5), and duration of the headache episodes. The Italian MMPI and the STAI, X1,2 were administered. The patients were then treated with antimigraine drugs, NSAIDs and antidepressants, as needed, for a period ranging between two and six months. The patients were re-examined six years later (Time 1) and the following tests were administered: MMPI-2, STAI Y1,2, and Beck Depression Inventory. In addition, a structured interview was performed using the SCID 1. If headache was still present, they were given the diary for three months. Twenty-seven patients could not be retrieved, and 2 refused to continue the program, leaving a total of 63 patients (5 men and 58 women) who completed the study. According to the pain parameters at Time 1, the patients were distributed in two groups: Group 1, with pain improvement (at least 50% improvement in at least one pain parameter) and Group 2, with no pain improvement. All data collected at Time 0 and Time 1 were assessed separately for the two groups, and the following issues were investigated: differences between group 1 and 2 in (1) MMPI scores, STAI scores and pain parameters at Time 0 (Student’s \( t \) test); (2) MMPI, STAI, and Beck scores at Time 1 (Student’s \( t \) test); (3) presence of anxiety, depression or other mental disorders as assessed with the SCID 1 at Time 1 (Fisher Exact Test).

Results The following items were found to be lower in Group 1 with respect to Group 2: STAI 1,2 and all MMPI scores at time 0 (significantly for Paranoia); STAI 1,2, all MMPI and Beck scores at Time 1 (all significantly, except Psychopathological Deviation, Schizophrenia and Hypomania). Moreover, Group 1 showed at Time 1 a significantly lower prevalence of major depression or dysthymic disorder. No difference of the pain parameters at Time 0 was found between the two groups.

Conclusions It is concluded that: (1) an association exists between personality changes and migraine, and (2) that this association seems to be bidirectional.

P1-C9

Epilepsy and atypical features in chronic headache

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Introduction There are several characteristics in headaches that should alert physicians to the possibility of an underlying brain lesion. These characteristics are, among others: aura that lasts more than 1 h (prolonged aura), strictly unilateral pain (not changing sides between the attacks), atypical features of the pain and the association of epilepsy or focal signs. It is not known, however, what is the prevalence of these characteristics in chronic idiopathic headache patients.

Objectives To determine the frequency of atypical headache features and epilepsy in a non-selected group of patients with chronic primary headaches.

Methods A prospective study, involving all consecutive patients with chronic headache, attending two headache clinics for the period of one month. A structured interview was conducted concerning: headache characteristics, atypical features, characterization of auras, presence of epilepsy (past and present) and family history of headache and epilepsy. Neurological examination was performed in all patients. The presence of central nervous system lesions was excluded, when suspected, by appropriate imaging studies (CT scan or MRI).

Results There were 71 patients, 50 women and 21 men, all dextrals, with a mean age of 38.5 years (ranging from 11 to 80 years). CT scans were done in 48 patients and cranial MRI in 11. In only two patients was there a brain lesion. One of these patients had a giant arteriovenous malformation (AVM) of the left hemisphere and had epilepsy and attacks of migraine-like headaches with a visual aura. The other one had a small (<3 cm) AVM and atypical strictly unilateral headache. In the primary headache patients, there were a high percentage of atypical headaches, as 33.8% did not fulfill International Headache Society diagnostic criteria. The most frequent headache types were migraine without aura (30.9%), chronic tension-type headache (17.6%), migraine with aura (10.2%), headache due to ergot/analgesic overuse (9.8%) and episodic tension-type headache (7.4%). None of the idiopathic headache patients had prolonged aura, only three had epilepsy (in one of them only during childhood), but a considerable number (22 patients) had strictly unilateral pain, not changing sides between headache attacks. Family headache history was frequent in primary headache (49 patients, 71%) and family epilepsy history was present in 14 patients.

Discussion The results of our study suggest that atypical features of headache and strictly unilateral pain are fairly common in primary headache and are not necessarily associated with brain lesions. On the other hand, the presence of epilepsy or prolonged auras (rare or absent in our population), should alert for the possibility of secondary headache.

P1-C10

Sleep disorders in headache sufferers: a screening of a headache clinic population


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Aim of the study Sleep and headache are known to be related in several ways. This prospective study investigates whether sleep and headache relations exist in known headache sufferers and to what degree possible sleep disorders influence the headache profile.

Patients and methods 650 headache sufferers were seen in the outpatient clinic of our headache centre, during a 1-year period, were interviewed about their headache and were classified according to IHS criteria. A short questionnaire was used and completed by each sufferer to detect possible
sleep disturbances. The sleep parameters recorded were sleep duration, insomnia, initial insomnia, early awakenings, sleepiness, snoring, restless sleep, hypersomnia, and sleep apnea. According to the type of headache, the sufferers were divided into those with: migraine, tension-type headache, cluster headache, chronic daily headache, and other types of headache. Considering sleep disturbances, two groups were distinguished: group A and group B, with and without sleep disorders, respectively. The patients in group A, based on a sleep questionnaire, were classified into three subtypes, according their sleep characteristics. We compared the two groups to a third ‘control’ group consisting of healthy employees of our hospital with similar age and sex profile. Polysomnographs had been done in selected cases.

**Results**
Sleep disorders in general have been recorded in the majority of all sufferers (74%). Sleep duration was shorter than that of the controls. Insomnia was reported in 37%, restless sleep in 53%, and snoring in 58%. Correlation between the different types of headache has shown more frequent sleep disorders in tension-type headache and chronic daily headache.

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**P1-C11**

**Headache symptoms in patients with Alzheimer syndrome**

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**Objectives**
There is often a complaint of headache by patients suffering from Alzheimer Disease (AD). In this study, we retrieved information from the pool of 487 patients followed at the Memory Disorders Outpatient Clinic of the Neurology Department of Athens General Hospital 'G. Gennimatas'.

**Materials and methods**
We present the data of 280 patients with AD, which were studied for the headache symptom. All cases were classified according to the IHS criteria and NINDS criteria for AD. We monitored the frequency, duration and severity of headache in correlation to the patient’s mental state and in relation to the previous headache history.

**Results**
Only 50 patients had history of headache attacks. The frequency and intensity of the attacks decreased as the AD progressed. The majority of the patients had the tension-type headache.

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**P1-C12**

**The prevalence of migraine in multiple sclerosis patients**


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**Objectives**
To determine the lifetime prevalence of migraine in patients with multiple sclerosis (MS). To assess the influence of MS on the frequency of migraine headaches.

**Methods**
We conducted a case-controlled-study enrolling 514 patients with clinical definite MS according to the Poser-criteria. 514 strictly age- and sex-matched subjects without any history of MS or any other neurological disease served as a control group. Subjects had to complete a questionnaire obtaining their headache history using the IHS-criteria. The prevalence was compared using the chi-squared test.

**Results**
The mean age in both groups was 42 (±11) years. 67.5% of the subjects in both groups were female. In the MS group, 14% suffered from primary progressive, 25% from secondary progressive, and 61% from relapsing-remitting MS. Mean duration of MS was 7.8 (±6.8) years. 33 MS patients and 42 controls had to be excluded from analysis because of missing data. 91 out of 481 MS patients (18.9%) fulfilled all IHS-criteria for the diagnosis of migraine vs 115 out of 472 controls (24.4%). The difference was significant (P=0.041). 29.2% of the MS patients with migraine reported that the migraine attacks stopped or became rarer after onset of MS. 27% reported no change in their migraine frequency, and 16.9% experienced migraine attacks more frequently after onset of MS. 5.6% (n=5, 1% of all MS patients) experienced their first migraine attack simultaneously with their first MS symptoms and 20.2% afterwards.

**Conclusions**
This is the first evaluation of lifetime prevalence of migraine in MS using the IHS-criteria. The results do not support previous findings of an increased migraine prevalence in MS patients which has been attributed to MS-related dysfunction of the serotoninergic system or activation of a migraine generator by MS lesions located in the brain stem. In contrast, our data show decreased lifetime prevalence of migraine in MS. Migraine as a presenting symptom of MS has been reported anecdotally, but, according to our data, seems to occur coincidentally in approximately 1% of MS patients. Concomitant MS seems to reduce rather than to intensify a pre-existing migraine.
POSTER SESSION I

D: Patterns of headache treatment

P1-D1
Treatment options in migraine: the patients' view
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Objectives To evaluate the experience with various treatment options and the assessment of these options in migraineurs and migraine-free controls.

Patients and methods Sixty-six consecutive patients suffering from migraine with and/or without aura and 45 migraine-free controls completed a semi-structured interview covering demographic data, headache characteristics and a total of 18 treatment options including OTC analgesics, prescription medication, household remedies, relaxation training, psychotherapy, acupuncture, homeopathy, sleeping, resting, taking a day off, diet, changes in lifestyle, physical activity and others. We asked all subjects to rate the efficacy of each treatment, and we differentiated between patients with and without experience with a certain treatment. All interviews were performed by one and the same person (JH) either personally or by telephone. For statistical analysis, SPSS-WIN 10.0 was used.

Results Patients and controls were comparable regarding age, sex, educational level and profession. Based on their own experience, migraine patients rated a day off (mean: 1.2, SD: 0.6; best = 1.0, worst = 3.0), rest (1.3, 0.7), prescription medication (1.5, 0.7) and modification of lifestyle (1.5, 0.8) best effective and diet (2.9, 0.3), unconventional treatments (2.6, 0.7), homeopathy (2.4, 0.8) and well-balanced nutrition (2.4, 0.8) least effective. Almost all treatment options were rated somewhat less effective by migraine patients compared to controls. The difference was statistically significant in OTC analgesics (P = 0.02) and homeopathy (P = 0.04). Compared to the patients experienced with a certain treatment, those without experience overestimated the efficacy statistically significant in 13 of 18 treatment options, and this overestimation was most marked (P < 0.001) in household remedies, other unconventional treatments, homeopathy, relaxation training, acupuncture and well-balanced nutrition. Interestingly, the efficacy of rest, sleep and a day off was rated similarly by patients with and without experience with these strategies.

Conclusions Migraine patients experience a day off, the opportunity to rest, prescription medication and changes in lifestyle as most helpful in coping with migraine, whereas they assess diet and unconventional therapies as least effective. Most treatment strategies tend to be rated less effective by migraineurs compared to controls, but this trend reaches statistical significance in OTC analgesics and homeopathy only. Patients inexperienced with a certain treatment usually overestimate its efficacy. This is particularly true for some popular non-pharmacological treatments.

P1-D2
Our own headaches: our own words
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Paediatric headache specialists commonly hold that both the severity of the problem and the suffering of the children with headache are underestimated, leading to delays in diagnosis and treatment. In an effort to go beyond textbook descriptions and focus on quality of life issues we have asked our patients for some perceptions, experiences and opinions so we might get an idea of their headaches, burdens and treatments in their own words. Each child attending our clinic with a complaint of headache was offered a chance to participate in the study. A parent or guardian gave written consent. No identifying data but age, sex, duration of headache disorder or diagnosis was recorded. Children were allowed to talk about their headaches, prompted by questions as needed or thought necessary. Replies were recorded and transcribed. No analysis of data was attempted. Replies were edited or abridged for clarity. A selection of the collection is presented in the hope that what these children have told us will show other children they are not alone, and perhaps encourage other sufferers to see how headaches may be alike and how they may be different. We hope in reading these words parents will increase their insight into their own child’s headaches and that physicians and other health care providers might learn more about their own patients by reading what these children have to say.

P1-D3
Preliminary results of the internet chat study: what are headache sufferers chatting about?
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Objective Thousands of internet chat rooms about chronic medical conditions exist; individuals can converse in real time with other people similarly diagnosed. No empirical data are available to evaluate the information shared in chat rooms. The current, ongoing study observes and categorizes statements made in chat rooms about various chronic medical conditions. Preliminary data regarding headache chat room activity are presented.
Materials and methods  A system designed to classify chat room statements was piloted. The final version includes four main categories (i.e. Disorder, Health Care Providers/Insurance, Treatment, and Unrelated) and several subcategories, rendering 33 possible rating categories. A training criterion of 100% agreement for the 4 main categories and 80% inter-rater agreement for the 33 subcategories was established. Only chat rooms having at least 3 chatters are rated. The rater enters an active chat room, does not interact, and instead reads each chat room statement aloud into an audiotape recorder. Upon completion of the chat session, the rater exits the chat room, the audiotape is played, and each statement is rated.

Results  Headache chat rooms have not been as active as other disorder-specific chat rooms (e.g. fibromyalgia, multiple sclerosis, etc.). The current results summarize 271 actual chat time minutes in headache-specific chat rooms (1344 ratings). Only one-third of the statements were headache-related. The majority (70%) of the headache-related statements involved self-disclosure about symptoms (48%) or treatments (52%). The overall ‘tone’ of the rooms was neutral; very few statements were classified as having a negative (<1%) or positive (4%) valence. Information-seeking was infrequent, as only 6% of the statements requested information from other headache sufferers. Likewise, advisement about headache management was rarely observed (6%), and of the 26 advisement statements, only 2 provided inaccurate information.

Conclusions  The preliminary data suggest that headache chat rooms are not as active as other chat rooms focused on chronic medical conditions. When active, many of the discussions were unrelated to headaches; self-disclosure of headache symptoms and treatments were the primary topics of headache-related discussions. The overall ‘tone’ of the chats was neutral. Advisement was rare, but when offered, it was generally accurate. Thus, the data do not support general perceptions that headache-specific chat rooms may be detrimental to headache sufferers or serve no useful purpose.

Data collection is ongoing, but initial results suggest that headache chat rooms may be a useful source of information if one can find an active chat.

P1-D4

Educating the headache patient: an integral therapeutic handling

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Objectives  To present ways of educating the headache patient to achieve better results in headache management.

Material and methods  This investigation consists of the clinical observation and the objective evaluation of the advancement of the therapeutics in 100 patients during one year from their first visit, onwards. (a) Medical history (including headache history, psychological questionnaire and physical and neurological exploration); (b) listen to what the patient says about his headaches; (c) explain what type of headache he has and what he can expect from his doctor. Explain what happens during a headache; (d) teach the patient about tolerance and addiction to medication. What is rebound headache; (e) explain what are prophylactic and abortive medications; (f) teach the patient the best way to take his pain medication, the importance of timing, and having them at hand; (g) the importance of managing stress and different ways to do it: biofeedback technique, suggestions on how to handle stress, exercises to relax the muscles of the neck; (h) explain why exercise is important and give the patient a personal exercise routine; (i) find out if psychotherapy is needed, refer; (j) teach the patient how to use a headache diary where he can measure: recurrence, intensity, frequency, duration, and relation with triggers; (k) teach the patient what kind of headache triggers there are, how to recognize them and, once recognized, to avoid them; (l) the patient signs an agreement committing himself to comply with all indications and he must know that the document is morally binding; and (m) the patient is shown an ‘Honour Roll’ in which the names of the patients who have improved are recorded. Motivate and encourage the patient to achieve that goal.

Results  Patients, who besides taking the medications were educated about their headache, reported an improvement, sometimes remarkable, but in general terms fast and lasting.

Conclusions  (1) Educating the patient about his ailment and how he can help himself accelerates his recovery. (2) Knowledge will give the patient control over his headaches. (3) Once the patient feels control, he will stop fearing his next attack because he knows what to do. (4) The most important facts the patient needs to learn are: (a) A headache is a disease and not something he made up or he is provoking on purpose (he is not to blame); (b) How and when to use his pain medications: timing and quantity; (c) Dangers of medication abuse; (d) Becoming conscious about his headache triggers, recognizing and avoiding them; and (e) The fact that there are many things he can do besides taking medication, this gives him responsibility for his improvement. (5) Surprisingly, the ‘Honour Roll’ is powerful, and encourages patients to follow indications. (6) By educating the patient we achieve faster, more effective and lasting results to relief headache, improving significantly the quality of life of the patient.

P1-D5

Academic headache practice in the USA: membership survey of the American Headache Society

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It is not known what constitutes the typical experience of an academic headache specialist in the USA. The majority of the membership of the American Headache Society (AHS) practices headache medicine in the private sector. We therefore undertook a survey of academic headache
specialists in the AHS. 181 surveys including questions about academic rank, departmental and institutional affiliation and time distribution were sent to members drawn from the 1999–2000 Membership Directory of the AHS whose primary address was a recognized academic institution or who, by reputation, had extensive academic affiliation. Additional questions about headache teaching, research and practice were included. 72 (39.7%) of the surveys were returned. 49 (40%) of the 122 US medical schools were represented. The most prevalent academic ranking was Professor (38%). Included were 2 departmental chairs, 1 division chief, a Vice Dean and one residency training director. 70.8% were neurologists. 72% spent at least 50% of their time in clinic. 79% spent 25% or less of their time on research. As well, 78% spent 25% or less of their time teaching. Institutionally, it appears that teaching occurs throughout the graduate and postgraduate years, though 19.7% (12/61) recorded no medical school lecture at their institution. Additional data on average practice (i.e. new and follow-up patient numbers and times/patient) will be presented. This preliminary survey offers the first study of academic headache specialists in the US academic medical system. Suggestions for future studies are discussed.

P1-D6

Acute migraine treatment: patterns of use in a clinical population
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Objectives To describe the pattern and efficacy of current treatment of acute medication use in patients with episodic migraine.

Methods Patients 18 years or older who met the International Headache Society criteria for episodic migraine and had treated a headache in the past month with medication. Excluded were those whose headaches duration was >3 days with treatment and had more than 14 headache days a month.

Results We identified 109 migraineurs from ages 19–69 (average 43.6); 81.6% were women and 93.6% were white. The average migraine frequency was 3.9 attacks per month (range: 4/year to 12/month). Pain was rated as severe (64.2%), moderate (33%), or mild (2.8%). Most (74.2%) patients were under our care; 70.6% were on migraine prophylactic medication. Patients waited an average of 1.6 h + 2.4 h before initiating medical treatment (range: 1 min–18 h). Among 109 subjects 56.9% retreated in 4.2 h + 4.2 h (median time 3 h; range 20 min–24 h); 51.7% used the same medication. Among those that used a different remedication, 50% used a triptan as the second drug. Following the second treatment 54.8% were headache free within an average of 2.7 h. A third treatment was needed for 28.4%; 67.7% of these patients became headache free in an average of 4.8 hours after taking the third medication.

Conclusions Patients wait an average of 1.6 h + 2.4 h before initiating treatment. Initial treatment with a triptan is more effective than with other medications (2 h headache free at 2 h headache recurrence).

P1-D7

Acute migraine treatment: factors affecting therapeutic decision making
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Background Epidemiological studies have shown that migraine is under recognized as a chronic debilitating neurological disorder. Even among migraine sufferers who present to physicians, barriers to care remain.

Objectives To evaluate physician perception and prescribing patterns of acute migraine agents.

Methods In 1999, 439 physicians who prescribed triptans were recruited by mail and agreed to participate in a telephone survey on therapeutic decision making in migraine. Physicians were asked to select medical records from 5 migraine patients for chart review and to respond to in-depth questions on each patient using information from the chart. Each physician selected one patient who was currently on one of 4 available oral triptans (in the US) and one patient who was on a non-triptan acute prescription medication. Chart review questions included socio-demographic data, headache characteristics and current and prior treatment patterns.

Results 439 physicians (272 primary care physicians [PCPs], 167 neurologists) completed the survey within 6 weeks generating 2158 patient reports for analysis. Sixty-one physicians were interviewed for the qualitative phase of the study. Physicians ranked the importance of 12 different attributes of acute migraine treatment by allocating a total of

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial treatment</th>
<th>Headache free at 2 h</th>
<th>Headache recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triptan</td>
<td>35.8%</td>
<td>51.3%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>13.8%</td>
<td>20.0%</td>
<td>66.7%</td>
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<tr>
<td>acetaminophen</td>
<td></td>
<td></td>
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<tr>
<td>and caffeine</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NSAID</td>
<td>26.6%</td>
<td>13.8%</td>
<td>12.5%</td>
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<td>Ergot</td>
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<td>Barbiturate</td>
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<td></td>
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<tr>
<td>and/or narcotic</td>
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</tbody>
</table>

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Changes in pattern of first intention analgesic use in a group of Spanish headache patients

M. J. Monzon, J. M. Lainez, J. Parra & C. Peiro

Objectives Acute treatment recommendations for primary headache have changed in recent years. There has been a campaign to prevent analgesic overuse and to introduce new patterns of treatment, such as avoiding combinations of multiple analgesics and narcotics, and the use of different triptans. We have analysed the pattern of analgesic use in a group of headache patients that came for the first time to the neurologist. We have examined the first intention analgesic group of headache patients that are most likely to benefit from seeing a neurologist, and whose referrals therefore should be accepted.

Materials and methods Primary headache patients first time attending a consultation in Neurology received a diary that recalled detailed data about the clinical characteristics of their headache and the treatment of every attack. Patients continued with their previous analgesic treatments and completed the questionnaire for every treated attack during a month and before returning for a consultation.

Results 80 consecutive patients (68 women and 12 men) were included in the follow up. The mean age at first observation was 39 years. 24 patients (30%) suffered from chronic daily headaches and 56 had migraine and/or episodic tension-type headache. 57% of the patients used NSAIDs, 36% paracetamol or aspirin (associated with caffeine and/or codeine in 40% of the cases), 14% used triptans and 7% ergots. We compared these results with the pattern of analgesic use in the group analysed 5 years before. We found an increase in the use of NSAIDs, a decrease in consumption of ergots and combinations of different analgesics, and the beginning of the use of triptans to treat migraine before the neurological intervention.

Conclusions We found a change in the pattern of analgesic use between the two analyses. Even though, NSAIDs and ‘over-the-counter’ analgesics (paracetamol and aspirin) continued to be the treatment most commonly used, and paracetamol and aspirin were still used in many cases in combination with caffeine or codeine. However, in accordance with recent recommendations, there had been a decrease in ergots use and combinations of analgesics and the introduction of triptans in first intention treatment of primary headache patients. These changes may be a result of a general informative campaign about headache treatments that had been made in Spain in the last few years, and better knowledge by primary care physicians concerning headache and its treatment.

P1-D9

Do headache patients benefit from a referral to a neurological centre?

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Objectives Most patients with headache never see a doctor for their symptoms. Even fewer are referred for a specialist evaluation. Specialized health care is not able to accommodate the needs of the vast number of patients suffering from headache. It is consequently important to identify the headache patients that are most likely to benefit from seeing a neurologist, and whose referrals therefore should be accepted.

Materials and methods Nordland, Troms and Finnmark constitute the Arctic region of North Norway. There are three neurological centers in this region, rendering service for a population of about half a million people. We mailed a questionnaire to all patients with a major diagnosis of headache referred for a neurologist at these centres during a 2-year period, asking for features of their headache disorder, whether they were satisfied with the consultation, potential reasons for dissatisfaction, and what kind of measure that was taken by the specialist. We wanted to see which groups of patients stated they had a benefit from seeing the specialist, and if recommended measures were approved by the patients.

Results 1403 patients with headache saw a neurologist in these centres during the 2-year period, and received a questionnaire. Of these, 1052 (75%) returned the questionnaire. 927 patients (628 women and 299 men) answered the most relevant questions in sufficient detail to be considered for the topics in question. The mean age of these responders was 40.8 years and the mean duration of headache 12.9 years. 189 of 277 patients (68%) with migraine claimed benefit from the consultation, while this was the case for only 321 of 612
Conclusions

associated with patient satisfaction.

received a new prescription of a triptan, while 11% was

with the consultation. Of 289 patients with migraine, 119

of a specific measure, and 189 of these (47%) were dissatisfied

claimed benefit from the referral. 399 patients had no advice

recommended by the neurologist, and 317 of these (66%)

some kind of measure (physiotherapy, drug, sick leave)

outcome of the specialist referral. 481 patients had

patients with tension-type headache (57%) was dissatisfied

ence). (38 patients did not answer this question.) A majority of

IHS criteria claim significantly more benefit from a specialist

Lariboisière Hospital, Paris, France. The population was

opened on 9/12/2000 in the Emergency Department of

Results

following data: sex, age and final diagnosis at discharge.

From 9/12/2000 to 12/12/2000 were reviewed for the

Patients and methods

computer records were reviewed to document triptan costs

Patients referred to the clinic first participated in group

Methods

A disease management approach to headache is
described. In addition to physician referrals, headache

Patients and methods

The files of all patients who were seen

from 9/12/2000 to 12/12/2000 were reviewed for the

results. A total of 3799 patients were seen during the

months, including a majority of females (72.6%). The

mean age was 36.9 years, and only 17% of the patients

were aged above 50. Primary headaches were diagnosed in

3299 cases (86.3%), secondary headaches in 244 (6.4%),
cranial neuralgias in 38 (1%) and no precise diagnosis could

be made on a emergency basis in 218 patients (5.7%).

There was a trend over the 3 months towards a decrease in

primary and an increase in secondary headaches. Attacks of

migraine accounted for 60.9% of cases, mostly in females

(85%). Episodic or chronic tension-type headache accounted

for 20.6% of cases. A total of 190 patients (5%) came for cluster

headache, mostly not previously diagnosed. Sinusitis was the

most frequent cause of secondary headache (66 patients,

1.7%), followed by post-traumatic headache (58 patients,

1.5%) and CSF hypotension (24 patients, 0.6%). Vascular

disorders were detected in only 20 patients (0.5%), including

subarachnoid haemorrhage (7), dissection of cervical arteries

(5) and cerebral venous thrombosis (2). For the remaining 76

patients with secondary headaches, as many as 20 different

causes were identified. Hospitalisation was necessary for 68

patients.

Discussion

Some interesting features may be discussed. First,

the majority of patients are females aged 21–50 years old,

reflecting the female preponderance in migraine. Second, the

high frequency of cluster headache was totally unexpected,
suggesting that cluster headache may be more frequent than

usually thought. Finally, serious vascular conditions such as
cervical artery dissection or cerebral venous thrombosis were

rare but often misleading, presenting only with headache and

without the other classical signs of these conditions. Recent

and new headaches should always prompt neuroimaging,

CSF studies and/or cervical duplex scanning and transcranial

Doppler before considering a primary headache.

The first 3 months of the Lariboisiere Emergency

Headache Center: a series of 3799 patients

A. Ducros1, M. El Amrani1, L. Ben Slamia1, C. Roos1, R. Djomby1, V. Domigo1, L. Morin1, V. Besançon1, M. G. Bousser2 & D. Valade1

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Background

An emergency headache center (EHC) was

opened on 9/12/2000 in the Emergency Department of

Lariboisière Hospital, Paris, France. The population was

informed by various media that the EHC would be open 24 h

for adults suffering an acute recent headache.

Objectives

To describe the main characteristics of all patients

seen in the EHC during the first 3 months.

Patients and methods

The files of all patients who were seen from

9/12/2000 to 12/12/2000 were reviewed for the

following data: sex, age and final diagnosis at discharge.

Results

A total of 3799 patients were seen during the

3 months, including a majority of females (72.6%). The

mean age was 36.9 years, and only 17% of the patients

were aged above 50. Primary headaches were diagnosed in

3299 cases (86.3%), secondary headaches in 244 (6.4%),
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cervical artery dissection or cerebral venous thrombosis were

rare but often misleading, presenting only with headache and

without the other classical signs of these conditions. Recent

and new headaches should always prompt neuroimaging,

CSF studies and/or cervical duplex scanning and transcranial

Doppler before considering a primary headache.

Impact of a comprehensive model of syndrome

management of headache

M. Maizels1, V. Saenz1 & J. Wirjo2

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Objectives

Migraine and drug rebound headache remain

widely underdiagnosed and undertreated. Application of

principles of disease management may improve the care of

patients with these chronic diseases.

Methods

A disease management approach to headache is
described. In addition to physician referrals, headache

patients were identified from emergency department records.

Patients referred to the clinic first participated in group

education, and later had individual consultation. Charts and

computer records were reviewed to document triptan costs

and headache-related visits for 6 months before and after the

clinic visit. A Brief Headache Screen assessed frequency and

disability of headache.

Results

Over the 13-month study period, 264 patients

attended the group, and 235 had a follow-up consultation.

Triptan costs for 264 patients and chart review for 250 were

available. Six-month triptan costs increased $5422 (19%) from

a baseline of $28 897. Increased costs for 46 new triptan users

($10 509) were balanced by savings of $5653 for 24 high

utilizers; 136 (52%) patients did not receive any triptan

prescription. Headache-related emergency department visits

were reduced by 120/239 (50%), (estimated savings $12 000).

Reduced frequency of severe headache was reported in 62/72

(86%) patients who initially had severe headaches more than

2 days/week. Patients identified by emergency department

screening accounted for 57/250 (23%) of the study group,

36% of the triptan costs, and 47% of the visits, at intake.

Conclusions

A disease management approach to a headache

population resulted in significant improvement in clinical

outcomes, with small increase in pharmacy costs balanced

by reduced clinic visits. Triptans were not prescribed for

52% of the group. Triptan costs, clinic visits, and severe

headache frequency were most improved in patients with the

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highest severity of each element at intake, but reductions in triptan costs and clinic visits occurred at the expense of one another. Emergency department headache patients had disproportionately high triptan costs and headache-related visits. Disease management offers an effective approach to the headache population, with little financial impact on a managed care organization.

PI-D12
Effective management of primary headache disorders through a group model of care
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Objectives To evaluate a group model of care for primary headache disorders by assessing patient responses, measured by quality of life surveys, subjective improvement, and use of narcotics and triptans. To assess primary care provider (PCP) satisfaction with the headache management program. To implement individualized headache guidelines to better manage headaches and reduce excessive narcotic use.

Background Primary provider visits are time restricted, prohibiting adequate headache evaluation and management. Alternative means of delivering care to a large volume of headache patients, in a cost-effective manner and with high levels of patient and physician satisfaction, need to be developed. The group model offers an educational forum that empowers patients to participate in the management of their headaches. The model creates a treatment plan for each individual patient that allows for long-term follow up in primary care. The model addresses rebound issues with decreased narcotic use and appropriate triptan prescribing.

Design and methods This was a prospective cohort study with defined outcome measures. PCP referrals are seen in a group model consisting of a headache class taught by a neurologist with a subsequent nurse practitioner (NP) consultation followed by a two month return visit. The NP optimizes headache treatment for each patient utilizing existing headache guidelines and in consultation with the neurologist. Thereafter, the PCP manages the patient. Outcome measures are by means of patient and PCP surveys. The Migraine Specific Questionnaire (MSQ) and the SF 36 and patient subjective improvement questionnaires are collected at baseline, at return visits and at 6 months after entry into the program. In addition, 161 patients’ narcotic and triptan use was compared 6 months pre-enrolment to 6 months post-treatment.

Results The first 213 patients who completed the program were analysed. The MSQ and SF 36 results show significant improvement at 2 months and 6 months compared to baseline measurements. At 2 months, patient improvement surveys showed 91% subjectively improved. Eighty PCPs whose patients have been treated in the program showed high levels of satisfaction. In the 161 patients whose narcotic/triptan use was assessed, narcotic use decreased by a statistically significant 26%. Triptan use increased, but not significantly.

Conclusions This data supports the concept that a group model of care with a headache specialist NP is a cost-effective method in providing care to patients with primary headache disorder. Headache guidelines are implemented with high levels of patient and PCP satisfaction. The model also facilitates a reduction in patient narcotic use and more appropriate triptan use.

PI-D13
Comprehensive headache management: preliminary outcome data from an intensive outpatient protocol
T. Tucker¹, M. Kavin¹ & J. W. Janata²
¹Neurology, University Hospitals of Cleveland and Case Western Reserve University School of Medicine, Cleveland, OH, USA, ²Psychiatry, University Hospitals of Cleveland and Case Western Reserve University School of Medicine, Cleveland, OH, USA

Management of complex, treatment-refractory headache remains a challenge for practitioners. In this paper we present preliminary outcome results of patients treated in an intensive, multidisciplinary outpatient protocol. Subject selection criteria included diagnosis of migraine or mixed headache and failure of more conservative neurological and psychological outpatient treatment. Exclusion criteria included physical limitations that would interfere with physical therapy and conditioning, and psychological diagnoses (e.g. moderate to severe major affective disorder, psychosis) that would preclude effective patient utilization of self-management strategies. Subjects were patients admitted serially to the programme. The treatment protocol consisted of an initial neurological and psychological evaluation to establish diagnoses and ensure patient appropriateness for participation. Patients were enrolled in a half-day programme weekly for four consecutive weeks, designed to minimize interference with work and family obligations. Treatment included: appointments with a neurologist to optimize medications to best suit patient needs, psychology sessions to provide pain self-management training, meetings with an RN to provide education regarding medications and nutrition, and physical and occupational therapy for strength, stamina and endurance training, and for ergonomic workstation evaluation. Pre and post-treatment outcome measures include headache frequency, rated intensity, medication utilization, SF-36 quality of life scores, Beck Depression Inventory scores, Pain Impact Questionnaire score, McGill Pain Inventory scores and patient satisfaction ratings. Results are interpreted conservatively, given the preliminary nature of the data, and directions for future research are delineated.
P1-D14
The relationship of headache attributions, medication adherence, and outcome among migraine headache patients
1Psychiatry, University of Michigan, Ann Arbor, MI, USA, 2Swedish Headache Center, Swedish Neurosciences Institute, Seattle, WA, USA, 3Psychology, Wayne State University, Detroit, MI, USA, 4Neurology, Henry Ford Hospital, Detroit, MI, USA, 5Psychiatry, Henry Ford Hospital, Detroit, MI, USA
Migraine headache is a problem that afflicts a large proportion of people each year. Although effective treatments exist, problems with treatment adherence appear to be a major cause of increased morbidity and treatment failure. This prospective study investigated the determinants of medication adherence and the relationship between medication adherence and headache frequency experienced 3 months after an initial medical evaluation. Patients were 90 migraine headache sufferers (82% female, mean age of 40, and mean education of 14 years) who were new referrals to a neurology headache specialty clinic. Baseline measures were analysed for their ability to predict medication non-adherence and headache frequency at 3 months, and medication adherence was assessed for its ability to predict outcome. Medication adherence ratings were determined by the investigator following an extensive interview regarding adherence behaviour during the 3-month follow-up period. Investigator ratings consisted of a composite of medication usage and were made on a scale from 0 to 7, with a mean rating of 4.61; and 71.1% of patients earning ratings in the adherent range. Analyses were controlled for age, gender, and education. Poorer medication adherence was significantly predicted by the patient’s rating that they believed biological factors caused their headaches at follow-up (r = 0.24, P < 0.05). Head pain frequency was assessed by self-report of the number of days patients experienced headaches during the 3-month periods. Overall, patients reported a significant reduction in pain frequency at 3-month follow-up (mean headaches = 21) compared to pain frequency during the 3 months prior to the initiation of treatment (mean headaches = 33), t (89) = 3.64, P < 0.001. Finally, medication adherence was significantly correlated with pain frequency during the 3-month follow-up period (r = −0.27, P < 0.01). This cross-sectional study provides information regarding medication adherence and outcome behaviours of migraine headache patients in a natural setting and suggests that patients with biological attributions for headaches are less adherent to medication regimens, and less adherent patients have more frequent headaches than adherent patients. Thus, adherence may serve as a mechanism linking baseline psychological beliefs with outcome. Investigation of a patient’s headache attributions may help headache clinics identify potential non-adherent patients upon entry into their programmes.

Acknowledgement IHC 2001 Travel Award. Supported through an unrestricted educational grant from Ortho-McNeil Pharmaceutical, Inc.

P1-D15
Survey on the use of complementary and alternative medicine among patients with headache syndromes
S. von Peter, W. Ting, J. S. Scriver, D. J. Obre, H. Okvat, E. Korkin, M. Gross, M. Oz & C. Balmaceda
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Background and methods To determine the knowledge, prevalence, perceived effectiveness and expectations in relation to the use of complementary and alternative medicine in patients with headache. Seventy-three patients with headache syndromes attending a head and neck pain clinic were interviewed using a standardized questionnaire.

Results Alternative medicine therapies were used by 85% of the patients for the relief of their head pain. In 60%, the therapies were perceived to have a benefit. All of the patients were familiar with one or more of the presented alternative treatments. Eighty-eight percent believed in at least one of the complementary treatments as a beneficial remedy for their headache condition.

Conclusion The exposure to and interest in complementary and alternative treatments is common among patients with headache syndromes, despite the lack of scientific evidence of benefit and assessment of risk for many of the treatments. Neurologists and general physicians should be aware of the increasing role of alternative medicine in the health care system. There is still the urgent need for objective, integrative and critical research with regard to complementary and alternative medicine in headache and other pain disorders.

P1-D16
Demographic, nosological and therapeutic characteristics in a headache outpatient clinic
Headache Center, University Hospital Zurich, Zurich, Switzerland

Introduction The Headache and Pain Clinic (HPC) in the Neurology Department, Zurich University Hospital, is a service for management of difficult headache. Since 1966, a main intention was to elevate thresholds for headache and migraine. For a study of the HPC population after 30 years, we selected the patients with migraine, tension type headache and combinations of both whose files had been started in 1966, 1997 and 1998 (n = 1625).

Main results We found an overrepresentation of women: 71.8%, 7% of all patients were aged 4–19 years, 48% 20–39 years, 41% 40–64 years, 3.6% 65–79 years, and 0.4%
80–86 years. 21.9% of all patients had primary education, 64.1% apprenticeship/trade school, and 9% tertiary education (5.1% unknown). Patients with migraine: 767, 47.2% (77.8% women); tension type headache: 326, 20.1% (51.8% women); both combined: 532, 32.7% (75.2% women). 57% of our migraines had been referred as migraine, 6% as tension type headache with or without migraine, and 36% as ‘headache’. 79% of our tension type headaches had been referred as ‘headache’, 17% as tension type headache with or without migraine, and 4% as migraine. Migraine: 28% reported less than 4 headache days per month (5% in tension type). Tension type: 61% reported daily headache (9.3% in migraine). 19.5% of the migraine patients had a loss of work/school days up to 1 month per year (6.1% in tension type). 83.4% of tension type patients had no loss of work/school days (57.8% in migraine patients).

Conclusions The considerable differences between diagnoses of referring physicians and HPC diagnoses imply there is still quite an important information deficit. Differences of drug treatment on referral and HPC treatment have been studied separately and will be included in the present discussion. The major differences between our data and standard epidemiological results as well as data from the general Swiss population will be discussed.

P1-D17

How well do primary care physicians know the guidelines for the diagnosis and management of migraine?

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Objectives Guidelines for the diagnosis and management of migraine were published in 1997 by the Canadian Headache Society. The paper examines Canadian primary care physicians’ awareness and knowledge of these guidelines.

Materials and methods Telephone interviews were conducted November 2000 with 100 Canadian GPs and family medicine physicians who see more than 100 patients a week and treat patients for migraine.

Results 62% were aware of the guidelines. Just 16% said they were very or extremely familiar with them. The guidelines’ recommendations for treatment of acute attacks vary according to the severity of the attack. A test of knowledge of the acute treatment guidelines was administered to those aware of them. They were read a list of classes of medications and asked ‘...[is drug class] recommended in the Canadian migraine treatment guidelines for the acute treatment of [mild/moderate/severe & ultra-severe] migraine attacks?’ The number of correct answers was tabulated. Expressed as test scores, just 9% of these physicians obtained an ‘A’ or score of 80% or more. An additional 14% achieved a ‘B’ (70–79%), 17% obtained a ‘C’ (60–69%), 12% received a ‘D’ (50–59%) and 48% either scored <50% or were unaware of the guidelines. The guidelines for moderate and severe attacks were least likely to be correctly understood. A common error was the belief that the guidelines indicate severe attacks should be treated with medications containing a combination of codeine, ASA or acetaminophen, and caffeine with or without a barbiturate. Other common misunderstandings include the beliefs that NSAIDS and ergotamine-containing compounds are recommended for severe attacks. For moderate attacks, the most common misperception is that the guidelines recommend the use of ASA or acetaminophen alone. Of those aware of the guidelines (n=62), 77% had read the CMAJ guideline article, 61% had read a summary, 52% had taken CME mentioning the guidelines and 34% had discussed them with a neurologist. Those who were exposed to 2 or more sources had better average test scores than did those who learned of the guidelines from only one source.

Conclusions There is a moderate level of awareness of the guidelines, but few physicians correctly understand all of the types of medications that are and are not recommended for acute attacks. These data suggest there needs to be greater effort put into promoting awareness and understanding of the guidelines, and that repeated exposure is needed to create a greater depth of knowledge.
P1-E1
The MIDAS perception study: MIDAS grade, use of health care and treatment needs
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1John Hopkins School of Public Health, Baltimore, MD, USA,
2Innovative Medical Research, Stamford, CT, USA

Objective MIDAS is a 7-item, self-administered questionnaire, co-developed with AstraZeneca, that is used to measure and grade headache-related disability (i.e. Grades I-IV). There is growing evidence that individuals in Grades III and IV have significant and unmet need for medical care, whereas, those with Grade I or II headaches have a lower need for care. In a population-based study, we examined whether individuals in lower MIDAS grades differed substantially in their ‘use of care’ and ‘satisfaction with treatments’ when compared to those in Grades III and IV.

Method A total of 2174 adults participated in a telephone survey using a quota sampling procedure to ensure representative sampling of the US population. The baseline interview was used to collect data on headache frequency and symptoms, together with information on the use of, and satisfaction with, medications and healthcare services. A sub-sample of the survey participants (n = 471) were invited to participate in the Perceptions Survey, in which they received a copy of the MIDAS Questionnaire by mail, followed by a telephone interview (n = 421; 168 without and 253 with migraine). Subjects were then interviewed regarding their healthcare use and treatment needs.

Conclusion In general, MIDAS grade I and II individuals exhibit a low use of medical care for headache. Most use OTCs, and most achieve relief, either often or always. In contrast, a substantial proportion of MIDAS grade III & IV individuals seek specialty care for headache and suffer recurrence more frequently. The grade IV individuals, in particular, tend to use prescription medications and do not achieve high levels of satisfaction with treatments. These results support the hypothesis that the higher MIDAS grades have significant and unmet needs for medical care.

Results See Table at foot of page.

Table for abstract P1-E1

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<th>Grade II (n = 62)</th>
<th>Grade III (n = 64)</th>
<th>Grade IV (n = 57)</th>
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<td>Saw a doctor in the last year for headache</td>
<td>7.6%</td>
<td>30.6%</td>
<td>31.2%</td>
<td>42.1%</td>
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<td>Saw a doctor more than once in the last year</td>
<td>3.0%</td>
<td>16%</td>
<td>23%</td>
<td>30%</td>
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<td>Use of specialty care</td>
<td>1.7%</td>
<td>3.2%</td>
<td>9.4%</td>
<td>10.5%</td>
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<td>Only use OTC meds or no meds at all to treat headache (use 1st and 2nd)*</td>
<td>87.6%</td>
<td>67.3%</td>
<td>51.7%</td>
<td>46.2%</td>
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<tr>
<td>Use prescription medication only (used 1st and 2nd)*%</td>
<td>4.3%</td>
<td>8.6%</td>
<td>10.3%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Satisfied with treatment*: extremely satisfied/somewhat satisfied</td>
<td>43.9%/45.2%</td>
<td>22.0%/49.2%</td>
<td>27.9%/41.0%</td>
<td>9.1%/60.0%</td>
</tr>
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<td>Dissatisfied with treatment: extremely satisfied/somewhat satisfied</td>
<td>2.6%/1.7%</td>
<td>13.6%/3.4%</td>
<td>18.0%/1.6%</td>
<td>16.4%/7.3%</td>
</tr>
<tr>
<td>Always or often got relief from first medication*</td>
<td>79.6%</td>
<td>50.0%</td>
<td>54.4%</td>
<td>32%</td>
</tr>
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<td>Recurrence often or always*</td>
<td>5.3%</td>
<td>15.4%</td>
<td>25.0%</td>
<td>26.7%</td>
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</tbody>
</table>

*Overall chi-squared analysis for variables p. Note: One patient failed correctly to complete the MIDAS Questionnaire and therefore, this MIDAS score was omitted from the analysis.

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understand, and also to assess the patients’ perception of its utility. **Results** 421 subjects successfully completed The Perception Study: 168 met the IHS criteria for migraine and 253 had other types of headaches. MIDAS grade I subjects reported less frequent headaches ($P<0.0001$), with shorter duration ($P=0.04$), which were predominantly mild in severity ($P<0.0001$). Individuals with a higher MIDAS grade (III, IV) reported more frequent headaches, lasting 3–72 h or longer. Of the 237 MIDAS grade I subjects, 8.4% had more than 6 headaches/year with severe pain intensity (grade II 33.9%, III 45.3%, and IV 57.9%). Specific headache characteristics significantly differed among MIDAS grades ($P<0.0001$: i.e. exacerbation, unilateral pain, periorbital pain, pounding/pulsating pain, nausea, photo- and phonophobia). The more common features in MIDAS grade I subjects included unilateral (31%) and pounding/pulsating pain (42%); less common features were nausea (20.2%). Of the MIDAS grade I patients, 90% used over-the-counter medications and 92% were satisfied or very satisfied with their usual acute treatment, with 80% always achieving relief from their medications. **Conclusion** The results indicate that almost all those with a MIDAS grade I have a mild headache condition characterized by infrequent, predominantly mild attacks of short duration. Individuals with MIDAS grade III and IV, on the other hand, tend to suffer from frequent, moderate-to-severe headaches of long duration. The need for medical care and prescription medications among MIDAS grade I patients is usually low. Occasionally, MIDAS grade I patients have infrequent, disabling attacks; MIDAS Question B, which asks about pain intensity, may help doctors identify such cases.

**P1-E3**

**The MIDAS preference study: quality of life and depression**

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**Objective** Population-based studies have shown that migraine and depression are co-morbid and that migraine sufferers have reduced health-related quality of life (HRQoL) that is independent of co-morbid depression. We hypothesized that, as headache-related disability (as assessed by MIDAS, a 7-item questionnaire, co-developed with AstraZeneca) increased, HRQoL (assessed by the SF-12 scale) would decline, and co-morbid depression (assessed by the Center for Epidemiologic Studies of Depression [CES-D] scale) would become increasingly common. **Method** Study participants ($n=1763$) were identified from a nationwide telephone survey that collected data on headache frequency and symptoms, in addition to medication and healthcare use. The SF-12 was administered at the end of the telephone interview. A follow-up questionnaire (i.e., MIDAS, CES-D) was mailed to selected participants. The study sample included individuals with ($n=168$) and without ($n=253$) IHS migraine, with a range of MIDAS scores. **Results** Participants were predominantly female (69.8%), Caucasian (84.3%), employed full time (58%) and married (64.9%). MIDAS grade-I participants had scores on the physical and mental health subscales of the SF-12 consistent with a general population mean. As the MIDAS grade increased, SF-12 scores decreased and CES-D scores increased (see table).

<table>
<thead>
<tr>
<th>MIDAS</th>
<th>MIDAS Score 0/1</th>
<th>MIDAS Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Grade IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12 Physical</td>
<td>53.05/52.36</td>
<td>49.78</td>
<td>44.47</td>
<td>41.47</td>
<td>41.47</td>
</tr>
<tr>
<td>SF-12 Mental</td>
<td>52.94/51.83</td>
<td>48.37</td>
<td>47.96</td>
<td>42.07</td>
<td>42.07</td>
</tr>
<tr>
<td>CES-D</td>
<td>5.52/7.08</td>
<td>13.17</td>
<td>16.05</td>
<td>21.76</td>
<td>21.76</td>
</tr>
</tbody>
</table>

(1) All groups are significantly different from each other except III and IV ($P<0.11$). (2) All groups are significantly different from each other except II and III.

**Conclusion** MIDAS grade-I headache patients suffer from depression at normal population rates and have HRQoL scores that are within the normal range. As MIDAS grades increase, HRQoL declines, suggesting that the most disabled groups account for most of the HRQoL impairment in headache sufferers. Increasing CES-D depression scores indicate that comorbid depression is also associated with disability in headache sufferers.

**P1-E4**

**The MIDAS perception study: patient’s perception of the utility of MIDAS**

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**Objective** The MIDAS instrument is a 7-item questionnaire, co-developed with AstraZeneca, to measure headache-related disability using units of lost days, in a manner that would be intuitive and meaningful both to clinicians and headache sufferers. Furthermore, MIDAS was intended to identify the more disabled segment of headache sufferers and motivate them to seek the appropriate level of medical care. Prior work demonstrates that MIDAS scores correspond to clinical judgement. The present study (1) assesses patient perceptions of the MIDAS Questionnaire and the MIDAS score; and (2) determines if perceptions vary as a function of MIDAS grade. **Method** Study subjects were selected for participation in a telephone survey using a quota sampling procedure to ensure representative sampling of the US population. Upon completion of the baseline survey, 471 individuals were invited to participate in the Perceptions Survey. These subjects were sent a copy of the MIDAS Questionnaire by mail, and were then interviewed by telephone (421 successfully completed the Perception Survey).

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**Results**
As MIDAS grade increased, participants were increasingly likely to agree or strongly agree that the MIDAS Questionnaire asked questions that were important to them (grades: I 66%; II 72%; III 89%; IV 97%; P < 0.001). Participants also felt that MIDAS helped them understand the impact of headache on their lives (grades: I 69.8%, II 83.9%, III 84.4%, IV 89.6%; P < 0.0002). When asked if the MIDAS Questionnaire would facilitate talking to a doctor about headaches, the percent of headache sufferers who agreed or strongly agreed was similar across groups (63.3% to 79.4%). MIDAS motivated a considerably higher proportion of the more disabled patients to indicate that they would seek medical care (grades: I 5.9%, II 26.6%, III 50%, IV 80%; P < 0.0001). Over 97% of study participants felt MIDAS was easy or very easy to score; over 95% had no difficulty understanding the questions; and over 90% reported that overall, MIDAS was very easy or easy to understand.

**Conclusion**
Perceptions of the relevance of the MIDAS Questionnaire increased as the MIDAS score increased. All groups felt the Questionnaire was easy to complete and easy to score. The MIDAS Questionnaire helped the majority of patients to understand the impact of their headaches and encouraged the most disabled segment to recognize the potential benefits of seeking medical care. These findings suggest that MIDAS should be a useful tool in public health interventions.

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**P1-E5**

**MIDAS: determining the efficacy of prescribed management strategies using disability assessment**

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**Background and objectives**
The Migraine Disability Assessment (MIDAS) Questionnaire quantifies the impact headaches have on patients’ lives in three activity domains: (1) paid or school work; (2) household work; and (3) family and leisure activities. Headache-related disability has been shown to correlate with physicians’ clinical judgement and intuition about the severity of illness. However, a good clinical measure should also show change in response to clinically relevant treatment. The aim of this ongoing study, therefore, is to explore the utility of MIDAS in monitoring treatment progress and benefit in clinical practice.

**Patients and methods**
Patients attending the City of London Migraine Clinic are asked to complete the MIDAS Questionnaire on or before their first clinic visit. The Questionnaire is reviewed by the doctor during the consultation to ensure that it has been completed correctly. Following recommendation of management strategies, patients are asked to complete a further MIDAS questionnaire 3 and 6 months later. Changes in the MIDAS score are noted and patients are asked whether or not there has been a relevant improvement or deterioration in their condition. Patients and doctors involved in the study are invited to comment on the usefulness of the MIDAS Questionnaire.

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**Results and conclusions**
Data are being collected and analysed and will be presented in the poster.

**P1-E6**

**Comparative evolution of MIDAS score after monotherapy with triptans**

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**Introduction**
Since the introduction of sumatriptan, newer triptans are in use; however, patients seem to respond in an unpredictable manner, with a response rate of 50–90%. In migraineurs MIDAS scoring seems to be a useful instrument for individualization of treatment needs.

**Aim**
In our retrospective study we tried to evaluate any differences found in the response to triptans, especially with regard to the changes of MIDAS score before and after treatment.

**Methods**
The charts of 64 migrainers (9 men, 55 women; mean age 40.7 years, range 16–63 yrs) were reviewed. History of headache was 20.2 ± 10.9 (3–46) years. 22 pts (34.4%) had aura and 11 pts (17.2%) had toxic cephalalgia. A comparison was done between pts treated with sumatriptan (Su: n=48) and those with naratriptan (N: n=11) or zolmatriptan (Z: n=5). Grading by MIDAS score (I: 0–5, II: 6–10, III: 11–20, IV: >20) was done before (A) and after (B) 3–6 months on treatment for all pts: pts on Su, pts on N + Z, pts with (Ma) or without (Mo) aura, and abused (Ab) or non-abused (N-Ab) migraineurs. Analysis of variance (ANOVA) was used.

**Results**
Percentage distribution of MIDAS score is seen in the table for the main studied groups.

<table>
<thead>
<tr>
<th>MIDAS</th>
<th>Total A</th>
<th>Total B</th>
<th>Su A</th>
<th>B</th>
<th>N+Z A</th>
<th>B</th>
<th>Su→N+Z A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>31.3</td>
<td>43.3</td>
<td>35.7</td>
<td>0</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>9.3</td>
<td>39.1</td>
<td>10.4</td>
<td>30.0</td>
<td>6.3</td>
<td>57.1</td>
<td>0</td>
<td>38.9</td>
</tr>
<tr>
<td>III</td>
<td>26.6</td>
<td>21.8</td>
<td>22.9</td>
<td>16.7</td>
<td>37.5</td>
<td>7.2</td>
<td>22.2</td>
<td>44.4</td>
</tr>
<tr>
<td>IV</td>
<td>64.1</td>
<td>7.8</td>
<td>66.7</td>
<td>10.0</td>
<td>56.2</td>
<td>0</td>
<td>77.8</td>
<td>11.1</td>
</tr>
<tr>
<td>n</td>
<td>64</td>
<td>64</td>
<td>48</td>
<td>30</td>
<td>16</td>
<td>14</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

At Ex B 18 pts (37.5%) changed from Su to N or Z with a worse grading at Ex A from those who remained on Su (P < 0.01).

**Conclusions**
From these preliminary results according to MIDAS score, it seems that the effectiveness of Su is comparable to that of newer triptans. Aura does not influence the effect of triptans, whereas pts with drug abuse headache are more resistant to them.

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A population-based study of headache-related disability in Florianopolis, Brazil

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Objective To estimate the degree of headache-related disability in a representative sample of the adult population of Florianopolis, Brazil, applying the Migraine Disability Assessment (MIDAS) questionnaire.

Participants and methods This is a cross-sectional, door-to-door direct interview, population-based study. In 300 randomly selected households of the central area of Florianopolis, 625 subjects (337 females and 288 males), aged 15–64 years, responded to a structured questionnaire about headache. The participation rate was 87%. The five questions comprising the MIDAS questionnaire and score were asked to those (418 subjects) who had headache within the last 3 months. The overall score was categorized into four grades of increasing disability: I, score of 0–5; II, score = 6–10; III, score = 11–20; and IV, score > 20.

Results Among subjects with headache in the last 3 months, 78.7% had the MIDAS score grade I, 9.3% grade II, 7.0% grade III and 5.0% grade IV. Among the 223 subjects with headache of the migrainous group (migraine + migrainous disorder), 66.8% had the MIDAS score grade I, 13.9% grade II, 10.3 grade III and 9.0 grade IV. Among the 161 subjects of the tensional group (tension-type headache + headache of the tension-type not fulfilling all criteria), 91.3% had the MIDAS score grade I, 4.3% grade II, 3.7% grade III and 0.6% grade IV. Both diagnostic groups had a highly significant linear trend ($P < 0.001$) of smaller proportions of subjects with headache as the disability increased. Comparing proportions, in each grade, of migrainous cases and tensional cases, migrainous headache was significantly less frequent in grade I ($\chi^2 = 31.74; P < 0.001$), and more frequent in grade II ($\chi^2 = 9.57; P = 0.002$), in grade III ($\chi^2 = 5.81; P = 0.016$), and in grade IV ($\chi^2 = 12.60; P < 0.001$). By linear trend test, strong association ($P < 0.01$) was noted between increased MIDAS score severity in subjects with headache in the last 3 months and assistance sought, medical consultation ever, medical consultation in the last year, diagnostic investigation done, and medication used.

Conclusions This is the first population-based study of headache-related disability applying the MIDAS questionnaire in Brazil. The MIDAS score was significantly different in migrainous cases and tensional cases. The utilization of health care resources was higher among headache sufferers with higher grades of disability.

Reliability of Albanian version of the MIDAS questionnaire

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Introduction Migraine causes significant impairment in life activities. Assessing the impact of migraine on individual patients may favourably influence health care delivery for migraine sufferers. The Migraine Disability Assessment Questionnaire (MIDAS) has shown to be valid and reliable in many countries. The aim of this study is to assess the reliability of the Albanian version of MIDAS.

Method A specialist in headache disorders translated the MIDAS questionnaire into Albanian. 98 patients (diagnosed as migraine without aura sufferers at our headache centre) entered the study. Mean age was 34.2 years (15–50, SD ± 7.4). They had different levels of medical education. They completed the questionnaire during a consultation and were asked to complete another identical one 4 weeks later, at home. Pearson’s and Spearman’s tests were used for statistical evaluation.

Results 92 patients returned the second form. The disability grades assigned at the first and second compilation were stable in 81 (88.4%) patients. The test-retest reliability was found to be good ($r = 0.89$, Pearson’s test; $r = 0.81$, Spearman’s test).

Conclusion The Albanian version of the MIDAS questionnaire is reliable in assessing migraine disability. It does not depend on the age or level of education.

Abstract withdrawn
Reliability and validity of the Japanese translation of the MIDAS questionnaire

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Background and objectives The MIDAS instrument is a 7-item questionnaire, co-developed with AstraZeneca, to assess migraine-related disability in routine clinical practice. Previous studies have demonstrated the original English language version of the MIDAS Questionnaire to be highly reliable and valid. For MIDAS to be useful in countries where English is not the official language, and to enable comparison of international data, translation of the questionnaire into the relevant language is necessary. Testing of a translation is also required to ensure that it is conceptually and semantically equivalent to the original English MIDAS Questionnaire. The aim of this study is to assess the test-retest reliability and validity of a Japanese translation of the MIDAS Questionnaire amongst a sample of Japanese migraine sufferers.

Patients and methods Patients attending the Kitasato University or an allied clinic and reporting six or more primary headaches per year were eligible for study entry. Patients were grouped into one of three bands depending on their baseline MIDAS score: 1–10 (low headache impact), 11–20 (intermediate headache impact) or >21 (high headache impact). The distribution of scores was reviewed after the first 50 patients were recruited to ensure that an acceptable split between the three bands was being achieved. Headache aetiology was also considered to ensure both migraine (including mixed type) and tension-type headache sufferers were included. For the reliability testing, participants completed the MIDAS Questionnaire on two occasions, approximately 2 weeks apart. No change in acute or prophylactic medication was permitted during this interval. All patients were also enrolled in a diary study to assess the validity of the MIDAS Questionnaire. For this, patients completed a daily headache diary for 90 days and also completed a MIDAS Questionnaire at the beginning and end of the 90-day period.

Results One hundred and one patients were recruited (81 women and 20 men). The distribution of baseline MIDAS scores was as follows: low 46%, intermediate 22% and high 32%. Test–retest Spearman correlations of individual items ranged from 0.59 to 0.80. The test–retest Pearson coefficient of the overall MIDAS score was 0.82.

Conclusions The current data show that the reliability of the Japanese MIDAS Questionnaire is comparable to the original English version. Establishing the reliability and validity of the Japanese MIDAS Questionnaire is important prior to its use in clinical practice in Japan.
Conclusions
Headache had a high prevalence in this population survey with over two-thirds reporting headache in the previous 3 months. Headache was found to be more common in women and younger respondents. Headache disability at least moderately affected 13.7% of the respondents lives in the 3 months prior to the survey. Despite this, only 9.2% of respondents reported seeking a healthcare professional’s advice about their headaches during this time. The likelihood of consultation increased with increased disability due to headache.

P1-E12

Use of the headache impact test (HIT®) with other health status assessments to identify patients with comorbid depression

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Objective The Internet HIT is a valid and reliable health status assessment tool that precisely measures the impact of headache on individuals’ lives with minimal respondent burden. A HIT score above 56 has shown specificity as a screener for IHS-diagnosed migraine. This study assessed whether HIT could be used in conjunction with an established first-stage screener for depression to identify respondents suffering from both migraine and depression, two conditions that epidemiological studies suggest are frequently comorbid.

The depression screener in this study was the Mental Component Summary (MCS) score of the Short Form-8 (SF-8), which was used in the landmark Medical Outcomes Study. Scores of 42 or less have shown specificity as a screener for depression.

Methods Responses from consecutive recent headache sufferers, who completed HIT and the SF-8 by accessing them on the Internet at http://www.amIhealthy.com, were summarized to determine whether respondents met criteria for possible migraine (HIT score greater than 56) and/or possible depression (SF-8 MCS score of 42 or less).

Results 1013 respondents completed both surveys. Respondents’ scores suggest that migraine and depression were each highly prevalent in this sample of patients, 70% of whom screened positive for migraine and 26% of whom screened positive for depression. Respondents’ scores also suggest that migraine and depression were frequently comorbid. Of respondents screening positive for migraine, 32% also screened positive for depression.

Conclusions These findings corroborate comorbidity data from epidemiological studies of depression and migraine. The results support further evaluation of the use of HIT and the SF-8 in clinical practice and warrant further exploration in relation to other depression screeners. Conjunctive use of these screeners appears efficiently to identify possible sufferers of comorbid migraine and depression and may be realized in more effective identification and treatment of patients with these comorbid conditions.

P1-E13

Impact of migraine relative to other headache types

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Objective The Internet-based Headache Impact Test (HIT®) applies modern psychometric methods to achieve matchless brevity and precision in measuring the impact of headache on respondents’ lives. Launched to the press at World Headache 2000 (September 2000), HIT has been taken by thousands of headache sufferers. This study compared the impact of migraine with that of other headache types on the lives of respondents taking HIT during the 3-month period after it was launched to the press.

Methods Descriptive statistics were used to summarize responses from all individuals who took HIT on the Internet from 1 September 2000 through 30 November 2000 and who completed 10 additional questions assessing demographic and health status information. In addition to self-reporting on headache-related variables, respondents were asked to report on their physicians’ or other health care providers’ diagnoses and reasons for their headaches.

Results 19 064 HIT surveys were completed; 13 966 of the HIT respondents also completed the additional survey questions. Migraine was the most common self-reported reason for headache (15.4% of respondents); stress, tension, and sinus headache were the next most common self-reported reasons (14.7%, 7.5%, and 7.0% of respondents, respectively). Similarly, migraine was the most common response for their physician-/provider-stated reason for headache (15.4% of respondents) followed by tension, stress, and sinus headache (5.7%, 5.2%, and 3.7% of respondents, respectively). Of the
The internet-delivered dynamic headache impact test (HIT):
profile of the first 19,000 + respondents
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1Diamond Headache Center, Chicago, IL, USA, 2Headache Care Center, Springfield, MO, USA, 3QualityMetric, Inc., Lincoln, RI, USA, 4GlaxoSmithKline, Research Triangle Park, NC, USA

Objective Modern psychometric methods allow the Internet-based HIT to measure the impact of headache on respondents’ lives with an unprecedented degree of precision via computerized administration requiring only 1–2 min. This study evaluated characteristics of respondents taking HIT from its press launch in September 2000 through 30 November 2000 and assessed the relationships between HIT scores and clinical parameters.

Methods Responses from all individuals taking HIT as well as those completing 10 additional questions on demographic and health status information from 1 September 2000 through 30 November 2000 were summarized using descriptive statistics.

Results 19,064 HIT surveys were completed; 13,966 respondents also completed the additional survey questions. The majority of HIT respondents were females (61.4%) between the ages of 25 and 44 years (56%). 61% of respondents suffered moderate/severe or severe headaches. Half of respondents suffered 1–2 (27.4%) or 3–6 (22.8%) headaches/week. Mean HIT scores were 57.4 for males and 61.0 for females. Scores did not vary with age for respondents ages 18 through 54 years but declined with increasing age for respondents 55 and older. As expected, HIT scores were directly related to self-reported severity of pain and frequency of headache (47 for mild pain to 67 for very severe pain; 47 for less than 5 headaches/year to 62 for headaches every day); lower for those taking over-the-counter medicines compared with prescription medicines for moderate/severe headache (59 vs 63); and lower in respondents taking no medicines for headache compared with those requiring bed rest (55 vs 61). HIT score exceeded the 56 + cutoff for migraine for twice as many women (63%) as men (32%) – a demographic consistent with that observed in epidemiological studies. HIT is scored such that the US population mean for recent headaches sufferers is 50, and the standard deviation is 10. It should be noted, therefore, that a score difference as little as 3 points is noteworthy, and 5 points is highly significant (representing 3–5 tenths of a standard deviation respectively).

Conclusions The widespread use of Internet HIT since its September 2000 press launch demonstrates the feasibility of using Internet-based dynamic assessments to measure health status. Data from the first 19,000 ‘real world’ takers of HIT complement results of previous studies by showing that HIT differentiates respondents on the basis of migraine diagnosis and headache characteristics such as severity and frequency. This information may be useful in clinical decision-making.

Health care-seeking behaviour of respondents after taking the headache impact test (HIT)
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Objective HIT was developed with the goal of providing headache sufferers with a precise yet practical tool that could facilitate communication with their physicians about the impact of headaches. The Internet-based HIT has been shown to measure precisely and reliably the impact of headache on respondents’ lives. HIT typically requires 1–2 min for the patient/consumer to complete and generates reports that are easily interpreted by patient and clinician. HIT was launched to the press at World Headache 2000 (September 2000). This study reports information on respondents’ descriptions of their health care-seeking behaviour after taking HIT.

Methods Follow-up surveys containing 10 questions about health care-seeking behaviour were e-mailed to a random sample of 1205 respondents who had taken HIT during September or October 2000. The average time between completion of HIT and the follow-up survey was 3.5 months.

Results 430 of the 1205 surveys were returned for a 35.7% response rate. Sixty-two percent (62%) of respondents indicated that they had visited a doctor since taking HIT; 19% had not yet seen a doctor but indicated that they plan to; 20% did not plan to see a doctor. Mean HIT scores were higher among those who had seen a doctor (63) than among those who had no plans to see one (57). Of the respondents who had visited a doctor, 46% had made an appointment specifically to talk about headaches; 83% had discussed headaches with their doctor with or without a specific
appointment; and 11% had discussed headaches and showed their doctor the HIT report. Mean HIT scores were higher among those who had discussed headaches with their doctor (63–65) than among those who had not (59). Regardless of whether they showed their doctor the HIT report, 85% of respondents who had discussed headaches with their doctor indicated that HIT was useful in communicating with their doctor about the impact of headaches on their life.

**Conclusions** The experience of taking HIT on the Internet motivated many in this sample of headache sufferers to seek medical care and facilitated headache-related communication between patient and doctor. Headache sufferers whose HIT scores reflect more severe headache impact were more likely to seek medical care than those with lower scores.

### P1-E16

**HIT-6 reliably measures the impact of headache**

W. H. Garber1, M. Kosinski1, C. Dahllof2, S. Tepper3, S. C. Kujavskii1, J. Ware1 & A. Batenhorst4

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**Background** It is important that tools for measuring headache impact be reliable so that the severity of disease experienced by headache sufferers can be accurately assessed. HIT-6, a self-administered short form survey for measuring the impact of headache, contains 6 questions psychometrically selected from the validated, internet-based Headache Impact Test.

**Objective** The objective of the research was to determine the reliability of HIT-6.

**Methods** HIT-6 items were administered via the internet to a general population of recent headache sufferers (N = 1108). Reliability was assessed in several ways: internal consistency (Cronbach’s alpha) at a point-in-time; test-retest (Pearson product moment and inter-class correlations over a 2-week interval); and stability of scores over time (based on the 95% confidence intervals around change scores).

**Results** The response rate for completion of both questionnaires was 49.5%. Internal consistency reliability (Cronbach’s alpha) of HIT-6 total scores at baseline was 0.89. At the level of the total score, HIT-6 showed good test-retest reliability based on the product moment correlation coefficient (0.83) and the intra-class correlation coefficient (0.80). At the level of the individual question, HIT-6 also showed acceptable test-retest reliability with Pearson correlation coefficients ranging from 0.60 to 0.71 and intra-class correlation coefficients ranging from 0.57 to 0.70. HIT-6 scores were stable, with 77.6% of respondents showing no significant change in score from time 1 to time 2.

**Conclusions** HIT-6, a reliable tool for measuring the impact of headache on patients’ lives, can help physicians more accurately individualize treatment according to headache impact.

### P1-E17

**Validity of HIT-6, a paper-based short form for measuring headache impact**

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**Background** Short, precise tools for measuring the full range of headache impact are valuable to assist in clinical decision-making. As treatment decisions are based upon diagnosis and severity of headache, tools that quantify headache impact must validly characterize these variables.

**Objective** The objective of the research was to test the validity of HIT-6, a self-administered short form survey for measuring the impact of headache on patients’ lives, in terms of how well it discriminates between those with and without migraine and across levels of headache severity.

**Methods** HIT-6 questions were administered via the internet to a general population of recent headache sufferers differing in migraine status based on International Headache Society symptom criteria and in headache pain severity as measured by an 11-point scale. The mean HIT-6 score for headache sufferers is 50 with an SD of 10.

One-way analysis of variance was conducted to test the statistical significance of mean HIT-6 across migraine status and headache pain severity groups.

**Results** Among recent headache sufferers, the mean HIT-6 score was 65.9 for respondents with migraine compared with 55.9 for respondents without migraine (F = 443.2, P < 0.0001). Mean HIT-6 scores among respondents with mild, moderate, and severe headache were 51.1, 59.8, and 69.9, respectively (F = 275.6, P < 0.0001).

**Conclusions** HIT-6 is a valid tool for differentiating the level of headache impact among those with and without migraine diagnosis and across levels of headache severity. HIT-6 can help clinicians identify migraine sufferers and customize therapy according to the severity of disease.

### P1-E18

**HIT-6 scores discriminate among headache sufferers differing in headache-associated workplace productivity loss**

M. S. Bayliss3, M. Kosinski1, M. Diamond2, S. Tepper3, W. H. Garber1, J. Ware1 & A. Batenhorst4

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**Background** While disabling migraine affects every aspect of life, the economic consequences are most apparent in the workplace due to absenteeism and reduced functioning.
Tools for measuring headache impact should differentiate patients with respect to workplace functioning. HIT-6 is a reliable, valid, self-administered short form survey for measuring the impact of headache.

**Objective** To determine whether HIT-6 scores can discriminate among headache sufferers differing in workplace productivity loss attributed to headache.

**Methods** HIT-6 and questions concerning workplace productivity loss in the past 4 weeks were administered to a general population of recent headache sufferers ($n = 648$). Based on HIT-6 scores, respondents were categorized as being minimally (scores $< 50$), mildly (scores $50–55$), moderately (scores $56–59$), or severely (scores $60$ or more) impacted by headaches. The mean score for headache sufferers is $50$ with an SD of $10$.) One-way ANOVA was conducted to test the significance of differences in mean hours of lost workplace productivity estimated across the 4 categories of HIT-6 scores.

**Results** The mean number of hours of lost workplace productivity in the past 4 weeks was directly related to degree of headache impact as measured by HIT-6. Respondents with HIT-6 scores reflecting minimal impact had $1.93$ h of lost workplace productivity. Those with HIT-6 scores reflecting mild and moderate impact lost $3.33$ and $7.83$ h, respectively. Those with HIT-6 scores reflecting severe impact lost $17.92$ h of workplace productivity. The difference in lost workplace productivity across the 4 headache impact groups was statistically significant ($F = 30.43$, $P < 0.00001$).

**Conclusions** HIT-6 scores are directly related to self-reported workplace productivity loss attributed to headache. These data demonstrate the practical utility of HIT-6 for assessing clinically relevant disability and indicating treatment needs according to the degree of headache impact.

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**P1-E19**

**Development of HIT-6, a paper-based short form for measuring headache impact**

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**Objective** To develop a practical, precise paper-based questionnaire from the Internet-based Headache Impact Test (HIT-DynHA) using a 3-pronged approach to ensure psychometric soundness, clinical relevance and cross-national adaptability. HIT-DynHA, derived from 4 widely used headache questionnaires, has demonstrated evidence of precision, reliability, and validity in the measurement of the impact of headache on sufferers’ lives. A paper-based version of the questionnaire was desirable for clinicians and patients with no access to the Internet.

**Methods** From a pool of 54 widely used questions and 25 questions commonly used in clinical practice, psychometric methods and discriminant validity tests were used to select 6 questions for the short form (HIT-6). Random samples of recent headache sufferers from the general US population ($n = 1617$) were administered a questionnaire including the total HIT question pool. A rigorous translation methodology was employed to establish conceptual equivalence of HIT-6 translations across 22 countries.

**Results** HIT-6 was psychometrically sound: Factor analysis produced substantial correlations between HIT-6 questions and the general headache impact factor from the total HIT question pool ($0.64–0.81$). The relative agreement between HIT-6 scores and scores estimated from the total question pool and the dynamic administration was very high (correlations of $0.91$ and $0.86$, respectively). HIT-6 questions cover $67\%$ of the range of headache impact covered by the total HIT question pool and include all 6 content areas covered by other headache surveys. Norm-based HIT-6 scoring is comparable to that of HIT-DynHA. HIT-6 questions measured clinically relevant aspects of headache impact: HIT-6 questions were among the best in the total HIT question pool at differentiating among groups of patients with and without a diagnosis of migraine, with different levels of headache severity, and with different levels of workplace productivity loss ($F = 17.9–556.6$, $P < 0.0001$). Revised HIT-6 questions were conceptually equivalent across languages: Linguistically appropriate translations were developed leading to modifications in the English version. Translations were understood well in pilot tests ($n = 60$).

**Conclusions** Psychometrically sound, clinically useful, and cross-nationally adaptable, HIT-6 provides clinicians with a practical, precise measure of headache impact that can be used to tailor treatment to disease severity.

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**P1-E20**

**Comparability of scores on the Headache Impact Test$^6$ (HIT) and HIT-6$^5$**

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**Objective** To interpret and compare norm-based scoring for the Internet delivered Headache Impact Test (HIT), and the 6-item paper version (HIT-6).

**Design and methods** The Headache Impact Test was developed to quantify the impact of headaches on a patient’s life. Internet-based HIT offers an innovative approach to testing, used in both education and psychology. Linking the Internet and Item Response Theory (IRT) produces a method which can quickly deliver a precise (95% confidence interval of $\pm 3$ points) norm-based score by selecting questions targeted to each individual’s level of headache disability. Norm-based scoring, which designates a standardized mean and standard deviation, yields a simplified approach that facilitates interpretation. HIT-6 was developed using the HIT question pool to create a short, yet precise and reliable, paper
based assessment for use in settings where access to the Internet is limited. A traditional additive scoring approach for HIT-6 was desirable. To simplify interpretation, clinicians recommended that scoring between the two versions be comparable. An algorithm was developed and tested through multi-trait scaling analyses to ensure score comparability. To assess the relationship between scores of HIT and HIT-6, a study was conducted using random telephone interviews where subjects completed both versions of HIT and additional questions on migraine according to the IHS criteria through random telephone interviews.

**Results** Of the 7510 households that were contacted, 2148 had an eligible respondent and 1016 completed the interview. Scores on the HIT and HIT-6 corresponded closely with a correlation of 0.91. Scores were calibrated to reflect a mean of 50 with a standard deviation of 10 in an adult US population of recent headache sufferers. Scores above 50 suggest a greater than average negative headache impact, whereas scores below 50 reflect lower than average headache impact. Each one-point change on HIT and HIT-6 corresponds to one-tenth of a standard deviation. For example, a change in a score from 58 to 51 represents an improvement from the 75th percentile to the 50th percentile. For scores 56 and higher, sensitivity and specificity for migraine diagnosis were 72.6 and 92.7, respectively.

**Conclusion** Scores for HIT and HIT-6 are easily interpretable and comparable. Depending upon available methods for delivery within a clinical practice, both offer precision and brevity which are useful to alert physicians to the degree of impact of headaches on a subject’s life.
POSTER SESSION I

F: Migraine treatment: dollars and sense

P1-F1

An assessment of the burden of migraine using the willingness to pay model

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Background and objective Migraine is a highly prevalent and painful condition that exerts a substantial impact on both the individual and society. We used a contingent valuation method to measure migraine sufferers willingness to pay (WTP) for medication for their most severe migraine attacks based on the characteristics of the migraine sufferer and various aspects of treatment benefits.

Methods A questionnaire was mailed to a population-based sample of 310 migraine sufferers, and 201 (65%) surveys were returned. The survey included questions on the demographics, migraine characteristics, and psychological disposition of the respondents, as well as several scenarios that explored the attributes of a hypothetical migraine medication.

Results Responders and non-responders were generally similar. Study subjects were willing to pay a median price of $5 for the best case migraine treatment that provided complete relief in 30 min and worked 100% of the time, with no side effects and no headache recurrence. Willingness to pay decreased as treatment attributes deviated from this ideal. For example, WTP declined to a median of $1 for complete relief in 2 h and to $0.25 for complete relief in 4 h. All of the medication attributes powerfully influenced WTP. Subjects who were more likely to be WTP for treatment included those who typically paid $5 or less or at least $11 for their prescription migraine treatments, subjects in MIDAS Group III, and those with headaches of long duration. Subjects who employed a greater number of coping skills were less willing to pay.

Conclusions Based on these estimates, migraine sufferers, on average, are WTP $225 individually, or $5.6 billion in aggregate each year for relief of their most severe migraine attacks. Patient demographics and migraine severity predict WTP, but attributes of treatment were important. As treatment improves, WTP for migraine medications is likely to increase.

P1-F2

Hospital costs of acute headaches in a Brazilian public emergency room unit

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Objectives To estimate the costs due to consultation, investigation and clinical treatment of the acute headaches in a Brazilian Emergency Room (ER).

Methods The headache (as the major complaint) cases seen during the year of 1996 in an emergency room unit at Ribeirão Preto, SP, Brazil, have been retrospectively studied. We calculated the following costs: (A) Costs due to consultation, investigation and clinical treatment; (B) Expenses related to laboratorial exams; (C) Costs of internments; (D) Surgical expenses.

Results During that year, 1254 patients visited the ER with major complaints of acute headache, among which 64 needed hospitalization. Primary headaches predominated among non-hospitalized patients (77.0%), whereas the percentage of headaches secondary to neurological disorders was higher among patients who required hospitalization (51.5%). Migraine was the most common diagnosis in both groups.

The estimated costs due to consultation, investigation and clinical treatment of the acute headaches was in the order of US$76,985.17. The expenses related to laboratory exams only were US$13,223.07. The surgical expenses were US$3,232.17. The total cost was US$80,217.34, which corresponds to US$63.97 per patient. Additional data are shown in the table. Almost 56% of the patients were not hospitalized, had no laboratory test performed, nor needed any kind of surgical procedure.

<table>
<thead>
<tr>
<th>Percentage of the costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeries</td>
</tr>
<tr>
<td>Laboratory tests</td>
</tr>
<tr>
<td>Hospitalization</td>
</tr>
<tr>
<td>Consultation and clinical treatment</td>
</tr>
</tbody>
</table>

Conclusions We conclude that the resolution power of the primary health care system in the Ribeirão Preto region in terms of the headache symptom is very low. It should be pointed out that this region is considered to be one of the best medical centres in Brazil. Thus, it can be seen that headache frightens general practitioners, generating insecurity among non-specialists, with consequent diagnostic difficulties. Since
well-established criteria (IHS) are available for headache and in most cases a diagnosis can be made without the use of laboratory tests, there is a pressing need for a more aggressive dissemination of these criteria, which would lead to decreased operational and individual costs in tertiary care units. This research instigates an additional discussion about the costs and effectiveness of the current public health policy in Brazil, as well as in other developing countries.

P1-F3

Prevalence and costs of headaches for the public health system in a town in the interior of the state of São Paulo, Brazil

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Objectives To determine the prevalence of headaches in the public health system of a town in the interior of the State of São Paulo, Brazil, as well as to estimate the costs resulting from its management.

Methods The city (Ipua˜) had an estimated population of 11,208 inhabitants. Data refer to the year of 1998 and were obtained according to the following steps: (1) territorial and demographic characterization; (2) characterization of the financial indices and welfare state; (3) budget characteristics of the municipality; (4) evaluation of the structuring of the medical service; (5) determination of the prevalence of headaches at the different patient care levels, and (6) calculation of its ensuing costs. The following costs were estimated: (A) costs at the primary care units (the estimated cost of one consultation times the total number of headache as the main complaint consultations); (B) costs of local emergency care. The same method as described above was used; (C) costs of local hospital admissions (secondary care) (same method as described above); (D) costs of emergency referral of headache patients to tertiary care units (about 60 miles away) – the town hall provided the estimates of the costs of these kinds of referrals; (E) costs of elective referral (same method as described above).

Results Territorial area is 564 km² and demographic density was 19.47 inhabitant/km². Birth rate was 20.58/1000 inhabitant/year. Health expenses were 24.5% of total town revenue (US$70.65/year/inhabitant). Headaches represented 7.9% of all visits at basic health units, 9.7% in the emergency room and 1.1% of hospital admissions. The total costs of headache management were US$42,565.65, corresponding to US$3.99/inhabitant/year. The breakdown of the costs is presented in the table.

<table>
<thead>
<tr>
<th>Service</th>
<th>Expenses (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care unit visits</td>
<td>19,716.90</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>19,350.50</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>2876.81</td>
</tr>
<tr>
<td>Emergency referrals</td>
<td>316.02</td>
</tr>
<tr>
<td>Elective referrals</td>
<td>305.62</td>
</tr>
<tr>
<td>Total</td>
<td>42,565.65</td>
</tr>
</tbody>
</table>

Conclusions The search for rationality in health expenses has been announced as the goal by most public and private managing agencies. In Brazil, these affirmations collide with the lack of effectively conducted epidemiological studies, and studies on the impact on life quality and their costs. These studies should be carried out and corrective measures should be implemented as soon as possible, especially in developing countries where the available resources are smaller than the necessities of the population.

P1-F4

Indirect costs of migraine for a state-owned Brazilian hospital

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Objectives Evaluate the indirect costs of migraine affecting workers of a state-owned Brazilian hospital.

Methods A randomized 1890-individual sample out of 4050 workers from Ribeirão Preto University Hospital (HC) were supplied a form in order to identify those people with migraine (fulfilling all IHS criteria) or with migrainous headache (fulfilling all but one criteria, the duration of the headache; i.e. subjects could not remember the exact duration of the attack). Only workers presenting at least one attack during the last year entered the study. A total of 846 (67% females and 33% males) individuals were found, 575 with migraine and 271 with migrainous headache. In this study, all 846 individuals were deemed to belong to the ‘migraine group.’ We used the Chronic Pain Index (Von Korff Index), which classifies chronic pain into four different categories, and the Lost Working Hours Equivalence Index (LHEI), which considers both the hours lost due to the absence from work and reduction in productivity. The LHEI was calculated by the following formula: $LHEI = F + [P \times (1\% \text{ loss of productivity due to pain})]$, where $F =$ number of hours lost due to absence and $P =$ number of working hours at reduced productivity. The work time was considered to be 20 h per week and 12 months per year.

Results From 846 subjects with migraine interviewed, 770 (91%) reported some loss of productivity when in pain (mean of the loss = 56.9%). The mean loss of working hours per month was 6.5 h (0.1 h due to absence and 6.4 due to loss of productivity). The resulting costs are shown at the table. Extrapolation of these data to the HC workers as a whole (4050 workers) led to the following results: 1830 HC workers will present migraine or migranous headache and 1665 will show loss of productivity. This would imply a loss of 129769.7 working hours per year, which would be $892,906.29 in US dollars. Thus, the indirect costs are US$218.31/worker/year and US$487.92/worker with migraine/year.
Conclusions The impact on a person's life and the costs for an institution (or employer) show that migraine must be considered a public health problem and thus measures should be adopted to reduce its impact upon the individual and society. This is a special problem in developing countries, where the financial resources are, by far, less abundant than would be desired.

P1-F5
Evaluation of the impact of migraine and episodic tension headache on the quality of life and performance of a university student population
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Objectives To determine the prevalence of migraine and episodic tension-type headache (ETTH) among university students as well as its impact on academic performance and quality of life.

Methods A total of 1022 students were interviewed. Two questionnaires were applied, a standard one, previously validated, that permitted a diagnosis of migraine and ETTH according to the criteria of the International Headache Society (IHS), and a second one consisting of a battery of the following tests: (1) Von Korff grading scale for chronic pain; (2) Short-Form 36 (SF-36); (3) Nine-item pain questionnaire derived from the Patient Assessment Questionnaire (PAQ); (4) Quality of life in migraine questionnaire (QoL). The questionnaire consisted of 45 questions that evaluate: (1) Frequency of pain; (2) Intensity of pain and interference with daily activities; (3) Interference with study; (4) Interference with daily activities during pain; (5) Quality of life between pain crises; (6) Impact on mood and behaviour; (7) Impact on, and limitation of, physical activity; and (8) Perception of health. Subitems 6, 7 and 8 were also applied to students who had no headache (control). Data were analysed statistically by the ANOVA test and by the 95% confidence interval for differences between proportions.

Results A total of 256 students (25%) had migraine and 336 (32.9%) reported ETTH. When in pain, migraine sufferers presented a 62.7% fall in study productivity, as opposed to 24% of those with ETTH. Fifty percent of migraine sufferers tried to study despite the pain, as opposed to 53.2% of those with ETTH. Mean percentage of fall in study performance in the presence of pain and number of days/student/6 months when the students did not study at home or missed classes due to migraine and ETTH crises, correlated with pain index, are presented in the table. With respect to all other items tested, there was a significantly higher impairment in the presence of migraine than in the presence of ETTH and in the presence of the latter compared to control.

Conclusions The present study confirms the profound impact of headache on the performance of university students, with this impact being much more evident among migraine sufferers but also important among students with ETTH.

P1-F6
Headache treatment outcome: a proposed paradigm for quantitative analysis
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Evaluation of the efficacy of multidisciplinary inpatient/outpatient treatment of chronic headaches is ideally documented utilizing objective, quantitative data. Outcome efficacy is measured using a variety of standardized instruments such as the Headache Impact Test (HIT), Global Response to Treatment evaluation (GRT), the Beck Depression Inventory (BDI) and a Patient Satisfaction Questionnaire (PSQ). Maximizing quantifiable programme outcomes, provides the program and referral sources with objective data. Identification of measurable program objectives is the first component of the programme evaluation paradigm. The threshold of no less that 80% is set and follow-up visits intervals are established at 3, 12, 24 and 52 weeks. (1) 'Reduce the number of headaches'. The indicator of attainment of this objective is the mean percentage of fall in study performance in the presence of pain and number of days/student/6 months when the students did not study at home or missed classes due to migraine and ETTH crises, correlated with pain index, are presented in the table. With respect to all other items tested, there was a significantly higher impairment in the presence of migraine than in the presence of ETTH and in the presence of the latter compared to control.

Conclusions The present study confirms the profound impact of headache on the quality of life and performance of university students, with this impact being much more evident among migraine sufferers but also important among students with ETTH.
Cost-effectiveness of sumatriptan therapy: early vs delayed treatment

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Objective: To evaluate the cost-effectiveness (CE) of early migraine treatment with sumatriptan when pain is mild vs delayed treatment when pain may be moderate to severe.

Materials and methods: We developed a decision analytic model to compare the costs and outcomes per attack for early vs delayed migraine treatment with 50 mg and 100 mg sumatriptan. For each patient group, the model determined: the proportion pain-free at 2 and 4 h after initial therapy; the sustained pain-free rate (proportion pain-free at 4 h with no recurrence); medical care costs; and work loss costs during a 24-h period. Total costs were medical care plus work loss costs. CE analysis (change in costs for early vs delayed migraine therapy compared to the change in outcomes) was performed from both a medical care perspective (including only medical care costs) and an employer perspective (including total costs).

Results: Early sumatriptan treatment resulted in substantial increases in pain-free rates at 2 and 4 h and sustained pain-free rates compared to delayed treatment. Treatment with 100 mg sumatriptan resulted in better outcomes than did treatment with 50 mg. Medical care costs for identical doses were similar for early and delayed treatment but work loss costs were substantially lower for early treatment, resulting in decreased total costs. The incremental CE of early vs delayed treatment with 50 mg sumatriptan from a medical care perspective ranged from $7.64 per additional pain-free patient at 2 h to $2.23 per additional sustained pain-free patient. From an employer perspective, early treatment with 50 mg sumatriptan resulted in decreased total costs and better outcomes than delayed treatment (i.e. early treatment dominated delayed treatment). Comparing the impact of treatment timing with 100 mg sumatriptan, early treatment dominated delayed treatment in both perspectives.

<table>
<thead>
<tr>
<th>Treatment timing</th>
<th>Early</th>
<th>Delayed</th>
<th>Early</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Pain-free at 2 h (%)</td>
<td>50.5</td>
<td>45.0</td>
<td>67.0</td>
<td>53.6</td>
</tr>
<tr>
<td>Pain-free at 4 h (%)</td>
<td>79.6</td>
<td>66.5</td>
<td>90.0</td>
<td>74.6</td>
</tr>
<tr>
<td>Sustained pain-free rate (%)</td>
<td>66.6</td>
<td>47.8</td>
<td>77.0</td>
<td>55.9</td>
</tr>
<tr>
<td>Medical care cost ($)</td>
<td>21.94</td>
<td>21.52</td>
<td>20.86</td>
<td>20.95</td>
</tr>
<tr>
<td>Work loss cost ($)</td>
<td>19.64</td>
<td>38.98</td>
<td>15.06</td>
<td>35.60</td>
</tr>
<tr>
<td>Total cost ($)</td>
<td>41.58</td>
<td>60.50</td>
<td>35.92</td>
<td>56.55</td>
</tr>
</tbody>
</table>

Conclusions: Model-based results indicate that on a treated attack basis, early treatment of migraines with sumatriptan leads to decreased costs and improved outcomes compared to delayed treatment. These results provide additional evidence of the value of educating patients to treat at the first sign of headaches.

The timing of triptan use and its effect on migraine-related disability

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Objectives: 1. Determine the effect of triptan use on disability associated with migraines. 2. Identify differences in migraine-related disability based on timing of triptan use.

Methods: Migraine sufferers (N = 70) treated at a private neurology practice reported their triptan use and headache-related disability for one migraine. Seven patients who
reported this particular migraine, which was not representative of their typical migraines, were excluded. Participants reported the level of migraine pain (mild, moderate, severe) at which they took a triptan. They also reported the number of disabled and partially disabled (at least 50% impairment) hours of paid work, unpaid work, and social activities experienced while suffering from this migraine. Data were analysed using one-way ANOVA.

Results Of the 63 patients, 37 were taking Imitrex (pill, nasal spray, or injection), 14 were taking Maxalt (pill or melt), 5 were taking Amerge (pill), and 7 were taking Zomig (pill). Seventy percent of patients reported 2 or more disabled hours and 63% reported two or more partially disabled hours in at least one area of functioning. 43% reported 2 or more hours of total disability (disabled hours + 0.5 partially disabled hours) from paid work activities (M = 3.56, SD = 5.86). In addition, 57% reported 2 or more hours of total disability from unpaid work activities (M = 4.35, SD = 6.28), and 48% reported 2 or more hours of total disability from social activities (M = 3.84, SD = 6.54). Total disability hours did not vary with the type of triptan used. 33% of the sample population reported taking a triptan at the mild level of migraine pain, 49% at the moderate level of pain, and 17% at the severe level of pain. Individuals who treated their migraines at the severe pain level reported significantly more total disability hours (M = 9.15, SD = 12.32) for social activities than people who treated when pain was at either a moderate (M = 3.17, SD = 4.12) or mild (M = 2.31, SD = 4.43) level (P < 0.05). Also, those who treated themselves when pain was severe reported a significantly greater amount of partially disabled hours for both unpaid and paid work compared with the other two groups (P < 0.05). Disabled paid or unpaid work hours did not vary with the level of pain at which a triptan was taken.

Conclusions Triptan use does not eliminate migraine-related disability. When patients take triptans while experiencing a mild level of migraine pain, they experience fewer hours of disability.

| Table for abstract P1-F9 |
|------------------------|-----------------|-----------------|---------------------|-----------------|
| Study and medication (N) | Odds ratio (95% CI) | Cost per tablet ($) | Proportion pts with successful outcome ($95% CI) | Cost per success ($) |
| Protocol 030 | | | | |
| rizatriptan 10 mg (385) | 1.7 (1.2, 2.3) | 14.86 | 0.31 | 47.94 (41.28, 55.04) |
| sumatriptan 100 mg (387) | | 16.01 | | 72.77 (59.30, 88.94) |
| Protocol 046 & 052 | | | | |
| rizatriptan 10 mg (1114) | 1.2 (1.1, 1.5) | 14.86 | 0.33 | 45.03 (41.28, 49.53) |
| sumatriptan 50 mg (1116) | | 16.01 | 0.28 | 57.18 (51.65, 61.58) |
| Protocol 901 | | | | |
| rizatriptan 10 mg (201) | 3.6 (2.1, 6.2) | 14.86 | 0.30 | 49.53 (40.16, 61.58) |
| naratriptan 2.5 mg (212) | | 16.74 | 0.11 | 152.18 (104.6, 239.1) |
| Protocol 902 | | | | |
| rizatriptan 10 mg (290) | 1.4 (1.0, 2.0) | 14.86 | 0.31 | 47.94 (40.16, 57.15) |
| zolmitriptan 2.5 mg (286) | | 14.74 | 0.24 | 61.42 (49.13, 77.58) |

© Blackwell Science Ltd Cephalalgia, 2001, 21, 336–342
Conclusion This analysis shows, based on the outcome measure of freedom from pain, functional disability and associated symptoms at 2 h, that rizatriptan 10 mg provides better value than other triptans with potential cost-savings from $12.15 to $102.65 per successfully treated attack.

P1-F10
Economic analysis of acute migraine: results from a controlled comparison of almotriptan and sumatriptan

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Objective To compare the costs associated with the treatment of an acute migraine attack with either oral almotriptan or sumatriptan.

Methods Patients meeting IHS criteria for acute migraine were enrolled in a double-blind, placebo-controlled trial. Patients were randomly assigned to either almotriptan 12.5 mg or sumatriptan 50 mg for the treatment of a single migraine attack. Clinical, quality of life, and resource utilization data were collected from patient diaries kept for 48 h following the onset of a treated migraine. A cost minimization analysis was conducted from both a payer perspective and a societal perspective. Average unit costs were used to convert resource use into monetary values. Statistical comparisons were conducted on log transformed costs because cost data were positively skewed.

Results 1073 patients were evaluated, 591 on almotriptan and 382 on sumatriptan. No significant baseline differences were noted between groups. Pain relief at 2 h was achieved in 58% of the almotriptan group and 57% of the sumatriptan group. Healthcare system log costs were significantly (P < 0.01) less with almotriptan than with sumatriptan. Societal log costs were not significantly (P = 0.08) different between treatment groups, although a trend favoured almotriptan. Assuming two to six acute migraine attacks per month, healthcare system payers might save $42.96 to $128.88 per patient per year.

Conclusion Healthcare system payers might realize significant cost savings with the use of almotriptan vs sumatriptan.

P1-F11
A cost-effectiveness analysis of eletriptan 40 mg and 80 mg vs sumatriptan 50 mg and 100 mg in the treatment of migraine attacks

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Objectives This study compares the cost-effectiveness of eletriptan with sumatriptan in the acute treatment of migraine.

Methods The analysis was based on data from the first treated attack in a randomised, double-blind, placebo-controlled study. This study compared oral eletriptan (40 and 80 mg) with oral sumatriptan (50 and 100 mg) and analysed them in terms of the cost per successfully treated patient. Successful treatment was defined as pain-free response at 2 h, with no recurrence and no use of rescue medication. In the cost-effectiveness equation, costs included the cost of the study drug and rescue medications. For patients who did not have headache recurrence, medications taken up to 24 h after the first dose were taken into account. For patients who experienced recurrence, medications taken up to 24 h after the treatment for recurrence were included. Prices for sumatriptan were obtained from the British National Formulary (September 2000 edition). In the absence of finalized prices, the same values were applied to eletriptan.

Results All data are listed in the order of eletriptan 40 mg, eletriptan 80 mg, sumatriptan 50 mg and sumatriptan 100 mg. A total of 513 patients were evaluated in this analysis (91, 80, 177 and 165, respectively). A greater proportion of eletriptan patients were defined as successfully treated than were sumatriptan patients (30%, 33%, 12% and 15%, respectively). When resource utilisation was taken into account, both eletriptan dosage strengths were associated with a significantly lower cost per successfully treated patient than was the case with the sumatriptan doses ($22.6, $33.9, $64.0 and $80.5, respectively; P < 0.03 for all comparisons of both eletriptan doses against each dose of sumatriptan).

Conclusions This economic analysis has employed a patient-focused measure of treatment outcome and shown that eletriptan is associated with a lower cost per successfully treated patient than sumatriptan at equivalent drug acquisition costs. Consequently, eletriptan has a potentially important role in the cost-effective management of migraine.

P1-F12
An economic decision model for chest symptom events associated with triptan use in migraine

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Objectives To estimate the direct medical costs of managing chest symptom side effects in acute migraine patients treated with almotriptan vs sumatriptan.

Methods An economic decision model was populated using data from a randomised clinical trial of almotriptan 12.5 mg and sumatriptan 50 mg in 1173 patients with acute migraine and from physician responses (n = 175) to a practice pattern survey. The model assessed the cost of evaluating chest symptoms following administration of the first medication dose. The probability of chest symptoms following the first oral dose of almotriptan or sumatriptan was 0.003 and 0.022 (P = 0.004), respectively. For modelling purposes, other
side effects were assumed to be equivalent between treatments. The model was developed from the perspective of the payer, and cost information was obtained from the 2000 Physician Fee and Coding Guide. The incidence of chest symptoms was varied in a sensitivity analysis, and a subgroup analysis by specialty was performed.

**Results** The average direct medical cost per patient for managing chest symptoms was $0.22 for almotriptan and $1.64 for sumatriptan. Thus, compared with treatment with almotriptan, sumatriptan adds $1.42 per patient for additional care required for chest symptom side effects. Sensitivity analysis revealed that the economic model was robust when the incidence of chest symptoms was varied. The incidence of chest symptoms with almotriptan would have to increase by a factor of 7 (from 0.003 to 0.022) before costs associated with chest symptoms were equal between the two treatments.

Subgroup analysis revealed that the cost of managing chest symptoms was higher among general practitioners compared with specialists. The incremental cost of managing chest symptoms was $0.27 for almotriptan and $1.97 for sumatriptan among general practitioners and $0.16 for almotriptan and $1.19 for sumatriptan among specialists. Compared with treating patients with almotriptan, management of chest symptom side effects adds $1.70 and $1.03 per patient to the cost of sumatriptan when patients are treated by general practitioners and specialists, respectively.

**Conclusions** Treatment with almotriptan was demonstrated to be economically more beneficial than with sumatriptan when considering differences in chest symptom side effects. Treatment with almotriptan is likely to reduce the need for patient assessment associated with chest symptoms and increase patient compliance and satisfaction with therapy.
POSTER SESSION I

G: Genetics and biomarkers

P1-G1

Major changes in the molecular composition of cerebrospinal fluid during migraine

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Slow calcium ion channel receptor mutations, vasogenic peptides and c-fos activation are important pathophysiological abnormalities in headache. Drugs that minimize the nitric oxide cascade and alter serotonergic or dopaminergic systems provide the most effective migraine treatments. However, the biochemical changes during headache remain largely unknown. This general ignorance may change with the new ability to determine the composition of biological samples in broad, discovery-based strategies. As a source to study brain function, cerebrospinal fluid (CSF) contains many molecules derived from brain and its surroundings, and is safely accessible on a repeated basis from consenting subjects. Because changes in this fluid should reflect molecular pathophysiological events, we have initiated CSF analyses from headache sufferers to discover new biomarkers and drug targets. We present the identification of more than 17 molecules that are clearly altered during a migraine attack, as well as an interpretation of their possible significance. Lumbar CSF from two migraineurs was collected during headache and when headache-free, as well as from ten controls with no migraine history and no abnormal brain symptoms. Diagnosis was based on the International Headache Classification. CSF was subjected to denaturing 2-D PAGE, and 1000–2000 proteins were analysed using Melanie 3 software. Significantly altered proteins were then identified by comparison with published maps, specific immunostaining or by protein sequence analysis. The two-dimensional profile of CSF from the headache-free migraineurs was similar to the profile from the control participants. By contrast, the profile from the same migraineurs during an acute attack revealed more than 10 proteins that exhibited a 5-fold or greater increase in quantity (including prostaglandin D synthase, orosomucoid, transferrin, an intermediate IgG γs chain and several apolipoproteins) and more than 7 proteins that decreased over 5-fold (including z1-antichymotrypsin, z2-macroglobulin, z-microglobulin, c₃ proactivator, hemopexin and cerebrin-50). It is noteworthy that these changes involved both brain- and meningeal-derived proteins and were not simply blood transudates. These major CSF compositional changes during acute migraine represent the molecular phenotype. The identity and function of these molecules may relate to migraine events: increased PGDS may produce more PGD2 and induce sleep; reduced cerebrin-50 (or MYT2) may have been consumed while inducing overall DNA synthesis. We anticipate that further identification and study of these molecules may help to elucidate the pathophysiology of migraine as well as provide objective biomarkers and potential new drug targets for headache treatment.

P-G2

Association of headaches and the metals

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Migraine is the essential chronic headache whose diagnosis is extensively underestimated and misdiagnosed. There also exists some controversy in the classification of headaches. Lack of specific biological markers constitute an important problem during diagnosis of different headache syndromes. The metals deserve attention in this field due to their diagnostic and therapeutic values in clinical medicine. Recently, some macro minerals and trace elements have started to gain importance as the biological parameters for diagnosis and during treatment. A close association of headaches with serum magnesium (Mg) and calcium (Ca) levels has been observed. Migraines and headache, which accompany ethanol ingestion, are associated with deficits in ionized Mg. Premenstrual tension-headache is also accompanied by deficits in ionized Mg and elevation in ionized Ca/Mg; MgSO₄ corrects headache and the deficit in ionized Mg. An important diagnostic role of serum ionized Mg is in the clinical division into daily migrainous headaches and daily tension-type headaches. A higher incidence of disturbed Mg metabolism characterized by low ionized Mg and high ionized Ca/Mg in patients with daily migrainous headaches was noted. There is evidence that sodium (Na) and fluid retention are associated with migraine. The blood Na level has been shown to increase before and during headache. Headache is also one of the symptoms of common cold for which zinc (Zn) may be effective therapy. It was noted that administration of Zn acetate reduced the duration and severity of cold symptoms of the common cold, including headache. The existing relationship between genetic markers of the cluster headache and the efficacy of lithium (Li) salts therapy differentiated responders and nonresponders to the Li therapy. A higher frequency of antigens HLA-B18 and HLA-A19 in the former and a higher frequency of antigen HLA-A1 in the latter subgroup were found. Headache and some other related symptoms have been found to be associated with toxic metals such as lead (Pb) and mercury (Hg). When the health effects of Hg were investigated, one of the most frequent symptoms was cephalalgia. There is a need for further investigations, including environmental...
monitoring of Hg and clinical evaluation tests to detect early effects. Continuous exposure to substantial amounts of Pb and other unidentified metals, along with health stresses, has led to increased blood and urine Pb levels with concomitant appearance of the subjective symptoms such as headache, fatigue, and dizziness. These clinical trials and laboratory measurements introduce metals as possible biological markers for the diagnosis and during therapy for different headache syndromes.

**P-G3**

**Association study between migraine and candidate genes related to signal transduction in CNS**

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**Objective** Various authors suggest the role of a dopamine receptor hypersensitivity in migraine. Our and other groups found an association between migraine and D2 dopaminergic receptor gene. The dopaminergic hypersensitivity could be related not only to a receptor altered function but also to an abnormal functioning of the signal transduction pathways. The dopaminergic receptors are coupled to GTP binding proteins, the G-proteins, consisting of \( \alpha \), \( \beta \), and \( \gamma \) subunits. Different types of G proteins exist, classified on the basis of distinct \( \alpha \)-subunits. After receptor activation G proteins dissociate in \( \alpha \) and \( \gamma \)-subunites, which are both biologically active and can regulate the functional activity of effector proteins. Through their coupling to Gs protein D1-like receptors (D1, D5) stimulate adenylyl cyclase that increase AMPc. D2-like receptors (D2, D3, D4) are coupled with G\( \gamma \) and inhibit adenylyl cyclase. In addition, dopamine receptor subtypes modulate phosphoinositide pathways and regulate activity of potassium and calcium channels.

**Materials and methods** We investigated the possible role of the \( \alpha \) subunit of the G protein Golf (GNAL), the G protein \( \beta \) subunit (GNB3) and the inositol polyphosphate 1-phosphatase (INPP1) genes in migraine without aura. We used a family-based approach to examine an isolated population such as Sardinians. We selected 100 trios constituted by a proband and both his parents with a Sardinian descent of at least four generations among the patients followed at our Headache Center, Department of Neurosciences, University of Cagliari. Proband’s diagnosis, according to IHS criteria, was migraine without aura. GNB3 and INPP1 polymorphisms were determined by PCR. The data were analysed by Transmission Disequilibrium Test (TDT).

**Results** Monte Carlo test revealed no association between migraine without aura and GNAL, GNB3 and INPP1 genes. There was no difference in allele frequency in INPP1 and GNB3 genes (\( P = 0.16 \) and \( P = 0.17 \) respectively).

**Conclusions** Our results do not support, at the moment, an association between migraine without aura and GNAL, GNB3 and INPP1. An association study between migraine without aura and G protein-coupled inwardly rectifying potassium channel gene (GIRK1) is in progress.

**P1-G4**

**Neuroendocrine effects of subcutaneous sumatriptan in patients with cluster headache**

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**Objectives** The purpose of this study was to evaluate the sensitivity of 5-HT1D receptors in patients with cluster headache (CH) using sumatriptan as a pharmacological probe. The drug, a selective 5HT1B/1D agonist, stimulates the secretion of GH and inhibits the release of ACTH, cortisol and prolactin. These effects may be used to explore the function of hypothalamic serotonergic systems *in vivo*.

**Material and methods** We administered sumatriptan (6 mg s.c.) and placebo to 10 patients with cluster headache (1 female and 9 males; mean age \( \pm S D \): 38.6 \( \pm \) 12.6 yrs), during the active phase of the disease, and to 12 healthy controls. CH was diagnosed according to the International Headache Society criteria. Blood samples were collected –15, 0, 15, 30, 45, 60 and 90 min. after injections. Plasma hormone concentrations were measured using commercially available RIA and IRMA kits.

**Results** Placebo had no effect on hormone concentrations. The sumatriptan-induced increase of GH concentrations, measured as AUC, was significantly \( (P < 0.001) \) lower in patients with CH than in controls. The decrease of prolactin concentrations induced by the drug was significantly \( (P < 0.05) \) lower in CH patients. No difference in remaining hormones was found.

**Conclusions** Our results suggest that cerebral serotonergic functions mediated by 5-HT1D receptors are significantly altered in patients with cluster headache and confirm previous studies indicating hypothalamic involvement in the disease.

**P1-G5**

**Recurrent headache in a nationwide twin population**

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**Objectives** Recurrent headache (RH) is a very common health problem in the population. To increase the
understanding of genetic and environmental contributions to this complex disease we have screened for RH in the Swedish population of twins from 55 to 64 years of age. This is the first report from the study.

Methods The Swedish Twin Registry is a population-based register of twins administered at Karolinska Institutet in Sweden. The present study population consists of approximately 16 000 twins born from 1935 to 1944. Trained lay personnel interviewed eligible twins on the telephone about common health problems including RH. Items regarding headache symptoms permitted IHS diagnoses of migraine, tension-type headache, and cluster headache (CH). Subtypes of migraine and tension-type headache were also diagnosed, i.e., migraine with aura (MA), migraine without aura (MO), episodic tension-type headache (ETTH), and chronic tension-type headache (CTTH). The twins were also asked directly whether they had ever had migraine, i.e. self-reported migraine. The lifetime prevalence, frequency of symptoms, and heritability was computed for different types of headache in an initial sample of 5680 twins.

Results The lifetime prevalence (%) of RH is tabulated below. About 93% of the RH sufferers have had more than 10 episodes of headache. Among those subjects that reported headache lasting for more than 3 days, the majority were classified as CTTH or remained unclassified. The following heritability estimates were obtained: 37% (RH), 47% (IHS-migraine), 0% (IHS-tension-type headache), and 51% (self-reported migraine).

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<td>RH</td>
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<tr>
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<td>6.9</td>
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<tr>
<td>MO</td>
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<td>8.5</td>
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<tr>
<td>IHS-Tension-type headache</td>
<td>7.2</td>
<td>11.7</td>
</tr>
<tr>
<td>ETTH</td>
<td>7.2</td>
<td>11.7</td>
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<tr>
<td>CTTH</td>
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<td>10.1</td>
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<tr>
<td>Self-reported migraine</td>
<td>10.9</td>
<td>26.4</td>
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</tbody>
</table>

Conclusions The present twin population seems to be representative for the general population in the lifetime prevalence of RH. A genetic contribution to migraine of about 50% as suggested previously is confirmed. Tension-type headache is not attributable to genetic effects. Thus, the database presently being established at the Swedish Twin Registry will be an important resource for genetic epidemiological research of RH.

P1-G6

Altered haemostasis in migraineurs with livedo reticularis

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Introduction Livedo reticularis (LR) is a term given to the violaceous netlike pattern of the skin related to arteriopathy at the dermis-subcutis border. Reported to occur with stroke (Sneddon’s syndrome), LR is also associated with migraine, particularly in female migraineurs, and in those with prior stroke. Vascular perturbation in migraine is implicated by our previously reported finding of elevated von Willebrand factor (vWF), even interictally. Our objective is to evaluate haemostasis in the subset of migraineurs who have LR using a newly developed dynamic flow system that simulates physiological conditions.

Methods From our headache clinic, we prospectively enrolled persons with a history of migraine (by IHS criteria) who were noted to have LR. We recruited age-matched healthy, headache-free, LR-free individuals as controls. Non-anticoagulated venous blood was drawn and immediately analysed by the Clot Signature Analyser, an instrument which evaluates global haemostatic function, including the response to collagen and to vessel injury under physiological conditions of flow and temperature. These measurements include platelet haemostasis time (PHT), collagen induced thrombus formation (CITF), and clotting time (CT). We also sent a venous plasma sample for analysis of vWF activity (turbidometric analysis) and antigen (latex immunofossay). Comparison between cases and controls was determined with unpaired t-test for continuous variables and chi-square for categorical variables.

Results We analysed data from 21 case subjects (mean age: 43.2±10 years, all female) 10 with migraine with aura, 11 with migraine without aura and 29 controls (mean age: 43.5±11.7 years, 26 women and 3 men). Vascular risks factors of hypertension, myocardial infarction, smoking, and birth control pill use were similar in both groups. Levels of vWF antigen (141% vs 104%, P= 0.002) and vWF activity (155% vs 103%, P < 0.001) were significantly higher in cases than in controls. The cases also had significantly shorter PHT (220 vs 279 s, P=0.02) and CITF (276 vs 310 s, P=0.04) than controls. There was a trend for prolongation of CT (1416 vs 1528 s, P = 0.065).

Conclusions Utilizing a unique new instrument, we have demonstrated that primary (platelet-related) haemostasis is shifted toward coagulation in female migraineurs with livedo reticularis. Furthermore, our findings suggest that: (1) this shift may be precipitated by endothelial perturbation with increased release of vWF, and (2) those with vascular damage and collagen exposure may be at particular risk. We speculate that migraine-associated vasculopathy and coagulopathy may play a role in the increased incidence of stroke in young female migraineurs.

P1-G7

Are there changes in neuroexcitatory aminoacids plasma levels in migraine suffers?

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Introduction and objectives The balance between excitatory and inhibitory mechanisms is altered on the basis of
migraine. The objective of our study is to identify possible differences in plasma levels of neuroexcitatory amino acids.

**Patients and methods** We study patients with migraine with and without aura (MA and M) and a control group (C). In the period without crises, blood was obtained by venipuncture and the plasma levels of aspartic (Asp) and glutamic (Glu) acids were determined. PICOTag (WATERS) test was employed and statistical analysis was performed using ANOVA test.

**Results** The study included 42 patients, 27 women and 15 men, aged between 18 and 62 years. Patients were distributed in three groups: MA 12 patients (31.3 ± 7.58 years), M 12 patients (30.4 ± 9.74) and C 18 patients (28.13 ± 2.26). The aminoacid plasma levels were higher in MA (Asp: 14 ± 12.67 and Glu: 57.22 ± 40.8). We only obtained statistical significance in aspartic plasma levels in MA group against C group (P < 0.005).

**Conclusions** These results reveal that aspartic acid presents variations in MA patients to M and C. It could have relation to spreading depression, so the patients with recurrent crisis show higher levels of this excitatory aminoacid. More studies are necessary to confirm the value of these results.

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**P1-G8**

Migraine without aura and migraine with aura are distinct disorders: a population-based twin survey

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**Objective** To investigate the co-occurrence of migraine without aura (MO) and migraine with aura (MA) in a population-based twin survey. MO and MA are multifactorial disorders. If MO and MA share common genes, co-occurrence of MO and MA should be observed more frequently than expected by the prevalence in the general population.

**Materials and methods** The study population included all living monozygotic (MZ) and same-gender dizygotic (DZ) twin pairs born 1953–1960, i.e. 5360 twins (2026 MZ, 3334 DZ). The sample included 2840 men and 2520 women. They received a posted questionnaire, and those with possible migraine were interviewed by trained physicians (VU or MG). Twins who had not responded to the questionnaire were contacted by phone, if their co-twin had possible migraine. The questionnaire response rate was 87% (4660/5360) and 90% (2035/2272) participated in the telephone interview. The physicians were blinded with regard to questionnaire answers, zygosity, and the clinical diagnosis of the co-twin. The criteria of the International Headache Society were used.

**Results** Lifetime prevalence in the twin sample: 7% of men and 19% of women had MO, while 7% of men and 8% of women had MA. Lifetime prevalence of MA in twin pairs with MO: MZ men 2% (1/47), MZ women 6% (5/90), DZ men 9% (7/75) and DZ women 10% (19/182). Lifetime prevalence of MO in twin pairs with MA: MZ men 3% (1/33), MZ women 5% (3/68), DZ men 9% (4/44) and DZ women 13% (10/76). The observed and the expected number of twins with co-occurrence of MO and MA based on the prevalence in the general population were not significantly different in men or women (men P = 0.1 and women P = 0.5).

**Conclusion** The results strongly support that MO and MA are distinct disorders. Thus, common genes for MO and MA cannot be expected to be found in future genetic research.

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**P1-G9**

A new locus for migraine with aura on Xq13


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**Background** Migraine is a common disorder with a genetic basis. Sex factors influence expressivity of migraine symptoms, but only one potential locus for nonhemiplegic migraine has been identified on Xq24–28.

**Objective** To study a potential linkage of migraine with aura (MA) to X chromosome markers in a large, four-generation pedigree cosegregating (MA) and X-linked Charcot-Marie-Tooth disease (CMTX1) with previously demonstrated C552T mutation in the connexin 32 gene (GJB1) at the Xq13 region.

**Patients and methods** 50 of 67 subjects were assessed for migraine symptoms according to IHS criteria, and genotyped using 11 markers (42 members) spanning the region Xp12 to Xq28; 8 members were evaluated for the C552T mutation only. Twenty two patients had MA and three had migraine without aura (MO) based on clinical evaluation. Nineteen members of those with MA had CMTX neuropathy. Three patients with neuropathy did not have headache. Two-point and multipoint analysis was done with VITESSE 1.1, assuming a dominant model with 80% penetrance, 5% phenocopies and a gene frequency of 0.1.

**Results** Nineteen members (11 females, 8 males) of the 24 patients with the GJB1 mutation suffered from MA, while 9 (7 females, 2 males) of the remaining 23 subjects without the GJB1 mutation showed either MA or MO. Linkage analysis was performed with the 50 subjects. Two-point LOD score was 3.74 at θ = 0.0 for the GJB1 marker, and multipoint analysis revealed a LOD score of 3.73 at the GJB1 marker (θ = 0.0, establishing tight linkage of migraine with aura to this locus, and excluding the Xq24–28 region in this family.

**Conclusion** Our study demonstrates linkage of MA to the Xq13 region in this family. Our data reach statistical significance for proposing Xq13 as a new migraine locus. Connexin 32 mutated families should be evaluated for migraine symptoms in other published CMTX1 pedigrees. Contribution of chromosome 1 and 19 loci will be discussed.

**Acknowledgement** This work was funded by ‘Marqués de Valdecilla’ Foundation Grants 20/00 and A23/00.
PI-G10

Expanding the phenotypic spectrum of the CACNA1A gene T666M mutation
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Objectives Familial hemiplegic migraine is a rare autosomal dominant subtype of migraine with aura, in which missense mutations in the CACNA1A gene on chromosome 19, encoding the α1A subunit of the P/Q-type calcium channel, are present in 50% of the families. Whereas most mutations are identified in one or two families, the T666M mutation occurs most frequently, so far being reported in 13 independent FHM families. All T666M FHM families reported so far have cerebellar ataxia.

Materials and methods In our ongoing genetic screening, CACNA1A mutation analysis was performed in 64 patients with hemiplegic migraine, 33 familial and 31 sporadic cases.

Results We identified the T666M mutation in five unrelated FHM families (15% of families) and one apparently sporadic patient with hemiplegic migraine (3% of sporadic cases). Four of six families showed additional cerebellar ataxia. In one family, not all affected members had hemiparesis during the attacks but presented with attacks of confusion. One family showed progressive cognitive dysfunction.

Conclusions This study confirms that the T666M mutation is a frequent mutation in the CACNA1A gene, being found in 15% of our sample of FHM patients. When including all FHM families and familial and sporadic cases described in the literature in which the mutation analysis has been performed, 19 of 33 families had the T666M CACNA1A mutation. When a mutation in this gene is suspected, screening for the T666M mutation should be considered as a first step. The families described in this study show a considerable clinical heterogeneity, probably due to other genetic and environmental factors.

PI-G11

Mitochondrial DNA 11084 A-to-G polymorphism is not a genetic risk factor for Japanese migraineurs
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Background Mitochondrial (mt) dysfunction has been reported in patients with migraine. MtDNA 11084 A-to-G transition, in which a coding region of NADH dehydrogenase 4 (ND4), a subunit of mitochondrial complex I, causes amino acid replacement from Thr to Ala. In a small study of Japanese patients submitted as an abstract form, 13 of 53 (24.5%) migraineurs had mtDNA 11084 mutation (1). The mtDNA 11084 polymorphism have been reported to be absent in Caucasians with/without migraine headache (2, 3). We surveyed leukocyte mt DNA A11084G polymorphism in 166 Japanese migraineurs and 483 Japanese controls.

Subjects and methods Forty-three suffered from migraine with aura (MWA, mean age 34.1±11 (SD) years, male: female = 13:30) and 123 from migraine without aura (MOA, 37.1±15.3 years; male:female = 15:108). The control group consisted of 483 healthy subjects (45.5±9.9 years; male:female = 242:241). All participants gave written consent. The diagnosis of migraine was established in accordance with the criteria of International Headache Society. Genomic and mitochondrial DNA was extracted from venous blood leukocyte by the standard DNA extraction method. Genotype of each sample was determined by polymerase chain reaction, restriction fragment-length polymorphism (PCR-RFLP) analysis. The sense and antisense primers used were; 5'-CTC CTA CCC CTC ACA ATC ATG GCA AGC-3' and 5'-ATT AGT GCC ATG AGT AGG GGA AGG GAC C-3'. The PCR products were digested by a restriction enzyme BsaM I. The 281-bp fragment derived from the A allele (wild) was not digested, whereas the fragment of the same length from the G allele (mutant) was digested by BsaM I into 169- and 112-bp fragments. The digested PCR fragments were electrophoresed in 1.5% agarose gels. Sequencing of some PCR-products confirmed that this PCR method provided amplification of the target mtDNA region.

Results The frequency of mt DNA11084 A-to-G transition was 7.2% (12/166) in the migraine group and 7.3% (35/483) in the controls. The frequency of the mutation was 4.7% in MWA and 8.1% in MOA. There was no significant difference among the groups (chi-square test).

Conclusions The mt DNA11084 A-to-G transition is more common in Japanese than reported in Caucasian, however, this polymorphism is not a genetic risk factor for migraine in Japanese patients.

Acknowledgement Supported by the Min. Edu. & Sci., Govt. of Japan.

References

P1-G12

Altered allelic distributions of the serotonin transporter and phenol sulfotransferase genes in migraine without aura patients

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The development of the serotonin (5-HT) hypothesis and the recent introduction into the therapeutics of several triptan compounds acting preferentially at the 5-HT receptors have made the latter ideal candidate genes in the pathogenesis of migraine, though with little success so far [ref. (1) for review]. Although not confirmed (2), the only positive finding in the 5-HT field concerned the 5-HT transporter (5-HTT) gene (3), despite controversial phenotypic reports [ref. (4) for review]. By contrast, platelet phenol sulfotransferase (PST) activities, for which 5-HT is one substrate, were always reported to be reduced in migraine patients, particularly in individuals who are susceptible to dietary triggers [ref. (5) for review]. We thus decided to investigate both 5-HTT and PST gene polymorphisms in 40 patients suffering from migraine without aura (IHS criteria) and 99 blood donors (control group) after receipt of their informed consent. DNA samples were prepared from peripheral blood leukocytes using standard procedure. A PST gene polymorphism as well as the two described polymorphisms of the 5-HTT gene, i.e. the variable number tandem repeat (VNTR) in intron 2 and the insertion/deletion in the linked polymorphic region (5-HTTLPR, 2 alleles l and s), were determined using well-assessed PCR procedures (6, 7). Allelic and genotypic distributions were compared using the chi-square test of homogeneity. Genotype distributions were in Hardy–Weinberg equilibrium for the three tested polymorphisms in patients and controls. For the 5-HTTVNTR polymorphism, no difference was observed for genotypic nor allelic distributions between patients and controls (P = 0.74 for genotypes, P = 0.50 for alleles) according to Montagna et al. (2), but at variance with Ogilvie et al. (3). However, the 5-HTTLPR II genotype was more frequent among patients (47.5%) than controls (30%) (P = 0.04), whereas no difference was observed between patients and controls for I and s alleles distribution, suggesting a recessive effect. In addition, for the first time to our knowledge, we report that the allelic distribution of the PST gene differed between patients and controls (P = 0.04), whereas no difference (P = 0.14) was evidenced for the genotypic distribution.

References


P1-G13

Glutathione S-transferase polymorphisms: as a candidate gene with the habituation of smoking in migraine without aura

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Background Migraine is considered as a polygenic multifactorial disease that is caused by various environmental and genetic factors. Cigarette smoking induces migrainous symptoms. Glutathione S-transferase (GST) plays an important role in the defense of the body against reactive compounds. This enzyme catalyzes the reaction of glutathione with a wide variety of organic compounds to form thioethers, a reaction that is sometimes a first step in a detoxification process leading to mercapturic acid formation. We investigated whether the GST-P1, M1, T1 polymorphisms had an association with exposure to smoking in Japanese headache sufferers.

Materials and methods 38 suffered from migraine with aura (MWA, mean age = 34.0 ± 11.8 (SD) years, male: female = 12 ± 26), 99 from migraine without aura (MWOA, 38.1 ± 15.1 years; male: female = 17 ± 82) and 47 from tension type headache (TH, 48.3 ± 17.0 years, male: female = 13 ± 34). The control group consisted of 338 healthy subjects (44.8 ± 11.1 years; male: female = 144 ± 194). All participants gave written consent. The diagnosis of migraine was established in accordance with the criteria of the International Headache Society. Genomic DNA was extracted from venous blood samples by the standard DNA extraction method. The information of the habituation of smoking with headache sufferers was obtained by questionnaires. The genotype of GSTP1Ile105Val polymorphism was confirmed by PCR-RFLP methods with AlW26I and GSTM1; T1 null polymorphisms were confirmed by multiplex PCR method described previously (P1: Menegon A et al.; T1, M1: Michael A et al.). The genotype frequencies were compared with chi-square test.

Results The P1 Val, T1, M1 null genotype frequencies were as follows: P1, 0.11; T1, 0.37; M1 0.47 in MWA, P1, 0.11; T1, 0.45; M1 0.63 in MWOA, P1, 0.11; T1, 0.38; M1 0.51 in TH and P1, 0.12; T1, 0.44; M1 0.46 in CTL. There was a significant difference between MWOA and CTL (P < 0.01). Among the smoking patients in MWOA (N = 19), M1 null genotype frequency was more increased (15/19, P < 0.05).

Conclusion Our data indicate that GST M1 may be one of the genetic risk factors for MWOA with cigarette smoking in the Japanese population.

Role of polymorphisms of P-selectin glycoprotein ligand-1 (PSGL-1) in migraine

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Background and objectives Very recently, it has been established that immunological mechanisms, such as enhanced lymphocyte-endothelium interactions, could be part of the migraine pathophysiology in humans. The first adhesive step of leukocytes is mainly propitiated by the interaction of a receptor, termed P-selectin glycoprotein ligand-1 (PSGL-1), with endothelial P-selectin. The presence of polymorphic variants of PSGL-1 has been recently described, based on the inheritance of a variant number of tandem repeats (VNTR) sequences (16 in A allele, the largest and most frequent; 15 in B; and 14 in C, the shortest and least common allele). Our group has demonstrated that these variations in the distance by which the active sites of PSGL-1 extend from the surface influence adhesion of leukocytes with other cells expressing P-selectin. Therefore, the main objective of this work was to investigate whether the VNTR polymorphisms of PSGL-1 gene could play a role in migraine.

Subjects and methods We studied 85 patients with migraine (43 with aura, and 42 without aura), and 183 healthy blood donors from the South of Spain. Detection of the VNTR PSGL-1 alleles was performed by genomic PCR method and direct electrophoresis on acrylamide gels.

Results The frequency of the PSGL-1 genotypes and alleles were similar in patients with migraine and controls (P = 0.57, P = 0.76, respectively). Moreover, we did not observe significant differences in these frequencies attending to the type of migraine (P = 0.58, P = 0.49, respectively).

<table>
<thead>
<tr>
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<td>C</td>
<td>0.02</td>
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</table>

Conclusions According to our results, the VNTR polymorphism of PSGL-1 gene does not play a significant role in migraine.

Genetic determinants of comorbid migraine and mood/anxiety disorders: focus on the WFS1 gene

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From the epidemiological standpoint, a strong association exists between migraine and mood and anxiety disorders, which appear to be comorbid in 10–25% of the general population. The clinical diagnosis of migraine is associated with a significant risk of psychiatric disease, and some prophylactic treatments are effective in both conditions. There are some observations to suggest that in general these disorders share common metabolic changes, and presumably also common genetic determinants. It is now accepted that mood and anxiety disorders recognize a clear genetic component, although there is uncertainty as to the genes specifically involved. This may be due to the fact that migraine and depression/anxiety are both complex disorders, and multifactorial in nature; thus, there is presently no definite model of genetic transmission. We have tested whether the psychiatric comorbidity of migraine may be accounted for by any polymorphism in wolframin gene (WFS1), involved in Wolfram’s disease. Subjects harbouring mutations in this gene often suffer from psychiatric and behavioural disturbances, approximately 26% of the heterozygous patients being admitted to psychiatric institutions for manic-depressive symptoms or severe depression. We selected consecutively 24 migraine patients, 18 with migraine without aura (MA-) and 6 with migraine with aura (MA+), according to the IHS criteria. All patients showed psychiatric manifestations also (assessed using SCID-P and MMPI questionnaires). In addition, in 8 of the patients (2M, 6F, mean age 42.3±3 year) one or more episodes of major depression had occurred prior to migraine onset. The presence of WFS1-R611H and WFS1-H456R polymorphism was evaluated in our sample using a PCR-RFLP technique with suitable commercially available primers. A reduced frequency of the h611 allele (WFS1-R611H allele) was found in MA- patients. These preliminary data suggest a possible link between MA- and sWFS1-RR genotype; thus, common genetic determinants may underlie the psychiatric comorbidity of migraine.

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Increase of structural brain change with higher migraine attack frequency: a population-based MRI study, the camera-project

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Objectives We conducted a population-based MRI study and examined the association of structural brain lesions and migraine. We found that migraineurs, notably those with aura symptoms, are at high risk for (silent) cerebellar infarcts. Secondly, we found that female, but not male migraineurs are at increased risk for subcortical white matter lesions. In this part of the study, we examined the influence of migraine attack frequency on the risk for structural brain change.

Methods The sample is from the GEM study, which is based on a cohort of 6039 Dutch adults, including 863 migraineurs, who participated in a population-based study of cardiovascular risk factors. Migraine diagnosis was assessed according to IHS-criteria in a multistage procedure including a semistructured clinical interview by telephone. From the cohort aged 30–60 year, we randomly selected for MRI of the brain, 134 migraineurs without aura (MO), 161 migraineurs with aura (MA) and 140 controls who were matched to the cases. One neuroradiologist, blinded to clinical status, read MR images to identify infarcts and to assess subcortical WML (using a semiquantitative scale that takes into account a fixed volume of small, medium and large WML). Total WML volume was dichotomized into the upper 20% vs the rest. We separately estimated the risk (Odds Ratio; OR) for cerebellar infarct and high WML load, respectively, in migraineurs vs controls, using logistic regression, controlling for demographic and cardiovascular risk factors. Data on migraine frequency and characteristics were assessed during a structured telephone interview, some days before MR examination.

Results Regardless of migraine subtype, migraineurs with higher attack frequency were at higher risk for cerebellar infarcts [OR = 5.1 (P = 0.17) for <12/ year and OR = 9.3 (P = 0.04) for ≥12/year]. The risk for infarct in the cerebellum varied strongly by both migraine type and attack frequency per year [OR = 7.1 (P < 0.1) for MO with ≥12/year, OR = 18.1 (P < 0.01) for MA with <12/year and OR = 25.4 (P < 0.004) for MA with ≥12/year]. These effects did not vary by sex. The risk for high WML load in female migraineurs compared to controls also varied with attack frequency [OR = 1.5 (P = 0.3) for <12/ year and OR = 2.6 (P < 0.01) for ≥12/ year]. In men, no association of high WML load to migraine was found [OR = 0.6 (P = 0.3)].

Conclusion In migraineurs, the risk for both cerebellar infarct and WML increased with increasing attack frequency. For cerebellar infarcts, MA with higher attack frequency were at highest risk.

POSTER SESSION I

H: Pharmacology

P1-H1

Immunohistochemical comparison of CGRP and substance P (peptides and receptors) and NMDAR1 and GLUR1 receptor distribution in the cat trigeminocervical complex

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Using immunohistochemistry, we sought to examine the relative distribution and cellular expression of neuropeptides: CGRP (and receptor); substance P (and NK-1 receptor) and markers of excitatory amino acid (EAA) neurotransmission: AMPA/kainate (GluR1 receptor) and glutamate (NMDAR1 receptor) in cat spinal cord and caudal medulla. Paraffin-embedded, 4% paraformaldehyde-perfused sections were processed, containing trigeminal nucleus caudalis (TNC) and cervical spinal dorsal horn regions of C1 and C2-encompassing the trigeminocervical complex (TCC). Following a modified peroxidase-antiperoxidase method, sections were reacted, respectively, with an antirat (raised in rabbit) CGRP antibody, an antimouse (raised in pig) CCRP receptor antibody, an antisynthetic peptide substance P antibody, an antirat NK-1 receptor antibody, an antirat GluR1 receptor antibody and an antimouse NMDAR1 receptor antibody; all raised in rabbit. DAB-Ni²⁺-enhanced (black/grey) and nonenhanced (brown) was employed as visualizing chromagen. We observed intense brown DAB staining of CGRP-immunoreactive (IR) axon fibres and punctate labelling (varicosities) in laminae I/II outer (of the spinal dorsal horn (C1 and C2) and TNC. In other sections of the same regions, black/grey DAB staining of CGRP receptor-IR was seen exclusively in cytoplasm of cell bodies, but with much less intensity, within the same laminae. Intense substance P staining was seen as brown DAB-labelled varicosities and neuropil in laminae I/IIo of the spinal dorsal horn and TNC. While Substance P (NK-1) receptors were seen distributed as black/grey DAB cytoplasmic cell body staining also in laminae I/IIo and throughout the TCC. GluR1 receptor-IR cell bodies were also noted within laminae I/IIo, resulting in a brown DAB deposit in the cytoplasm of these neurons; there was also some intense punctate (varicosity and axon fibre) staining as well. Finally, NMDAR1 receptor-IR was predominantly distributed within the neuropil, across laminae I/IIo throughout TCC, as a uniformly intense, but diffusely spread grey/grey DAB deposit. Occasionally some moderately labelled cell perikarya were discernible amidst the neuropil staining. Using immunohistochemistry, we detected the relative locations of IR specific to various receptors and neuropeptides within laminae I/IIo of the TCC. Localization of neuropeptide and EAA receptors in the TCC has implications for future development of pharmacological treatments for conditions like migraine.

P1-H2

Neurogenic vasodilation of dural blood vessels in the anaesthetized rat is not mediated by cholinergic transmission

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Objectives To test the hypothesis that dural vessel dilation induced by closed cranial window electrical stimulation is in part mediated by cholinergic transmission.

Introduction Dural vessel dilation induced by activation of trigeminal sensory fibres may be responsible for some component of the migraine attack. Electrical stimulation of a closed cranial window in the anaesthetized rat provokes dilation of dural vessels that can be tracked by intravital microscopy. The presence in some patients with migraine and cluster headache of clinical features, such as lacrimation, suggests cranial parasympathetic activation and poses the question as to whether neurogenic meningeal dilatation has a cholinergic component.

Methods Rats were prepared according to the technique described by Williamson et al. (1) in order to record on-line the diameter of a middle meningeal artery branch through a closed cranial window using an intravital microscope coupled to a video dimension analyser. In the first experiment, Acetylcholine (ACh; 1 µg, IV) was administered before and after muscarinic blockade (n=5) with scopolamine (2 mg/kg, IV) or nicotinic blockade (n=6) with mecamylamine (4 mg/kg, IV). In the second experiment (n=8), vasodilation was induced by electrical stimulation of the cranial window surface before and after muscarinic blockade with IV scopolamine. Nicotinic blockade was not used in the second experiment as it did not alter the response to ACh in the first one. The effect of ACh infusion and cranial surface electrical stimulation on dural vessel diameter was calculated as the maximum percentage increase in relation to baseline. Student’s t-test for paired samples was used to compare the means of the values obtained before and after the cholinergic blockade, and differences were considered significant when P<0.05.

Results The mean dural vessel percentage increase caused by Acetylcholine stimulation was significantly different before and after muscarinic blockade (P=0.045). Moreover, there was no difference between the after blockade values and those obtained after vehicle infusion (P=0.431). In contrast, no difference was detected in the effect of ACh
before and after nicotinic blockade (P = 0.688). In the second experiment, when the effect of muscarinic blockade on the neurogenic dilation model was assessed, no significant difference was demonstrated (P = 0.538).

**Conclusion** Cholinergic dilation of the rat dural arteries is mediated by muscarinic receptors, but this mechanism does not play a significant role in the rat dural vessel dilation induced by closed cranial window electrical stimulation.

**Reference**


**P1-H3**

**Inhibitory effects of adenosine A1 agonists on the cat trigeminovascular system: a new target for anti-migraine drugs?**

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**Introduction** Interest in the fundamental mechanisms underlying headache, particularly the pathophysiology of migraine and cluster headache, has led to the study of the physiology and pharmacology of the trigeminovascular system. The triptans, 5-HT1B/1D agonists, were substantial advances for many patients. They have both vasoconstrictor and neuronal mechanisms of action. There is considerable literature to suggest that adenosine receptor agonists may have antinociceptive effects; they have no vasoconstrictor actions. We sought to explore their role in trigeminovascular nociceptive transmission.

**Methods** Cats were anaesthetized (x-chloralose 60 mg/kg, intraperitoneally and halothane), and prepared for physiological monitoring. The superior sagittal sinus (SSS) was isolated from underlying cortex and stimulated electrically after the animals had been paralysed with gallamine (6 mg/kg, intravenously). Units linked to stimulation were recorded with a tungsten-in-glass microelectrode placed in the trigeminocervical complex. Signals from the neurons were amplified, filtered and passed to a microcomputer where poststimulus histograms were constructed online to analyse the responses to stimulation and the effect of drug administration. Blood was sampled from the external jugular vein to determine levels of calcitonin gene-related peptide (CGRP) release before and after drug administration.

**Results** Units responded to SSS with a typical latency of 8–10 ms. Intravenous administration of the highly selective adenosine A1 receptor agonist GR79236 (3, 10, 30 and 100 mg/kg) (1) had a dose-dependent inhibitory effect on SSS-evoked trigeminal neuronal activity. The maximal effect was seen at 100 mg/kg with an 80±6% reduction in probability of firing. There was a transient 10% reduction in blood pressure at this dose. The inhibitory effect could be substantially reversed by the selective A1 receptor antagonist DPCPX (300 mg/kg i.v.; P <0.05). SSS stimulation increased cranial CGRP levels from 33±2 pmol/L to 64±3 pmol/L, an effect blocked by pretreatment with 30 mg/kg i.v. GR79236 (44±3 pmol/L, n=6; P <0.01).

**Conclusion** It can be concluded that in two models of trigeminovascular nociceptive activation after SSS stimulation, the A1 receptor agonist GR79236 showed potent inhibitory activity. These studies suggest the adenosine A1 receptor as a novel, nonvasoconstrictor target for the development of acute antimigraine treatments.

**Reference**


**P1-H4**

**The effect of histamine and histamine antagonists on rat dural meningeal vessels**

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**Background and objectives** Histamine infusion causes an immediate headache and migraine attack several hours after infusion. The mechanism of action is believed to involve the activation of nitric oxide synthase, and consequently conversion of L-Arginine into nitric oxide (NO) with consequent dilation of cranial blood vessels. Mepyramine, an H1-receptor antagonist is an effective inhibitor of this dilation, but not at inhibiting NO-induced headache. This study has used the intravital microscopy technique to measure dural meningeal vessel diameter after histamine infusion and the effect of various histamine receptor antagonists and nitric oxide synthase inhibitors. We also studied the effect of the same histamine receptor antagonists on neurogenic stimulation of dural vessels.

**Methods** Rats were anaesthetised with 60 mg/kg i.p. sodium pentobarbitone and cannulated for measurement of blood pressure and intravenous administration of experimental drugs and supplementary anaesthesia. The parietal bone was thinned to form a cranial window through which the diameter of the middle meningeal artery or one of its branches was measured with a video dimension analyser (1)

**Results** Infusion of histamine at 10 μg/kg/min for 15 min yielded an immediate and reproducible dilation of the dural blood vessels. This dilation was inhibited by both H1- and H2-receptor antagonists, Mepyramine (2, 4 and 8 mg/kg) and Famotidine (0.1, 0.3, 1.0 and 3.0 mg/kg), respectively. The dilation was also blocked by the nitric oxide synthase inhibitor i-nitroarginine methylester (L-NAME; 40 mg/kg). Mepyramine, but not famotidine, only at the largest dose 10 mg/kg, had a small inhibitory effect on neurogenic vasodilation.
Conclusion The histamine-induced prolonged meningeal vessel dilatation has a similar time course to the transient headache response found in patients. Both the H1-receptor antagonist and the H2-receptor antagonist blocked histamine-induced meningeal dilatation. These data reinforce the view that both H1- and H2-receptors mediate dilation of meningeal arteries. Also, the inhibitory response of L-NAME indicates that NO synthase is activated by histamine infusion. The modest effect of H1-receptor blockade on neurogenic vasodilation is consistent with the histamine infusion. The modest effect of H1-receptor antagonist and the H2-receptor antagonist blocked histamine-mediated dilation of meningeal arteries. Also, the inhibitory response of L-NAME indicates that NO synthase is activated by histamine infusion. The modest effect of H1-receptor blockade on neurogenic vasodilation is consistent with the histamine infusion. The modest effect of H1-receptor antagonist and the H2-receptor antagonist blocked histamine-mediated dilation of meningeal arteries. Also, the inhibitory response of L-NAME indicates that NO synthase is activated by histamine infusion.

Conclusion GTN infusion provoked early mild headache in volunteers with no history of migraine but no alterations in R2 component of the nociceptive blink reflex at 15 and 45 min. This suggests that in humans GTN induced mild headache through vasodilation of the cranial vasculature but not sufficient to produce changes in central trigeminal transmission as detectable by nociceptive blink reflex measurements.

Reference

P1-H5

Nociceptive specific blink reflex and glyceryl trinitrate infusion in healthy volunteers

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Introduction Intravenous infusion of the nitric oxide donor glyceryl trinitrate (GTN) induces early headache in healthy subjects. In an animal model, subcutaneous administration of GTN increased c-fos expression in laminae I and II of the trigeminal nucleus caudalis and in periaqueductal grey matter caudal ventrolateral column, areas known to be involved in trigeminal pain processing. As the R2 component of the blink reflex is mediated by wide dynamic range interneurons from the nucleus trigeminalis caudalis, GTN may potentiate the R2 blink reflex component in healthy volunteers. The novel blink reflex technique described recently by Kaube et al. (1) theoretically offers advantages in this setting because of its nociceptive selectivity (A-delta fibres).

Methods Eight healthy volunteers with no history of migraine by IHS criteria were studied. Nociceptive blink reflex was elicited and recorded according to the above technique using a concentric stimulation electrode (0.6–1.5 mA). GTN (0.5 mg/kg/min IV 30 min) and placebo (saline 0.9% IV 30 min) were administered sequentially in a randomised double-blind design with a 30-min interval. Blocks of 6 sweeps were recorded at baseline and at 15 min and 45 min after starting each infusion. Area under the curve (AUC) of the R2 blink reflex component was calculated using custom written software (Matlab 5.1, MathWorks USA). The absolute R2 (AUC) values of all subjects were calculated and the percentage change of the absolute R2 values between each condition and baseline were compared using Friedman test analysis of variance for related samples.

Reference

P1-H6

Sensitisation of trigeminal nucleus caudalis neurones by dural prostaglandin E2 application in the anaesthetized rat

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Current animal models of migraine do not provide an accurate representation of the clinical disease. Recent evidence suggests that both peripheral sensitization of dural nociceptors innervating the pain-producing cerebral arteries and central sensitization of second order neurones within the trigeminal nucleus caudalis (TNC) may account for the extracranial hyperalgesia and alloydina that frequently accompany a migraine attack. Hence, the aim of this study was to create a sensitized animal model which will first provide a greater insight into the mechanisms underlying the pathogenesis of migraine, and secondly provide a means of more accurately determining clinical efficacy of novel drugs. In brief, extracellular recordings were made from single units within the TNC responding to nocuous electrical stimulation of the trigeminal afferent fibres innervating the middle meningeal artery (MMA), as well as innocuous (brush) and noxious (pinch) stimulation of the facial receptive field (FRF), in the anaesthetized rat. Topical application of prostaglandin E2 (PGE2), 0.1 µmol to the closed cranial window overlying the MMA enhanced the response to electrical stimulation, reaching a maximum 10 min after PGE2 treatment of 88 ± 15% (n = 8) over saline-treatment values (P < 0.05). Only 3 of the cells tested were spontaneously active and all showed an increased firing rate following PGE2 of 116 ± 31% (n = 3) over saline-treatment values. Facilitation was also seen in the FRF, following both innocuous and noxious stimulation, with a maximum increased response of 332 ± 103% and 402 ± 102%, respectively (n = 8); occurring at a median time point of
60 min after PGE$_2$ application in a range of 45–75 min (P<0.05 cf saline, n=4). Naratriptan (3 mg/kg i.v.) coadministered with PGE$_2$ significantly inhibited neuronal activity 20 min after application, but this was not significantly different from the effect of naratriptan alone. Naratriptan had no significant effect on the response to stimulation of the FRF in either saline- or PGE$_2$-treated animals. These data indicate that PGE$_2$ may cause direct activation of dural nociceptors as well as sensitizing the response to other stimuli. The peripheral sensitization evident in the increased response to MMA stimulation following PGE$_2$ may generate a central hyperexcitability reflected by the increased response to facial stimulation. With further characterization this model may be useful in the preclinical evaluation of future antimigraine drugs.

**P1-H7**

Opioid receptors modulate nociceptive neurotransmission in the trigeminocervical complex

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**Objectives** Opioid agonists have been used for many years to treat all forms of headache, including migraine. We have sought to characterize the opioid receptors involved in craniovascular nociceptive pathways by *in vivo* microiontophoresis of μ-receptor agonists and antagonists onto neurons in the trigeminocervical complex of the cat.

**Methods** Cats were anaesthetized with α-chloralose (60 mg/kg, i.p. and 20 mg/kg, i.v. supplements), after induction and surgical preparation using halothane. A midline craniotomy and C$_1$/C$_2$ laminectomy were performed allowing access to the superior sagittal sinus (SSS) and the recording site in the cervical spinal cord. Extracellular recordings of activity in the trigeminocervical complex evoked by supramaximal electrical stimulation of the SSS were made. Seven- or nine-barrelled glass micropipettes incorporating a central, tungsten recording electrode were used for microiontophoresis of test substances onto cell bodies.

**Results** Cell firing evoked by microiontophoretic application of L-glutamate (n=8 cells) was reversibly inhibited by [D-Ala$_2$, N-Me-Phe$_4$, Gly-$\alpha$-ol$_3$]-Enkephalin; H$_2$N-Tyr-D-Ala-Gly-N-Me-Phe-Gly-ol (DAMGO) (n=7), a selective μ-receptor agonist, in a dose-dependent manner, but not by control ejection of sodium or chloride ions from a barrel containing saline. Cells received wide dynamic range (WDR) or nociceptive specific (NS) mechanism receptor input from cutaneous receptive fields on the face or forepaws. The inhibition neurons activated with L-glutamate could be antagonized by selective μ-receptor antagonists D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH$_2$ (CTOP) or D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH$_2$ (CTAP), or both, in all cells tested (n=4 and 4, respectively).

**Conclusions** μ-Receptors modulate nociceptive input to the trigeminocervical complex. Characterizing the subtypes of opioid receptors that influence trigeminovascular nociceptive transmission is an important component to understanding the pharmacology of this synapse, which is pivotal in primary neurovascular headache.

**P1-H8**

CGRP receptors: comparison of human and rat pharmacology using a novel non-peptide antagonist

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**Objectives** Both rat and human CGRP receptors require the proteins CRLR (calcitonin-receptor-like-receptor) and RAMP1 (receptor-activity-modifying-protein 1) to associate with a G-protein in order to represent a functional selective receptor (1). However, the study of species differences and functional pharmacology has been performed using CGRP(8-37) the peptide CGRP-receptor antagonist which has limitations, e.g. susceptibility to degradation (2). In the current study, Compound1 (4-(2-Oxo-2,3-dihydro-benzimidazol-1-yl)-piperidine-1-carboxylic acid [1-(3,5-dibromo-4-hydroxy-benzyl)-2-oxo-2-(4-phenyl-piperazin-1-yl)-ethyl]-amide, WO 98/11128) is a novel nonpeptide antagonist that has been used to further characterize CGRP receptors in isolated intracranial, extracerebral blood vessels, the human middle meningeal artery (HMMA) and rat basilar artery (RBA).

**Methods** Ring segments of HMMA (obtained from neurosurgery patients with ethics committee approval) and of RBA were mounted for isometric tension recording either in organ baths (HMMA) or a Mulvany myograph (RBA) containing Kreb’s physiological salt solution (with 10 μM thiorphan), 37°C. Cumulative concentration-effect curves to human αCGRP were performed on separate precontracted segments either in the absence or presence of human αCGRP(8-37), 3 μM, or Compound 1 (rat, 3 μM; human, 100 nM). A matched pairs protocol was used to avoid desensitization due to multiple exposure to CGRP. Responses were calculated as a percentage of a reference response.

**Results** In both HMMA and RBA, Compound1 caused a similar noncompetitive inhibition of the hαCGRP-evoked vasodilation (=50% reduction in the max), although different concentrations were required (3 μM and 100 nM for RBA and HMMA, respectively). hαCGRP(8-37), on the other hand, had a similar effect on responses in HMMA and RBA (apparent P$_A$: 7.2 and 7.7, respectively).

**Conclusion** The novel selective nonpeptide CGRP-receptor antagonist, Compound1 displays a difference in CGRP receptor pharmacology when comparing RBA and HMMA and this was not demonstrated by hαCGRP(8-37), in this study. This difference may be due to the presence of different combinations of CRLR and RAMPs 1, 2 & 3 in the two vessel types or it may be due to rat and human CRLR and/or RAMP1 being functionally different, hence highlighting species differences.

Confirmation of functional CGRP receptors in human isolated middle meningeal arteries using BIBN4096BS

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Objectives During migraine, elevated CGRP levels are normalized by sumatriptan, concomitant with headache relief; BIBN4096BS (1) is the first CGRP receptor antagonist to undergo clinical trials for migraine. For the CGRP receptor family, calcitonin-receptor-like-receptor (CRLR) and receptor-activity-modifying-proteins (RAMPs) are necessary for receptor expression, functionality and pharmacology (2). Human middle meningeal artery (HMMA) not only contains mRNA coding for CRLR & RAMP1, 2 & 3 but also has utility in predicting antimigraine efficacy. Therefore, HMMA has been used to establish whether BIBN4096BS is a functionally selective antagonist for CGRP receptors.

Methods Ring segments of HMMA (obtained from neurosurgery patients with ethics committee approval), were mounted for isometric tension recording in Kreb’s physiological salt solution (with thiorphan at 37°C). Cumulative concentration-effect curves were performed on segments precontracted with prostaglandin concentration-effect curves were performed on segments precontracted with prostaglandin F2α (10 µM), to either human α-CGRP, human β-CGRP, adrenomedullin, amylin or calcitonin. For antagonist studies, matched pair experiments were performed and human α-CGRP was tested in the absence or presence of BIBN4096BS (1 nM or 10 nM) or human α-CGRP(8-37) (3 µM) and adrenomedullin in the absence and presence of BIBN4096BS (10 nM).

Results In HMMA, human α-CGRP, human β-CGRP, adrenomedullin and amylin caused vasodilation and were similarly potent (−log EC50: 7.7, 7.5, 7.8, 7.5, respectively) whereas, their maximum relaxant responses were different (65.3, 78.3, 55.2, 94.9, respectively) relative to prostaglandin F2α (=100%); calcitonin had little or no effect (−log EC50 7.2 and max 3.8). BIBN4096BS (10 nM) and human α-CGRP(8-37) (3 µM) inhibited human α-CGRP mediated vasodilation, causing about 50% reduction in the maximum relaxation. BIBN4096BS (10 nM) had no effect on adrenomedullin responses.

Conclusions In HMMA, CGRP and related peptides acted as potent vasorelaxants and the functional pharmacological profile to these peptides differs from that seen in other cerebral vessels; this may be due to the complexity of receptor and accessory protein expression in the different vessels. Nevertheless, in HMMA, BIBN4096BS blocked CGRP relaxations (and not adrenomedullin) and therefore, acted as functionally selective antagonist.

Acknowledgements Thanks to J. Elliot for his chemistry input.

References
to 155±23 pg/mL (1.46±0.12 fold increase n=10). This increase was also significantly different (P= 0.002 paired t-test) to that observed in vehicle controls (1.16±0.08).

**Conclusions** This study has demonstrated that BK causes the release of both PGE2 and CGRP from cultured rat trigeminal neurones. Since indomethacin abolished BK-induced PGE2 release but had little effect on CGRP release, the data suggests that BK-induced CGRP release was independent of the release of PGE2.

**References**

**P1-H11**

**Characterization of the novel, non-peptide CGRP receptor antagonist BIBN4096BS, in rat**

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The vasodilatory peptide calciton gene–related peptide (CGRP) has been implicated in the pathophysiology of migraine. Clinical studies show plasma CGRP levels to be elevated during migraine attacks (1). We have recently developed a novel, nonpeptide CGRP antagonist, BIBN4096BS (2) with subnanomolar affinity for primate CGRP receptors (3). In the marmoset, BIBN4096BS potently inhibits facial skin blood flow (FSBF) evoked by electrical stimulation of the trigeminal ganglion (TG). Here, we report on the characterization of the binding and functional properties of BIBN4096BS in rat. First, the affinity of BIBN4096BS to CGRP receptor binding sites in various rat tissues was evaluated. Compared to the high affinity found for BIBN4096BS at the primate CGRP receptor, the binding affinities of [3H]-BIBN4096BS to the rat CGRP receptor were markedly lower (nanomolar range), indicating species selectivity. Furthermore, rat nucleus accumbens and spinal cord have been reported to contain receptors for the members of the calcitonin-related peptide family, namely CGRP, calcitonin, amylin and adrenomedullin (ADM). We therefore also investigated the binding characteristics of BIBN4096BS in these tissues as a displacer of [125I]-human CGRP, [125I]-salmon calcitonin, [125I]-rat amylin and [125I]-rat ADM. Only CGRP was displaced with nM affinity, while the other peptides were displaced with μM affinities, indicating that BIBN4096BS is indeed a highly selective CGRP antagonist. In functional studies, the effect of BIBN4096BS on blocking FSBF evoked by electrical stimulation of the TG was investigated. An elevated FSBF triggered by tonic stimulation of the TG was potently reversed by application of BIBN4096BS (0.03–0.3 mg/kg).

CGRP has been suggested to play a role in mediating re-perfusion after acute myocardial infarction. We hence tested the effect of the CGRP antagonist BIBN4096BS on myocardial ischaemia provoked by coronary artery occlusion, followed by re-perfusion in anaesthetized rats. In this model, BIBN4096BS had no influence on the infarct size.

Furthermore, the effects of BIBN4096BS were tested in a model of cerebral blood flow (CBF) autoregulation. CBF autoregulation was tested by measuring CBF while lowering the blood pressure by blood withdrawal. BIBN4096BS, at a concentration maximally effective in the FSBF model, had no effect on CBF autoregulation.

In summary, we have shown that BIBN4096BS, whilst most potent at the primate CGRP receptor, is also a useful, high-affinity tool to study CGRP receptor biology in rodents.

**References**

**P1-H12**

**C-fos expression within rat trigeminal nucleus caudalis (TNC) induced by bradykinin through nitric oxide (NO) release is not altered by 5HT-1B/D agonists**

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**Introduction** We have previously reported that intracarotid injection of bradykinin (BK) in slightly anaesthetized dogs, triggers a dose-dependent pain response consisting in hyperpnoea, hypotension, bradycardia, neck muscles contraction and vocalization through activation of BK2 receptors localized in the occipital artery territory. BK2 activation of endothelium cells induces the synthesis and release of an l-arginine derived NO compound, probably S-Nitrosocysteine (S-NOC), which appears to modulate the activation of perivascular primary afferent by BK. Intracarotid injection of BK and S-NOC induced the expression of c-FOS in neurons of the rat TNC, which was significantly reduced by pretreatment with L-NAME, NO syntase inhibitor. The aim of the present study was to analyse the effects produced by 5HT-1B/D agonists, antimigraine drugs, upon BK induced c-FOS expression in the TNC.

**Materials and methods** The drugs were injected intracarotidally in 56 rats (250–300 g) anaesthetized with urethane (1.25 g/kg i.p.). All animals survived for 2 h after which they were sacrificed, perfused and fixed with paraformaldehyde (4%). Free floating sections of its brain were processed by immunohistochemistry as described by Nazaly et al. 1992. Four sham rats were injected with 10 μL saline solution, the same volume in which BK (3 μg n=6 and 10 μg n=12), S-NOC (40 μg, n=12) and 3-morpholinyl-sidoneimine (SIN-1), a NO donor (30 μg n=12) were injected in absence and in
presence of L-NAME (10 mg/kg i.p.). Rizatriptan 10 mg (n = 5) and zolmitriptan 2.5 mg (N = 5) were administrated by oral route 2 h before of the BK or S-NOC injection.

**Results** In sham rats, only a few c-FOS positive cells (mean = 12.7 cells) were detected in TNC. On the other hand, after BK (mean = 57.8 cells) and S-NOC (mean = 81 cells) injections, the number of positive cells in TNC increased significantly. SIN-1 (mean = 34.1 cells) also induced a substantial c-FOS expression; while pretreatment with L-NAME reduced the c-fos expression in the TNC induced by BK and SIN-1 but not by SNOC. The triptans compounds (rizatriptan and zolmitriptan) were not able to reduce the BK (mean = 49.8 cells) and S-NOC (mean = 74.16 cells) induced c-FOS expression.

**Conclusion** The present findings suggest that 5HT 1B/D agonists do not affect the activation of TNC neurons elicited by intracarotid BK and S-NOC.

**PI1-H13**

**Ethanol excites capsaicin-sensitive rat trigeminal ganglion neurons and releases SP and CGRP**

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Alcohol ingestion is one of the most common triggering factors of migraine and cluster headache attacks. However, the mechanism by which ethanol precipitates a migraine and cluster headache attack is not completely understood. Here we have investigated whether ethanol stimulates a subset of primary sensory neurons characterized for the content in neuropeptides, substance P (SP) and calcitonin gene-related peptide (CGRP), and for the expression of the capsaicin receptor (vanilloid receptor-1, VR1). We measured the release of SP and CGRP immunoreactivity (LI; fmol/g/20 min) from slices of rat trigeminal ganglia and the mobilization of intracellular Ca2+ ([Ca2+]i) in trigeminal neurons in culture obtained from newborn rats. Ethanol (0.1-3%) caused a concentration-dependent increase in CGRP-LI and SP-LI release. The release of SP-LI and CGRP-LI by 3% ethanol was 14 ± 3 and 97 ± 22, respectively (n = 8), and was abolished by capsaicin pretreatment (10 μM for 40 min) (2 ± 2 and 8 ± 3, respectively; n = 6, P < 0.05). Ethanol-induced SP-LI and CGRP-LI release was also reduced significantly in a Ca2+-free medium (4 ± 1 and 9 ± 4, respectively; n = 4, P < 0.05). Ethanol (0.1-3%) increased [Ca2+]i in isolated trigeminal neurons in a concentration-dependent manner. All the cells that responded to ethanol (3%) were viable and responded to capsaicin (1 μM). The increase produced by 3% ethanol was 48 ± 5% of ionomycin and that produced by capsaicin was 76 ± 7% (n = 85). After pretreatment with capsaicin (10 μM for 40 min) 3% ethanol failed to increase [Ca2+]i. Ethanol (10%) produced massive release of neuropeptides and mobilization of Ca2+. However, after exposure to 10% ethanol, neurons were no longer viable and able to respond to capsaicin.

Ethanol also increased [Ca2+]i in non-neuronal cells (human hepatocytes and HEK293). However, maximum increase was 13% of ionomycin, and the effect of ethanol in these cells was not affected by capsaicin-pretreatment. Thus, ethanol causes excitation (Ca2+ mobilization) in different cells, but this effect is particularly evident in capsaicin-sensitive sensory neurons. Neuropeptide release resulting from ethanol-induced excitation of trigeminal neurons may contribute to the ability of ethanol to trigger attacks of migraine and cluster headaches.

**PI1-H14**

**Propranolol shows no reduction of glyceryl trinitrate (GTN) induced headache and migraine in migraine patients or healthy volunteers: a double blind cross-over study**

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**Objective** Prophylactic trials in migraine are long-lasting and expensive. Before they can be done, long-term toxicology must be available and this considerably delays drug development. A human migraine model would be helpful in testing new drugs. Glyceryltrinitrate (GTN) evoked headache has been well characterized in migraine patients and healthy volunteers. Besides an immediate headache during infusion, migraine patients experience a delayed headache that resembles the patient’s normal spontaneous migraine attacks, and fulfills IHS criteria. The effect of established prophylactic antimigraine drugs on GTN evoked headache has not been reported previously. Here we report experience obtained with propranolol.

**Methods** 21 subjects with migraine without aura and 16 healthy volunteers were included in a two centre randomized double blind cross-over study. Propranolol 160 mg or placebo was given daily for 14 days, followed by a 20 min intravenous infusion of GTN 0.25 μg/kg/min on both study days. Headache was registered for 12 h after the infusion and its intensity was scored on a verbal rating scale from 0 to 10 and fulfilment of IHS criteria was recorded up till 24 h.

**Results** 14 subjects with migraine and 14 healthy volunteers completed both study days and were evaluable. All 14 migraine subjects developed headache after GTN (peak headache mean, 5.3 range 2–10). No reduction of peak headache was found after propranolol (mean 3.6, range 0–7) compared to placebo (mean 4.3, range 0–10). 8 migraine subjects developed IHS 1.1 migraine after GTN. 2 subjects on both days, 3 subjects only after placebo and 3 subjects only after propranolol. No reduction of GTN evoked IHS migraine was found after propranolol compared to placebo (5 vs 5). Subsequent analyses of migraine patients fulfilling IHS 1.1 or 1.7 after GTN did not reveal any difference between placebo and propranolol (9 vs 7). All healthy volunteers developed...
headache after GTN (peak headache mean 2.7, range 1–7). No reduction of peak GTN was found after propranolol (mean 2.6, range 1–5) compared to placebo (mean 2.6, range 1–7). 2 subjects fulfilled IHS criteria 1.1 of migraine without aura after propranolol but not after placebo. The fulfilment was short lasting and did not require rescue medication.

Conclusion We observed no effect of propranolol on GTN evoked headache and migraine in migraine patients or in healthy volunteers. This could indicate that GTN induces migraine at a different level than the prophylactic effect of propranolol on migraine.

P1-H15

Experience with SB-220453 in the glyceryltrinitrate (GTN) migraine model, interaction with GTN

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Background SB-220453 is a novel benzopyran compound which in animal models inhibits neurogenic inflammation, blocks propagation of spreading depression and inhibits trigeminal nerve ganglion stimulation-induced carotid vasodilatation. It is therefore potentially a new nontriptan antimigraine drug. Here we investigated SB-220453 in a human migraine-model.

Methods 15 patients with migraine without aura were included in a two centre randomised double-blind cross-over study. SB-220453 40 mg or placebo was followed after 60 min by a 20 min intravenous infusion of glyceryltrinitrate (GTN) 0.5 μg/kg/min on both study days. Headache was registered for 12 h after the infusion. Its intensity was scored on a verbal rating scale from 0 to 10. Fulfilment of IHS criteria was recorded up till 24 h.

Results 9 evaluable patients had GTN infusion on both study days. The administration of GTN was consistent in producing both immediate and delayed headache and migraine that resembled the patients’ usual spontaneous migraine. Delayed peak headache score showed a trend towards reduction after SB-220453 compared to placebo (mean 3.8 vs 5.0). However, no clear reduction was seen in the number of subjects experiencing delayed headache (8 vs 8), number of subjects reporting migraine (6 vs 8), migraine attacks fulfilling IHS criteria 1.1 or 1.7 (6 vs 7) or IHS 1.1 alone (4 vs 5). 4 subjects had a hypotensive episode after SB-220453 plus GTN but none after GTN alone. The reaction was unexpected since animal models had shown no vascular or sympatholytic activity. The study was terminated prematurely due to this potential interaction.

Conclusion SB-220453 had no significant acute antimigraine activity compared to placebo in this human model of migraine. SB-220453 may augment the hypotensive effect of GTN.

P1-H16

Rizatriptan inhibits neurogenic dural vasodilation in guinea-pigs via an action at 5-HT1D but not 5-HT1F receptors

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Objectives Vasodilation within the meningeal vasculature resulting from activation of the trigeminovascular system and release of calcitonin gene-related peptide (CGRP) has been implicated in the pathogenesis of migraine. Clinically effective 5-HT1B/1D agonists such as triptans inhibit neurogenic dural vasodilation in rats prejunctionally to inhibit release of CGRP, an observation which parallels clinical studies showing that sumatriptan normalises CGRP levels concomitant with headache relief. However, species differences between the 5-HT1B/1D receptor distribution within the trigeminovascular system of rats and humans, make observations in rats difficult to extrapolate to man. In contrast, the distribution of 5-HT1 receptors in the guinea-pig trigeminal nerve is similar to humans with the 5-HT1D and 5-HT1F receptor subtype predominating. These studies investigated the pharmacology neurogenic dural vasodilation in guinea-pigs using the CGRP receptor antagonist CGRP(8–37) and the 5-HT1 agonists rizatriptan (5-HT1B/1D), PNU-142633 (5-HT1D) and LY334370 (5-HT1F).

Materials and methods Guinea-pigs, anesthetized with pentobarbitone were cannulated for measurement of blood pressure and i.v. administration of drugs. Following introduction of a closed cranial window, the dural blood vessels were visualised and the diameter measured using a video dimension analyser. Prior to dilation of the dural blood vessels with CGRP (1 μg/kg) or electrical stimulation (300 μA, 5 Hz, 1 ms for 10 s) the blood vessels were constricted with endothelin-1 (3 μg/kg, i.v.).

Results In guinea-pigs pretreated with CGRP(8–37) (0.3 mg/kg, i.v.) the vasodilator response to electrical stimulation was inhibited by 85%. Dural vasodilation was also blocked (up to 62%) by the 5-HT1B/1D agonist rizatriptan (100 μg/kg) with estimated plasma levels (40 nM) commensurate with concentrations required for antimigraine efficacy in patients. In contrast, rizatriptan did not reverse the dural dilation evoked by CGRP. Neurogenic dural vasodilation was also blocked (up to 52%) by the 5-HT1D agonist PNU-142633 (100 μg/kg) but not by the 5-HT1F agonist LY334370 (3 mg/kg).

Conclusions These studies demonstrated that neurogenic dural vasodilation, mediated predominantly by CGRP release, was inhibited by rizatriptan via a presynaptic action to inhibit CGRP release from trigeminal sensory fibres innervating the dural blood vessels. Furthermore, the receptor mediating these inhibitory effects of rizatriptan was the 5-HT1D but not the 5-HT1F subtype, suggesting that if these mechanisms are relevant to the antimigraine actions of the triptans the guinea-pig is an appropriate species to investigate the pharmacology of neurogenic dural vasodilation.

P1-H17
Pharmacological profile of mechanisms involved in the external carotid vascular effects of the acute antimigraine agent isometheptene in anaesthetized dogs
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The present study set out to investigate the external carotid vascular effects of isometheptene in vagosympathectomized dogs, anaesthetized with pentobarbital. 1 min intracarotid infusions of isometheptene (10, 30, 100 and 300 μg/min) produced dose-dependent decreases in external carotid blood flow, without affecting blood pressure or heart rate. The vasoconstrictor responses to 100 and 300 μg/min of isometheptene were clearly attenuated in animals pretreated with reserpine (5000 μg/kg). Moreover, after reserpine (an α1-adrenoceptor antagonist; 100 μg/kg), the responses to isometheptene remained unaltered in either untreated or reserpine-treated dogs. In contrast, the responses to isometheptene were attenuated by rauwolscine (an α2-adrenoceptor antagonist; 300 μg/kg) in untreated animals, and were practically abolished in reserpine-treated dogs. Further investigation of the specific α2-adrenoceptor subtypes, using selective antagonists, showed that BRL44408 (2A) and MK912 (2C) markedly attenuated this response, while iminoxan (2B) was ineffective. The involvement of 5-HT1B and 5-HT1D receptors seems highly unlikely since antagonists at 5-HT1B (SB224289) and 5-HT1D (BRL15572) receptors (both at 300 μg/kg) were ineffective. On this basis, it is concluded that isometheptene-induced canine external carotid vasocstriction is mediated by both indirect (a tyramine-like action) and direct (acting at receptors) mechanisms, which mainly involve α2A- and α2C-adrenoceptors. The involvement of α1- and α2B-adrenoceptors as well as 5-HT1B/1D receptors seems limited, if any.

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P1-H18
Characterization of sumatriptan-induced contractions in human isolated blood vessels using selective 5-HT1B and 5-HT1D receptor antagonists and in situ hybridization
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Objective To study the role of 5-HT1B/1D receptors in sumatriptan-induced contractions of blood vessels of importance in migraine.

Methods Ring segments of human middle meningeal artery (6 patients), temporal artery (3 patients), right epicardial coronary artery (6 heart valve donors, who died of noncardial disorders) and saphenous vein (6 patients) were suspended in organ baths (37°C), containing Krebs solution enriched with a cocktail of atropine, prazosin, mesulergine, imipramine, mepryazine (all 1 μM), corticosterone (10 μM) and pargyline (100 μM). Contraction was recorded isometrically and was expressed as percentage of contraction to 1 μM prostaglandin F2α (middle meningeal and temporal artery) or 100 mM K+ (coronary artery and saphenous vein). Segments were incubated with either the 5-HT1B receptor antagonist SB224289, the 5-HT1D receptor antagonist BRL15572, both antagonists (all 1 μM) or vehicle for at least 30 min prior to construction of a cumulative concentration response curve to sumatriptan. In addition, we have also attempted to localize mRNA for 5-HT1B and 5-HT1D receptors in these blood vessels (except the temporal artery) via non-radioactive in situ hybridization.

Results Sumatriptan caused concentration-dependent contractions of the middle meningeal (pEC50: 6.7 ± 0.2; Emax: 85 ± 15%), temporal (pEC50: 6.7 ± 0.3; Emax: 68 ± 28%) and coronary (pEC50: 5.7 ± 0.1; Emax: 13 ± 2%) arteries as well as the saphenous vein (pEC50: 6.1 ± 0.1; Emax: 62 ± 4%). In temporal artery, SB224289 completely abolished contraction to sumatriptan. In middle meningeal artery and saphenous vein, SB224289 blocked sumatriptan-induced contraction in an insurmountable fashion. In contrast, SB224289 acted as a weak surmountable antagonist in coronary artery (pKd: 6.4 ± 0.2). BRL15572 was unable to antagonize sumatriptan-induced contractions in any of the blood vessels and incubation with both antagonists together revealed no additional antagonism. The mRNA for the 5-HT1B receptor was clearly expressed in both the smooth muscle and endothelium of middle meningeal artery and to a lesser extent in coronary artery and saphenous vein. The 5-HT1D receptor mRNA was very weakly expressed in any of the blood vessels examined.

Conclusion We conclude that the 5-HT1B/1D receptor agonist sumatriptan contracts human isolated middle meningeal and temporal artery and saphenous vein predominantly by 5-HT1B receptors. The weak antagonism by SB224289 in coronary artery suggests that 5-HT1B receptors that are susceptible to SB224289 play a minor role in contraction to sumatriptan in coronary artery.

P1-H19
Characterization of the contractile effects induced by triptans on post-mortem human basilar arteries
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Ischaemia due to vasocostriction has been one of the most severe adverse reactions found for triptans. Therefore, this study aimed to verify the contractile effects of 5-HT, sumatriptan and zolmitriptan in isolated postmortem...
human basilar arteries, characterizing their receptor subtypes. From dead bodies of individuals submitted to autopsies (average of 21 h post-mortem), basilar arteries were obtained, carefully dissected and cut into rings. Then, they were suspended under a basal tension of 19.6 mN in organ baths filled with Krebs-Henseleit solution aerated with 5% CO2–95% O2 and maintained at 37°C. Vessel segments containing distinct, macroscopically visible atherosclerotic lesions were not used. Isometric contractions were then recorded. Following a 2-h equilibration period, three concentration-response curves were performed with the different triptans and 5-HT in the presence of 0.01 mM cocaine, 0.04 mM desoxycorticosterone and 0.25 mM L-NAME. 30 min before the third curve 0.01 mM pindolol (5-HT1A/1B antagonist), 0.001 mM ketanserin (5-HT2 antagonist) and 0.0001, 0.001, 0.01 and 0.05 mM of BRL 15572 (selective 5-HT1D antagonist) were added. In each assay, control rings were used. Contractile responses of the third curve were expressed as a percentage of the maximum contraction obtained in the second curve. Data were also analysed to obtain values of E_max and pEC50 in terms of mN of tension of the second curve. All the agonists produced concentration-dependent contractions of the post-mortem human basilar artery preparations. The rank order of agonist efficacy was: 5-HT > sumatriptan > zolmitriptan, with E_max-values (mean ± SEM) of 5.55 ± 0.42 mN (n = 8), 4.44 ± 0.57 mN (n = 6) and 3.12 ± 0.19 mN (n = 6), respectively. The pEC50-values (mean ± SEM) were 6.60 ± 0.07 (n = 8), 6.44 ± 0.03 (n = 6) and 6.31 ± 0.08 (n = 6) for 5-HT, zolmitriptan and sumatriptan, respectively. Concerning the characterization of the 5-HT receptor subtype, 0.01 mM pindolol or 0.001 mM ketanserin did not alter the contractile responses induced either by 5-HT, sumatriptan or zolmitriptan; 0.01 mM BRL 15572 did significantly antagonize in an unsurmountable way the contractile responses induced by sumatriptan but not those induced by zolmitriptan, although there was also a reduction of the maximum contractile response to zolmitriptan. These findings indicate that on one hand zolmitriptan has less contractile capacity than sumatriptan in the post-mortem human basilar artery and on the other hand this vessel has a population of 5-HT1D receptors mediating the contractile response to triptans. Probably some of the ischaemic adverse events found for sumatriptan are due to its capacity of vasoconstriction.

P1-H20

Vascular reactivity to triptans in human isolated coronary and cranial arteries and its relevance to clinical administration of these drugs

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Vasoconstriction can be mediated through activation of 5-HT1B receptors, and in cranial arteries this effect may be important for the antimigraine activity of the triptans. Triptans may also produce lesser effects in other vascular beds, and coronary side-effects, although rare, remain a concern. We assessed the vasoreactivity of human isolated cranial and coronary arteries to triptans and made comparisons of vasoconstrictor potency in the human vessels with plasma levels achieved after clinically relevant oral doses of these drugs. Changes in isometric tension caused by cumulative drug additions were measured in isolated ring segments of middle meningeal, middle cerebral, and coronary arteries. Mean concentration-effect curves were obtained and nonlinear regression analysis (GraphPad Prism) was used to calculate vasoconstrictor potency. For each drug, the ratio (Cmax/EC50, with 95% confidence limits) between vasoconstrictor potency (EC50) and maximum plasma levels (Cmax) obtained after oral administration of clinically relevant doses was calculated (using published and available clinical trial data, see table).

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg)</th>
<th>Plasma nM**</th>
<th>Coronary a. ratio</th>
<th>Cranial a. ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>100</td>
<td>183</td>
<td>0.24</td>
<td>2.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.12–0.47)</td>
<td>(0.89–7.48)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>10</td>
<td>74</td>
<td>0.07</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.04–0.14)</td>
<td>(0.44–1.26)</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.5</td>
<td>16</td>
<td>0.05</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.03–0.07)</td>
<td>(0.13–1.09)</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>40</td>
<td>262</td>
<td>0.17</td>
<td>6.58</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.08–0.35)</td>
<td>(3.3–13.12)</td>
</tr>
</tbody>
</table>

For cranial arteries the pEC50 (± standard error) values for sumatriptan, rizatriptan, zolmitriptan, and eletriptan were 7.15 ± 0.2, 7.0 ± 0.1, 7.37 ± 0.2 and 7.4 ± 0.13*. In coronary arteries pEC50 values were approximately 10-fold lower: 6.11 ± 0.13, 6.0 ± 0.12, 6.46 ± 0.08, and 5.8 ± 0.14 (from Massen Van Den Brink et al., 1998) respectively. The analysis supports the view that vasoconstriction is an important antimigraine mechanism, because in general the Cmax/EC50 ratios in cranial arteries were not significantly different from unity. In contrast, in coronary arteries the ratios were low, showing that triptans are weak vasoconstrictors in this artery. Thus these studies in human isolated arteries demonstrate that triptans possess craniovascular over coronary artery selectivity.
Changes in cerebrovascular reactivity following infusion of glyceryltrinitrate in rat

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Infusion of glyceryltrinitrate (GTN) can provoke a migraine attack in migraineurs 4–6 h after GTN infusion. In an experimental rat model, we found an increase in inducible nitric oxide synthase (iNOS) in dura mater beginning 4–6 h after GTN infusion. We have in the present study used this rat model to investigate vascular reactivity to 5-HT, CGRP, and GTN in the basilar artery in vitro 4 h after GTN infusion.

Materials and methods Twenty-one anaesthetized rats were infused with GTN at 2 mg/kg/min for 30 min, and 18 rats served as controls and were infused with saline (0.2 mL/kg/min for 30 min). For RT-PCR the animals were exsanguinated at 30 min, 2, 4 and 6 h after infusion. For in vitro pharmacology the animals were exsanguinated 4 h postinfusion. The brains were quickly removed and the cerebral arteries were carefully dissected with the aid of an operating microscope. The basilar artery was mounted in a sensitive in vitro system for studies of vasomotor responses. The cerebral arteries were immersed in 1 mL RNA later (Ambion, USA) for RT-PCR.

Results There was no significant difference in blood pressure during GTN infusion compared with infusion of saline. Using a set of primers selective for iNOS, RT-PCR showed an increase in mRNA for iNOS 2–6 h after GTN infusion. Contraction induced by 5-hydroxytryptamine was significantly \( \text{pEC}_{50} = 7.23 \pm 0.10 \) compared with arteries from controls \( \text{pEC}_{50} = 6.83 \pm 0.14 \). There was no difference in maximum amount of contraction to 5-HT between the two groups. In contrast, the relaxant response to GTN was significantly depressed and shifted towards higher GTN concentrations in arteries from GTN-treated rats \( \text{pEC}_{50} = 6.54 \pm 0.14; \text{E}_{\text{max}} = 37 \pm 3\% \) as compared to control animals \( \text{pEC}_{50} = 7.19 \pm 0.18 \) \( \text{E}_{\text{max}} = 66 \pm 6\% \) \( \text{P} = 0.0007 \). The relaxation induced by CGRP was slightly but significantly \( \text{P} = 0.0087 \) more potent in arteries from GTN-treated rats \( \text{pEC}_{50} = 8.60 \pm 0.08 \) than in arteries from controls \( \text{pEC}_{50} = 8.31 \pm 0.08 \). There was no difference in maximum amount of relaxation to CGRP between the two groups.

Conclusion The results suggest that intracranial arteries become more sensitive to 5-HT-induced contraction four hours after an infusion of GTN. There also seems to be a slight increase in sensitivity to the vasodilator CGRP. In contrast, arteries from GTN-treated animals were less responsive to GTN-induced relaxation, possibly due to desensitization. It is possible that similar changes in cerebrovascular reactivity could be involved in the development of a migraine attack after GTN infusion in migraine patients.

References
Frovatriptan has been shown to have a broad therapeutic index (TI) in clinical pharmacology and migraine patient studies. In healthy subjects effects on blood pressure were seen only at 80 and 100 mg, i.e. 32–40 times the intended clinical dose of 2.5 mg. Single doses of up to 40 mg were well tolerated by migraine patients, although the incidence of adverse events (AEs) was dose proportional. In order to evaluate more thoroughly the TI of frovatriptan, a review of the clinical pharmacology safety database was performed, and AEs were reviewed in relation to frovatriptan exposure.

Methods Frovatriptan C max levels were used to define exposure. AEs occurring within 48 h of the final dose from each treatment period were related to their respective C max level and assigned to one of seven groups. These were placebo, 0–5, >5–9 (corresponds to mean blood levels for a 2.5-mg dose), >9–15, >15–25, >25–50 and >50 ng/mL. The incidence of all AEs as well as moderate or severe AEs was determined.

Results Twenty-one studies comprising 369 subjects were included in the analysis. In all, 651 treatment periods were analysed. The incidence of AEs was higher in the frovatriptan periods than in the placebo periods. There was no clear relationship between blood frovatriptan concentration and AE incidence for frovatriptan levels <50 ng/mL for either all AEs or moderate/severe AEs. A similar pattern was seen for the incidence of chest pain and throat tightness, although the numbers were small (see Table 1). Four subjects who withdrew early due to AEs and for whom C max levels were available had levels between 41 and 312 ng/mL.

Conclusion Frovatriptan has a broad TI. The incidence of AEs increased noticeably only at C max values >50 ng/mL. These concentrations correspond to mean blood levels attained at 6–10 times the intended clinical dose of 2.5 mg.

### Table 1 Incidence of AEs

<table>
<thead>
<tr>
<th>Blood C max (ng/mL)</th>
<th>All AEs (%)</th>
<th>Moderate or severe AEs (%)</th>
<th>Chest pain (%)</th>
<th>Throat tightness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0–5</td>
<td>30</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5–9</td>
<td>41</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;9–15</td>
<td>39</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>&gt;15–25</td>
<td>32</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;25–50</td>
<td>41</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;50</td>
<td>54</td>
<td>14</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

1 Chest pain includes tightness and thoracic pain.

Central cholinergic challenging of migraine by testing second generation anticholinesterase drugs

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The antinociceptive activity of donepezil, a novel cholinesterase inhibitor, was investigated in the mouse hot plate test. Donepezil (5–10 mg/kg i.p.) induced a dose-dependent antinociception, which reached its maximum effect 15 min after injection. Donepezil antinociception was prevented by the antimuscarinic drug scopolamine. At analgesic doses, donepezil did not alter animals’ gross behaviour. These results indicate that donepezil is endowed with muscarinic...
antinociceptive properties, indicating this compound as a potential therapeutic approach for the treatment of painful pathologies. We therefore investigated donepezil effect in migraine. To this aim two different clinical trials were performed. In TRIAL I 156 volunteers suffering from migraine without aura (66 males, 90 females; mean age 34.6 ± 3.7 SD) were enrolled. After one month run-in, a two months propranolol therapy (40 mg twice a day, oral route) or a two months therapy with donepezil (5 mg, evening assumption, oral route) were randomly assigned. TRIAL II consisted of a large sized open study. 357 volunteers (208 females, 169 males, mean age 34.3 ± 2.9; 152 suffering from M without aura with no less than 4 M attacks a month, 42 affected by M with aura associated to M without aura with no less than 4 M attacks a month, 142 characterized by chronic daily M) were included in the study which consisted in 1 month run-in period, 2 months donepezil treatment. A two months follow-up period was planned both for TRIAL I and TRIAL II. Donepezil, in TRIAL I, resulted effective as prophylactic agent in migraine sufferers by reducing the number of hours with pain (from 72.9 ± 24.6 to 27.4 ± 22.5), the number of attacks (from 3.4 ± 1.2 to 1.5 ± 0.9) and the severity of the pain attack (from 88.5 ± 11.8 to 73.8 ± 9.8) determined on a 0–100 VAS. The efficacy of donepezil was compared to that of the β-blocker propranolol showing higher activity. In TRIAL II, including also chronic-nearly chronic migraine sufferers, donepezil reduced the number of hours with pain (from 757.2 ± 27.1 to 397.9 ± 19.6), the number of attacks (from 8.29 ± 0.2 to 3.89 ± 0.2) and the severity of the pain attack (from 78.3 ± 0.8 to 31.7 ± 1.0). Response rates of this large sized open study (TRIAL II) devoid of entry criteria regarding migraine subtypes suggest the drug as an excellent prophylactic compound for migraine in general practice. Clinical results also indicate that the activation of the cholinergic system can represent a novel prophylactic approach to migraine.

P1-H26
5-HT 1 B/D receptor function in pupillary dynamics of iris sphincter muscle in animal and man

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5-HT 1 B/D receptor activity on iris sphincter muscle was studied in 8 cats (5 females, 3 males; all 7 months old), in 9 headache-free migraine sufferers (5 females, 4 males; age range 31–43) as well as in 9 control subjects matched for sex and age (5 females, 4 males; age 32–43 years). The experience was carried out in agreement with Helsinki Declaration and statements for animal research – IASP 1983, Cunningham 1993. Pupillary investigation was performed in subjects – animals and humans – free from any drug since at least 3 days before the treatment. Measurements were done before and after the conjunctival instillation and after the instillation of 2 drops (= 400 μg/administration) sumatriptan succinate previously ascertained by 3 different University Structures in 4 self-testing experiences as an absolutely not noxious eyedrop solution. Following conjunctival administration in the right eye, pupillary maximum ray and area were measured in standard light condition at 3 min, 6 min, 9 min, 15 min in cats and at 5 min, 10 min, 15 min, 30 min, 60 min, 90 min, and 120 min in humans. Both in cats and humans sumatriptan induced a mydriatic response which peaked at 5 min (P < 0.1) in cats, at 15 min both in migraine sufferers (P < 0.01) and controls (P > 0.1). Comparison between migraine sufferers and controls evidenced a shorter (P < 0.0001) and lower (P > 0.05) degree of mydriasis. The results suggest: (i) the occurrence of 5-HT 1B/D receptor sites in the iris sphincter muscle of cats and humans, (ii) a physiological role of 5-HT 1B/D receptors in dynamic functions of iris sphincter muscle. The outcomes of the comparison between migraine sufferers and controls seems to indicate a super-sensitivity of 5-HT 1 B/D receptor sites in migraine sufferers’ iris.

P1-H27
Selective 5-HT1F agonists, LY334370 and LY397584, inhibit both central and peripheral branches of trigeminal sensory afferents in rats

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Serotonin agonists with affinity for the 5-HT1B, 1D, and 1F receptors have been efficacious in the treatment of migraine. Their activity has been ascribed to their ability to contract vascular tissues and/or to inhibit trigeminal sensory afferents, neurons that have been hypothesized to conduct migraine pain to the CNS. Using the neurogenic dural inflammation model of migraine pain and correlational analysis of compound potency with receptor affinity and activity, our data suggests that the serotonin receptor subtype responsible for inhibiting the peripheral aspects of trigeminal neurons is the 5-HT1F (Johnson, 1997). Inhibition of the central aspects of trigeminal sensory neurons was also assessed using trigeminal stimulation-induced c-fos activation of brainstem second order nociceptive neurons. Two highly selective 5-HT1F agonists, LY334370 (Ki = 1.6 nM) and LY397584 (Ki = 5.5 nM), were examined for their ability to inhibit the peripheral and central branches of the trigeminal neurons. One-hour oral pretreatment with LY334370 attenuated dural protein extravasation with an ID50 value of 30 μg/kg, whereas LY397584 showed an ID50 of 120 μg/kg. In the c-fos expression model, oral LY334370 pretreatment significantly decreased the number of brainstem neurons staining for Fos protein with a minimal effective dose (MED) of 1 μg/kg. An oral MED for LY397584 was determined to be 1 mg/kg. The potency difference seen in the c-fos model may be attributed to differences in the ability of these compounds to penetrate the blood–brain barrier. These data suggest that 5-HT1F receptors, when activated, inhibit both the peripheral and central branches of trigeminal sensory neurons thought to participate in the transmission of migraine nociception.
P1-H28

Functional effects of frovatriptan on human recombinant 5-HT_{1B} and 5-HT_{7} receptors

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Objectives Frovatriptan is a novel 5-HT_{1B/1D} agonist which, in experiments using human vascular tissues in vitro, shows selectivity for basilar over coronary arteries (1). The cerebroselective action of frovatriptan may be due in part to its activity at 5-HT_{7} receptors. In this study the functional activity of frovatriptan and three other 5-HT_{1B/1D} agonists were investigated using human recombinant 5-HT_{1B} and 5-HT_{7} receptors stably expressed in clonal cell lines.

Materials and methods Human 5-HT_{1B} receptor cDNA was transfected into a CHO-K1 cell line expressing the promiscuous G_{i6} protein. The human 5-HT_{7} receptor was coexpressed with the chimeric G_{a16} protein in HEK-293 cells. Concentration response curves were generated using a fluorometric imaging plate reader (FLIPR) as the G_{a16} and G_{i6} proteins successfully coupled both receptors to a transient calcium signal (2,3). Concentration response curves were performed in order to determine the functional potency and efficacy of frovatriptan and reference compounds (relative to 10 μM 5-HT) as described previously (4).

Results At 5-HT_{1B} receptors, all compounds tested were potent full agonists eliciting the same maximal response as 5-HT. The rank order of potency at 5-HT_{1B} receptors was frovatriptan > sumatriptan = zolmitriptan > rizatriptan. At 5-HT_{7} receptors, frovatriptan was a high efficacy partial agonist eliciting a maximal response 76% of that elicited by 5-HT. In contrast, zolmitriptan and sumatriptan elicited only low efficacy partial agonist responses (47% and 51%, respectively, when compared to 5-HT). Rizatriptan did not elicit a detectable agonist response in this assay system. The rank order of potency at 5-HT_{7} receptors was frovatriptan > zolmitriptan > sumatriptan.

<table>
<thead>
<tr>
<th>Compound</th>
<th>5-HT_{1B} pEC_{50}</th>
<th>5-HT_{1B} relative efficacy</th>
<th>5-HT_{7} pEC_{50}</th>
<th>5-HT_{7} relative efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>8.77</td>
<td>1.02</td>
<td>7.92</td>
<td>0.97</td>
</tr>
<tr>
<td>±0.06</td>
<td>±0.01</td>
<td>±0.17</td>
<td>±0.02</td>
<td>±0.03</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>8.78</td>
<td>0.99</td>
<td>7.15</td>
<td>0.76</td>
</tr>
<tr>
<td>±0.07</td>
<td>±0.01</td>
<td>±0.05</td>
<td>±0.03</td>
<td>±0.10</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>8.72</td>
<td>0.90</td>
<td>5.47</td>
<td>0.51</td>
</tr>
<tr>
<td>±0.20</td>
<td>±0.01</td>
<td>±0.17</td>
<td>±0.10</td>
<td>±0.03</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>8.71</td>
<td>0.94</td>
<td>6.18</td>
<td>0.47</td>
</tr>
<tr>
<td>±0.07</td>
<td>±0.02</td>
<td>±0.07</td>
<td>±0.06</td>
<td>±0.06</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>8.17</td>
<td>0.95</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>±0.06</td>
<td>±0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions Frovatriptan was the most potent agonist with the highest relative efficacy at the 5-HT_{7} receptor. It was also the most potent agonist at the 5-HT_{1B} receptor. Functional potency and relative efficacy at human 5-HT_{1B} and 5-HT_{7} receptors. Results are mean ± SEM of 5–8 experiments performed in duplicate in a 96 well plate. The compounds were prepared identically and assayed at the same time. NR – no agonist response.

References

P1-H29

Systemic infusion of glyceryl trinitrate (GTN) in the rat produces sensitization of first and second-order trigeminovascular neurons

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Continuous intravenous infusion of glyceryl trinitrate (GTN), a pro-drug for nitric oxide (NO) has been shown to cause an acute short-lasting headache episode in nonmigraineurs. Migraine patients, however, treated with GTN develop a worse but also a delayed migraine-like headache. It has been suggested that NO-mediated vasodilation of cerebral and extra-cerebral blood vessels accounts for the GTN-related migraine-like headache. However, it is also likely that NO plays a role in sensitizing peripheral and central trigeminovascular neurons. The specific aim of this study was to elucidate whether systemic GTN infusion promotes sensitization of mechanosensitive dural afferents and second order neurons that process sensory information that originates in both the dura and skin. Extracellular recording techniques were used to identify changes in response properties of peripheral and central trigeminovascular neurons following 30 min intravenous infusion of GTN (2 μg/kg/min). Mechanosensitive dural primary afferents showed an immediate and either a transient or prolonged sensitization period with increased responsiveness to mechanical stimuli. In some units there was also a delayed but prolonged sensitization period commencing 1–3 h following GTN infusion. None of the units, however, displayed an increase in their spontaneous activity. Central neurons with convergent input from the dura and facial skin were also sensitized. There was evidence for increased responsiveness to mechanical stimulation of the dura and mechanical and thermal stimulation of the skin. Increases in the rate of spontaneous activity were also evident. These responses were always delayed and developed usually 1–2 h following infusion. Our findings suggest that GTN infusion, likely associated with NO release, promotes an acute and transient, but also a delayed and prolonged sensitization of dural afferents. The delayed sensitization of central neurons...
coinciding with increased responsiveness of primary afferent units suggests a role for peripheral input in driving central neurons. We cannot, however, exclude the possibility that NO, by acting directly on central pathways, also promotes central sensitization. Both peripheral and central mechanisms thus may promote GTN-induced headache.

PI-H30
Bradykinin both activates and sensitizes trigeminal ganglion neurons
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Bradykinin is an established sensitizer and activator of nociceptive sensory neurons. Its role in the pathophysiology of migraine is, however, unclear. Aberrant electrical activity and the release of the neuropeptide CGRP from sensory neurons of the trigeminal ganglia (TGNs) have been implicated in the aetiology of migraine. Using electrophysiological techniques we have investigated the effects of bradykinin on the membrane potential (Vm) of TGNs. Neurons were acutely dissociated from adult rat trigeminal ganglia and maintained in tissue culture up to 7 days prior to use. Vm was measured using the perforated-patch variant of the whole-cell patch-clamp technique. Only neurons with processes and a somal diameter between 19 and 28 μM were patched. These are known to contain CGRP and belong mainly to the C-fibre type of sensory neurons. Results are presented as mean±SEM and are from 13 neurons tested with bradykinin. Statistical significance was determined using the Student’s t-test. The mean cell capacitance was 25±1.4 pF and series resistance was 5.0±0.7 MΩ. Under control conditions, the neurons were electrically silent with a Vm of −56±2.0 mV and an input resistance of 131±17 MΩ. Action potential activity could be evoked by membrane depolarization produced by positive current injection through the patch-clamp electrode or by bath application of 100 nM capsaicin, an agonist of the vanilloid receptor. The neurons varied widely in the duration and shape of their action potentials. Within 23±3 s of application of 100 nM bradykinin, the Vm depolarized by 5.3±1.3 mV to −50±2 mV (P = 0.002) which was associated with an increase in input resistance of 18±8.8 MΩ. In 3 neurons, spontaneous action potentials were evoked. Although no effect was observed on the shape or duration of electrically stimulated action potentials and their after-hyperpolarization, bradykinin shifted the voltage threshold for action potential activity from −26±1.8 mV to −28±1.7 mV (P = 0.0002). Bradykinin did not affect the magnitude of the depolarization in Vm produced by 100 nM capsaicin (29±5 mV compared to 16±4 in control) but increased the percentage of neurons that fired action potentials in response to the vanilloid from 29% to 69%. These effects were not due to the ability of bradykinin to stimulate PGE2 production from the neurons since these effects were not mimicked by bath application of 1 μM PGE2. The combined effects of bradykinin to depolarize the membrane potential and lower the voltage threshold for action potential firing may underlie the ability of the peptide to stimulate CGRP release from TGNs. In conclusion, bradykinin both activates and sensitizes action potential activity in TGN and therefore has the potential to be involved in the aetiology of migraine.

PI-H31
Pharmacological exploration of nitrogen pathways in migraine and cluster headache
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Drugs which are direct or indirect donors of nitrogen oxide (NO) evoke a specific headache attack in the patients affected by migraine and cluster headache. The attacks are not simultaneous with the peak action of the drugs but occur with a consistent latency. This suggests a possible trigger mechanism. This is one of the principal indications for the involvement of NO in the pathogenesis of migraine and cluster headache. The cellular action of NO is mediated by the activation of the cyclic guanyll-monophosphate which is inactivated by the phosphodiesterase 5. Sildenafil was introduced in the therapy of the erectile dysfunction because it potentiates the NO action by inhibiting the phosphodiesterase 5 at the vascular level. We have studied the effect of glycerol-nitrate 0.3 mg sublingual) and sildenafil (20 mg oral dose) in two groups of patients: one affected by migraine without aura (10 subjects, 6 women and 4 men; mean age 37.5±6.75) and another by cluster headache (9 subjects, 6 men and 3 women; mean age 43.26±4.35). GNT induced a specific attack (migraine and cluster headache) after a period of time from 60 to 120 min Sildenafil induced a light, nonspecific and transitory (2–3 min) episode of headache which occurred 50–70 min after drug administration in 7 migraine and 8 cluster headache patients. A migraine patient showed a migraine attack 4 h after drug administration. No one else showed a specific attack within 6 h (the time limit arbitrarily chosen to relate the attack to the drug action). We show that even if the transitory and nonspecific headache induced by sildenafil was frequent in migraine and cluster headache patients (more of what is reported in the literature), the drug, unlike GNT, was unable to induce specific attacks. These results indicate that if NO is involved in the pathogenesis of migraine, it is not through cellular mechanisms (which are inhibited by sildenafil).
P1-H32

Effect of baclofen and sodium valproate on rat brain GABA levels: a dose response study

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Objectives Sodium valproate (SV), a GABA-mimetic drug, is an established prophylactic agent in migraine. Baclofen, a GABAB agonist, also appears to have a similar effect. They have no direct effect on serotonin. GABA may have an indirect role in the pathogenesis of migraine. The purpose of this investigation was to study the effects of chronic medication with oral baclofen and SV on GABA levels in rat brain.

Materials and methods The investigation was carried out in 36 Sprague-Dawley adult male rats and was divided into 2 studies for dose-related effects. In study I, the intended daily doses of baclofen and SV were 400 mg and 6 mg per 100 g of body weight, respectively. In study II, these were 7 mg and 30 mg per 100 g of body weight, respectively, for baclofen and SV. These corresponded to the upper range of the therapeutic doses (study I) and a midpoint of upper range of therapeutic doses and LD50 doses for rats (study II). There was a no treatment control group. Study treatments were allocated to 3 groups of rats according to a predetermined randomisation code. Baclofen and SV were added to drinking water for 6 days. Rats were sacrificed on day 7. GABA levels were studied in the prefrontal cortex, septum, striatum, hypothalamus, hippocampus, and substantia nigra. Brain slices (300 mm-thick sections) were prepared and above 6 specific brain regions were microdissected. GABA levels were measured by a high performance liquid chromatography (HPLC) method.

Results In study I, the average daily doses of baclofen and SV consumed by rats were 0.39 mg and 6.68 mg per 100 g body weight, respectively. In study II, these were 3.99 mg and 116.07 mg per 100 g body weight, respectively, for baclofen and SV. In study I, the highest concentrations of GABA were found in the striatum in all 3 experimental groups. No drug-related changes in GABA levels were observed. In study II, compared to SV and control groups, an increase ($P<0.05$) in GABA level was observed in the prefrontal cortex in rats treated with baclofen. A dose-related increase in GABA levels in the septum ($P=0.026$), hippocampus ($P=0.026$), and substantia nigra ($P=0.0022$) occurred in the baclofen group. No such change was observed with SV. Mean ($\pm SD$) serum baclofen levels in study I were 145.25 ($\pm 76.62$) mg/L, but this was not measured in study II. No measurable amount of SV was found in study I and low levels, 44.10 ($\pm 16.83$) mmol/L were observed in study II.

Conclusion Baclofen at a daily dose of approximately 4 mg/100 g body weight significantly increased GABA concentrations in the prefrontal cortex of rats. No change in SV group may be related to poor oral bioavailability.

P1-H33

The effects of selective voltage gated calcium channel blockers on trigeminal sensitization responses to dural artery dilation in the rat

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Background and objectives Mutations of P/Q-type voltage gated calcium channels (VGCCs) have been implicated in the pathogenesis of familial hemiplegic migraine (1) and in the modulation of nociceptive information from primary afferent neurons into the central nervous system (2,3). The effects of selective N-type and P/Q-type channel blockers o-conotoxin GVIA and o-agatoxin TK were tested in an electrophysiological assay of trigeminal central sensitization in the anaesthetized rat to evaluate the potential utility of VGCC blockers as antimigraine drugs.

Methods Male Sprague-Dawley rats (300–350 g) were anaesthetised with pentobarbitone (80 mg/kg i.p.; followed by 20 mg/kg i.v. infusion) and surgically prepared for single unit extracellular recordings from caudal trigeminal neurons; the femoral artery and vein and trachea were cannulated and the caudal brainstem was exposed. The parietal skull was then thinned and a stimulating electrode was placed over the middle meningeal artery. Neurones were selected that responded to electrical stimulation of the dura mater and to innocuous stimulation of the face. Air-jet pulses were applied to the vibrissa to evoke reproducible responses of single trigeminal neurones.

Results After a stable period of neuronal activity, CGRP (calcitonin gene-related peptide) was administered i.v. (1 $\mu$g/kg) to dilate the cranial vasculature; this resulted in a potentiation of vibrissal responses with 9/14 cells (mean change $+40 \pm 15\%$, $n=5$ rats). In separate groups of animals, either the N-type blocker, o-conotoxin GVIA (1 $\mu$M), or the P/Q-type channel blocker, o-agatoxin TK (1 $\mu$M) were applied to the surface of the brainstem in a volume of 50 mL, and the effects of CGRP evoked dilation were compared with control animals. In the presence of o-conotoxin GVIA ($n=7$ rats), CGRP-evoked dilation caused an increase in vibrissal responses with 10/16 cells (mean change of $+5\% \pm 1.8\%$). Similarly, in animals treated with o-agatoxin TK ($n=5$ rats), CGRP evoked dilation facilitated vibrissal responses with 6/12 cells (mean change of $+12\% \pm 5\%$). Neither of the peptide toxins had any effect on baseline responses to vibrissal stimulation.

Conclusions These data suggest that both N- and P/Q-type VGCC are important in the transmission of nociceptive inputs from distended meningeal afferents but are not involved in transmission from low threshold facial afferents. Future drugs that target these subtypes of VGCC could have potential therapeutic antimigraine utility.

References

P1-H34

Recombinant porcine 5-HT₁ receptor subtypes: structural and pharmacological profile in relation to human 5-HT₁ receptor subtypes

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Objectives To clone, sequence and pharmacologically characterize the porcine 5-HT₁₆, 5-HT₁D and 5-HT₁F receptor subtypes and to compare with recombinant human receptor subtypes.

Methods Total cellular RNA was isolated from cerebral cortex and trigeminal ganglion. Poly(A⁺) mRNA was purified from total RNA and used for cDNA synthesis and amplification of porcine 5-HT₁ receptor subtypes by RT-PCR. Oligonucleotide primers were designed from other species and the 5′ and 3′ ends of porcine receptor subtypes were verified by inverse PCR. For pharmacological studies, the cDNA inserts of the above receptors were subcloned into pcDNA3 vector, transiently expressed into Cos-7 cells and binding studies were performed on cell membranes.

Results Using RT-PCR, we amplified different bands of expected size for 5-HT₁ receptor subtypes. Nucleotide sequence of 1173 bp, 1134 bp and 1101 bp products encoded 390, 377 and 366 amino acid protein of porcine 5-HT₁₆, 5-HT₁D and 5-HT₁F receptors, respectively. The 5′ and 3′ ends of three cDNAs were also verified by inverse PCR. These recombinant porcine receptors showed high homology (92–95%) with human receptor subtypes as well as with other species. In pharmacological studies, the rank order of the affinity constant (pKᵢ) of 5-HT receptor ligands for porcine 5-HT₁ receptor subtypes showed a high correlation with the recombinant human subtypes. However, porcine 5-HT₁D receptor showed less affinity for specific 5-HT₁D antagonist BRL15572 and porcine 5-HT₁F receptor for few triptans.

Conclusion We have cloned and pharmacologically characterized porcine 5-HT₁₆, 5-HT₁D and 5-HT₁F receptor subtypes, which could be of further use as a tool for studying potential therapeutic agents.

P1-H35

Assessment of selective 5-HT₁B/1D-receptor agonist-induced peripheral vascular effects in humans

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Objectives Although selective 5-HT₁B/1D receptor agonists are effective and generally well tolerated antimigraine drugs, they are known to cause systemic vasoconstriction. A novel antimigraine drug that demonstrates efficacy without causing systemic vasoconstriction would have a major advantage. Therefore, in the development of new antimigraine drugs, sensitive techniques are needed to detect drug-induced vascular effects. In the present study, the sensitivity for detecting sumatriptan-induced peripheral vascular effects was investigated by measuring changes in dorsal hand vein (DHV) diameter, toe-arm systolic blood pressure gradient, systolic (SBP) and diastolic blood pressure (DBP).

Materials and methods A single-center, randomized, double-blind, placebo-controlled, 3-way cross-over study was performed in 12 healthy male volunteers. Dosing occasions were separated by 1-week wash-out periods. Vascular effects were measured at baseline, every 5 min for 30 min and at 40 and 60 min after subcutaneous administration of placebo and sumatriptan 3 or 6 mg. DHV diameter was measured using a technique for recording compliance of human hand veins as described by Aellig. Toe-arm systolic blood pressure gradient was measured with occlusion plethysmography using mercury-in-rubber strain-gauges placed on the arm and ipsilateral great toe. SBP and DBP were recorded using an oscillometric device.

Results Based on weighted mean and compared to placebo, sumatriptan 3 and 6 mg increased SBP by 3.3 mmHg (P=0.023) and 6.4 mmHg (P<0.001), respectively, and DBP by 5.0 mmHg (P=0.006) and 7.5 mmHg (P<0.001), respectively. This increase in blood pressure appeared to be dose dependent. Sumatriptan 3 and 6 mg decreased DHV diameter by −1.8 mV (P=0.015) and −1.7 mV (P=0.016), respectively, but this decrease did not appear to be dose dependent. Toe-arm systolic blood pressure gradient did not change (P=0.309 and 0.652 after sumatriptan 3 and 6 mg, respectively). Peak change in blood pressure and DHV diameter were recorded within 10 and 15 min after drug administration, respectively.

Conclusions In contrast to DHV diameter and toe-arm systolic blood pressure gradient, SBP and DBP increase dose-dependently after subcutaneous sumatriptan. In addition, SBP and DBP appear most sensitive for detecting sumatriptan-induced peripheral vascular effects and are much easier to assess. Consequently, until validation of more sensitive techniques, blood pressure is the parameter of choice to evaluate 5-HT₁B/1D-receptor agonist-induced peripheral vascular effects in humans.
POSTER SESSION II

I: Preventive treatment

P2-I1
Evaluation of the glyceryltrinitrate (GTN) human migraine model as a possible tool for prophylactic drug development: effect of valproate in a double-blind cross-over study

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Objective Due to the intermittent and unpredictable nature of migraine, a human model would be helpful in the study of new migraine compounds. GTN evoked headache has been fully investigated in migraine patients. Besides an immediate headache during infusion, migraine patients experience a delayed headache that resembles the patients’ spontaneous migraine attacks and fulfills IHS criteria. Efficacy of valproate in the GTN model would support the usefulness of this model in drug development.

Methods 12 subjects with migraine without aura, in a randomized double-blind cross-over study. Valproate 1000 mg or placebo was given daily for a minimum of 13 days, followed by a 20-min intravenous infusion of GTN 0.25 µg/kg/min on both study days. Headache was registered for 12 h after the infusion and its intensity was scored on a scale from 0 to 10. Fulfillment of IHS criteria was recorded up till 24 h.

Results 12 subjects completed the study. The response was identical on both study days in 6 subjects. Of these 1 did not develop headache at all, 2 took rescue medication at the onset of delayed headache and did not fulfill IHS migraine criteria on either study day. 2 reported migraine that fulfilled IHS 1.1 on both study days. 1 reported migraine on both study days that fulfilled IHS 1.1 except having only photophobia and not phonophobia before taking rescue medication. Of the remaining 6 subjects, 4 fulfilled IHS 1.1 after placebo but not after valproate. 2 reported migraine after placebo but not after valproate. However, it did not quite fulfill IHS criteria. After valproate a non-significant reduction compared to placebo were seen in subjects with GTN evoked migraine IHS 1.1 (2 vs 6, P = 0.09). Also a non-significant reduction of peak headache was seen after valproate compared to placebo (mean 4.8 vs 3.1, P = 0.10). IHS criteria 1.1 is a very hard endpoint since the subjects could treat their headache/migraine at any time and before fulfilling IHS 1.1. Subsequent analyses of the data revealed, however, that on placebo, 9 subjects reported migraine, fulfilling IHS 1.1 or 1.1 except only having photo- or phonophobia and not both before taking rescue medication. This was reduced to 3 subjects after valproate (P = 0.01).

Conclusion Valproate reduced all headache parameters, but none of the primary endpoints to a statistically significant degree, possibly due to the small number of subjects. The size of the effect was similar to that of valproate in clinical trials. The study therefore suggests that the GTN migraine model is valid and could be suitable for the testing of future prophylactic migraine drugs. Several possibilities exist for further improvement of the model.

P2-I2
The cost-effectiveness of a prophylactic migraine programme as contrasted to pharmacological migraine treatment

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Objective To compare the cost-effectiveness of utilizing the Mundo Method Programme with conventional therapy for patients in a managed care practice who were migraine sufferers receiving chronic maintenance care.

Background Migraines afflict 24 million Americans usually women between 10 and 40 years of age. The Mundo Method Programme, a self-care prophylactic oriented educational programme, seeks to prevent and control migraines by emphasizing body-mind awareness, elimination of headache triggers and stress reduction. Mundo therapy training, similar to biofeedback, is self-applied touch therapy with focused concentration to abort migraines.

Methods A retrospective analysis of programme questionnaires, baseline and follow-up (n = 78) 1995 through 1999 of clients who self-assessed their headaches as migraines according to IHS criteria. Number of headaches reported before and after the programme, use of medications, and the use of the Mundo therapy were collated. 87% were women, age range 17–62. Encounter data for this group was not available to link cost of prior maintenance treatment. A second retrospective review analyzed the cost of migraine pharmacological therapy for 10 patients being treated over 1 year (9/1999 to 9/2000) identified through pharmacy profiles and billing data. The mean cost of abortive medications and office visits for migraines was $2187/year. Adding the cost of emergency visits and diagnostic imaging increased this to $2639.

Results Analysis of the 78 cases in the Mundo programme showed a 65% reduction in the number of headaches and 52% decreased use of abortive medication. Of note, prior to programme, only 17% (9% after) were on prophylactic drug treatment. 97% reported greater self-control of their headaches. Cost was $210 per person to the managed care network. Applying this projected 65% reduction in the number of headaches to the medically managed group...
($2187) would realize a potential cost reduction of $1421 per patient.

**Conclusion** Cost reduction is noted in the decreased cost/client/year as evidenced by a decreased use of abortive and acute therapy and increased self-control. The benefits of the programme in increased personal quality of life and increased social quality of life through decreased days lost to missed work/school/social activities are related to the reduction of migraine occurrence in the survey comments. The findings that biofeedback, stress reduction, relaxation and trigger avoidance reduce frequency of headaches is consistent with the literature. A pretest/post-test design identifying encounter costs, prophylactic contrasted with pharmacological, is recommended.

**P2-I3**

**Quality of life, disability and migraine prophylactic therapy**

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**Introduction** Migraine prophylactic therapy is indicated to diminish frequency and intensity of crises when migraine attacks are more than two a month. MIDAS and SF-36 questionnaires could be powerful instruments for physicians to evaluate the disability and quality of life of migraineurs. Their use has shown how these features are ameliorated after prophylactic therapy.  

**Objective** We performed a study to evaluate the quality of life and disability in a group of migraineurs before and after prophylactic therapy. We evaluated the utility of both questionnaires in clinical practice and the impact of a chronic drug therapy on the quality of life.  

**Materials and methods** A prophylactic therapy, either with propranolol, lisuride, amitriptyline and flunarizine, was prescribed to 43 outpatients, attending the Headache Center, Department of Neurosciences, University of Cagliari. Patients were evaluated with MIDAS and SF-36 questionnaires before and after three months of therapeutic regimen. Statistical analysis was performed using Student's *t*-test.

**Results** Following therapy, 43 patients showed a statistically significant (*P < 0.05*) average decrease of MIDAS score of 19 points. An average, statistically significant (*P < 0.05*) elevation of total score was evident in every domain of the SF-36 scale, particularly in RF, RE, AS, and DF areas.

**Conclusions** This study has demonstrated that prophylactic therapies have a relevant role in decreasing disability and ameliorating the quality of life in migraineurs, and also that the chronic use of a drug does not interfere with the quality of life. The questionnaires are also valid tools to specify practical guidelines and give an estimate of economical costs of migraine. Further information given by SF-36 could integrate the clinical evaluations in fields of interest not investigated by MIDAS such as the reasons for disability that are not related only to pain.

**P2-I4**

**Carbamazepine, controlled-release, for migraine prophylaxis**

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**Objective** To study a new dosage form of a well-established anticonvulsant as a prophylaxis agent for migraine headache previously refractory to prior conventional therapies.

**Study design and methods** 30 patients were entered into this study, all with at least IHS-criteria migraines (1.1,1.2, 1nd 1.7). Many (*n = 20*) had coexistent tension-type headaches for an average duration of 5.2 years. All patients had at least 4 migraine headaches per month; 8 patients had chronic daily headaches in addition to migraines. Most (*n = 24*) had been tried on other anticonvulsant prophylaxis therapy, including divalproex sodium, gabapentin, tiagabine and even carbamazepine. Controlled-release carbamazepine (Carbatrol) was started at 200 mg in the evening once daily and titrated by 200 mg each week to 400 mg per day. At times, 200 mg in the morning and 400 mg in the evening was the regimen, depending on how it was tolerated. Some patients were also increased to 400 mg twice a day. After initial titration of therapy, the average duration of active therapy was 4 months. Patients kept headache diaries and rated the severity of their headaches on a 0–10 numeric rating scale (NRS).

**Results** 14 patients reported an average of 67% reduction in frequency of their migraines. 4 patients reported no change in the pattern of their headaches. 4 patients dropped out due to side-effects (nausea and GI disturbance) and 10 patients are still in the titration phase of the study. 10 patients were able to taper off or reduce the dosage of their other anticonvulsant prophylaxis medications.

**Conclusions** This open-label study demonstrates effectiveness of controlled-release carbamazepine as a prophylaxis agent for refractory migraines and other headaches. This is complementary to its action in reducing other pain syndromes, such as neuropathic pain and trigeminal neuralgia. It is well tolerated and may be tried as prophylaxis even when other neuronally active agents have not been successful in reducing headache severity and frequency. The preliminary results in an ongoing study extend our available option for treating resistant migraines and they warrant further research using double-blind methods.

**P2-I5**

**A retrospective chart review demonstrating the efficacy of topiramate for prophylaxis of migraine**

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**Objective** Topiramate is a novel agent approved for treatment of epilepsy. Open-label reports and pilot double-blind trials suggest a role for topiramate in migraine
prophylaxis. We had previously reported a chart review of 98 refractory migraine patients treated with topiramate. For this chart review we utilized topiramate prophylaxis earlier in the treatment sequence.

Methods A chart review was performed on patients started on topiramate between 5/4/99 and 11/17/00. 107 patients were included who were diagnosed with migraine (with or without aura) and on topiramate for migraine prophylaxis with at least one follow-up visit at four or more weeks. Charts were reviewed for frequency of mild or moderate/severe headaches and side-effects at baseline and all follow-up visits.

Results The 28-day headache frequency was reduced from 21.0 ± 8.7 to 17.1 ± 9.6 (P = 0.0001) for all types of headache; mild headaches were reduced from 7.5 ± 6.9 to 5.7 ± 6.4 (P = 0.02) and moderate/severe headaches were reduced from 13.4 ± 7.4 to 11.4 ± 8.6 (P = 0.02). A subgroup analysis of patients failing >5 prior preventives (n = 54) demonstrated a reduction in all types of headache from 19.9 ± 9.9 to 15.2 ± 9.3 (P = 0.0004); mild headaches were reduced from 6.9 ± 7.3 to 5.3 ± 6.4 (P = 0.09) and moderate/severe headaches were reduced from 12.9 ± 7.2 to 9.9 ± 7.3 (P = 0.004). Patients failing 35 prior preventives (n = 53) proved more refractory; all types of headache were reduced from 22.1 ± 7.3 to 19.1 ± 9.5 (P = 0.04); mild headaches were reduced from 8.2 ± 6.5 to 6.2 ± 6.5 (P = 0.09) and moderate/severe headaches were reduced from 13.9 ± 7.7 to 13.0 ± 9.5 (P = NS). Of patients experiencing a ≥50% reduction in headache frequency, the response rate for each type of headache was: mild headaches (36%); moderate headaches (37%); severe headaches (39%) and all types of headache (23%). The ≥50% reduction rate for patients receiving topiramate as their only migraine preventive (n = 40) was as follows: mild headaches (33%); moderate headaches (25%); severe headaches (43%) and all headaches (23%). The most common adverse effects (AEs) were drowsiness, paresthesias, decreased memory, altered taste and decreased appetite. Average patient weight was reduced from 183 to 177 lb (P = 0.0001) with 76% of patients experiencing weight loss. 27 patients (25%) discontinued topiramate therapy; 12 due to lack of efficacy and 15 due to AEs. The median topiramate dose was 75 mg daily (range 25–300 mg/day).

Conclusions The results demonstrate the clinical efficacy of topiramate in migraine prophylaxis. In contrast to our previously reported series in which patients with mild headache obtained less benefit, topiramate therapy was significantly able to reduce the frequency of both mild and moderate/severe headaches.

P2-I7

Topiramate: a case series study in migraine prophylaxis

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Objective To determine the efficacy and tolerability of topiramate for the prophylaxis of episodic and chronic migraine, based upon a retrospective chart review.

© Blackwell Science Ltd Cephalalgia, 2001, 21, 368–383
Methods Patients diagnosed with either episodic migraine (EM) or chronic migraine (CM) who had continued topiramate therapy for at least 6 weeks were selected from an electronic medical record system. The parameters examined included demographics, headache frequency, headache severity, concomitant use of other medications, and incidence of adverse events. A paired t-test was used to compare parameters before and after treatment.

Results Seventy-four patients were identified (6 males and 68 females). Fifty patients were diagnosed with CM and 24 with EM (6 with aura and 18 without). Among patients with CM, mean headache frequency was 25.7 ± 28 days. Mean headache severity was 6.3 on a scale of 0–10, with 10 representing the most severe pain. Among patients with EM, mean headache frequency was 9.9 ± 28 days. Mean headache severity was 6.0. Eighty-six percent of all patients used abortive migraine medication at least 3 days/week. Among all patients, 15 (20%) were on monotherapy and 59 (80%) were on polytherapy. Sixty of 74 patients (81%) began topiramate therapy at 25 mg/day for the first week, which was increased by 25 mg/week to 100 mg bid (200 mg/day). Fourteen patients began topiramate therapy at 15 mg/day for the first week, which was increased by 15 mg/week. The mean daily dose for all patients was 208 mg, and the mean duration of treatment prior to analysis was 133 days. Mean headache frequency decreased from 20.6 ± 28 days to 13.6 for all patients (P < 0.001), from 9.9 to 5.1 for EM patients (P < 0.02) and from 25.7 to 17.7 for CM patients (P < 0.01). Headache severity was reduced by at least 50% in 44.6% of all patients, 58.3% of EM patients, and 38.0% of CM patients. Among all patients, headache severity was reduced from 6.2 to 4.8 (P < 0.001). Headache severity was reduced in EM patients (6.0–4.8, P < 0.001) and in CM patients (6.3–4.8, P = NS). Seventy-four percent of patients reported using less abortive medication. Migraine duration was shorter for 58% of EM patients. The number of years with CM, a diagnosis of depression, and the presence of a more severe psychiatric disorder did not correlate with a change in headache frequency (P = NS). The most common adverse events were paresthesias (25%), cognitive difficulties (15%), dizziness (4%) and nausea (4%). Six patients (8%) discontinued topiramate due to adverse events and 4 due to ineffectiveness. Mean weight loss was 6.9 lb.

Conclusions These study results suggest topiramate is effective in reducing headache frequency, severity, and duration in patients with CM and EM. Psychiatric comorbidity did not effect treatment outcome.

P2-I8

Topiramate: effective prophylaxis treatment for refractory migraines and mixed headaches

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Introduction In the prophylaxis treatment of migraine headaches, virtually all anticonvulsants that are currently marketed (perhaps more properly termed neuronal stabilizing agents or neuromodulators) have been shown to have efficacy. This may be concordant with the theory that migraines and perhaps other headaches are reflective of a brain disorder. Topiramate has unique mechanisms of action: blockade of sodium channels and AMPA/kainate glutamate receptors, agonist activity at GABA-A receptors, together with weak carbonic anhydrase activity. Preliminary evidence from this ongoing study, and from other investigators, has suggested that topiramate may be effective for migraine prophylaxis.

Methods Patients with chronic migraines, with or without other headache types were recruited from the population of a headache clinic and were enrolled in this open-label study. Topiramate was started at 25 mg per day, with weekly titration to 100–150 mg per day over 4–6 weeks. Active treatment continued over at least three months, although some patients have been treated up to a year or longer. Additional dosing titration was accomplished during ongoing treatment with topiramate. The average dose for successfully treated patients was 325 mg per day, usually in two doses (range 75–1600 mg). Patients were instructed to keep headache diaries, rating the frequency and severity of their migraines and other headaches. They used a 0–10 numeric rating scale (NRS) to rate the severity of their symptoms.

Results Ninety-eight patients were placed on topiramate. Most (76) had failed attempts at prophylaxis with neuronal stabilizing agents such as divalproex sodium, gabapentin, carbamazepine and other agents. Many (n = 49) had coexisting cervical or lumbar neuropathic pain syndromes. In 60 evaluable patients, migraines decreased in frequency by an average of 70.5% per month. Remaining headaches were about 57% less severe, on a 0–10 NRS. Sixteen patients dropped out due to side-effects, mainly paresthesias, cognitive difficulties or non-benefit. Eight patients were just begun on therapy or did not follow the protocol instructions; 6 were lost to follow-up.

Conclusions Topiramate prophylaxis therapy was well tolerated and effective in reducing the frequency and severity of chronic migraine headaches in a refractory headache clinic population. Double-blind, placebo-controlled studies are warranted.

P2-I9

Topiramate is indicated in cluster-migraine

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Objective Determine whether topiramate is indicated for preventative treatment of cluster-migraine.

Background Topiramate demonstrates migraine efficacy in randomized controlled trials and in open label clinical experiences. Unfortunately, preventative selection is often difficult and usually determined by comorbid illnesses. However, it would be helpful if migraine diagnosis could define an appropriate preventative agent. Topiramate has shown efficacy in migraine and cluster headache, thus it may have efficacy in the cluster-migraine overlap syndrome, migraine with cluster features (MWCF).
Methods MWCF represents unilateral International Headache Society migraine associated with at least one symptom of ipsilateral orbital-nasal autonomic dysfunction (lacrimation, conjunctival injection, ptosis, eyelid edema, rhinorrhea or nasal congestion). Chart review was performed on all MWCF patients who were treated with topiramate from October 1997 to October 2000. The primary endpoint was defined as ≥50% reduction in migraine frequency. A significant reduction in headache or aura severity represented secondary endpoints. Endpoints were assessed after two to three months of treatment.

Results Fifteen subjects were identified, all women. Age range 38–62 years, mean 51.3 years. Five had chronic or transformed migraine and 10 episodic migraine. Aura was present in three; one multiple auras and another prolonged aura. Topiramate was adjunctive in 13, and monotherapy in two. Topiramate dose range 25–400 mg/day; mean 112.5 mg/day. Migraine improved in 14 (93%). Twelve (80%) had significant improvement with ≥50% reduction in migraine frequency. Two improved per secondary endpoints. Only one patient failed, a chronic migraine sufferer on adjunctive treatment. In chronic migraine sufferers there was no significant change in daily headache when assessed at three months. However, at six months one had a reduction in daily headache to once weekly. One monotherapy patient dropped out after two weeks of treatment because of dizziness and paresthesias but was assessed at two months with ≥50% reduction in migraine frequency. There were no other dropouts. Paresthesias occurred in two others, and one each had dysgeusia and drowsiness, and another had anxiety, depression and confusion. Seven patients had weight loss.

Conclusions Topiramate demonstrates efficacy, safety and tolerability in the treatment of migraine with cluster features. The high efficacy suggests a possible selection bias in favor of a migraine variant or phenotype likely to be topiramate responsive. Thus, specific migraine diagnosis or characteristics may define which preventative is most appropriate. This preliminary report suggests that topiramate is indicated for cluster-migraine prevention. However, randomized controlled trials are recommended.

P2-I10

Long-term therapy with topiramate reduces migraine frequency and severity: a retrospective chart analysis

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Objective To assess long-term efficacy and tolerability of topiramate for the prevention of migraine, utilizing a retrospective chart review.

Background Several antiepileptic drugs, including topiramate, appear to have utility in a variety of neurologic conditions such as neuropathic pain and migraine. Long-term efficacy and tolerability of these agents for the prevention of migraine have not been widely reported.

Design and methods Patients treated for >1 year with topiramate for migraine prevention were included. Chart review included demographics, baseline headache frequency, prior preventive medications, topiramate dose, reduction in migraine frequency (≥50%) and severity (≥2-point reduction on a 4-point migraine severity scale; 0 = no pain, 3 = severe or debilitating pain), and incidence of adverse events (AEs).

Results Thirty-seven female patients were included in the analysis, ranging in age from 19 to 60 years (mean = 42). Seventeen patients (46%) had migraine with aura. The mean number of years with migraine was 20 (range 3–50). Twenty-seven patients (73%) failed one or more (mean = 3.2) prior preventive medications. The mean duration of therapy was 2.3 year (range 1.3–3.9). The mean daily dose of topiramate was 295.3 mg (range 50–1600); 14 patients (38%) received ≤100 mg/day and 8 patients (22%) received 125–200 mg/day. Most patients (92%) received topiramate monotherapy. Only 3 patients (8%) received combination therapy. Thirty-one patients (84%) experienced a ≥50% reduction in monthly migraine frequency and 28 of 37 patients (76%) experienced a ≥2-point reduction in migraine severity while on topiramate therapy. No serious AEs were reported. The most common AEs were paresthesias (n=8), and confusion (n=4). Six patients discontinued therapy; 4 for lack of efficacy and 2 for AEs (diarrhoea, confusion). Sixteen patients experienced weight loss (mean 18.4 lb, range 10–68 lb).

Conclusions To our knowledge, this is the first report on the long-term utility of topiramate in migraine prevention. Topiramate therapy was well tolerated. A large majority of topiramate-treated patients experienced fewer, less severe migraine headaches.

P2-I11

Neuromodulation of late life migrainous accompaniments with topiramate therapy

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Objective To describe neuromodulation of late life migrainous accompaniments using prophylactic topiramate therapy.

Background Late life migrainous accompaniments – scintillating scotomas, numbness, aphasia, motor weakness and dysarthria – may occur for the first time after the age of 45 and complicate the diagnosis of cerebrovascular disease, particularly transient ischemic attacks. Treatment can be difficult for many reasons but cardiac disease and drug tolerability pose challenges in choosing a prophylactic medication for the older patient.

Topiramate is being evaluated currently as a migraine prophylactic agent. As a neuromodulator, topiramate blocks repetitive firing, enhances GABA inhibition, reduces glutamate, and affects voltage-gated Na⁺ and Ca⁺⁺

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channels, all of which may be important in interrupting migraine. Those characteristics, in combination with its cardiac safety profile, make topiramate an appealing drug to evaluate in the older patient with persistent migrainous accompaniments.

**Design and methods** Ten patients with persistent periodic neurologic phenomena (scintillating scotoma, parasthesias, vertigo) were identified. All were over 65 years of age and one had a previous history of migraine with aura. After thorough evaluation to exclude causes of transient ischaemia, topiramate therapy was begun. Patients were treated with dosages beginning at 15 mg/day, increasing by 15–30 mg every four days, up to 100 mg BID. No significant adverse events were reported by the patients.

**Results** All 10 patients achieved complete resolution of their neurologic symptoms within 2 weeks of initiating topiramate.

**Conclusions** The anticonvulsant, topiramate, may represent an effective and safe therapy for treatment of late life migrainous accompaniments by modulating cortical hyperexcitability.

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**P2-I12**

**Levetiracetam as prophylaxis for resistant headaches**

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**Introduction** Levetiracetam, a new anticonvulsant, was recently introduced in the USA for the treatment of seizures. It has an unknown mechanism of action. Using the rationale that virtually all commercially available anticonvulsants have shown efficacy in the treatment of migraines and other headache types, we decided to utilize this agent in the treatment of a headache clinic population with chronic refractory headaches. This initial open-label study with a neuronal stabilizing agent such as levetiracetam was undertaken on the premise that migraines and perhaps other headaches are a manifestation of an underlying neuronal dysfunction in the brain.

**Methods and study design** 30 patients from an existing headache clinic population were chosen for prophylaxis therapy with levetiracetam. All had been treated with other neuronal stabilizing agents (anticonvulsants) and had failed or responded poorly to these attempts at prophylaxis therapy. Each patient in the study had tried at least two agents and 18 patients had tried up to 4 different agents. Most (n = 25) were on at least one agent at the time levetiracetam was added. All patients had an average of at least 2 migraine episodes per week (IHS criteria) with additional tension-type headaches. 16 patients had additional cervical or lumbar radiculopathy symptoms, cervical whiplash injuries, failed neck surgery or traumatic brain injuries prior to onset of their severe headache pattern. Levetiracetam was started at 250 mg in the evening, with weekly increases. A one-month run-in period to 1000 mg twice a day was used. Further dosage adjustments were then made during active therapy. Patients kept headache diaries and rated severity of headaches on a 0–10 numeric rating scale (NRS).

**Results** 14 patients reported a better than 50% reduction in their migraine frequency and severity with 3 months of active therapy. Dosage was adjusted in some cases to 4500 mg per day in two or three doses. 12 patients were able to discontinue or taper the bulk of their prior prophylaxis medications during treatment with levetiracetam. 8 patients had no response, or discontinued the medication due to side-effects (n = 3). 4 patients had 25–50% decreases in their headache patterns and 4 are in the run-in phase.

**Conclusions** These preliminary results from an ongoing study using levetiracetam as migraine prophylaxis may add a new therapeutic strategy to existing available therapies with neuronal stabilizing agents. This may be very useful in treating refractory headache patterns that have failed multiple prior attempts at headache stabilization using neuronally active agents. These results may warrant a double-blind trial of levetiracetam in migraine prophylaxis.

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**P2-I13**

**Levetiracetam for preventive treatment of migraine**

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**Objective** To assess the efficacy of the new anticonvulsant levetiracetam (Keppra, LEV) for preventive treatment of migraine.

**Background and methods** Antiepileptic drugs are increasingly recognized to be helpful in migraine treatment. LEV, a promising anticonvulsant of unknown mechanism, has been tried in a small number of headache patients. We gave 62 patients with refractory migraine with (10) and without aura (40) as well as daily headache (12) LEV beginning at 500 mg BID and increasing as needed to 1500 mg BID. Other preventive and abortive medications were continued. Patients reported headache frequency, duration and severity as well as side-effects at 1, 2 and 3 months.

**Results** Ten patients discontinued LEV because of side-effects (drowsiness, nausea, increased headache, tics and ‘weird’ feelings) or lack of efficacy. Headache frequency and severity were significantly less on LEV, although not in the first month and not at doses below 1500 mg/day. The infrequent side-effects increased at the more effective higher doses.

**Conclusions** LEV reduced the frequency and severity of refractory migraine with modest side-effects. Gradual titration to relatively high doses of this antiepileptic drug may be required for migraine therapy. Further study of LEV in headache and pain is appropriate.
P2-I14

Lamotrigine efficacy in migraine prevention

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Objective To show that lamotrigine has efficacy in the treatment of migraine with and without aura and chronic daily headache.

Background In a randomized controlled trial, Steiner et al. showed a lack of preventative migraine efficacy for lamotrigine. However, that study was flawed by the exclusion of 50% of the study population on the basis of being placebo responders or non-compliant during the single-blind placebo run in phase, too high a lamotrigine starting dose (200 mg/day), and changing the lamotrigine dose during the trial. Subsequently, open label studies by D'Andrea et al. and Lampl et al. suggested efficacy for migraine aura and migraine with aura, but not for migraine without aura.

Materials and methods Sixty-five patients with migraine or chronic daily headache seen between September 1999 and August 2000 were compassionately prescribed lamotrigine. Data was collected regarding demographics and efficacy was recorded after two or three months of treatment. The primary efficacy endpoint was a ≥50% reduction in severe headache frequency. Secondary endpoints included a ≥50% reduction in mild and moderate headache frequency or aura frequency.

Results 30 patients were excluded from analysis; 10 were non-compliant (six never started the medication), eight were lost to follow-up, one lack of benefit, and 12 adverse events (4 increased headache, 3 rash, 2 abdominal discomfort, 1 pruritus, 1 ataxia). 35 patients had adequate lamotrigine therapy, and efficacy was assessed at three months in 30 and two months in five. There were 26 women and nine men; age range 32–79 years, mean 48.4 years. 24 patients had transformed or chronic migraine, seven episodic migraine and four had hemicrania continua. Lamotrigine dose ranged from 25 to 200 mg/day, mean 55.1 mg, median 50 mg/day. Treatment was adjunctive in 34 patients. 48.6% (17/35) of patients showed significant improvement with a ≥50% reduction in severe headache frequency, the primary endpoint. However, overall efficacy was 57.1% (20/35). 18 patients had aura and 66.7% (12/18) had a ≥50% reduction in headache frequency. There were nine analgesic rebound or overuse patients and only one improved significantly. There were seven non-rebounding chronic migraine without aura patients and eight with aura; 28.6% (2/7) without aura and 50% (4/8) with aura improved significantly. Surprisingly significant improvement was noted in 75% (3/4) of hemicrania continua patients.

Conclusion This open label experience suggests supplementary evidence in favor of lamotrigine efficacy as a migraine preventative. Effectiveness was improved when aura was present and diminished by analgesic overuse. In some intractable populations, chronic migraine with aura and unexpectedly hemicrania continua, benefit was demonstrated. On the basis of these findings, additional randomized controlled trials are recommended.

P2-I15

Preventive treatment of migraine with zonisamide

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Objective To assess the efficacy of the new anticonvulsant zonisamide (Zonegran, ZNS) for migraine prevention.

Background and methods ZNS is a new antiepileptic drug which reduces glutamate-mediated excitatory neurotransmission, inhibits excessive nitric oxide production, scavenges hydroxyl and nitric oxide radicals and inhibits carbonic anhydrase. These mechanisms may be relevant to migraine as well as epilepsy. We gave ZNS to 34 patients with migraine with and without aura who were resistant to other preventive and abortive treatments. ZNS was begun at 100 mg/day and increased as tolerated to 400 mg daily. Other medications were continued, including abortive treatments but not analgesics. Patients reported frequency, duration and severity of headaches as well as side-effects at 1, 2 and 3 months.

Results Headache severity was significantly reduced, and the other measures decreased with ZNS treatment. Paresthesias, fatigue, anxiety and weight loss were acceptable side-effects which often resolved; more bothersome side-effects were agitated dysphoria (2) and difficulty concentrating (2), which prompted discontinuation. Nine other patients discontinued ZNS because of perceived lack of efficacy.

Conclusions ZNS, like other neuromodulating anticonvulsants, may be efficacious for migraine prevention. It reduced headache severity and was well tolerated; at least some of the patients who stopped it due to apparent inefficacy may have responded with a longer trial. Prospective study in a larger population is appropriate.

P2-I16

Zonisamide in the treatment of headache disorders

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Introduction Zonisamide, an anticonvulsant recently introduced in the US has a unique combination of pharmacologic actions: it inhibits voltage-gated Na+ channels and also blocks T-type calcium channels. Both of these mechanisms may play a role in headache and pain modulation, possibly via neuronal stabilization.

Methods 33 patients, taken from an active headache clinic population, were selected for open-label treatment with zonisamide. All had refractory migraines and mixed headache disorders, by IHS criteria. All had failed, or had responded poorly to prior trials with other anticonvulsants as prophylaxis therapy, and most (n=27) had failed at least 2 such agents. 8 had chronic migraines alone, with an average of 9 migraines per month. The rest of the patient sample had tension-type headaches along with migraines (average of 7.7 episodes per month).
Zonisamide was started as add-on therapy to other prophylaxis agents. 100 mg was given in the evening or at bedtime every third day for 4–5 doses. Then, it was increased to every other day for the same number of doses before beginning on a daily regimen. Dosage was changed every 2–3 weeks and in some cases was as high as 600 mg/day. Headache frequency and severity were reported by patients using diaries. Severity was reported on a 0–10 numeric rating scale (NRS).

**Results** 6 patients reported a 65% or better decrease in frequency of migraines and other headaches; 8 reported 25–50% decrease in their symptoms. 9 patients did not respond or were non-compliant with the protocol; 4 of these patients stopped the medication due to side-effects. 10 patients have just been started on the medication and are in the titration phase of therapy.

**Conclusions** Zonisamide may have efficacy in a difficult-to-treat refractory headache population. These initial data, generated open-label and ongoing, suggest zonisamide may, like virtually all other neuronal stabilizing agents (anticonvulsants), have efficacy where older agents have failed to provide relief of headache symptoms. This potentially useful agent for headache prophylaxis should be studied in a double-blind manner.

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### P2-I17

**Asthma + migraine in childhood and adolescence: prophylactic benefits with leukotriene receptor antagonist**

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**Objective** To evaluate the prophylactic benefits of montelukast, a potent cysteinyl leukotriene receptor antagonist on asthma plus migraine patients.

**Materials and methods** Treatment of 6 outpatient asthma + migraine sufferers (3 males and 3 females, aged between 9 and 13 years) were evaluated on a prospective open-label study design using sodic montelukast 5 mg (SINGULAIR®) once at night for 24 weeks. Prophylaxis and diagnosis was established for asthma according to the International Consensus Report on Diagnosis & Management of Asthma (1992) and for migraine using the IHS criteria (1988) modified by Winner et al. (1995). Frequency of attacks was measured by patients’ notes on a standard calendar currently adopted at DITH.

**Results** All patients experienced a decrease in asthma attacks during treatment. No relevant side-effect was reported. Patient data and migraine improvement are presented in the table at the foot of the page, where M = male; F = female; MA = migraine with aura; MO = migraine without aura.

**Conclusions** Leukotrienes are pro-inflammatory mediators derived from the metabolism of arachidonic acid via 5-lipoxygenase. Leukotriene antagonists for asthma prophylaxis are currently available. Perivascular inflammatory reaction in the intracranial trigeminovascular system is accepted in the pathophysiology of migraine attack. Sheftell et al. (ASH meeting 1999, oral presentation) reported a greater than 50% decrease in frequency and intensity of attacks during two months of prophylactic use of montelukast 10 mg in 10 of 14 adults migraine sufferers. The results suggest a beneficial effect of montelukast toward decreasing the frequency of migraine and asthma attacks during 24 weeks of medication in this small sample of young patients. This treatment indicates safe and efficacious benefits from prophylactic control of asthma migraine comorbidity.

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### P2-I18

**Preventative treatment of migraine headache with rofecoxib and montelukast**

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**Introduction** The use of NSAIDs has long been known to be effective in migraine prevention. Work by Sheftell (1) has demonstrated partial efficacy of montelukast in migraine prevention.

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Study purpose To assess the efficacy of a COX-2 inhibitor, NSAID, rofecoxib combined with montelukast in migraine prevention.

Study design Prospective, open label of rofecoxib 12.5 mg daily combined with montelukast 10 mg daily for 12 weeks in migraine without aura. Patients had 2–12 migraine attacks per month. Interval headaches were less than 15 days per month and distinguishable from their migraines. Previous preventative medications were allowed if dose had been stable for 8 weeks prior to study initiation.

Results There were 33 patients enrolled, 25 females and 6 males. 31 patients had evaluable data. 2 patients dropped out in the first month of treatment due to adverse effects. The mean number of migraine attacks at initiation was 6.4 attacks per month. At the end of 12 weeks, the migraine frequency was reduced to 2.3 per month (P<0.001). 25 of 31 patients had at least a 50% reduction in their migraine frequency. 2 patients had transient adverse effects but continued on the study. There were 6 patients who had been on previous preventative medication. There was no statistical difference in their response rate compared to patients on no prior preventative medication (P<0.05). There was no change in the occurrence rates of interval headache. Long-term use of 4–40 weeks additional use demonstrated no increased risk of adverse effects nor diminution in the response rate.

Conclusion The combination of rofecoxib and montelukast was a highly effective, well-tolerated preventative treatment for migraine headache. The combination of the 2 agents produced more favorable results with less adverse events than have been found in previous clinical trials of an NSAID or montelukast alone.

Reference
1 Sheftell F et al. Headache, 1999; 39:381.

P2-I19
Rofecoxib for migraine prophylaxis
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Objective To demonstrate the effectiveness of rofecoxib in the prevention of migraine.

Methods and materials Rofecoxib was prescribed to a series of patients presenting to an outpatient clinic with complaint of migraine headaches. The study was conducted in a retrospective chart review fashion. 25 patients with IHS criteria for migraine headache were treated with rofecoxib 25 mg per day, in addition to their usual abortive medications. Migraine types include migraine with and without aura, mixed migraine/tension and post traumatic migraine. Initial headache frequency was recorded. On subsequent follow-up (range 4–8 weeks), headache frequency was again recorded, as well as adverse side-effects or reason for discontinuation.

Results 16 of 25 patients (64%) reported a significant reduction in frequency of their headaches post-treatment, defined by reduction in frequency of at least 50%. Rofecoxib appeared to be equally effective for all migraine subtypes. Rofecoxib appeared to be well tolerated at the dose of 25 mg per day. 4 of 25 patients discontinued the medication, and only 2 (8%) did so because of untoward side-effects. Side-effects reported were pelvic pain and malaise. No patient discontinued rofecoxib because of GI intolerability. Two patients discontinued rofecoxib due to poor response. One patient discontinued rofecoxib because her migraines were completely controlled resulting in headache recurrence after discontinuation. After reintroducing rofecoxib, complete migraine control was once again achieved.

Conclusion Rofecoxib appears to be an effective, well-tolerated medication for the prophylaxis of migraine headache. Additional investigation of this medication on a larger scale is warranted.

P2-I20
Prophylactic treatment of migraine with tizanidine
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Objective To assess the efficacy of the alpha-2 adrenergic antagonist tizanidine (Zanaflex, TZD) as an adjunct to the prophylactic treatment of refractory migraine.

Background and methods TZD has been widely used to treat spasticity, tension headache, analgesic rebound headache, and as an adjunct to the multifaceted treatment of transformed migraine. It may also have a role in migraine preventative therapy, and with early use may prevent the emergence of daily headache. We gave TZD to 22 patients with frequent episodic migraine with and without aura who had not responded to anticonvulsants or antidepressants, and whose attacks were incompletely controlled by abortive agents. TZD was started at 4 mg nightly and increased to 16 mg nightly or in divided doses as tolerated. Other migraine medications were continued but analgesics were not. Patients reported headache frequency, duration and severity as well as side-effects after 1, 2 and 3 months.

Results TZD in doses of 4–16 mg per day significantly reduced the severity and duration of headaches, and caused a less marked reduction in their frequency. Thirteen of the 22 patients could not continue the effective TZD dose or chose to stop TZD due to sedation, fatigue or weakness.

Conclusions TZD may be a useful adjunct to other preventative medications for the prophylactic treatment of migraine. We found the sedative effects to be limiting, however, even with bedtime dosing. More gradual titration and the recent availability of a smaller size may improve the tolerability of TZD for sensitive patients.

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P2-I21

Acute effect of acetazolamide on familial hemiplegic migraine (FHM)

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Background Acetazolamide, a carbonic anhydrase inhibitor, is a treatment effective in the episodic ataxia type 2 and it has already been used successfully in FHM prophylaxis. Distinct types of mutations in the CACNA1A gene have been identified in these different autosomal dominant disorders.

Objective To evaluate the efficacy and tolerance of acetazolamide in the treatment of acute FHM attacks.

Material and methods We studied a 15-year-old male affected, since the age of 11 years, with attacks of scotoma in the peripheral visual field, lasting 15–20 min, followed by right (occasionally left) hemiparesis, including the hemiface and the hemitongue, hemiplegia and aphasia. These symptoms usually persist for 24 h. A migraineous throbbing headache, with nausea and vomiting, develops 30–60 min after the beginning of visual aura. Attacks may be provoked by trivial trauma or by stressful events. Brain MR and interictal neurological examination were normal. His mother had suffered two attacks of migraine with visual aura, hemiplegia and aphasia. The patient was treated with simple analgesics (acetyl salicylic acid or nimesulide) for five consecutive FHM attacks, in two associated with zolmitriptan (2.5 mg), and for three other consecutive attacks with acetazolamide (500 mg per os) at the beginning of aura symptoms, and zolmitriptan (2.5 mg) at the beginning of the migraineous headache.

Results Simple analgesics with or without zolmitriptan, were without benefit on aura symptoms, which still lasted 24 h, and gave limited headache relief. Duration of aura symptoms, including the hemiplegia, were significantly shortened to 1.5–2 h after acetazolamide. Zolmitriptan was effective on headache and associated symptoms in 1–1.5 h. No adverse events were reported.

Conclusion This preliminary study suggests that acetazolamide is a safe and effective acute treatment of prolonged and disabling neurologic symptoms of FHM, especially when prophylaxis is not feasible due to a low frequency of attacks.

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P2-I22

Flunarizine and migraine: a prospective study on long-term prophylactic effectiveness

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Introduction In a previous naturalistic study, we evaluated the efficacy of prophylactic treatments and the existence of a post-treatment remission period in a group of outpatients affected by migraine with or without aura attending our headache centre.

Objective The objective of this study was to evaluate the long-term effectiveness of prophylactic therapy with flunarizine and the presence of a well being period after repeated cycles of therapy.

Materials and methods We chose our sample from a group of 61 responding patients out of a number of 114 subjects who performed the first preventive treatment with flunarizine. Thirty-two patients affected by migraine responding to the first preventive treatment with flunarizine (5 mg/day for at least three months) were followed up prospectively for 2–5 years during repeated cycles of preventive flunarizine therapy. We evaluated the efficacy of flunarizine using migraine index (frequency x intensity) before and after treatment and these data were statistically analysed with two-tailed Wilcoxon test for paired data. The percentage of patients who reported a period of partial (>50% decrease in the frequency of attacks) or total (lack of attacks) as well as the presence of side-effects during preventive therapy were detected.

Results All 32 patients repeated another prophylactic treatment with flunarizine: 30/32 patients (93.7%) responded during therapy and the post-treatment remission period was described in 19/30 patients (63.3%). A group of these patients were submitted to other preventive cycles of flunarizine therapy. The only side-effect observed was weight gain.

Conclusions Our data suggest that the efficacy of flunarizine during therapy was maintained in repeated preventive treatments and the partial or total remission period is present in at least 60% of patients even if its duration is reduced progressively.

P2-I23

The effect of mianserin on quality of life survey in migraine patients

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Migraine is one of the most observed primary headache types with a pronounced effect on general health and on the ability to take part in social activities. The management of migraine patients does not focus only on treatment of the headache but also on improvement in the quality of life. The purpose of this study was to evaluate the effect of mianserin, a tetracyclic antidepressant (2×10 mg), combined with a non-steroidal anti-inflammatory drug on quality of life survey in migraine patients. Fifty-four migraine patients, evaluated according to IHS criteria, were enrolled in this study (45F, 9M; mean age, 34±1.2). Mianserin was combined with a non-steroidal anti-inflammatory drug (naproxen sodium 2×275 mg [n=34] or nimesulide 2×100 mg [n=20]) and used for approximately 1 month. Quality of life survey was assessed using Medical Outcome Study (MOS) Short Form Health Survey (SF-36).
Patients and methods

Ten female migraine patients, aged 18 years of age and older. Evaluated parameters are physical functioning, limitations due to physical health, limitations due to emotional problems, energy-fatigue, emotional well being, social functioning, pain and general health. Mianserin therapy combined with non-steroidal anti-inflammatory drug, in migraine patients for one month improves significantly all the parameters assessed and related to quality of life. As it is well known that migraine diminishes quality of life, the management of migraine should also be addressed to the effect of the therapy on quality of life. In this study, we present the beneficial effect of mianserin (2×10 mg) on quality of life in migraine patients.

P2-I24

Buspirone as an adjuvant therapy in the prophylaxis of refractory migraine: case studies

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Objectives Stress is a recognized precipitating factor in migraine. It has been suggested that the physiological and psychological responses to stress in migraine patients are different from the non-sufferers (1). Buspirone, a 5-HT2a agonist, is an effective anxiolytic drug with many pharmacological effects. Buspirone has been observed to be effective in tension headache (2). The aim of this pilot open study was to assess buspirone’s efficacy as an adjuvant therapy in the prophylaxis of migraine attacks.

Patients and methods Ten female migraine patients, aged between 22 and 85 years, were prescribed buspirone 10 mg twice daily initially for 6 weeks in an open study. They all had normal CT/MRI scan of head, but EEG was abnormal in 2 patients. 5 were suffering from migraine with aura and 3 had migraine without aura. Three others fulfilled the criteria for chronic tension-type headache (CTH) (IHS, 1988). Buspirone was prescribed when all other pharmacological treatment options were exhausted. The concomitant prophylactic drugs were sodium valproate, verapamil, baclofen, a non-selective beta adrenoceptor blocking drug and pizotifen. Patients were not taking any other regular medication. They were seen at an outpatient clinic and were instructed to keep a migraine diary. The average frequency of attacks per month were 4 in migraine and 20 in CTH patients. Patients who improved and were able to tolerate the medication, received buspirone for 12 months or longer depending on the clinical progress.

Results At the end of 6 weeks’ treatment, the average frequency of attacks per month were reduced to 1.5 and 8 in migraine and CTH groups, respectively. Six patients observed 30–90% (average 62%) reduction in the migraine frequency and 4 patients maintained the improvement for 7–12 months. They were selected for long-term therapy. The attacks were also of shorter duration and less severe, but they were not specifically monitored. Buspirone was discontinued for adverse reactions, such as spacing out and general slowness, in 2 patients. One patient suffered from a seizure following 2 weeks’ medication and buspirone was stopped. Two other patients did not take buspirone for longer than 2 weeks due to poor motivation and/or fear of side-effects.

Conclusion In the dosage used, in this open pilot study buspirone appears to be an effective adjuvant therapy for the prophylaxis of migraine and related headaches. However, clearly further long-term placebo-controlled study involving a larger patient population is necessary to verify buspirone’s efficacy in migraine prophylaxis.

References

P2-I25

Use of chlordiazepoxide/amitriptyline combination for long-term migraine prophylaxis

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Forty-four migraine patients who had more than 5 migraine attacks per month were given 5 mg chlordiazepoxide and 12.5 mg amitriptyline combination as migraine prophylaxis. Patients ranged in age from 20 to 75 years and were followed for 5 years. Migraine abortive drugs were allowed for acute attacks, but no other prophylactic drug was permitted. All patients had at least a 50% reduction in frequency of attacks over the 5-year period. Duration and intensity were also reported to be less. No serious side-effects were reported. The combination drug appears to be as effective as higher doses of amitriptyline and prophylaxis occurs at much lower doses when combined with chlordiazepoxide. This study suggests that the combination drug of 5 mg chlordiazepoxide and 12.5 mg amitriptyline is an effective migraine prophylactic agent working as effectively as higher doses of amitriptyline alone, but without the accompanying side-effects.

P2-I26

Preventing headache by intervening during prodrome: what predicts success?

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Objective To review patient diaries from a previously reported study to determine if one is able to characterize the prodrome symptoms that were associated with success in terms of preventing moderate to severe headaches.

Methods Prodrome precedes headache by up to 48 h, is characterized by a variety of symptoms, and is distinguished from aura. Migraineurs who are able to recognize prodrome symptoms may be able to intervene and prevent headache.
Naratriptan, a long-acting 5HT-1 agonist, has been shown to prevent headache in patients with documented prodrome (1). Adult migraineurs who were aware of prodrome symptoms preceding headache by 4–24 h recorded onset of prodrome and symptoms, time of naratriptan 2.5 mg administration, and headache onset and severity. A posthoc analysis was conducted to compare prodrome symptoms that preceded headaches that were successfully prevented with those prodrome symptoms that were followed by headache, despite intervention with naratriptan.

**Results** 20 patients documented 84 prodromes and took naratriptan 2.5 mg at the point when they felt the headache was inevitable. A moderate or severe headache was prevented in 68/84 (81%) prodrome treatments. Of the successfully treated prodromes, 54/68 (79%) were not followed by headache and 14/68 (21%) were followed by mild headache. Successful intervention (none or mild headache) was most frequently preceded by the following prodrome symptoms: irritability 29/68 (43%), change in nausea 29/68 (43%), and muscle pain/tenderness 27/68 (40%). Similar prodrome symptoms were reported for those headaches that were not prevented, suggesting that further research is needed to identify which prodrome symptoms may predict success, in terms of preventing headache. However, time of naratriptan administration may be more important for preventing headache than recognizing specific prodrome symptoms.

**Conclusion** Preventing headache by intervening during prodrome may be possible if the intervention can be administered at an optimal time. This requires that migraineurs are able to recognize prodrome symptoms that predict success. More studies are needed to determine these symptoms and to optimize the timing of the intervention.

**Reference**
1 Cephalalgia 2000; 20:122–6.

**P2-I27**

The role of naratriptan as a prophylaxis to the menstrual migraine: a pilot comparative to naproxen study

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**Objectives** Menstrual migraine is a monthly nightmare for many young women, starting 1–3 days before or after the menstruation onset. Triptans are the treatment of choice for attack therapy, but a small percentage of them require specific prophylaxis. NSAIDs drugs, as well as estrogen supplements, have been used for this purpose. Naratriptan, a second-generation triptan without associated adverse events and rebound phenomena, could be used as a short duration prophylactic treatment. The aim of this study is to evaluate the usefulness of Naratriptan as prophylaxis for true menstrual migraine.

**Patients and methods** Fifteen young women, mean age 29-year-old, with regular cycle and menstruation as the only trigger of migraine, were enrolled in this open study, comparative to NSAIDs study, which lasted 6 months. During the first 3 months, they were requested to keep a headache and menstruation diary card and were under treatment with NSAID (Naproxen 500 mg/day) that started 3 days before the expected onset of menstruation and was taken the 3 first days of bleeding. During the second quarter, all patients were under treatment with Naratriptan, 2.5 mg/day for 6 days (−3 up to +3 days from the menstruation onset). The results of the second quarter were compared with those of the first one for each patient.

**Results** 12 of the 15 women (80%) treated with Naratriptan and 8/15 (54%) treated with Naproxen had no attack. Three women under Naratriptan had an attack of mild intensity and short duration.

**P2-I28**

Can vagus nerve stimulation help migraine?

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**Objective** To investigate whether epileptic patients treated with vagus nerve stimulation (VNS) and suffering from migraine experience relief of headaches following VNS implantation.

**Background** The mechanism of action of VNS used for control of epilepsy is not completely understood. Hypotheses include secondary activation of multiple central nervous system structures by the Nucleus Tractus Solitarius (NTS), including reticulating system and cerebral cortex. NTS also projects to amygdalo-hippocampal complex, thalamus, hypothalamus, and spinal trigeminal nucleus, all structures implicated in migraine. It is therefore suggested that vagus nerve stimulation could potentially help control migraine by modifying the activity of these different structures.

**Methods** We identified all the patients in the VNS registry of the department of Neurology of the University of Oklahoma (n = 34). These individuals were contacted and information was collected by telephone with standard form by the first author (M.E.L.). Patients were screened for diagnosis of migraine according to IHS criteria. The outcome measurement used was the average monthly frequency of migraine attacks, which was assessed in three time periods: (I) 3 months before VNS placement; (II) 3 months immediately after VNS placement; (III) 4–6 months after VNS placement. Improvement was defined as at least 50% reduction in the frequency of attacks from before to after VNS placement. Patients unable to give accurate answers were excluded.

**Results** Of the 34 identified patients in the registry, 5 could not be contacted and 4 were excluded for lack of accurate information due to mental retardation. Of the 25 patients from whom adequate information was obtained, 10 (5M/5F) had...
P2-I29
A randomized, double-blind placebo-controlled parallel group study of thioctic (or alpha-lipoic) acid, 1600 mg po in migraine prophylaxis

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Objectives To assess the prophylactic antimigraine effect of thioctic acid (Thioctacid®) in a randomized controlled trial (RCT). Thioctic acid (alpha-lipoic acid) is known to enhance energy metabolism in mitochondria and of proven benefit in diabetic neuropathy. Impaired mitochondrial phosphorylation potential may play a role in migraine pathogenesis (Montagna et al., 1994) and enhancers of mitochondrial energy metabolism, such as high-dose riboflavin, are effective in migraine prophylaxis. After an open pilot study indicated a possible benefit, we performed an RCT of oral thioctic acid in the prophylactic treatment of migraine.

Material and methods Five Belgian centres recruited 54 migraineurs (48 migraine without aura, 10 with aura; mean age 38 ± 8 year; 7 males). They received placebo for a 1-month run-in period and were included in the randomized double-blind phase, if they had presented at least 1 attack. Forty-four patients received either placebo (n = 18) or thioctic acid 600 mg p.o./day (n = 26) for 3 months. Seven patients dropped out after 2 months (2 in the placebo arm, 5 in the verum); their data were included according to the last-value-carried-forward method. The trial was interrupted before the planned 80 patients were enrolled, because of slow recruitment in some centres and time limitation in drug quality.

Results Monthly attack frequency was reduced between run-in and the third month of randomization after thioctic acid, but not after placebo (P = 0.034). There was, however, no significant difference in attack frequency between the first run-in month and the average of the randomized 3 months, nor in headache days. The proportion of responders (50% reduction in monthly attack frequency) was not significantly different between placebo (11%) and thioctic acid (19%). Within group analyses showed a significant reduction of attack frequency (P = 0.002), headache days (P = 0.008) and headache severity (P = 0.042) on average in patients treated with thioctic acid, but no significant reduction in the placebo group. No adverse effects were reported. The reasons for drop-outs were inefficacy and in 1 patient rhinitis.

Conclusions This RCT does not demonstrate a clinically meaningful advantage of thioctic acid over placebo in migraine prophylaxis. On various secondary outcome measures, there is nonetheless an indication for a beneficial effect of thioctic acid. As this study was underpowered because of premature interruption, a large multicentre trial of this compound, which has an excellent tolerance, may be worthwhile.

P2-I30
Open-label trial of high-dose Coenzyme Q10 as a migraine preventive

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Objectives To assess the efficacy of high-dose Coenzyme Q10 as a preventive treatment for migraine headaches.

Background The true pathogenesis of migraine is unknown. Clues from magnetic resonance spectroscopy studies and DNA analysis suggest that migraine, in a subset of individuals, is a direct result of mitochondrial impairment. At present, there are very few efficacious migraine preventives and fewer without significant side-effects. Coenzyme Q10 is a naturally occurring substance and an essential element of the electron transport chain. It has been the most extensively studied agent for the treatment of mitochondrial disorders. If indeed migraine results from mitochondrial dysfunction, then Coenzyme Q10 could be a successful migraine preventive.

Methods 32 patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with Coenzyme Q10 at a dose of 150 mg/day. Study subjects had to have had a migraine history for at least one year and have experienced between 2 and 8 migraines per month. No one was on preventive therapy within two months of Coenzyme Q10 administration. Total study length was four months with a one-month baseline period and three-month therapy phase. Each patient kept a study diary to monitor migraine frequency and intensity.

Results 31 of 32 patients completed the study. One patient was lost to follow-up. 61.3% of patients had a greater than 50% reduction in number of days with migraine. 93.5% had at least a 25% reduction in number of days with migraine. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after three months of therapy which was a statistically significant response (P < 0.0001). Mean reduction in migraine frequency after one month of treatment was 13.1% and this increased to 55.3% by the end of three months of therapy. There were no
side-effects noted with Coenzyme Q10. Because of the small number of males in the study and individuals less than age 30, we were unable to comment on any sex or age group differences in response to Coenzyme Q10. In the attacks that did occur, Coenzyme Q10 did not appear to significantly reduce headache intensity.

Conclusion From this open-label investigation, Coenzyme Q10 appears to be a good migraine preventive. The data suggest that Coenzyme Q10 starts to work within four weeks of initiation but usually takes five to 12 weeks to yield a greater than 50% reduction in days with migraine. Placebo-controlled trials are now necessary to determine the true efficacy of Coenzyme Q10 in migraine prevention.

P2-I31

Creatine phosphate as a prophylactic agent in migraine. A pilot study

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Objective To determine the efficacy and safety of creatine in the prevention of migraine in a pilot study.

Background 31P-MR spectroscopy has shown decreased levels of phosphocreatine, the high energy phosphate buffer, in the brains of migraineurs. Creatine is a precursor of phosphocreatine, and it is used to increase mass and aerobic fitness of muscles.

Design and methods Eight patients suffering from migraine without aura (2 males and 6 females, aged 29–42 year) gave informed consent to a pilot double-blind vs placebo study of creatine. After a run-in time of 6 months, patients were randomly allocated in a cross-over design to a placebo or creatine phosphate, 5 g per os 4 times a day in soluble form for one week followed by 5 g once a day for 3 months (wash out period of 3 months). The number and intensity of the migraine attacks, the days free from migraine and the consumption of analgesic medications were calculated for each trial period. Patients underwent standardized lactic effort tests prior to and at the end of each trial period. Statistical analysis was performed by means of Paired Student’s t-test.

Results All patients finished the study and there were no untoward clinical or laboratory effects. Creatine administration resulted in no statistical differences in any of the variables analysed. Peak effort lactic levels were reduced after creatine.

Conclusion Creatine administration was safe but did not show beneficial effects in the prevention of migraine attacks, at least at the dosages and treatment duration used here. Further studies, on more patients, and with different dosages may be needed.

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P2-I32

Effect of changes in nutrition and lifestyle on migraine: the patient’s experience

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Objectives To evaluate the effect of changes in nutrition, consumption of alcohol, lifestyle and environmental factors in migraine patients and migraine-free controls.

Patients and methods Sixty-six consecutive patients suffering from migraine with and/or without aura and 45 migraine-free controls completed a semistructured interview covering demographic data, headache characteristics, changes in nutrition (including alcohol, cheese, dairy products, chocolate, cereals, caffeine, food additives, fruits, vegetables, nuts, etc.) and lifestyle or environmental factors (including stress, sleeping habits, intake of meals, hunger, smoking, oral contraceptives, physical activity, exhaustion, bright light, noise, etc.) and the effect of such changes on headache. Patients with overuse of analgesics, ergotamines and/or triptans as well as patients with relevant organic and/or psychiatric disorders were excluded. The subjects gave informed consents. All interviews were performed by the same person (JH) either personally or by telephone. For statistical analysis, SPSS-WIN 10.0 was used.

Results Patients and controls were comparable regarding age, sex, educational level and profession. In migraine patients, 19.7% had changed nutrition and 35.4% had changed lifestyle because of headache; another 19.7% and 23.1%, respectively, reported changes because of other reasons. In the controls, the corresponding percentages were 4.4% and 6.7% (changes due to headache) and 35.6% and 42.2% (other reasons). Changes in nutrition most commonly included alcohol, red wine, chocolate, coffee and caffeine. Statistically significant differences between migraineurs and controls were found in only 2 of 19 factors, i.e. alcohol (P < 0.001) and red wine (P < 0.05). Changes in lifestyle most commonly comprised stress, oral contraceptives, smoking, sleep, and intake of meals. None of a total of 12 factors differed between patients and controls. Changes in nutrition were rated effective by few subjects (migraineurs: 11.5%, controls 5.6%). Changes in lifestyle, however, were rated effective significantly more often (migraineurs: 41.0%, P<0.05, controls: 22.7%, P < 0.05). The difference in the efficacy of lifestyle changes between patients and controls was on the border of statistical significance (P = 0.05).

Conclusions Between 40 and 60% of patients with migraine and migraine-free controls change nutrition and/or lifestyle in order to improve their headaches. Changes in nutrition are rated effective by few subjects, whereas changes in lifestyle are related to an improvement of headache by more than 40% of the migraine patients and by more than 20% of the migraine-free controls.
P2-I33

Nutritional profile and intermediate metabolism of B12 vitamin: a novel physiopathological and therapeutic approach for migraine. An open study on 70 patients

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Objective The aim of our study is to evaluate in migraineurs eventual alterations in food behaviour, gastrointestinal problems with or without clinical evidence of nutrient deficiency (above all, vitamins and minerals), repercussion of corrective therapy on migraine, and possible physiopathological interpretation.

Materials and methods During the period from January to December 2000 we studied 70 consecutive patients (48 F) with a mean age of 33.8 (SD 12.6) years who were suffering from migraine with or without aura (IHS 1988 criteria). We did an open study in 5 stages: T0: first visit; T1: starting of corrective therapy; T2, T3, T4: follow-up controls.

Results 80% of patients followed an unbalanced diet (excessive consumption of animal proteins, acid fats, simple carbohydrates rather than complex ones; small quantities of vegetable proteins, vitamins and mineral salts) and disproportionate consumption of main meals and snacks. The average water consumption was 781.4 mL/24 h without thirst (37.1%). In 91% of cases at least one gastroenteric symptom was present (14.3% diarrhoea, 63% nausea and/or gastralgia). Furthermore, symptoms of lack of vitamin A were found (photophobia 72%; nyctalopia 48.6%), of vitamin B12 and cobalt (cold feet 48.6%; limb cyanosis 14.3%; joint and muscle pain 54.3%; cold hands 34.3%; cramps 48.6%; and paraesthesiaes at upper and lower limbs 45.7–40%). Clinical data were confirmed by following laboratory results: increase of plasma osmolarity (38.6%); reduction of B12 vitamin serum concentration (64.3%); and serum concentration of cobalt below normal limits (57.1%). After the therapy aimed to correct these deficiencies, migraine index values were found significantly reduced (P < 0.001) with respect to basal ones. Conclusions The crucial point from a physiopathological point of view is represented by a possible dysfunction of vitamin B12; other mechanisms can be the production of abnormal vasoactive substances by bacterial flora and change of the homeostatic balance.

P2-I34

A placebo-controlled, double-blind trial of magnesium with riboflavin and feverfew for the prevention of migraine headaches

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Introduction Current prophylactic agents for migraine have limited efficacy and a high side-effect profile. Three ‘natural’ supplements – magnesium, riboflavin, and feverfew – have each demonstrated efficacy for migraine prevention in placebo-controlled trials. Differences in therapeutic mechanisms suggest the possibility that a combination of these agents may offer further efficacy with a low side-effect profile.

Methods Some 120 patients are to be randomized in a 1:1 ratio to receive either the combination supplement or placebo, in order to produce evaluable results for 96 patients. Patients log their headache frequency and severity for a one-month run-in, and then a 3-month trial period. The primary endpoint measure is change in number of migraine attacks. Secondary endpoints include: per cent of patients with at least 50% decrease in migraine attacks; and changes in number of: migraine attacks month 1 and month 3, migraine days, doses of triptan medication, and migraine quality-of-life scores.

Results Statistical design allows for an evaluation of the data after a total of 48 patients have completed the study. Results for the first 48 patients will be reported.

Conclusion A new therapeutic product which combines magnesium, riboflavin, and feverfew is evaluated.

P2-I35

Fish oil vs olive oil in the management of recurrent migraine headaches in adolescents

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Objective To examine whether dietary supplementation with fish oil rich in very long-chain n-3 polyunsaturated fatty acids (PUFA) can alleviate recurrent migraine headaches in adolescents.

Background Recent reports have suggested that increasing dietary intake of n-3 PUFA results in formation of less potent inflammatory mediators, and attenuates inflammatory processes that may affect adolescents.

Design and methods 27 adolescents with frequent migraine headaches for at least 1 years (mean 4½ ± 1 years) participated in a randomized, double blind, crossover study consisting of 2 month fish oil, 1 month washout period, and 2 month placebo (olive oil). Participants self-assessed severity and duration of headache episodes throughout the study. At the end of every 2-month treatment period, participants rated the effectiveness of treatment on a 7-point Likert Scale (1 ‘not
effective, not worthwhile’; 4 ‘moderately effective, moderately worthwhile’; 7 ‘totally effective, totally worthwhile’). A score of >4 was considered as improvement.

**Results**

23 adolescents (16 girls, 7 boys, mean age 15.1) completed the study. Compared with frequency of headaches before the study, there was a significant (P<0.0001) reduction in headache frequency during fish oil treatment and during olive oil treatment but no significant (NS) difference between treatments. Likewise, self-assessment on the 7-point faces pain scale revealed a significant reduction in headache severity during fish oil treatment (2.9±0.5, P=0.01) and during olive oil treatment (3.5±0.4, P=0.03) compared with headache severity before the study (5.0±0.3), and no significant difference between treatments. Patients’ ratings revealed that 87% experienced reduction in headache frequency, 74% experienced reduction in headache duration, and 83% experienced reduction in headache severity during fish oil treatment, compared with 78% who experienced reduction in headache frequency, 70% who experienced reduction in headache duration, and 65% who experienced reduction in headache severity during olive oil treatment (NS). About 91% would recommend fish oil to friends/relatives with headaches vs 91% who would recommend olive oil (NS).

**Conclusions**

Patients experienced a similar reduction in frequency, duration, and severity of headaches during treatment with fish oil and during treatment with olive oil. The overwhelming improvement suggests that the effect should not be dismissed as simply a placebo effect. In fact, results of this preliminary study suggest that both fish oil and olive oil may be beneficial in the treatment of recurrent migraine headaches in adolescents. Further studies are warranted to compare each of these treatments with other interventions.
POSTER SESSION II

J: Pathophysiology

P2-J1
Modular headache theory: a unified approach to headaches
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Objective To present a new theory of brain function for the primary and some of the secondary headaches.

Background In practice, one primary headache disorder may have a feature of a second primary headache disorder. An example is cluster with aura. Headaches may have mixed features, behaving and responding as an amalgam of two disorders, for example cluster-tic. Headache patients may fail to exhibit a diagnostically important feature of a primary headache, yet function like this disorder, e.g. migraineur disorder. One headache disorder may be completely subsumed by another. For example, idiopathic stabbing headache is a disorder in itself, or a symptom of migraine or cluster headache. The principle of parsimony suggests these, and many other variant headaches, are not all fundamentally unique headache syndromes.

The model Any primary headache and some secondary headaches may be described as a group of modules, with one module for each of the main clinical manifestations. Modules are anatomically and functionally linked to one another, and become activated in a characteristic manner for the individual. Neuronal learning, with bidirectional reinforcement of specific modules and links, explains some of the individual’s headache stereotypy. A module is a group or network of neurons within the brain, sometimes associated with blood vessels or other organs, that produce a feature or symptom of headache. Several modules are activated during most headaches. Suspected modules are throbbing vascular pain, non-throbbing pain, cervical muscle tenderness and pain, eye pain, stabbing pain, tic-like pain, allodynia, nausea/vomiting, photo-phono-osmophobia, ptosis/miosis, lacrimation/nasal congestion, prodrome, lysis (headache termination), time-diurnal, time-seasonal, unilateral/suppressor, and postdrome. Most of these modules are active in more than one headache type. A link is the connection between modules. Links have a neuroanatomical basis and coordinate the sequential or concurrent activation of modules.

Significance of the model Modular headache theory explains how individual headache features are shared by different headache disorders. It has consequences for research, treatment and classification.

P2-J2
Modulation of cephalic pain as physiological approach to headache therapy
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The ‘pain gating theory’ (PGT) implies that, in somatoesthetic areas, pain is controlled by the activity of either peripheral proprioceptors or the central descending inhibitory pathway of tronco-cephalic origin. In the present report, an interdisciplinary study between basic and clinical researchers has singled out a novel therapeutic approach to relieve cephalic pain (headache) based on the concept of a ‘PGT’ modulating the nociception in the cephalic area. Physiological analyses have been carried out with the aim of clarifying whether jaw proprioceptors might exert an inhibition on neurons of the caudal nucleus of trigeminal spinal nuclei where all the nociceptive afferents converge. In single healthy individuals of both sexes, the threshold to painful stimulation applied to periodontal spots in the mouth has been evaluated in the absence and presence of proprioceptive activity obtained with extreme opening of the mouth for 3–5 min. Such opening, either active or passive, triggers massive proprioceptive afferents. Our results demonstrate that this natural autostimulation brings about an enhancement of threshold for pain perception in healthy subjects. In a second series of experiments the pain threshold in patients with tension headache has been calculated. Preliminary data have shown significant changes of pain threshold in these patients. Such results have allowed us to start with a therapeutic protocol in 15 young patients (aged between 10 and 18-year-old) with cephalic painful syndromes. In order to trigger the inhibitory proprioceptive pathways of jaw areas we have set up a particular ‘bite plane’ opportunistically modified to this goal by one of us (M. Zampino). This apparatus, by inducing the extension of jaw muscles, produces a lasting and constant proprioceptive autostimulation. We have observed that this peculiar autostimulation was able to gradually reduce the number of painful episodes by decreasing both the intensity and the duration of each episode and in almost all the cases produced a complete relief of symptoms in about 20–30 days. This physiological autostimulation seems to be a very effective therapeutical treatment.
Urinary nitric oxide metabolites and lipid peroxidation by-products in migraine

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Objectives Among the possible pathogenic mechanisms of the migraine-related cerebral blood flow changes, an enhanced endothelium nitric oxide (NO) bioavailability associated to an increased superoxide anions release has been suggested. This study examines the possibility that assaying urinary levels of NO stable metabolites (NOx) and lipid peroxidation by-products might help to determine in vivo modifications of the oxidative status in migraine, during and after the attack and the headache-free period.

Materials and methods Thirty subjects suffering from migraine with and without aura and 20 healthy controls, were enrolled. Three urine samples, collected throughout 24 h, during and after the migraine attack, and during the headache-free period, were assayed for NOx and thiobarbituric acid reactive substances (TBARS). NOx were measured by reducing nitrate to nitrite and measuring nitrite by a fluorimetric test. NOx and TBARS corrected by creatinine excretion were expressed as mmol/mmol Creatinine and as imol/mmol Creatinine, respectively. Student’s unpaired t-test and two-way ANOVA test were utilized for statistical analyses.

Results Urinary NOx (0.75 ± 0.14 vs 0.28 ± 0.15 mmol/mmol Creatinine; P < 0.05) and TBARS (0.40 ± 0.19 vs 0.26 ± 0.13 µmol/mmol Creatinine; P < 0.05) levels were higher in all the migraine sufferers during the headache-free period as compared with the healthy controls. NOx urinary excretion (0.75 ± 0.14 mmol/mmol Creatinine) was higher during the headache-free period with respect to levels measured during (0.50 ± 0.17 mmol/mmol Creatinine; P < 0.05) and after (0.58 ± 0.15 mmol/mmol Creatinine; P < 0.05) migraine attack. Urinary TBARS were increased during the attack (0.59 ± 0.17 µmol/mmol Creatinine; P < 0.05) with respect to the headache-free period (0.40 ± 0.19 µmol/mmol Creatinine; P < 0.05), to decrease after the attack (0.49 ± 0.14 µmol/mmol Creatinine; P < 0.05). No differences were observed in the same parameters between patients with migraine with (n = 12) and without aura (n = 18).

Discussion As suggested by our results the simultaneous release of NO and superoxide anions might determine the oxidative status of migraine sufferers. Besides, the ictally decreased NOx levels might follow the reaction of NO with superoxide anions produced during migraine-related changes of cerebral blood flow. Therefore, the enhanced excretion of oxidative metabolites appears to parallel the process that leads to a decreased NO bioavailability during the attack. The usefulness of urinary NOx and TBARS as markers of their systemic levels might be promising to evaluate the increased vulnerability to oxidative stress in migraine.

Autonomic nervous system dysfunction occurs in migraine only with co-existing anxiety

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Objective Autonomic nervous system (ANS) dysfunction in migraine has been postulated, but inconsistently observed. However, ANS dysfunction is reliably observed in generalized anxiety disorder (GAD), frequently comorbid with migraine. We hypothesized that inconsistent findings have resulted because ANS dysfunction is actually associated with comorbid anxiety rather than with migraine.

Methods Screening (over 1000 college students) followed by face to face diagnostic interviews for headache (IHS) and anxiety disorders (Prime MD (1); Primary Care Evaluation of Mental Disorders) yielded 80 female college students (N = 80; M age = 19) who were separated into four groups: 1, migraine without aura (IHS 1.1) with GAD symptoms (M Trait Anxiety = 49; N = 19); 2, migraine without aura with no GAD symptoms (M Trait Anxiety = 36; N = 21); 3, migraine-free with GAD symptoms (M Trait Anxiety = 49; N = 21); and 4, migraine-free with no GAD symptoms (M Trait Anxiety = 32; N = 19). All subjects participated in a 1-h lab stress procedure (mental arithmetic and cold pressor). A spectral analysis (fast Fourier transformation) of time-series EKG interbeat intervals (2) during seven 2.5-min assessment periods during the lab stress procedure (rest, mental arithmetic, rest, cold pressor, rest, rest) was used to assess ANS function. Sympathetic nervous system (SNS) activity was assessed by the lower frequency component of the power spectra of IBIls divided by the higher frequency component (Lo/Hi); parasympathetic nervous system (PNS) activity was assessed by the higher frequency component divided by total frequency of the IBI power spectra corrected for respiration cycle (Hi/Tot).

Results ANOVAs demonstrated a significant interaction between anxiety and assessment periods for SNS and PNS indicators, as well as HR during mental arithmetic tasks (P < 0.05). HR and SNS indicator were higher in the high anxiety group than in the low anxiety group during the stress procedure (rest, mental arithmetic, rest, cold pressor, rest, rest) was used to assess ANS function. Sympathetic nervous system (SNS) activity was assessed by the lower frequency component of the power spectra of IBIls divided by the higher frequency component (Lo/Hi); parasympathetic nervous system (PNS) activity was assessed by the higher frequency component divided by total frequency of the IBI power spectra corrected for respiration cycle (Hi/Tot).

References

P2-J5

Nociceptin and human pain perception
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Objectives The neuropeptide nociceptin has been identified in human spinal dorsal horn and very recently also in the trigeminal ganglion. The mode of action of nociceptin in pain perception seems rather complex and has only been studied in animals. The aim of study I was to examine a possible local pain reaction after injections of nociceptin into the temporal muscles of healthy subjects. In study II the nociceptive actions were examined after injections of nociceptin into tender trapezius muscles of healthy subjects.

Materials In study I four healthy subjects (2m, 2f) with a median age of 24 years were included. In study II 10 healthy subjects (4m, 6f) with a median age of 26 years and a total tenderness score (TTS) of more than 9 and a local tenderness score (LTS) on the non-dominant side of more than 2 were included. Five different doses – 12.5, 25, 50, 100, and 200 pmol per 0.2 mL of nociceptin – were used.

Methods In study I each subject received 3 injections of different doses of nociceptin in an open-labeled design into the temporal muscle. In study II, subjects received 1 injection with 200 pmol of nociceptin in a randomized, double-blind, placebo-controlled design into the non-dominant trapezius muscle. Local pain and tenderness, stimulus-response relations, LTS, TTS, hardness, and pressure pain detection thresholds in the temporal region and on the finger were registered during a 1-h observation period.

Results In study I no pain or changes in mechanical thresholds were detected after injections of either dose of nociceptin into the temporal muscle. In study II the LTS increased 5 min after injection of nociceptin compared with placebo (P = 0.025). Likewise, a trend of increased local tenderness in the observation period (60 min) (P = 0.085), increased TTS after 5 min (P = 0.066), and increased LTS after 60 min (P = 0.083) were identified compared with placebo. No pain or changes in hardness or thresholds were identified after nociceptin compared with placebo.

Conclusion Nociceptin may have an algesic effect in human tender muscle. Further exploration of the mode of action and the possible algesic effect of nociceptin is thus warranted.

P2-J6

Clinical signs of neuromuscular hyperexcitability in migraine patients
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Objectives The study was focused on the detection of the clinical signs of neuromuscular hyperexcitability in migraine patients due to a described association between migraine and increased neuromuscular excitability or latent tetany, respectively.

Materials and methods 42 subjects (40 women and 2 men, mean age of 40.5 years, age range 12-55 years) with the diagnosis of migraine with or without aura (according to IHS classification criteria), repeatedly followed-up in a pain centre during the last 2 years, underwent a neurological examination focused on the signs of neuromuscular hyperexcitability. In all of them, the presence of the Chvostek’s sign and in 28 of them, the presence of the Tromner’s sign were assessed. These signs have been frequently detected in subjects with tetanic syndrome.

Results A repeatedly positive Chvostek’s sign (CS) was proven in 28 of the subjects under study (66.6%). An inconstant presence of this sign was detected in 5 subjects (12%). A negative CS was registered in 9 subjects (21.4%). A repeatedly positive Tromner’s sign (TS) was proven in 15 of 28 subjects (53.6%). An inconstant presence of this sign was detected in 3 subjects of this subgroup (10.7%). A negative TS was registered in 10 subjects (35.7%). Common regular occurrence of both the CS and the TS was registered in 8 subjects in a subgroup of 28 patients (28.6%). Inconstant common occurrence of both these signs of neuromuscular hyperexcitability was detected in 5 subjects (5/28, 17.8%). Regular, as well as inconstant common occurrence of these two signs was registered in 13 of 28 subjects (46.4%).

Conclusions The frequent detection of the positive CS and TS in the subjects under study is consistent with the hypothesis of the central hyperexcitability in migraine. For migraine patients, special attention should be given to these easily detectable clinical signs of an increased neuromuscular excitability and it is desirable to carry out a biochemical study focused on magnesium metabolism and EMG ischaemic test for the detection of tetanic syndrome. On the basis of the results obtained in this study, a relatively frequent association between migraine and the tetanic syndrome could be supposed.

P2-J7

Electrophysiological evidence for trigeminal neuron sensitization in migraine
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Background The trigemino-nociceptive system is considered to play a crucial role in the pathogenesis of migraine.

Objectives Study of the electrically elicited corneal reflex, via detection of the tactile perception (Ttp), reflex (Tr) and pain (Tp) thresholds, allows a quantitative evaluation of the sensorimotor function at the trigeminal level.
Materials and methods  Forty-eight patients suffering from migraine without aura were investigated during the interictal phase. The corneal reflex was elicited by electrical stimuli delivered via a thin cotton thread soaked with saline solution and connected to the cathode of a constant-current stimulator. The examiner touched the cornea with the thread floating on the corneal thin layer of tears, so that, after a brief period of adaptation, no sensation was evoked by this procedure. A pulse of 1 ms duration was delivered randomly (8–40 s), and attention was paid to spontaneous blinking. The muscular response was recorded from the orbicularis oculi muscle.

Results  Significantly different Ttp, Tr and Tp emerged between patients with bilateral migraine and controls (MANOVA; P < 0.001). In patients with unilateral migraine, Ttp, Tr and Tp values on the symptomatic side were lower than those on the non symptomatic side, although the differences were not statistically significant. In the same group, all thresholds on the symptomatic side (MANOVA; P < 0.0001) were significantly lower than those in controls and in patients with bilateral migraine, while the thresholds on the non symptomatic side were significantly lower only compared to controls. The Pearson correlations coefficients between Tp and Tr in each subgroup were highly significant and ranged from r = 0.72 to r = 0.80 (P < 0.001). Plotting Tp against Tr values, the regression line turned out less steep in migraineurs (regression coefficient range: beta = 0.9–1.0) than in controls (beta = 1.6). A direct multivariate analysis using the Hotelling’s T2 test with Bonferroni’s adjustment revealed significantly different distribution of Tp in unilateral migraine patients compared to controls on the symptomatic side (P < 0.022).

Conclusions  These abnormalities we found suggest an hyperexcitability of the trigeminal pathway which further support the view of a central sensitisation in migraine.

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P2-J8

Visual evoked MEG fields in migraine aura patients

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Objectives  We used an 8 Hz stimulus pattern to elicit visual aura and evaluate the hyperexcitability of the occipital cortex in migraine with aura (M + A) patients.

Methods  Visual evoked cortical magnetic fields (VECMF) were recorded during 18 min of continuous visual stimulation in M + A patients and normal subjects (N). M + A patients and N subjects were visually stimulated with a black and white circular checkerboard pattern, reversing at 8 Hz. Magnetic fields were monitored with a whole head neuromagnetometer (4D Neuroimaging Magnes 2500) for 18 min (sampled at 254 Hz; filtered 1–30 Hz). Data were separated into 3 averaged epochs, each containing ~500 pattern reversals. One epoch was created from the first 3 min; the second from minutes 8–10 and the third from the minutes 15–18 of data. Two Dimensional Inverse Imaging (2DII) was used to determine the sources for the latencies and location of the VECMF for each epoch. The three epochs for M + A patients were compared to the other M + A patients and normal subjects.

Results  The latencies of the VECMF throughout 20 min of visual stimulus were consistent across normal subjects, with peaks at 35 ms, 75 ms and 145 ms. Peaks were localized to a small focal area of the striate cortex. In the M + A group peak latencies varied between epochs and were different for each subject. M + A patients also showed no consistent peak amplitudes. Finally, VECMF peaks were imaged in extended areas of the striate cortex and extra-striate cortex.

Conclusions  Visually evoked cortical activation, of inconsistent amplitude, latency and waveform, was observed in widespread areas of the occipital cortex in M + A patients in contrast to consistent and physiological focal striate cortex evoked responses in normal subjects. These findings suggest that neuronal hyperexcitability underlies the potential for triggering abnormal neuroelectric events such as spreading depression throughout extensive regions of the occipital cortex of M + A patients.

P2-J9

Acetazolamide improves SFEMG abnormalities in migraine patients

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Objectives  Acetazolamide is effective in episodic ataxia type 2 (EA-2) and it has some utility in familial hemiplegic migraine (FHM). Both FHM and EA-2 are caused by mutations in the CACNA1A gene (chromosome 19p13) coding for the a1A-subunit of P/Q Ca2+ channels. There is indirect evidence that the same locus is implicated in the more common forms of migraine. By single fibre EMG (SFEMG) recordings, we found mild abnormalities of neuromuscular transmission in migraineurs with prolonged or complex aura and hypothesized that this could be due to dysfunctioning P/Q Ca2+ channels at the neuromuscular junction. The objective of this study was thus to search for an effect of a prolonged treatment with acetazolamide on the SFEMG abnormalities found in migraine patients.

Materials and methods  We selected 5 migraineurs (1 without aura [MO], IHS code 1.1; 4 with aura [MA], IHS code 1.2; median attack frequency = 4/month, range 2–20). All MA patients had sensorimotor symptoms and/or loss of balance during the aura. The MO patient suffered from interictal episodic vertigo. Stimulation SFEMG was derived from m. extensor digitorum communis (±18 fibres). Results were expressed as the ‘mean value of consecutive
data were acquired by a 4-wavelengths frequency-domain across the stimulation block and across all 14 cycles. NIRS-performed in each subject. VEPs were recorded from Oz, O1 1 min resting period (presentation of a black screen) were evoked by a checkerboard reversing at a rate of 3 with aura and 14 healthy volunteers) were investigated. 12 interictal migraine patients (9 without aura, patients and volunteers. We did not find any evidence for vascular habituation which may indicate that there is a difference in neuro-vascular coupling between the two groups.

**References**


P2-J10

**Is deficient interictal VEP-habituation accompanied by an altered vascular response in migraine patients?**

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**Objective** The present study compared regional concentration changes in oxy- and deoxy-haemoglobin by means of near infrared spectroscopy with simultaneously acquired visual evoked potentials during prolonged stimulation in migraine patients and volunteers.

**Methods** 12 interictal migraine patients (9 without aura, 3 with aura and 14 healthy volunteers) were investigated. VEPs were evoked by a checkerboard reversing at a rate of 3 Hz. Fourteen cycles consisting of 1 min stimulation and 1 min resting period (presentation of a black screen) were performed in each subject. VEPs were recorded from Oz, O1 and O2 referenced to Fz and analysed in terms of peak-to-peak amplitudes of N1-P1 and P1-N1 to assess habituation across the stimulation block and across all 14 cycles. NIRS-data were acquired by a 4-wavelengths frequency-domain monitor (ISS Inc., USA, modulation frequency 110 MHz) and concentration changes in oxy-Hb and deoxy-Hb were calculated from intensity as well as from phase shift values (2). To assess the ‘vascular habituation’, the oxy-Hb- and deoxy-Hb responses to the individual VEP-blocks of 1 min were analysed and mean amplitude was checked for habituation effects.

**Results** Across all stimulation blocks N1-P1 amplitude was markedly increased in migraine patients whereas the volunteers showed a stable N1-P1 amplitude. Across all cycles N1-P1 absolute amplitude in migraine patients was initially smaller than in the volunteers and increased slightly, whereas it decreased initially in the volunteers reaching its minimum after eight cycles. P1-N2 amplitude remained stable in migraine patients but showed the same pattern as N1-P1 amplitude in the volunteers. On the contrary neither group showed an alteration of the vascular response.

**Conclusion** Though probably due to a different stimulation protocol, the previously reported habituation in volunteers could not be reproduced, we have shown a clear electrophysiological difference between migraine patients and volunteers. We did not find any evidence for vascular habituation which may indicate that there is a difference in neuro-vascular coupling between the two groups.

P2-J11

**Repetitive transcranial magnetic stimulation of the occipital cortex modifies habituation of visual evoked potentials in healthy volunteers and migraineurs**


**Objective** To study the excitability of occipital cortex in healthy volunteers and migraineurs by recording pattern-reversal visual evoked potentials (PR-VEP) before and after low and high frequency repetitive transcranial magnetic stimulation (rTMS). rTMS is able to decrease or increase cortical excitability depending on stimulation frequency. It is controversial whether and in which direction cortical excitability is modified in migraine. Between attacks, habituation of PR-VEPs can be reduced or reversed (i.e. potentiation) which we have attributed to cortical hypoexcitability.

**Material and methods** We performed rTMS of the visual cortex in healthy volunteers ($n=12$) and in patients suffering from migraine with ($n=2$) or without aura ($n=6$) in the interictal period with a focal figure-of-eight magnetic coil placed over the occipital scalp. We delivered 900 pulses at two different frequencies in a randomized order: 1 Hz rTMS
(15 min) and 10 Hz rTMS (18 train of 5 s, with an intertrain-interval of 10 s). Stimulus intensity was set to the phospheneprovedihreshold. Before and after rTMS the PR-VEPs were sequentially averaged in blocks of 100 responses during 3 min of uninterrupted stimulation at 3.1 Hz and analysed in terms of latency and peak-to-peak amplitude of N1-P1 and P1-N2 peaks.

**Results** There were no significant differences in N1, P1 and N2 latencies before and after rTMS neither in normal volunteers nor in migraineurs. After 1 Hz rTMS, amplitudes of N1-P1 and P1-N2 in the first block were decreased in 70% of healthy volunteers and 50% of migraineurs. After the 1 Hz rTMS there was a significant reduction of the habituation or even a potentiation in healthy volunteers, but the potentiation observed in migraineurs was not modified. After 10 Hz rTMS, 1st block amplitudes of N1-P1 and P1-N2 were increased in 50% of healthy volunteers and 75% of migraineurs. There was no significant change of habituation in healthy volunteers, but in migraine patients we observed a reduction of potentiation or even appearance of habituation.

**Conclusion** The decrease of cortical excitability induced by 1 Hz rTMS in normal volunteers is associated with loss of habituation or even potentiation of PR-VEPs. The increase of cortical excitability which follows the 10 Hz rTMS produces in migraineurs less marked potentiation or even habituation. Taken together, these findings suggest that the deficient habituation of EPs found interictically in migraine is due to a reduced preactivation level of sensory cortices, and not to hyperexcitability.

**P2-J13**

**Somatosensory trigeminal evoked potentials in unilateral migraine**

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**Objectives** Migraine headache is usually half-sided but the painful side can change between different attacks. Rarely, patients always experience the pain on the same side of the head. The aim of the study was to investigate brainstem reflexes in patients with strictly unilateral headache to detect side-to-side differences in stimulus processing.

**Methods** 25 patients (22 male, 3 female; mean age 38.5 years) with strictly unilateral migraine without aura (>90% of the attacks with the pain on the same side) were enrolled. The diagnosis was made according to the IHS criteria. 21 patients (19 female, 2 male) with migraine without aura and pain on alternating sides in different attacks served as controls. The potentials were evoked by routine laboratory methods on both sides outside a migraine attack. The P1 latencies of the trigeminal somatosensory evoked potentials (SEP) and the R1, ipsilateral R2, and contralateral R2 of the blink reflex (BR) were evaluated on both sides of stimulation. The values were compared by nonparametric statistical methods.

**Results** In patients with strictly unilateral pain, the P1 latencies of the SEP were significantly longer on the symptomatic side compared to the contralateral side and without aura (n=6). IDAP was computed from N1-P2 amplitudes of 90 averaged responses at stimulation intensities of 40, 50, 60 and 70 dB above perception level, at a frequency of 0.5 Hz. During uninterrupted stimulation at 3.1 Hz, PR-VEPs were sequentially averaged in four blocks of 50 responses and amplitudes of the N1-P1 peak were measured. We compared the modifications in N1-P2 amplitude at 40 dB, the IDAP slope, PR-VEP N1-P1 amplitude in the first block and the PR-VEP habituation over 4 blocks, before and after hyperventilation.

**Results** Hyperventilation induced a slight decrease in the N1-P2 amplitude at 40 dB (14% in normal volunteers; 4% in migraineurs). All healthy volunteers and 60% of migraineurs presented an important increase of IDAP slopes after hyperventilation. After the hyperventilation, the PR-VEPs potentiation was aggravated in 60% of migraineurs and there was a decrease in PR-VEPs habituation or even a potentiation in all healthy volunteers.

**Conclusion** In healthy subjects, hyperventilation decreases (or may invert) PR-VEP habituation and increases IDAP. Between attacks it augments PR-VEP potentiation and IDAP slopes in a large subgroup of migraine patients but not in all. A reduced performance of Ca2+ channels due to hypocapnia, acidosis and reduced iCa2+ levels may explain these electrophysiological changes. It remains to be seen whether hyperventilation may increase the prevalence of abnormal EP findings in migraine or help to identify pathophysiologically different subgroups of patients.
(P1: 19.5 ± 2.5 ms on the symptomatic side vs 18.3 ± 2.2 ms on the contralateral side, P = 0.007). In patients with alternating pain localization, the P1 latencies were 18.7 ± 2.5 ms on the left and 18.5 ± 2.2 ms on the right side. We could not detect any significant differences between the latencies of the different BR potentials.

Conclusion We have previously shown that patients with cluster headache during the cluster episode and outside an attack have significantly longer tSEP on the symptomatic side. These data show that an asymmetry of cerebral somatosensory stimulus processing is not a unique feature of cluster headache. It also occurs in migraine, given the rare situation that the pain is strictly unilateral, occurring always on the same side of the head. The BR is a trigeminal-facial reflex activating an oligosynaptic pathway (R1) and polysynaptic pathways (R2) located in the brainstem. The tSEP measures a pathway from the trigeminal nerve via brainstem and contralateral thalamus to the primary sensory cortex. Our findings of prolonged tSEP on the symptomatic side but no side differences in BR in patients with strictly unilateral primary headache disorders suggest that an alteration of stimulus processing has its origin in cerebral regions located more rostrally than the brainstem.

P2-J14

Visual stress in migraine: autonomic reactivity and subjective complaints associated with exposure to intensive visual stimulation

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Objectives Migraine sufferers experience more visual discomfort associated with bright lights, grating patterns and flickering visual stimulation than those who do not get migraines. Intense visual stimulation can also trigger migraines. The mechanism for visual sensitivity and its link to migraine remain unclear. It has been suggested that autonomic dysregulation may be involved. This study compared autonomic responses (heart rate variability and electrodermal responses), somatic and visual complaints, and anxiety in migraine sufferers and controls exposed to intense and mild visual stimulation.

Methods 24 migraine sufferers (M) and 24 nonmigraine controls (NC), all females, were tested during a headache-free interval. Participants were exposed to 5-minute periods of 2 intense visual stimuli (bright light and a high contrast, rapidly flickering grating) and 2 mild visual stimuli (dim light and a low-contrast, slowly flickering grating). Five-minute baseline periods preceded and followed each condition. Consecutive cardiac interbeat intervals (IBI) and electrodermal activity were recorded during each condition. Heart rate variability (HRV) and electrodermal responses (EDR) were assessed offline. Participants rated anxiety, and somatic and visual complaints on a visual analogue scale (VAS) before the first baseline, after each viewing condition, and after the last baseline.

Results ANOVAS compared initial and final baselines (group × baseline period), and reactions to the 4 viewing conditions (group × stimulus × intensity). The M group had lower IBI (i.e., higher heart rate) across all conditions (P < 0.01) when compared to NC. No significant effects were detected for HRV variables. While no difference in number of EDRs was detected at baseline, M had more responses than NC across all viewing conditions (P < 0.05). Both groups had more EDRs during the intense viewing conditions as compared to the mild conditions (P < 0.05). VAS responses indicated that M described a significant increase in headache and tired/sore eyes from beginning to end of the study, and more headache and visual complaints (e.g., distortions and after-images) associated with the 4 stimuli as compared to NC. Reported anxiety was not higher in M before testing, but was increased during the intense visual conditions. This pattern was not detected in NC.

Conclusions While migraine sufferers reported more somatic and visual symptoms, and anxiety when exposed to different types of visual stimulation, no clear pattern of autonomic reactivity emerged. The results will be discussed in relation to theories of autonomic dysfunction in migraine, as well as theories that link visual complaints to migraine pathophysiology.

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P2-J15

Trigeminal reflex hyperactivity in migraine patients

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Introduction Activation of the trigemino-vascular system as well as of the central trigeminal nuclei that control the pain that arises from the head are thought to play an important role in the pathophysiology of migraine attacks. The blink reflex can give information on peripheral and central trigeminal functions. This reflex may be conditioned and habituates readily.

Objectives To assess the blink reflex habituation responses in migraine patients and controls.

Methods The 'blink reflex habituation test' was performed in 15 headache-free migraine patients and in 15 control subjects. A Micromed device with an 'ad hoc habituation test program' permitted us to elicit and record the reflex activity on both sides bilaterally and to repeat the stimulation at decreasing time intervals in order to induce habituation.

Results Whereas R1 and R2 latencies, amplitudes and areas were similar in patients and control subjects, the blink reflex habituation response was markedly reduced in migraine patients. A statistically significant difference (P < 0.001) was found between patients and controls when stimuli were delivered at intervals shorter than 10 s.

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Conclusions  Our data suggest that in migraine patients the pathways involved in the blink reflex are hyperactive. This may be due to a central brainstem activation that may predispose patients to migraine attacks.

P2-J16
Assessment of trigeminal nociceptive function in headache: brain responses evoked by CO₂ laser stimulation in migraine and tension-type headache patients

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Although the cerebral responses after stimulation of different modalities have been studied in migraine patients, the central nociceptive system has never been investigated. We recorded CO₂ laser evoked potentials (LEPs) in 13 patients suffering from migraine without aura (MA) and 20 patients affected by tension-type headache (TTH), according to IHS criteria (1988). Twenty normal controls were also evaluated. LEPs were collected after stimulation of the hand and of the perioral and supraorbital regions on both sides. Three averages of 30 or 15 trials were recorded after stimulation of each hand or trigeminal regions, respectively. The different averages were separated by a time interval of 5 min, while 10 min divided the different stimulation. The N1 response in the temporal region contralateral to the stimulation and the simultaneous P1 potential in the frontal lobe were recognized. Later, the N2a component, reaching its maximal amplitude on the Cz vertex, and the N2b potential in the frontal region were identifiable. Lastly, the P2 response showed a widespread topography with the highest amplitude on the vertex. In healthy subjects, the LEP components recorded on the Cz vertex (N2a/P2) showed a progressive amplitude reduction across the three averages for each stimulation site. Moreover, the N2a response had a later latency in the third than in the first average after stimulation of both hands and perioral regions. The vertex LEP components (N2a/P2) tended to have a higher amplitude in both MA and TTH patients than in healthy subjects. This tendency was statistically significant only for the P2 potential after stimulation of the left perioral region in MA patients. Moreover in MA patients, there was a significant reduction of the N2a/P2 amplitude in the third average only after stimulation of the left hand and of the left perioral region and the N2a latency was significantly increased in the third average only after stimulation of the right perioral region. As previously shown with the non-nociceptive evoked potentials, we failed in demonstrating any specific LEP abnormality in MA and TTH patients. The increased vertex LEP amplitudes might be due to a lower degree of habituation of these responses, clear in MA patients. Previous studies demonstrated a reduced habituation of evoked potentials of different modalities in migraine patients: the LEPs findings could confirm a dysfunction of adaptation capacity to repetitive stimulation as an interictal cortical dysfunction probably predisposing to migraine.

P2-J17
Migraineurs show visual field defects on motion coherence perimetry during the interictal period

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Objectives (a) To assess interictal visual field sensitivity in migraine patients compared to nonheadache controls using a motion perimetry task; (b) to compare visual sensitivity in migraine on the motion perimetry task to a conventional luminance-based measure.

Methods Forty subjects diagnosed with migraine (20 with aura [MA], 20 without [MO]) and 20 nonheadache controls (NC) were tested. Migraineurs were tested at least 1 week after an episode. A computerized global dot motion test was employed to measure motion sensitivity separately in each eye, at 15 discrete locations covering the visual field. This test uses a four-alternative forced choice procedure in which the goal is to detect the overall global direction of coherent motion in a noisy pattern of dots.

Results For foveal stimulus presentations, mean motion sensitivity was significantly elevated in both migraine groups (MO greater than MA) compared to NCs (P = 0.007). There was no statistically significant difference in the ratio of foveal thresholds between the eyes (P = 0.19). Across specific peripheral locations, motion thresholds were significantly elevated in migraine patients compared to NCs (P = 0.001). Global motion perimetric measures revealed that almost twice as many migraineurs (70% MA, 65% MO) had at least one region of reduced sensitivity (≥2 standard deviations above the NC mean), than NCs (35%). Periperal defects were primarily unilateral and nonuniformly distributed across the visual field with only a small percentage of homonymous deficits in each group (15% MO, 10% MA, 16% NC). Furthermore, 3 MOs and 1 MA showed a general depression in both visual fields. This did not occur in any NCs. The global motion perimetry task identified significantly more abnormal visual field locations than conventional luminance-based perimetry, where controls and migraineurs performed similarly and in the normal range.

Conclusions Motion sensitivity, but not static luminance sensitivity was selectively depressed in some locations of the visual field in migraineurs. This suggests abnormalities in the magnocellular visual pathway. Field defects in global motion perimetry have also been described in glaucoma patients and glaucoma suspects using a similar motion perimetry task.

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P2-J18

Spatial and temporal properties of interictal visual discomfort in migraine

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Objectives Heightened visual sensitivity has been indicated in migraine not only during episodes, but also interictally. Complaints include discomfort and sometimes pain in the presence of flickering stimuli and striped patterns, the spatial temporal characteristics of which have not been fully characterized and may help clarify visual cortical pathways involved. Here we employ a well controlled computerized test to assess spatial-temporal characteristics of visual discomfort in migraine and compare them to nonheadache controls.

Methods 40 subjects diagnosed with migraine (20 with aura [MA], 20 without [MO]) and 20 nonheadache controls were tested. Migraineurs were tested ≥1 week after an episode. The task measured visual discomfort thresholds elicited by a circular patch of square wave grating. Stimulus contrast steadily increased over a brief exposure period with discomfort indicated by a mouse press that would terminate the pattern. Twenty different stimuli covering a range of spatial (0–16 cpd) and temporal frequencies (0–30 Hz) were presented, including spatial-temporal combinations to assess relative involvement of the magnocellular (M) and parvocellular (P) visual pathways.

Results Static patterns: Across spatial frequencies sampled, mean visual discomfort thresholds were significantly lower in MO (89%) and MA (80%) than NCs (97%; P = 0.02). Visual discomfort was evoked by at least 1 pattern in over half of migraine patients, and 20% of NCs. A main effect was found for spatial frequency (P = 0.001), with greater visual discomfort at middle spatial frequencies in all groups (P = 0.01). Temporally modulated patterns: Overall mean discomfort thresholds were significantly lower in MOs (67%) and MAs (62%) than NCs (89%; P = 0.005). Visual discomfort was elicited by ≥1 flickering pattern in most migraineurs (80% MOs, 95% MAs) and a large proportion of NCs (60%). However, a larger proportion of patterns induced discomfort in migraine (MO = 62%, MA = 54%, NC = 38%). A main effect was found for temporal frequency (P < 0.001), with greater visual discomfort at higher temporal frequencies in all groups, that was significantly greater in MO and MA (P = 0.04). Spatial–temporal interactions: All groups showed significantly greater mean discomfort to the stimuli designed to invoke relatively greater M than P processing (P < 0.05). This difference was significantly greater in migraine than NCs (P = 0.001).

Conclusions Although interictal visual discomfort in migraine patients has been previously described, the present results suggest that heightened visual sensitivity is not a ubiquitous feature of migraine and also occurs in individuals without headache. Further, the spatial-temporal characteristics of visual discomfort in migraine implicate an abnormality in temporal processing.

P2-J19

Longitudinal assessment of cortical excitability in women with menstrual migraine

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Objectives To pilot a method of assessing interictal occipital cortical excitability longitudinally around the migraine attack.

Background Occipital excitability is increased in the migraine interictum, and some authors have found this to be correlated to attack frequency. Thus, the onset of a migraine attack may be preceded by a rise in excitability, possibly facilitating cortical spreading depression.

Methods We studied six females with menstrual migraine without aura (one with infrequent attacks with aura) using transcranial magnetic stimulation (TMS). Cortical excitability was assessed by stimulating the occipital region, and finding the threshold for reports of phosphenes. Assessments were scheduled on the 3 days before the expected onset of migraine, which was predicted by the peak urinary LHRH concentration. Additional stimulations were performed on days 1 and 2 after the cessation of the attack, and on days 7, 14, 21, and if possible, day 28 after its onset. Three subjects had had TMS on the 3 days before the attack and one subject was studied on four consecutive premigraine days. The remaining two subjects were studied 2 days and 1 day prior to attack onset. In the postattack period, two subjects had a non-menstrual migraine attack, which was separated by at least two days from the nearest assessment.

Results One subject revealed a marked decrease in phosphenic threshold from the first to the second assessment, which remained stable afterwards. As this drop did not occur in proximity to the attack, this was most likely due to a learning effect. Preliminary analysis using ANOVA revealed that overall, no significant changes in phosphene threshold occurred during the menstrual cycle, nor in relation to the migraine attack. However, for the one subject with infrequent attacks with aura, there was a considerable fall in phosphene threshold of 9% over the 3 days before the attack, which gradually returned to ‘normal’ in the week after the attack. This particular attack was not, however, characterized by a migraine aura. Data from non-migrainous age matched control subjects are currently being assembled.

Conclusion In a small series of migraine without aura patients, we have found no evidence for increases in cortical excitability in the few days before the attack. However, in migraine with aura, an increase in excitability may occur, which in turn might increase the risk of spontaneous spreading depression in the occipital cortex in migraine with aura. This study provides grounds for further longitudinal investigations of migraine with aura, and demonstrates the feasibility of the methods used.
Cortisol and prolactin response to M-CPP test in prolonged menstrually related migraine attacks

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Background and objectives During the perimenstrual period, migraine attacks can last longer than 72 h, and may be extremely severe and poorly responsive to analgesics. However, little is known on the neuroendocrine milieu as a possible factor influencing the clinical expression of menstrually related migraine (MM) attacks.

To assess neuroendocrine correlates of MM and perimenstrual status migrainosus (SM) we evaluated cortisol and prolactin responses to the direct central serotonergic agonist m-CPP administered orally during the follicular and luteal phases of the menstrual cycle.

Methods Ten women (age: 39.4±7.7; body mass index (BMI): 21.9±3.9; duration of menstrual cycle: 27.7±0.9) with MM (duration: 4.6±0.7 days) received oral m-CPP (0.25 mg/kg) at 8.30 a.m. during the follicular (+3, +7) and the luteal (−7, −2) phase of the menstrual cycle. Nine women (age: 37.1±7.0; BMI: 23.7±2.2; menstrual cycle: 27.9±0.8) with MM attacks (duration: 1.7±0.7 days) and six healthy (C) women (age: 35.8±7.0; BMI: 22.2±2.6; duration of menstrual cycle: 28.3±1.0) were also studied throughout the cycle and served as controls. Blood samples were taken at times −30, 0 and every 30 min over 4 h.

Results The major findings were as follows: (a) Prolactin response to m-CPP was significantly blunted in SM compared to MM and C in both phases of the menstrual cycle (f=2.5, P<0.003 follicular; f=4.2, P<0.001 luteal). Basal plasma prolactin levels were similar in the two groups. Prolactin area under the curve (AUC) was significantly lower in SM than in MM and C during the follicular phase (f=11.5, P<0.001), but not in the luteal, being lower only compared to C (P<0.003).

(b) Cortisol response to m-CPP was absent in SM as opposed to MM and C in both phases of the menstrual cycle (f=7.5, P<0.001 follicular; f=4.5, P<0.001 luteal). Basal plasma cortisol levels were significantly higher in SM compared to C during the follicular (P<0.01) and luteal phase (P<0.05), slightly higher in the follicular and superimposable in the luteal phase compared to MM. As a consequence, no significant differences were found in cortisol AUC between groups.

Conclusions A derangement of serotonergic control of prolactin and particularly of cortisol release occurs in women with perimenstrual SM. Such dysfunction does not seem to be specific of any menstrual cycle phase.

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Homocysteine in patients with migraine
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Introduction Although the pathophysiology of migraine has not been thoroughly elucidated, it has been postulated that the aberrant vascular function is closely concerned. Recent evidence has shown that homocysteine plays an important role in a variety of vascular diseases as an independent risk factor of endothelial damage, activation of platelets, and so forth. However, its implication in migraine is largely unknown. In the present study, we measured the plasma concentrations of homocysteine and its related products including cofactors in patients with migraine during the interictal period.

Materials and methods 9 patients with migraine with aura (McA), 9 patients with migraine without aura (MsA), and 5 healthy volunteers (C) were studied. Blood samples were drawn from the brachial artery after 30 min of bed rest. After centrifugation, plasma was separated. The concentrations of homocysteine and methionine were measured by high performance liquid chromatography (HPLC). Those of folic acid and vitamin B12 were measured by chemiluminescent immunoassay (CLIA).

Results Each plasma concentration was as follows: homocysteine (nmol/mL): McA 9.9±6.4, MsA 5.9±1.6, C 7.1±1.3; methionine (nmol/mL): McA 2.2±0.6, MsA 1.9±0.4, C 2.6±1.0; folic acid (ng/mL): McA 7.3±3.0, MsA 9.8±5.5, C 6.0±1.1, vitamin B12 (pg/mL): McA 570.0±73.3, MsA 511.7±184.2, C 473.4±97.9. As regards all the substances examined, there were no significant differences among McA, MsA, and C.

Conclusions The concentrations of homocysteine and its related products showed no significant differences among McA, MsA, and C. Further investigation should be required to clarify the implication of homocysteine in the migraine pathophysiology.

Up-regulation of inducible nitric oxide synthase (NOS-2) and cyclooxygenase type 2 (COX-2) switches to TH2-type response in migraine
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Nitric oxide synthases (NOS) play a role in CNS neurotransmission and in the regulation of cerebral circulation. Inducible NOS (iNOS) expression is activated by cytokines (LPS, PGE2). Central and peripheral pathomechanisms that work in migraine recognize in NO one of their drivers. NO
modulates Th1/Th2 cell subset balance. Th1 releases IL2, IFN-gamma and lymphotoxin; Th2 releases IL4, IL5 and IL10. Th1/Th2 cytokines may influence the spreading of pain-producing processes in migraine. Eleven migraine without aura (MwoA) patients (9F, 2M) and 10 age-matched healthy controls (C) (8F, 2M) have been enrolled in this clinical study. Blood samples were taken at baseline (T0) and during an induced (5 mg isosorbide dinitrate) migraine attack (T1). Total RNA from peripheral blood lymphocytes (PBLs) was isolated by Trizol reagent and RNA (2 μg) was reverse transcribed to prepare complementary cDNA. COX-2, NOS-2 and β-actin were amplified, using PCR, with specific primers. After gel electrophoresis, signals were quantified by acquiring samples with the CCD camera instrument Gel Doc 2000. MwoA and C PBLs were stimulated or not (4 h at 37°C) with phorbol 12-myristate 13-acetate plus ionomycin in presence of Brefeldin A. Cells were washed and stained with fluorochrome conjugated anti-CD3 and anti-CD8 MoAbs fixed and permeabilized and intracellularly stained with fluorochrome conjugated anti-IFN-gamma or anti-IL4 MoAbs. The level of cytokine expression was analyzed by gating on CD4+ subset. Th1 and Th2 cytokines (IFN-gamma, IL2, IL4) were directly assayed by ELISA. The results of this study seem to indicate the following: NOS-2 is overexpressed in PBLs from MwoA (T1 vs C, P < 0.002; T0 vs C, P < 0.001). Th1 subset is lowered in both MwoA phases (T0 vs T1 = n.s.; T0 or T1 vs C, P < 0.001). Th2 subset is increased in both MwoA phases (T0 vs T1 = P < 0.05; T0 vs C, P < 0.001; T1 vs C, P < 0.003). IL2 serum levels are lowered in MwoA (T1 vs C, P < 0.05); IL4 serum values were increased in MwoA (T1 vs C, P < 0.05); IFN-gamma serum values did not show any difference (T0 vs T1 = n.s.; T0 or T1 vs C, n.s.). These results show a regulatory effect played by NO on T cells, shifting the balance within Th1/Th2-type activity toward Th2 response. This unbalance may be interpreted as a biomolecular defense signal against the NO-induced sterile inflammation pathway. An induced Th2 anti-inflammatory activity may represent a new modality in MwoA treatment.

P2-J23
Nitric oxide synthase expression in platelets of migraine subjects

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The increased production of nitric oxide (NO) may explain many of the events that occur during a migraine attack. Thus, it has been found that: (a) cGMP and nitrite levels, reflecting NO formation, are increased during migraine attacks; (b) donors of NO induce headache and migraineurs are very sensitive to these compounds; (c) NO is involved in pial artery dilatation elicited by the cortical spreading depression; (d) NO can dilate human cranial vessels and the cerebral arterial tree is frequently innervated by nitricergic neurons, whose stimulation induces relaxation; (e) migraine attacks have been associated with intra- and extracranial arterial dilation; and (f) NO can also influence sensory nerve endings. The increased production of NO can result from the stimulation of the constitutive (nNOS and eNOS) and/or of the inducible NO synthase (iNOS). Until now, studies have suggested the involvement of the constitutive NOS in migraine but there are no studies about the role of iNOS in this disease. Therefore, the objective of this work was to quantify the constitutive and the inducible NOs in platelets of women with migraine without aura or healthy controls. The selection of migrainous women (without any drug preventive or symptomatic treatment) and controls was made taking into account the International Headache Society criteria. Written informed consent was obtained from each subject. Blood was collected in the morning (9:00 a.m.), at the same time for migraineurs and controls, and platelets isolated by differential centrifugation. The nitric oxide synthase expression was determined by Western blot. Thus, after incubation, platelets were homogenized and protein fractionated electrophoretically in polyacrylamide gel at constant voltage. Pre-stained standards are used as molecular weight markers and run in a parallel lane. Proteins are transferred to nitrocellulose membranes in a Mini-Trans Blot Cell at constant current for 2 h. After buffer, membranes are incubated with a specific antibody. After washing, membranes are incubated with goat antirabbit secondary antibody conjugated to horseradish peroxidase. Specific protein bands are detected with the detection reagent on special autoradiography films. The control (n = 8) and migraine groups (n = 8) did not differ regarding regular physical activity and age. Concerning the platelet constitutive NO synthase expression, there was no significant difference between migraineurs and controls. On the contrary, the expression of the platelet inducible NO synthase was significantly higher in the migraine group. Although preliminary, our results suggest that in migrainous subjects there is a higher NO synthase activity contributing to migraine pathophysiology.

P2-J24
Anaerobic exercise provokes headaches in patients with migraine, activating the system of L-arginine-nitric oxide

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Background and objectives Nitric oxide (NO) is probably involved in the central process of pain and plays an important role in the vascular tone. Many authors have suggested its involvement in the pathophysiology of migraine. This is the first study in which the production of NO in patients with migraine subjected to physical exercise is determined and in which the production of NO is correlated to headaches triggered by exercise. This study aims to correlate the

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production of nitrates by platelets (when stimulated by lipopolysaccharide plus interleukin-1α) and the plasma levels of nitrates plus nitrates [and indirectly the activity of NO synthases (NOS)] with the triggering of headaches by exercise in patients with migraine.

**Material and methods** The studies have been carried out in a group of 21 women suffering from migraine without aura (MWOa) and an age-matched control group of 12 women without chronic headaches. For 30 s, they performed the Wingate anaerobic test (WanT). Platelet nitrates and plasma nitrates plus nitrites have been determined before and 5 and 30 min after the WanT.

**Results** In migrainous women, exercise triggered headaches 4.5–5.5 h after the WanT. A significant increase from the basal time to the 30 min in the production of platelet nitrites (1.39 ± 0.25–3.01 ± 0.20 nM NO2/109 platelets) in the migraine group and a statistical difference between the two groups in the plasma determinations (basal: 20.0 ± 2.8 and 12.6 ± 1.6; 5 min: 24.1 ± 3.1 and 14.4 ± 1.3; 30 min: 22.7 ± 2.4 and 14.3 ± 1.7 μM/L in MwoA patients and controls, respectively) has been observed.

**Conclusions** Results suggest that patients with migraine without aura have a significantly increased production of NO, reflecting an increased activity of the constitutive NOS, and that exercise is a triggering factor of migraine attacks, probably stimulating the inducible NOS.

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**P2-J25**

**Analysis of blood flow velocities in migraineurs undergoing biofeedback therapy**

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**Introduction** Biofeedback/relaxation therapy (BFRT) is a frequently employed nonpharmacological therapy for migraine, a common disorder with a neurovascular basis. The objective of this study is to determine if migraineurs with aura respond differently to BFRT than migraineurs without aura, and if such a difference can be explained on the basis of blood flow velocity (BFV).

**Methods** Diagnoses of migraine were based on IHS criteria. A group of migraineurs, 6 with aura (MA) and 12 without aura (MO) underwent BFRT (10 sessions and home practice over a 12-week period). A control group (7 MA and 12 MO) were told to ‘relax’ but given no formal instruction. Using transcranial Doppler (TCD), two measurements of left and right side middle cerebral artery BFV were obtained before and after the BFRT/control periods while subjects were migraine free. Pretest and post-test measurements were made of forehead muscle tension, hand temperature, and heart rate. Subjects also completed inventories assessing depression (Beck), anxiety (State-Trait Anxiety), and daily pain. Subjects’ successful responses to BFRT/control were defined as a 50% reduction in the pain score.

**Results** The group receiving BFRT (both MA and MO) showed significant (P < 0.05) reductions in pain, depression, and anxiety compared to the control group. Pain score decreased from 0.53 ± 0.31–0.32 ± 0.30 in the BFRT group and from 0.51 ± 0.42–0.47 ± 0.43 in the controls. Depression score decreased from 9.8 ± 5.6 to 4.3 ± 4.5 in BFRT; controls decreased from 10.5 ± 9.9–9.0 ± 11.8. Anxiety score decreased from 40.4 ± 8.9–34.4 ± 8.9 in the BFRT group, while the controls did not change. There were no significant differences in BFV by group or period. Stratified by migraine type, MA showed significant (P < 0.05) left to right BFV differences, whereas MO did not. Overall, left (L) and right (R) maximum BFV were significantly higher (P < 0.05) in MA (L = 102.2 ± 14.2; R = 97.1 ± 11.6) than in MO (L = 90.9 ± 19.0; R = 94.2 ± 17.5). Pearson correlation showed the following significant (P < 0.05) relationships. Trait Anxiety score was correlated with heart rate (r = 0.61) as predicted. There was also an inverse correlation (r = −0.36) between trait anxiety and maximum BFV.

**Conclusion** BFRT is an effective therapy regardless of migraine type, and the benefit is not related to changes in BFV over the course of therapy. Left to right variation and maximum values of BFV were higher in MA. The inverse correlation of anxiety and BFV may be related to hyperventilation-induced vasoconstriction.

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**P2-J26**

**Could asymptomatic cerebrovascular syndrome cause headache?**

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**Background and objectives** Whether the so called ‘asymptomatic multiple lacunae’ may cause headache is not yet elucidated. It is also not known if the pathogenesis of lacunar infarction such as hypertension, arterial sclerosis and cerebral ischaemia may become the cause of headache. The purpose of this study is to investigate the possible role of chronic cerebral hypoperfusion in the mechanism of headache.

**Materials and methods** In a serial 161 patients (65 men, 96 women, mean age of 59.1 ± 18.4 years) who underwent brain MRI study at our hospital between 10/04/2000 and 19/01/2001, clinical characteristics, subjective symptoms, neurological findings and MRI findings were evaluated. Correlation between ischaemic MRI lesion and headache was closely evaluated.

**Results** 57 of 161 patients (35.4%) suffered from headache. The patients with headache (17 men, 40 women, mean age of 51.1 ± 20.5 years) were younger than the patients without headache (48 men, 56 women, mean age of 63.4 ± 17.9 years). In 102 (43 men, 59 women) of 161 patients (63.4%), neurological findings were negative. The ratio of negative neurological findings of the patients with headache (91.2%) was significantly higher than those patients without headache (48.1%). One or more risk factors of cerebrovascular disease (hypertension, diabetes mellitus, hyperlipidaemia, and
hyperuricaemia) existed in 75 of 161 (46.6%) patients. In patients with negative neurological findings, 15 of 52 (28.8%) patients with headache had one or more risk factors for cerebrovascular disease and 24 of 50 (48.0%) patients without headache had the risk factors, and that difference was statistically significant \((P<0.05)\). Brain MRI showed prior cerebrovascular disease in 27 of 57 (47.7%) patients with headache and in 61 of 104 (58.7%) patients without headache. In patients with negative neurological findings, the difference in the ratio of cerebrovascular lesions of MRI was not significant between the patients with headache \((23/52, 44.2\%)\) and the patients without headache \((26/50, 52.0\%)\).

**Conclusions** There was no univariate correlation between cerebral ischaemic lesion and headache. However, among patients with asymptomatic MRI lesions, headache sufferers were younger, were more often women, and had less artherosclerotic risk factors or neurological findings than nonheadache sufferers. These results suggested a correlation between asymptomatic cerebrovascular disease and headache.

**P2-J27**

**Sympathetic nervous system and migraine: a TCD study**

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Patients with migraine have an impairment of the sympathetic nervous system (SNS). During the cold pressor test (CPT) and head up tilt (HUT) the SNS is activated. We measured the cerebrovascular reactivity (CVR) to CPT and HUT by transcranial Doppler sonography (TCD) in order to detect the dysfunction of SNS. 15 patients with migraine without aura (mean age 36.9 ± 2.89 years) participated in our study. A control group comprised 16 healthy volunteers (mean age 35.9 ± 5.2 years). Tests consisted of a 5-min baseline period, 3-min immersion of the right hand in ice water (CPT) and HUT to 90° for 5 min. In both middle cerebral arterial vessels, vm was monitored by bitemporal 2 MHz probes using the TCD Multi-Dop X4 system. At the same time, the mean arterial pressure (MAP) and heart rate (HR) were continuously monitored by finapres and ECG while end-tidal CO₂ (Et-CO₂) was followed by a capnograph. A computer program (TCD 8) was utilized to determine vm over a 2-min time interval at rest, during 3-min of CPT and 5-min of HUT. Differences in cerebral (Δvm) and systemic parameters (ΔMAP, ΔHR, ΔEt-CO₂) during CPT and HUT were calculated. Student's \(t\)-test and model of logistic regression were used. ΔvmCPT was significantly lower in migraine \((P<0.01)\) while ΔMAPCPT, ΔHRCPPT and ΔEt-CO₂ CPT did not differ significantly. ΔHRHUT was significantly lower in migraine \((P<0.01)\) and ΔvmHUT, ΔMAPHUT, and ΔEt-CO₂ HUT did not significantly differ between the groups. The MAP in both groups was in the autoregulatory range during CPT and HUT. In the CPT and HUT model of logistic regression, migraine (yes, no) was entered in as a dependent variable while Δvm, ΔMAP, ΔHR and ΔEt-CO₂ were independent variables. Data of the model fitted very well \((P=0.89)\) for CPT and moderately for HUT \((P=0.10)\). dvmCPT appeared to be significant in the models \((P<0.01)\). The cerebrovascular reactivity to CPT and HUT is altered in migraine. It is likely that patients with migraine have hypofunction of the SNS.

**P2-J28**

**Functional 1H-MRS in migraine: evidence for a mitochondrial disorder?**

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**Purpose** The study was aimed at investigating brain metabolite changes due to visual cortex activation in migraineurs and normal subjects by 1H-MRS.

**Subjects and methods** 7 patients with migraine with aura (MwA), 9 patients with migraine without aura (MwoA) and 8 control subjects were studied. 1H-MRS was carried out using a whole-body scanner (GEMS LX system) with a standard head coil. The volume of interest (about 8 cm³) was placed in the visual cortex area and the data were acquired over 36' 40''. The visual stimulus was applied using MR-compatible goggles with a flashing red light: frequency = 8 Hz and intensity = 14 lux. ANOVA with least significant difference (LSD) test were used for statistical analysis.

**Results** The minimum of N-acetylaspartate (NAA) signal was reached within the first 4 min of visual stimulation in MwA patients but later in MwoA (10 ± 8.5 min) and controls (20 ± 12.3 min). The rate of NAA signal decrease, with respect to its first value (measured during the off status) was greater in the MwA patients (14.61% ± 3.70) compared with MwoA patients (5.04% ± 0.25) and control group (7.47% ± 2.63). A statistical significance emerged for the difference between the mean NAA decrease detected in MwA patients and that detected in the other two groups \((P<0.02)\), but not between NAA decrease in MwoA patients and NAA decrease in controls. A significant difference between the total creatine (tCr) peak of the MwA and that detected in the other two groups \((P<0.05)\) was found only at the time needed to reach the minimum (MwA = 8.5 ± 3.5 min, MwoA = 16.0 ± 5.65 min, Controls = 16.0 ± 4.24 min). No significant difference emerged between the lactate peak of both patient groups and controls.

**Conclusions** Reduction in brain NAA levels has been associated with mitochondrial disfunctioning (1,2). Accordingly, the dramatic decrease \((-14.61\%)\) in the NAA signal in the MwA within < 4 min after visual stimulation suggest the occurrence of a mitochondrial disturbance and a less efficient response of the visual cortex to the metabolic shift induced by sensory stimulation in the patients affected.

**References**

P2-J29

Mechanism of magnesium infusion therapy on migraine attack by using magnetic resonance angiographic technique

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Objective
We have demonstrated that magnesium infusion therapy dramatically ameliorated both migraine and cluster attacks. The mechanism of magnesium infusion therapy on migraine attack has been considered to be dilation of cerebral vessels. No direct evidence, however, has been demonstrated during migraine attacks in patients. Therefore, by using magnetic resonance angiographic (MRA) technique, we investigated whether magnesium really dilated cerebral vessels of patients during migraine attacks.

Subjects and methods
Three patients with migraine without aura (cases 1, 2 and 3) were examined by magnetic resonance angiography. In case 1, MRA was performed before and after magnesium treatment during headache period, and it was done in the non-headache period. In cases 2 and 3, MRA was performed before and after magnesium infusion to investigate the action of magnesium on cerebral vessels in the non-headache period.

Results
In the case 1, MRA during migraine attack showed marked dilatation of optic artery of the painful side, compared to MRA in the non-headache period. The dilated optic artery did not change its diameter even after magnesium infusion when headache was ameliorated. In the case 2 and 3, no changes in the diameters of any cerebral vessels were shown before or after magnesium infusion in the non-headache period.

Conclusion
The mechanism of magnesium infusion therapy on migraine attack is not by changing the diameter of the cerebral vessels. This is the first evidence of the action of magnesium on the cerebral vessels during the migraine attack in patients.

P2-J30

Evidence for increased visual cortex excitability in migraineurs in response to angle perception: a functional MRI visual activation study

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Objective
Due to its uniqueness, one of the most intriguing topics in neurology is the mechanism of visual aura in migraine. There is evidence suggesting that cortical hyperexcitability plays a key role in fortification spectra, but the ultimate reason for this malfunction is obscure. Noteworthy is the particular distribution of bright lines with varying angulations, reflecting perhaps the activity of a particular sets of hyperexcited neurons. In the present study, a functional MR (fMR) paradigm was designed to address the visual perception of angles in both hemispheres in migraineurs as compared to controls.

Subjects and methods
Five normal subjects and five IHS migraine with aura patients were studied interictally. Fortification spectra were right sided in two individuals, left sided in one, and alternating in two. Blood oxygen level-dependent contrast (BOLD) fMRI was used to compare brain activation during a computerised visual stimulation with patterns composed by rows of oblique bars oriented in parallel, alternating 90° in a rhythmical and congruent way (control condition); and two other identical patterns, except by bars forming 60° in either right or left hemifield (RH and LH ‘angle’ conditions). A factorial design taking subject group, side of visual aura and side of ‘angle’ presentation as main variables was employed. Linear contrasts across these variables were performed according to the Theory of Random Gaussian fields.

Results
Significant interaction between subject group, stimulated hemi-field and side of visual aura on brain activation was observed. Using a threshold of \( P < 0.001 \), there was activation in the visual cortex contralateral to the hemi-field stimulation only when the stimulated hemisphere was contralateral to the symptomatic cortex in side-locked aura subjects. Similarly, both hemispheres were activated in response to contralaterally presented ‘angles’ in the side alternating aura group. In the control group, activation was only observed in the nucleus accumbens, but not in the visual cortex.

Conclusions
Our results, albeit preliminary, strongly support the hypothesis of abnormal cortical excitability in migraineurs, and suggest that this effect is mainly restricted to the affected hemisphere in patients with unilateral aura locked in one side. This effect also suggests that seeing ‘angles’, as compared to parallel bars, may provide an efficient way of evoking this selective response.

P2-J31

Abstract withdrawn
P2-J32

Functional magnetic resonance imaging during sustained visual stimulation: less habituation-like changes of the BOLD signal in migraine with aura

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Objective To study habituation-like changes of the MRI-BOLD signal in the visual cortex during prolonged visual stimulation in migraine with typical aura (MA).

Background One of several mechanisms of interictal migraine pathophysiology involves deficient habituation in cortical information processing as shown by visual evoked potential studies (Schoenen et al., 1995; Afra et al., 1998).

Design and methods Eleven healthy volunteers (HV) and 8 MA patients (interictally) were investigated using functional MRI with a 1.5T Philips ACS-NT system. A reversing checkerboard (8 Hz) was used for visual stimulation. Activated cortical areas were determined using a fMRI protocol (P < 0.001) [single shot EPI, TR = 3 s, TE = 40 ms, nominal voxel size = 0.07 cm3] with a repetitive block paradigm (3 periods: 30 s darkness - 30 s stimulation) showing an increase in BOLD of about 2%. A second fMRI protocol [single shot EPI, TR = 5 s, TE = 40 ms] was used to investigate the time course of activation in sustained visual stimulation (paradigm: 2 min control (dark), 10 min stimulation, 2 min control). Motion correction and spatial filtering was applied to all data. The slope of the activation time course during the sustained activation period was determined by a linear fit and compared between HV and MA.

Results The slopes of the BOLD signal during sustained visual stimulation were −0.0114 (−1.1% over 10 min) for HV and −0.0016 (−0.16% over 10 min) for MA with a significant difference (P < 0.05) between MA and HV.

Conclusions We found a less pronounced decrease of the BOLD signal during sustained visual stimulation in migraine with aura patients compared to healthy volunteers. This seems to reflect a smaller decrease in cortical activation in migraine with aura patients which is in line with previous studies showing diminished electrophysiological habituation during sustained visual stimulation in migraine with and without aura patients. Whether our observations are also true for migraine without aura remains to be determined. Further experiments are directed to correlate our fMRI results with established electrophysiological methods in the same migraine patients.

P2-J33

Does focal white matter lesion correlate with vascular abnormality in primary headache?

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Focal white matter lesion (WML) on MRI is often detected in patients with migraine or other primary headaches. Although the mechanism is unknown, the possible role of chronic ischemia or hypoperfusion has been suggested. Transcranial Doppler (TCD) is useful to evaluate intracranial vascular abnormality, and previous studies have reported frequent TCD abnormality in interictal migraineurs, which may implicate the chronic vascular instability or subclinical vasospasm. We try to reveal the correlation between WML and TCD abnormality to validate the ischemic hypothesis of WML in primary headaches. Brain MRI and interictal TCD was performed for 15 patients with migraine (M:F = 6:9, 38 ± 10 years) and with other (11 tension-type, 1 cluster, 1 idiopathic stabbing, 1 paroxysmal hemicrania, 1 unclassifiable) primary headaches (M:F = 3:12, 44 ± 10 years). Focal WML was graded on T2-weighted MRI as normal, mild, moderate, and severe. TCD abnormality was defined as increased mean flow velocity (>2SD) or side-to-side difference of middle cerebral artery flow velocity (>25%), and the number of abnormal vessels were counted. Compared with other headache groups, WML (73% vs 33%, P = 0.03) and TCD abnormality (73% vs 27%, P = 0.01) were more frequent in the migraine group. However, WML showed no correlation with...
TCD abnormality ($P = 0.40$), age ($P = 0.62$) or sex ($P = 0.29$) by logistic regression analysis. Severity of WML also had no correlation with severity of TCD abnormality (Pearson correlation $= 0.07$, $P = 0.71$). Although WML or TCD abnormality is more frequent in migraine among primary headaches, correlation was not found between two parameters. These results do not support the role of chronic ischemia or vascular abnormality for pathogenesis of WML in migraine and other primary headaches.

P2-J34

Single and double pulse transcranial magnetic stimulation demonstrate hyperexcitability in migraine

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Introduction Occipital cortex hyperexcitability in migraine [M] sufferers was demonstrated recently using single pulse [SS] transcranial magnetic stimulation [TMS]. Double-pulse stimulation [DPS], that performed at low intensity with short interstimulus intervals [ISI] can assess cortical inhibition, so far has not been studied in the visual cortex in M. Accordingly we extended our studies to evaluate if the hyperexcitability is due to reduced cortical inhibition.

Methods Twelve M patients and 15 C were recruited. TMS was performed using a Magstim 200 Bistim machine. Subjects were blindfolded and experiments performed in a dark room. A 13-cm circular coil was applied tangentially to the scalp 7 cm above the inion. Stimulator intensity [SI] was increased in increments of 10% until subjects reported visual phenomena or 100% SI was reached. In subjects where the latter occurred, no further stimulation was given ($n = 9$ (all C)). In the remaining subjects 15–20 SS were given at random SI. Subjects were asked to report the phosphene intensity [PI] on a scale of 0–4. Phosphene threshold [PT] was the SI where a scale of two was consistently achieved. Double stimulation [DPS] was delivered with an ISI 3 ms at SI 10–20% above PT.

Results The difference between M and C in the proportion with phosphene was significant ($P = 0.001$, Fisher’s exact test). An analysis of variance (ANOVA) to test SS and DPS showed different trends in M ($P = 0.05$) and C ($P = 0.02$). Also, in M there was a difference in PI scale of 3 ($P = 0.02$) and 4 ($P = 0.0004$); no differences were found in C.

Conclusion The SS continues to demonstrate a reduced phosphene threshold, an increased intensity of phosphenes and increased excitability of visual cortex in M. The increased response to DPS may be indicative of neuronal hyperexcitability which has been demonstrated by other experimental paradigms (1). In accord with recent psychophysiological experiments, double-pulse stimulation at low intensity did not support reduced neuronal inhibition as a mechanism of increased excitability in migraine sufferers.

Reference


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P2-J35

Cyclic-GMP is the final effector of the dual neurovascular effect of nitroglycerin in the rat brain

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Background Nitroglycerin is a nitric oxide (NO) donor which consistently induces spontaneous-like migraine attacks with a latency of several hours when administered to migraineurs during their headache-free phases. During the past years we have demonstrated that systemic administration of this NO-donor causes neuronal activation in selected brain areas which are either involved in the control of cardiovascular activity or regulate central nociceptive function. Nitroglycerin is believed to act directly and/or indirectly on the central nervous system, through the release of NO. In many instances NO mediates its biological effects by activating guanyl cyclase and increasing cyclic guanosine monophosphate (cGMP) synthesis.

Aim The present study was aimed at demonstrating whether nitroglycerin effect of the Central Nervous System is mediated by an increased synthesis of cGMP.

Methods The localization of cGMP after systemic administration of nitroglycerin was detected immunohistochemically in the brain of rats that had been systemically treated with nitroglycerin or vehicle.

Results The immunohistochemical analysis revealed lack of cGMP immunostaining in the brain of vehicle-injected rats, whereas NTG dramatically increased this staining at 2 and 4 h in fibers located in the wall of cortical blood vessels as well as in lamina I and II of nucleus trigeminalis caudalis.

Conclusions The present findings confirm the proposed dual (neuronal and vascular) effect of nitroglycerin on the rat brain. cGMP emerges as the mediator of this complex activity and it is likely to accumulate in specific vascular and neuronal sites as a consequence of the stimulating effect of exogenous (nitroglycerin-derived) or endogenous (nitroglycerin-induced) NO.
P2-J36

Trigeminal cerebrovascular neurogenic vasodilatation is regulated by 5-hydroxytryptamine 1B/1D receptor mechanism: development of a novel experimental model of migraine

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Although involvement of the trigeminovascular system is obvious in migraine pathogenesis, the realization of migraine in the animal models has been one of the most complicated issues. In this study, we approach the nasociliary nerve (NCN), a branch of the first division of TG, which has been elucidated to be a cerebrovascular branch of the trigeminal nerve in rats (1). The blood flow increase elicited by NCN stimulation has been demonstrated in the rat (2) and is the most intriguing issue from a viewpoint of nociception-cerebral blood flow association in pathological conditions of migraine. In order to elucidate the pathogenesis of migraine, we established an experimental model of migraine and explored the receptor mechanisms in the trigeminal neurogenic vasodilatation utilizing sumatriptan, 5-hydroxytryptamine (5-HT) 1B/1D receptor agonist, in this animal model. Twelve male Sprague-Dawley rats were anaesthetized and ventilated mechanically with room air. Both parietal cortical blood flow (CoBF) and striatal blood flow (StBF) in the right side were continuously monitored with Laser-Doppler flow meter system. NCN was approached from the orbit in the right side and stimulated electrically near its entrance to EF. Stimulation of NCN, under intravenous injection of vehicle (0.8 mL saline) followed by sumatriptan (25 µg/kg in 0.8 mL saline). No significant change in physiological parameters was observed. Both CoBF and StBF were increased upon electrical stimulation of NCN. CoBF was significantly increased by 5.9 ± 1.0% (P<0.05) at 15 s, 6.7 ± 1.0% (P<0.01) at 20 s, 7.1 ± 0.9% (P<0.01) at 25 s, and 6.5 ± 0.8% (P<0.01) at 30 s from the initiation of stimulation, and this increase was suppressed by sumatriptan. StBF was also significantly increased by 6.3 ± 0.7% (P<0.05) at 25 s after initiation of stimulation and this increase was also suppressed by sumatriptan. This study demonstrated that 5-HT 1B/1D receptor agonist abolished the blood flow increase elicited by trigeminal activation. This is attributed to roles of 5-HT 1B receptor agonist, either stimulating presynaptic 5-HT1D receptor to inhibit the release of SP/NKA/CRGP from trigeminal nerve terminals, or activating postsynaptic 5-HT1B receptor to constrict smooth muscle cells in the cerebral blood vessels. Thus, 5-HT 1D/1B receptor mechanism is significantly involved in the neurogenic vasodilatation/blood flow increase upon trigeminal activation.

References

P2-J37

The effect of systemic nitroglycerin administration on 5HT and CGRP innervation of the rat spinal trigeminal nucleus

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Nitric oxide (NO) may play a role in migraine pathogenesis. Nitroglycerin (NTG), an NO donor, can induce attacks in migraineurs. Subcutaneous NTG injections in rats induce nNOS activation in the spinal trigeminal neurons (Pardutz et al., 2000). Activated neurons belong to the trigemino-vascular system, but the cellular mechanisms causing the neuronal activation are not known. Our aim was to provide further details in rats on the effects of NTG with special emphasis on the CGRP and serotonin (5HT) containing fibres innervating the spinal trigeminal nucleus, which receives most of the afferents from intracranial vessels. Adult male Whistar rats were given subcutaneous NTG (10 mg/kg) or its vehicle. Four hours later, the animals were perfused, and C1-C2 segments of the cervical spinal cord were removed for analysis. 30-µm thick cryostat sections were made throughout the samples, and immunohistochemistry for CGRP and 5HT was performed. The area innervated by immunoreactive fibres was measured by an image analyser. We found a significant increase of 5HT- and decrease of CGRP-immunoreactive fibres in laminae I-III of the C1-C2 part of the spinal trigeminal nucleus (P<0.05) after NTG injection compared to the vehicle. According to our data, NTG is able to decrease CGRP immunoreactivity of primary nociceptive trigeminal neurons and increase the 5HT immunoreactivity of descending pathways terminating in the spinal trigeminal nucleus. We conclude that these mechanisms are relevant for the understanding of NTG-induced attacks and the natural migraine triggers.

P2-J38

Inhibitory influences of nucleus raphe magnus on the responses of trigeminovascular second-order neurons and the role of 5HT1B/D receptors

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The influence of the nucleus raphe magnus (nrm) on responses of trigeminal and cervical spinal cord neurons to dura mater stimulation was studied in 103 neurons from 34 cats. Cats were anaesthetized with chloralose and multi-barreled electrodes used to record action potentials from the upper cervical cord or trigeminal nucleus. The sagittal sinus, middle meningeal artery, tooth pulp or occipital nerve was stimulated electrically. An electrode in the nrm delivered trains of shocks prior to peripheral sensory stimulation.
Electrical stimulation of dural vessels activated neurons in the trigeminal nucleus caudalis and the C2 region of the cervical spinal cord with latencies in the A-delta range. Neurons received convergent input from facial receptive fields, tooth pulp and the occipital nerve. Activation of second-order neurons was suppressed prior to electrical stimulation of the nrm, with maximum efficiency at about 40 ms. In some neurons suppression occurred independently of any activation produced by nrm stimulation, but in many the suppression depended upon occurrence of a action potential produced by nrm stimulation. In such cells, stimulation of any sort, from any convergent input or even the occurrence of a spontaneous action potential, could suppress responses to subsequent sensory input. Inter-event histograms of the spontaneous discharge of such neurons revealed a post-discharge inhibition lasting 10–500 ms, with a maximum trough at 40 ms. The suppression of responses by nrm stimulation could be mimicked by systemic or local iontophoretic application of antimigraine drugs such as ergotamine and naratriptan. Both nrm-induced and naratriptan-induced suppression could be antagonised by iontophoretic application of the 5HT1B/1D antagonist GR127935 (50 nA). We conclude that trigeminovascular second-order neurons can be suppressed by activation of a descending serotonergic neuronal system, originating in the nrm and mediated through 5HT1B/1D receptors and that antimigraine drugs can mimic this suppression. In addition, most trigeminovascular second-order neurons display a recurrent inhibition initiated by their own discharge, which can complicate the interpretation of inhibition produced by other influences on subsequent responses to sensory stimulation.

P2-J39
Fos expression in the rostral medulla and caudal pons after periaqueductal grey stimulation: comparison with superior sagittal sinus stimulation

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Introduction The periaqueductal grey (PAG) region of the brainstem is a modulator of craniovascular nociception and integrates behavioural and autonomic responses associated with adjustment of pain thresholds. It is included in the region identified in human functional imaging studies in migraine and is a key candidate for involvement in the disorder. We have previously shown, using Fos immunohistochemistry, structures in the rostral medulla and caudal pons which respond to superior sagittal sinus (SSS) stimulation. These include the trigeminal nucleus, nucleus raphe magnus, superior salivatory nucleus and areas within the reticular formation. The PAG communicates with many structures in the medulla and pons and may mediate its effect on neurons in the trigeminal pathway through these structures.

Objectives In this study we sought to identify structures in the caudal medulla and rostral pons involved in craniovascular nociception and affected by periaqueductal grey stimulation.

Methods Fos immunoreactivity was counted in structures in the caudal medulla and rostral pons of cats after either of two interventions: (i) PAG and SSS stimulation for 2 h, or (ii) PAG stimulation for 2 h. Counts in the medulla and pons were compared as ipsilateral vs contralateral relative to the side of stimulation in the PAG.

Results After PAG and SSS stimulation, Fos immunoreactivity was seen in the trigeminal nucleus, nucleus raphe magnus, infratrigeminal nucleus and specific loci in the reticular formation. Most activity in the trigeminal nucleus was ipsilateral to the side of PAG stimulation. After stimulation in the PAG, Fos was seen in the infratrigeminal nucleus and in low levels in the nucleus raphe magnus and reticular formation.

Conclusion The trigeminal nucleus, nucleus raphe magnus, infratrigeminal nucleus and specific loci in the reticular formation may be involved in trigeminal and periaqueductal grey activation during craniovascular pain. These structures may play a role in integrating the processes of migraine.

P2-J40
Stimulation of the greater occipital nerve (GON) enhances responses of dural responsive convergent neurons in the trigemino-cervical complex in the rat

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Introduction Headache patients often report pain that involves the front of the head, innervated by the first (ophthalmic) division of the trigeminal nerve, and the back of the head, innervated by the greater occipital nerve (GON) that is a branch of the C2 spinal root. The physiology of this interaction is crucial to an understanding of most primary headaches. The aim of the study was to examine mechanisms of convergent trigemino-cervical input in a model of cranial nociception by describing a population of neurons that receive convergent input from the dura as well as from the GON.

Methods Rats were anaesthetised with Pentobarbitone (65 mg/kg), paralysed and artificially ventilated with O2-enriched air. The brainstem and spinal cord at the level of C2 were exposed and neurons in the dorsal horn of C2 were recorded with Tungsten microelectrodes. The parietal dura above the middle meningeal artery was stimulated through a closed cranial window (10–70 V (0.5–3 mA), 0.2–2 ms, 0.7 Hz). The cutaneous branch of the GON was exposed in the neck and stimulated (2–20 V, 2 ms, 0.6 Hz).

Results Recordings were made from 34 neurons (30 wide dynamic range-WDR/4 nociceptive specific-NS) which responded to electrical stimulation of dura and the greater occipital nerve (GON). The majority of neurons showed latencies between 2 and 15 ms, which corresponded to A-fibre input and 20–100 ms, which corresponded to C-fibre input. Most neurons had additional cutaneous receptive fields corresponding to the ophthalmic division of the
trigeminal nerve and the GON territory. Neurons were found in superficial and deep laminae of the dorsal horn. The degree of convergence between dural and ipsilateral GON input was 38%. All convergent neurons tested received input from the ipsilateral as well as from the contralateral GON (n = 4). Chemonociceptive stimulation of GON innervated muscles by i.m. injection of formalin (5%, 50 μL) excited 6/6 neurons. Brief electrical stimulation of the GON (20 stimuli, C-fibre strength) enhanced responses to electrical stimulation of dura responsive neurons in 4/8 neurons.

Conclusions These results show (i) a considerable population of neurons showing convergent input from both dura as well as cervical cutaneous and muscle territories which supports the view of a functional continuum between the caudal trigeminal nucleus and upper cervical roots involved in cranial nociception, and (ii) neurons responding to dural stimulation show an enhanced response after conditioning stimulation of the GON suggesting a central sensitizing mechanism at the second order neuron level. An understanding of the physiology and pharmacology of this important interaction has implications for most forms of primary headache.

P2-J41
5-HT1B/1D receptor positive cells in human trigeminal ganglion: characterization and colocalization with CGRP and NOS
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In human intracranial vessels, antimigraine drugs cause vasoconstriction via 5-HT1B receptors. Detailed analysis using immunocytochemistry with specific 5-HT1B/1D antibodies has revealed the presence of 5-HT1B immunoreactivity in smooth muscle cells and endothelial cells of human cerebral and middle meningeal arteries. Studies of the main intracranial sensory ganglion, the trigeminal ganglion, have, with RT-PCR of the entire tissue, revealed mRNA encoding for both 5-HT1B and 5-HT1D receptor subtypes expressed in both man and guinea pig. Considering the functional division of the trigeminal ganglion into large (mainly mechano-receptive) and small (mainly nociceptive) cells we though it important to analyse which cells contain the 5HT1 subreceptors, which cells contain CGRP/NOS and which cells show colocalization. By using selective antibodies, we detected that 5-HT1D receptors are predominantly expressed in medium (50% of positive cells, 60–90 μm) and small neurons (40% of positive cells, 30–60 μm). About 10% of 5-HT1D receptor positive cells are large (>90 μm). 5-HT1B receptor antibodies showed weaker staining and lower cell number compared to 5-HT1D receptors. Using double immunostaining we showed that 5-HT1D receptors colocalize with CGRP and around 55 + 16% of the CGRP positive cells in size of 30–60 μm are 5-HT1D receptor positive. Around 20% of the 5-HT1D receptor positive cells stained for NOS as examined by NADPH diaphorase staining. In conclusion, both 5-HT1B and 5-HT1D receptors are expressed in human trigeminal ganglion. 5-HT1D receptors are mainly expressed in medium and small sized cells where they colocalize with CGRP and NOS.

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P2-J42
Demonstration of nociceptin positive cells and opioid-receptor LIKE-1 in human trigeminal ganglion
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Background Opioid-receptor like-1 (ORL-1) is a potential target for new analgesics. ORL-1 has no special affinity to opiates whereas the recently discovered neuropeptide nociceptin seems to act as a natural ligand. In this study, we wanted to characterize the distribution of nociceptin in human trigeminal ganglia and cerebral blood vessels as well as nociceptin receptor expression at mRNA levels. In addition, we analysed the effects on cerebral blood vessels.

Methods Trigeminal ganglia and cerebral arteries were obtained from man and cats (n = 4). The study was approved by the local Ethics committees. The obtained tissues were either fixed for indirect immunocytochemistry or snap-frozen in liquid nitrogen immediately for RT-PCR. For in vitro experiments, human cerebral cortical arteries and cat cerebral arteries were used.

Results About 70% of neuronal cells in human trigeminal ganglia were nociceptin immunopositive. The cells were predominantly expressed in medium-sized cells (78% of positive cells in size of 30–60 μm). 14% of the nociceptin positive cells were seen in small-sized cells (<30 μm) and 8% in large-sized cells (>60 μm). Double immunostaining in human trigeminal ganglia showed that nociceptin colocalized with calcitonin gene-related peptide (CGRP), substance P (SP), nitric oxide synthase (NOS) or pituitary adenylate cyclase activating peptide (PACAP). 61% of nociceptin positive cells contained CGRP, 54% contained SP, 50% contained NOS and 68% contained PACAP. Immunoreactivity to nociceptin was not detected in human cerebral blood vessels. Similar results were observed in the trigeminal ganglia and cerebral blood vessels from cat. RT-PCR revealed the expression of nociceptin receptor mRNA in human trigeminal ganglia. To further examine whether there was nociceptin receptor activity in blood vessels, a pharmacological study was done, where cerebral arteries of cat and man revealed strong contraction by 60 mm K+ and U466152.
Nitric oxide regulation of CGRP gene expression in trigeminal ganglia neurons

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We have begun to investigate the role of nitric oxide in regulating the synthesis and release of the neuropeptide calcitonin gene-related peptide (CGRP) from primary trigeminal ganglia neurons. CGRP levels are elevated in all types of vascular headaches, including migraine. CGRP is thought to play an important role in the underlying pathophysiology of migraine due to its ability to regulate cerebral blood flow, to mediate neurogenic inflammation within the meninges, and to relay nociceptive signals to the CNS. Another agent implicated in migraine pathology is nitric oxide (NO). Glycerol trinitrate, an exogenous NO donor, triggers migraine attacks, while blockade of NO synthesis aborts acute migraine attacks. We hypothesized that the cerebrovascular effect of NO may be mediated by stimulation of CGRP synthesis and release from trigeminal neurons. Primary cultures of trigeminal ganglia neurons were treated with the spontaneous exogenous NO donors sodium nitroprusside (SNP) or NOC-18 and the amount of secreted CGRP measured by radioimmunoassay. Both SNP and NOC-18 treatment caused a >4-fold increase in the amount of CGRP released compared to unstimulated cultures. To determine whether NO could also stimulate CGRP gene expression, trigeminal cultures were transiently transfected with luciferase reporter plasmid DNA containing 1.3 kb of the CGRP promoter and reporter activity measured. Cotransfection with an inducible nitric oxide synthase (iNOS) expression vector or treatment with SNP caused a >3-fold increase in CGRP promoter activity. Cotreatment with the serotonergic antimigraine drug sumatriptan significantly repressed NO-stimulated promoter activity and secretion. These results demonstrate that CGRP gene expression is directly regulated by NO and the stimulatory effect of NO can be repressed by sumatriptan. The specific NO-responsive sequences in the CGRP promoter and signal transduction pathways (cGMP, MAP kinase, and PI3 kinase) thought to be involved in NO-mediated regulation of CGRP are being investigated. Results from our studies will provide valuable insight into the molecular mechanisms by which NO controls CGRP gene expression and contributes to migraine pathogenesis.

Conclusion
Nociceptin is expressed in both human and cat trigeminal ganglia but not cerebral blood vessels. Nociceptin is colocalized with CGRP, SP, NOS and PACAP. Nociceptin receptor mRNA is expressed in human trigeminal ganglia. These indicate a role of nociceptin in ganglia function.
P2-J45

The dilator effect of serotonin in the middle meningeal artery of the cat and the role of 5-HT receptor sub-types

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In 42 male and female cats, we studied the vascular effects of intravenous and intracarotid injections of 5-HT on the middle meningeal artery (mma) and the way in which it was modified by a series of 5-HT antagonists. Cats were anaesthetized with chloralose. A catheter was inserted into one carotid artery via a lingual artery and drugs injected in bolus doses through it. Both middle meningeal arteries were exposed and laser Doppler probes used to record ‘volume’, Doppler velocity and bulk blood flow. Intravenous injections of 5-HT, 1–100 μg/kg, produced a dose-dependent fall in blood pressure (−32±8% at 20 μg/kg), a rise in meningeal blood flow (+29±6%) and a fall in mma resistance (−31±4%). Blood flow changes were the result of a local dilatation because the ‘volume’ signal recorded by the probe increased without red blood cell velocity increasing. Intracarotid injections of 5-HT, 5–50 μg, produced similar systemic and craniovascular responses, the latter changes being much larger in the ipsilateral mma. Dose–response curves of vascular resistance changes were not significantly affected by WAY100635 (5-HT1A antagonist), GR127935 (5-HT1B/1D antagonist), methiothepin (5HT3C and 5-HT7 antagonist), ketanserin (5-HT2A antagonist) or methysergide, but were blocked by the 5HT3 antagonist ICS205930 (tropisetron). No drug had significant effects on blood pressure, flows or resistances by itself. Intravenous injections of the 5HT1 agonist antimigraine drugs sumatriptan, eletriptan, naratriptan, zolmitriptan and alniditan (1–1000 μg/kg) produced a mild degree of meningeal constriction, with very flat dose–response curves. Naratriptan was the most potent of these drugs and alniditan the least potent. The vasoconstriction produced by these agents was less than that produced by the antimigraine drug DHE. We conclude that 5-HT is a vasodilator in vivo and that the dilation is not mediated by 5HT1, 5HT2 or 5HT7 receptors, but possibly by another type, including 5-HT3. Of the presently used or putative antimigraine drugs, only DHE has a significant vasoconstrictor effect upon the mma artery in vivo. The results suggest that vasoconstriction is not a significant mechanism of antimigraine activity for the triptans.

P2-J46

Estrogen regulation of gene expression following cortical spreading depression (CSD)

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Objectives The goals of the study were to develop an animal model of menstrual migraine and to examine effects of estrogen on gene expression following cortical spreading depression (CSD).

Materials and methods Ovariectomized female C57BL6×129 vehicle control mice (ovxV) and ovx female mice undergoing estrogen replacement (ovxE), 10–11-weeks-old, were anesthetized with Avertin and four episodes of CSD were induced at 5 min intervals by application of 300 mM KCl on the left hemisphere. No CSDs were observed in controls where NaCl was applied to the cortex. The mice were sacrificed 2 h after the last episode of CSD or the last NaCl application. The left cerebral cortex plus thalamus were flash frozen in liquid nitrogen for RNA extraction. The differential gene expression of 1176 known mouse genes was analyzed by using the AtlasTM Mouse 1.2 cDNA Array from CLONTECH and analyzed using Atlas Image 1.5 software. Differential RT-PCR with respect to beta actin was also used to examine selected genes not represented on that array.

Results Of the 1176 genes assessed using the cDNA array, only a small number were affected by estrogen levels. The genes differentially expressed in ovxE mice relative to ovxV mice after CSD included transhyretin precursor, glutathione-S-transferase 5, major prion precursor (PRP), glutathione-S-transferase 5, GM-CSF receptor, cathepsin D, insulin-like growth factor binding protein-6 and protein kinase C inhibitor protein 1. Neuropeptide Y, a vasoconstrictor, was expressed at higher levels in the ovxE mice than in ovxV mice. Atrial natriuretic peptide (ANP), a vasodilator, was highest in ovxE NaCl, lower in ovxE CSD and lowest in ovxV CSD.

Conclusions Several genes were differentially expressed in ovxE vs ovxV following CSD. Interestingly, mutations in transhyretin (Garzuly et al., 1997), and high GM-CSF levels (Martelletti et al., 1993) have been associated with migraine. Estrogen treatment alters CSD-induced changes in gene expression of proteins involved in signal transduction, response to oxidative stress and control of blood flow.

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**POSTER SESSION II**

K: Triptans

**P2-K1**

Efficacy of six oral triptans at 1 h post-dose: a meta-analysis

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Objectives Patients rate rapid onset and complete relief of pain among the most important attributes of acute migraine treatment. Therefore, we used a meta-analytic database to investigate in headache response (HR) and pain free rates (PF) at 1 h among six oral triptans and 12 doses.

Material and methods Pharmaceutical sponsors and investigators sent raw patient data on 1 h pain-free and 1 h response of all double-blind, randomized, placebo or active controlled, clinical trials with oral triptans. Eligible studies were randomized, double-blind studies of marketed or to be marketed triptans at clinical doses. Differences in endpoints between triptans and placebo were assessed with random effects models.

Results 42 of the 53 trials included in the meta-analysis assessed 1 h efficacy data. Mean results (and 95% confidence intervals) for sumatriptan 100 mg were 32% [30–34] for 1 h HR (improvement from moderate or severe to mild or no pain) and 8% [7–10] for 1 h PF (improvement to no pain); placebo subtracted proportions (= therapeutic gain) for 1 h HR were 13% [10–16] and for 1 h PF were 5% [3–7]. Compared to the absolute sumatriptan 100 mg data, naratriptan 2.5 mg (24% [21–26]; 6% [4–7]) and eletriptan 20 mg (24% [20–27]; 4% [2–5]) showed lower, and rizatriptan 10 mg (43% [41–45]; 11% [10–13]), zolmitriptan 2.5 (39% [36–41]; 10% [8–11]), zolmitriptan 5 mg (40% [37–43]; 10% [8–12]) and eletriptan 80 mg (35% [33–38]; 12% [10; 14]) showed higher 1 h HR and/or 1 h PF rates. Almotriptan 12.5 mg (35% [31–38]; 10% [8–13]), rizatriptan 5 mg (38% [35–40]; 9% [8–10]) and eletriptan 40 mg (32% [30–34]; 6% [5–7]) showed no differences. After placebo subtraction only rizatriptan 10 mg (20% [16–22]) and eletriptan 80 mg (22% [18–27]) showed higher 1 h HR proportions than sumatriptan 100 mg. Eletriptan 80 mg showed a better 1 h PF proportion (11% [8–14]). In comparison, the mean absolute 1 h response of 6 mg subcutaneous sumatriptan is 76% (placebo-subtracted: 51%) and the mean 1 h pain free is 48% (placebo-subtracted).

Conclusions After placebo subtraction at 1 h, both rizatriptan 10 mg and eletriptan 80 mg were superior to oral sumatriptan for HR; eletriptan was also superior for 1 h PF response. In comparison with subcutaneous sumatriptan, all the oral triptans showed lower 1 h-efficacy rates.

**P2-K2**

Placebo in triptan trials: efficacy, tolerability and consistency

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Objectives Inclusion of placebos in migraine clinical trials might be justified by variation among studies in placebo response rate. Herein, we summarize placebo response rates for efficacy, tolerability and within subject consistency of response using a meta-analytic database.

Material and methods Forty-two placebo-controlled oral triptan trials (9 Glaxo Wellcome [GW]-sumatriptan studies, 6 Astra-Zeneca [AZ]-zolmitriptan studies, 4 GW-naratriptan studies, 12 Merck Sharp & Dohme [MSD]-rizatriptan studies, 9 Pfizer-eletriptan studies and 3 Almirall-almotriptan studies) were included according to placebo response, pain-free (PF), sustained pain-free (SPF), and any (ANY-AE), chest related (CHEST-AE), and central nervous system related adverse events (CNS-AE). In 2 GW-sumatriptan, 1 GW-naratriptan, 3 Pfizer-eletriptan and 1 Almirall-almotriptan studies, consistency of placebo response and consistency of placebo pain free was investigated.

Results Mean (and 95% confidence intervals) placebo response (improvement from moderate or severe to mild or no pain) at 2 h was 29% [28–31], PF (improvement to no pain) at 2 h was 8% [7–9], SPF (improvement to no pain at 2 h, without recurrence of headache within 24 h and without the use of rescue medication) was 6% [5–6]. Mean placebo adverse events were ANY-AE 27% [26–28], CHEST-AE 1.2% [0.9–1.5], and CNS-AE 11% [10–12]. Compared to these data, Pfizer-eletriptan studies showed lower placebo HR (25% [23–28]), PF (5% [4–6]) and SPF (4% [3–5]), and Almirall-almotriptan studies showed higher HER 36% [31–40], PF 15% [11–18] and SPF 11% [8–14]. These differences in placebo efficacy could not be explained by differences in the severity of the baseline attack nor the chance to get placebo at baseline. Pfizer-eletriptan studies showed higher ANY-AE rates (35% [32–38]), but no differences in the other AE measurements. Almirall-almotriptan studies showed lower ANY-AE rates (12% [9–16]) and CNS-AE (4% [2–6]). The mean consistency of placebo-response in 2 of 3 attacks was 22% [19–25] and 8% [6–10] in 3 of 3 attacks. The mean consistency of placebo-pain free in 2 of 3 attacks was 6% [4–9] and 2% [1–4] in 3 of 3 attacks.

Conclusions The placebo efficacy and tolerability measurements of Pfizer-eletriptan studies and Almirall-almotriptan studies differ from the mean placebo values. There were no
differences in study design or population to explain these differences. Variation in results among studies highlights the need for including a placebo arm in migraine clinical trials.

P2-K3
Triptans vs analgesics: patient preference
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The purpose of this study was to determine the current choice of abortive migraine medication in a large number of patients who had been prescribed triptans in the past. The triptans included sumatriptan, naratriptan, rizatriptan, and zolmitriptan. Each of the 663 patients in the study had used a triptan for at least one migraine headache. The patients were asked whether they currently prefer to use triptans, analgesics, both, or neither. The analgesics included: 1. over the counter medications that are utilized for headache, particularly aspirin and caffeine combinations, aspirin, ibuprofen, naproxen, acetaminophen (with or without caffeine), ketoprofen, and sinuses or allergy preparations, and 2. prescription non-steroidal anti-inflammatory, narcotics (such as various forms of codeine, propoxyphene, hydrocodone, etc.), butalbutal medications (both with and without codeine), orphenadrine with aspirin and caffeine, and Stadol N.S. In the 'neither' category was Midrin, dihydroergotamine, and various forms of ergotamine preparations. The patients were also asked why they currently prefer to use triptans, analgesics, both, or neither. The analgesics included: 1. over the counter medications that are utilized for headache, particularly aspirin and caffeine combinations, aspirin, ibuprofen, naproxen, acetaminophen (with or without caffeine), ketoprofen, and sinuses or allergy preparations, and 2. prescription non-steroidal anti-inflammatory, narcotics (such as various forms of codeine, propoxyphene, hydrocodone, etc.), butalbutal medications (both with and without codeine), orphenadrine with aspirin and caffeine, and Stadol N.S. In the 'neither' category was Midrin, dihydroergotamine, and various forms of ergotamine preparations. The patients were also asked why they prefer triptans or analgesics. 52% (344/663) of the patients preferred using a triptan alone. 21% (140) used analgesics alone, while 18% (121) used both triptans and analgesics within one hour of each other. 9% (58) of patients did not prefer triptans or analgesics. 70% of patients exposed in the past to triptans chose to continue utilizing them, either alone (52%) or in combination (within one hour) with an analgesic (18%). The primary reasons for choosing one modality over the other was efficacy. This study indicated a high degree of satisfaction among migraineurs for the triptans.

P2-K4
Migraine headache recurrence: relationship to clinical, pharmacological and pharmacokinetic properties of triptans
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Background and objectives The use of all triptans is associated with headache recurrence. The mechanism by which recurrence occurs is not clear and the incidence of recurrence varies with the triptan used. Clinical, pharmacological and pharmacokinetic characteristics, which could affect headache recurrence, were investigated. These were therapeutic gain (TG), elimination half-life, 5HT1B and 5HT1D functional potency and binding affinity.

Methods Data for binding affinity and potency were taken from a direct comparison study (1). For each triptan, the elimination half-life quoted in the data sheet was used and the mean recurrence rate and mean TG were calculated using the results from their individual placebo controlled pivotal studies. TG was calculated at the time point used to define recurrence in each study. Rank correlation with recurrence rate was performed for each of the test parameters. (see table at foot of page.)

Results Mean headache recurrence rate ranged from 17% for frovatriptan 2.5 mg to 40% for rizatriptan 10 mg; mean TG ranged from 26% for almotriptan 12.5 mg to 45% for eletriptan 80 mg; 5HT1B potency ranged from pEC50 7.0 for sumatriptan and rizatriptan to 8.6 for eletriptan, and binding affinity from pKi 7.8 for sumatriptan and rizatriptan to 8.6 for eletriptan, reported decreased side-effects as the reason for their preference. 40% stated that both efficacy and less side-effects influenced their decision. 5% did not give any reason. In conclusion, 70% of patients given triptans chose to continue utilizing them, either alone (52%) or in combination (within one hour) with an analgesic (18%). The primary reasons for choosing one modality over the other was efficacy. This study indicated a high degree of satisfaction among migraineurs for the triptans.

<table>
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<th>Triptan</th>
<th>Recurrence % (range)</th>
<th>Half-life (h)</th>
<th>5-HT1B potency (pEC50)</th>
<th>5-HT1B affinity (pKi)</th>
<th>Therapeutic gain % (range)</th>
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<tr>
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<td>7.6</td>
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<tr>
<td>Frovatriptan 2.5 mg</td>
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</table>

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naratrant and zolmitriptan; 5HT\textsubscript{1D} potency ranged from pEC\textsubscript{50} 7.8 for almotriptan to 9.2 for eletriptan and binding affinity from pK\textsubscript{I} 7.6 for almotriptan to 8.8 for eletriptan. Elimination half-life and recurrence were highly correlated ($r = -0.98$, $P = 0.0024$) and there was also a significant correlation between 5HT\textsubscript{1B} potency and recurrence ($r = -0.75$, $P = 0.021$). 5HT\textsubscript{1B} receptor binding affinity and recurrence were not correlated ($r = -0.38$, $P = 0.26$), nor were 5HT\textsubscript{1D} receptor potency ($r = -0.23$) or binding affinity ($r = -0.20$). Therapeutic gain was not correlated to recurrence ($r = +0.29$) (see table).

**Conclusion** Headache recurrence is not inversely correlated with efficacy but does appear to be influenced by certain pharmacological and pharmacokinetic properties of triptans. Long half-life and high 5HT\textsubscript{1B} receptor potency appear to be associated with a low rate of headache recurrence.

**Reference**


## P2-K5

**Clinical efficacy and cost-effectiveness of oral triptans: an updated meta-analysis incorporating data for almotriptan**

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**Objective** We recently published a systematic review and meta-analysis of the clinical efficacy and cost-effectiveness of oral triptan therapy, which was based on the published evidence base to the end of 1999. Since publication, a new agent – almotriptan – has been launched in the UK. This study incorporates published aggregate data for almotriptan into the analysis, to help guide rational prescribing decisions.

**Method** Randomized placebo-controlled clinical trials of oral triptans currently licensed for use in the UK were identified for the original meta-analysis. To this base have been added two additional studies: a comparative controlled trial of zolmitriptan 2.5 mg, rizatriptan 10 mg, and placebo, the results of which have been published since the original study was completed, and an aggregated database of phase II/III studies involving almotriptan 12.5 mg, the newly licensed dose available in the UK. After qualitative appraisal of the constituent studies, a meta-analysis was performed to ascertain the following outcomes: proportion of patients rendered pain-free within 2 h of the index dose; number needed to treat to achieve this outcome; and cost-effectiveness ratio, based on current UK drug costs.

**Results** 24 qualifying studies were identified, consisting of 32 active treatment arms and 24 placebo arms, and involving a total of 9509 patients. Within these studies, rizatriptan 10 mg emerged as the most clinically effective treatment (NNT 3.1; 95% CI: 2.9–3.4), followed by zolmitriptan 5 mg (NNT 3.3; 95% CI: 2.8–4.0), sumatriptan 50 mg (NNT 4.0; 95% CI: 3.4–4.9), sumatriptan 100 mg (NNT 4.3; 95% CI: 3.7–5.0), almotriptan 12.5 mg (NNT 4.6; 95% CI: 3.8–6.0), zolmitriptan 2.5 mg (NNT 4.9; 95% CI: 4.0–6.2), and naratriptan 2.5 mg (NNT 9.2; 95% CI: 5.8–22.7). The mean expenditure required to render one patient pain-free at two hours (UK prices) was least for rizatriptan (£13.85), followed by almotriptan (£15.00), sumatriptan 50 mg (£15.92), zolmitriptan 2.5 mg (£19.49), zolmitriptan 5 mg (£26.65), sumatriptan 100 mg (£34.07), and naratriptan (£36.75).

**Discussion** Based on this analysis, almotriptan 12.5 mg falls in the mid-range of clinical efficacy amongst the oral triptans, being significantly less effective than either rizatriptan 10 mg or zolmitriptan 5 mg. Its low purchase price, however, means that it has a cost-effectiveness ratio comparable to that seen with rizatriptan. These data are, of course, derived from protocol-driven clinical trials. Only assessment based on actual clinical experience with almotriptan can clarify whether its lesser clinical efficacy may result in a higher dose consumption per attack, with consequent adverse effect on the true cost effectiveness ratio.

**P2-K6**

**Comparison of therapeutic gains over sumatriptan for eletriptan, naratriptan, rizatriptan and zolmitriptan: a review of six clinical studies**

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**Objective** To determine the relative efficacy of four newer triptans (eletriptan, naratriptan, rizatriptan, zolmitriptan) vs sumatriptan by comparing therapeutic gains (i.e. headache response of the new triptan minus sumatriptan response).

**Background** Since the launch of sumatriptan, which was the first triptan approved for the treatment of migraine, several newer triptans have been developed. Comparative studies between these newer triptans and sumatriptan have shown the advantages of using these triptans over sumatriptan when compared with therapeutic gain.

**Methods** This review summarizes the headache response results at 2 h postdose for six published placebo-controlled studies that compared sumatriptan, with each of four newer triptans. The therapeutic gains over sumatriptan (25 mg and 50 mg or 100 mg) were compared with either eletriptan (20 mg, 40 mg, and 80 mg), naratriptan (1 mg, 2.5 mg, 5 mg), rizatriptan (5 mg and 10 mg), or zolmitriptan (5 mg), respectively.

**Results** Eletriptan 80 mg had the greatest gain (22%) compared with sumatriptan 100 mg, followed by eletriptan 40 mg and, naratriptan 5 mg and 10 mg, which were 10%, 2% and 5%-6%, respectively. Sumatriptan 100 mg had a respective 6% and 8% higher therapeutic gain than naratriptan 5 mg and 2.5 mg. Rizatriptan 10 mg had a 10% and 4% greater therapeutic gain than sumatriptan 25 mg and 50 mg, respectively. Rizatriptan 5 mg had a 6% greater therapeutic gain than sumatriptan 25 mg. However, sumatriptan 100 mg had therapeutic gains ranging from 1%–2% greater that eletriptan 20 mg, zolmitriptan 5 mg and naratriptan 1 mg.

**Conclusion** Based on sumatriptan comparative studies the rank order of clinical efficacy of the triptans is eletriptan, rizatriptan, sumatriptan, zolmitriptan and naratriptan.
P2-K7

Which triptan would you like? A retrospective triptan preference study

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Introduction Ever since second generation triptans such as naratriptan (N), zolmitriptan (Z) or rizatriptan (R) were introduced treating physicians observed that triptans are not interchangeable despite similar pharmacology.

Patients (Pts.) in our headache center, like elsewhere, seem to respond somewhat unpredictably to different triptans with a generally high response rate. We studied charts of Pts. that were exposed at least once to triptans in 1999 and 2000. Analyses were used for group comparison to test the influence of gender, diagnosis (migraine with aura, MA, migraine without aura, MO), frequency of attacks, work loss on the number of changes between oral triptans. We defined preference when a certain triptan prescription was repeated.

Results Charts of 176 patients (72% female) were available for analysis. Mean age was 44 years (men 42, women 45). MA was found in 61 (13 males) and MO in 115 (34 males), according to IHS criteria. Mean triptan changes in MA were 0.93, in MO: 1.32 (P < 0.05). Numbers of pts per triptan were: S = 49, Z = 40, N = 40, R = 2. Number of changes between triptans were: 0 in 58 pts, 1 in 78, 2 in 29, 3 in 16. Women switched triptans more often (P < 0.05) and showed a different triptan preference. Mean changes per substance were: S = 0.36, N = 0.49, Z = 1.16. Influence of preference on number of changes was P < 0.001. Substance per gender preference: Z = 83% female, N = 70% female, S = 65% female. Proportions of MA over MO per substance: S = 46%, N = 42%, Z = 30%.

Conclusions Women tend to prefer Z over N or S and switched between substances more often than men. More patients with MA were using S. No triptan was showing significantly higher preference over the other two. Although the number of switches are high, recommendations for initial use of any particular triptan can not be derived from our study. This means that several triptans need to be tried out in case of no response. However, analysing a larger group of patients may suggest certain sequences of triptans and whether other factors such as diagnosis, gender, age, etc. can be used to facilitate the choice of a triptan.

P2-K8

Comparative effectiveness of newer triptans (naratriptan and zolmitriptan) against sumatriptan

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Introduction Almost 10 years ago the introduction of sumatriptan (Su), a 5-HT agonist, started a new era in migraine treatment. Since then newer triptans were introduced but it seems that pts respond unpredictably.

Aim In this retrospective study we tried to find common characteristics, if any, in the use of different triptans and to evaluate the pts’ responses to them.

Methods We reviewed the charts of 64 pts with migraines (9 men, 55 women; mean age 40.7 year, range 16–63 year) with a headache history of 20.2 ± 10.9 year (3–46). Auras presented 22 pts (34.4%) and 11 pts had drug abuse. A comparison was done between pts treated with Su vs those treated with naratriptan (N) and/or zolmitriptan (Z). Changes in the frequency of crises before (A) and after (B) 3–6 mos on treatment were noted for all pts: pts on Su, pts on N+Z, pts with (Ma) or without (Mo) aura, abused (Ab) and non-abused (N-Ab), and those who changed from Su to N and/or Z. Frequency of crises was categorized as 1: 1–2/mo, 2: 1/w, 3: 2–4/w, 4: daily.

Results Percentage distribution of main categories studied is seen in the table at the foot of the page. Aura does not influence the responsiveness to triptans, whereas pts who have abused drugs have a better outcome with triptans.

Table for abstract P2-K8

<table>
<thead>
<tr>
<th>Frequency of crises</th>
<th>Total A</th>
<th>Total B</th>
<th>Su A</th>
<th>Su B</th>
<th>N + Z A</th>
<th>N + Z B</th>
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</table>

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Conclusions These preliminary results indicate that pts starting on N+Z have a similar response with Su; drug abuse pts have better outcome with any of the triptans.

P2-K9

Triptans and blood pressure

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Even if triptans have dramatically improved the perspective of the migraine attacks, many coexisting situations limit their use in clinical practice. An important restriction is represented by the presence of high blood pressure in a large number of migraineurs (above all, over forty). First, we evaluated cardiovascular variation induced by the triptans which were administered during a migraine attack in normotensive patients. Forty-five patients, suffering from migraine without aura, were divided into 3 groups of 15 patients (age- and sex-matched). Each group was treated during a migraine attack with a different triptan: the 1st with sumatriptan (50 mg oral dose), the 2nd with zolmitriptan (2.5 oral dose) and the 3rd with rizatriptan (10 mg oral dose). Systolic and diastolic blood pressure (expressed as mean pressure) and cardiac frequency were measured before and at the peak of drug action. An evaluation of the intensity of migraine attack was made (numeric scale 1–100, 100 = the highest intensity of previous migraine attack). A score below 30 was considered as a value indicating a significant therapeutic effect. Sumatriptan was effective in 13 patients, zolmitriptan in 11 patients and rizatriptan in 9 patients. A significant (even if mild) increase in mean arterial pressure was found after sumatriptan (basal values: 92.34 ± 6.75; after drug 101.01 ± 5.64) and after rizatriptan (basal values: 91.37 ± 7.56; after drug 100.04 ± 6.73). The variation induced by zolmitriptan was not significant (basal values 92.31 ± 4.56; after drug 95.49 ± 4.56). Heart frequency was never significantly changed (data not shown). On the basis of these findings (and after carefully examining each patient) we evaluated the effect of zolmitriptan on headache attack and on the cardiovascular parameters in a group of 12 patients affected by migraine without aura and mild hypertension (values of diastolic pressure between 95 and 100 mmHg). The patients were not under antihypertensive therapy. Zolmitriptan was able to control the migraine attacks in 10 of the subjects. The increase of blood pressure was not significant (mean pressure: basal values: 108.87 ± 6.75; after drug 110.08 ± 5.78). Heart frequency did not change. Therefore, zolmitriptan seems to be a relatively safe drug in patients with mild hypertension since it does not induce a significant blood pressure increase. Caution is still needed.

P2-K10

Similarity of dizziness and pain/pressure adverse responses after oral 5HT1B/1D agonist administration

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President, EBD Group, Carlsbad, CA, USA

Objective Comparison of oral 5HT1B/1D agonists to cause a central and a peripheral adverse event.

Background The various ‘triptans’ are known to differ in their tolerability profiles. These differences are not dependent upon either lipophilicity or (absolute dose x lipophilicity) for this class of drugs (1,2). ‘Triptan’ efficacy differs much less, and is presumed due to the captioned receptor subtype. Receptor-mediated agonism is characterized by relatively small absolute dose size in comparison with, for example, anesthetic gases or ethanol. Comparison of rank orders of potency is a commonly employed method of pharmacological analysis. Similar rank orders for different response types, using the same range of drugs with non-identical potency, is strong evidence that the responses are mediated by similar molecular mechanisms. Dizziness is a classic central nervous system adverse event type. After ‘triptan’ administration, pain or pressure can be reported in the chest and extremities, especially around the upper limb girdle and neck; in the overwhelming majority of patients, it is not of coronary origin (3) and is presumably a peripheral adverse event.

Methods Adverse events in clinical trials’ databases are reported using standardized dictionaries. US product labeling uses standardized tolerability tables for drugs in this class, and shows active- and placebo-associated adverse event rates (AAER and PAER, respectively). An adverse event rate increment: AERI (%) = AAER (%) – PAER (%) can be used to compare drugs and doses, and is analogous to the calculation of therapeutic gain for comparisons of efficacy. Least squares correlation was used.

Results Among the 10 drug-dose combinations in current labelling, AERIs for ‘dizziness’ and ‘pain or pressure’ were correlated (Kendall’s R = 0.88); for nine degrees of freedom (d.f.; 10 drug-dose combinations and two adverse event types), t = 5.33, and P < 0.001. For one and nine d.f., F = 27.0 and P < 0.001.

Conclusions This similarity in rank order of potency suggests that these central and peripheral adverse event types are due to a similar receptor-mediated mechanism. It is not likely to be the 5HT1B/1D receptor.

References
P2-K11

Cognitive efficiency following migraine therapy
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Clinical trials have shown that triptan tablets are efficacious agents in the acute treatment of migraine. Since migraine is known to impose restrictions on migraineurs’ cognitive efficiency, a comparison of the effects of a migraine-specific medication (rizatriptan, 10 mg) with a non-specific medication (a butalbital agent) on migraineurs’ cognitive efficiency was conducted using a crossover design. The Headache Care Center-Automated Neuropsychological Assessment Metrics was administered to 25 migraineurs, three times without a migraine, twice during a migraine, and three times after the administration of either rizatriptan (10 mg) or Fiorinal (1 or 2 tablets). The results indicated a significant drop in cognitive efficiency during a migraine. Recovery of cognitive efficiency occurred significantly with rizatriptan but more slowly with Fiorinal over a two-hour period.

P2-K12

Triptan efficacy and preference: results of a randomized, multi-centre, open-label, crossover study of sumatriptan, naratriptan, rizatriptan, and zolmitriptan tablets in acute treatment of migraine
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Introduction Historically, the triptans have been evaluated and compared on the basis of strictly defined clinical efficacy parameters. An open-label patient preference trial may provide a complementary approach to traditional drug comparator trials by assessing differences between multiple therapies in a more natural setting.

Objectives The primary objective of this study was to assess patient preference for sumatriptan 100 mg. The secondary objectives were to assess preference for sumatriptan 50 mg, naratriptan 2.5 mg, rizatriptan 10 mg, and zolmitriptan 2.5 mg. Other secondary objectives included assessment of efficacy, safety, tolerability, patient satisfaction, and reasons for preference.

Methods Some 390 patients aged 18–65 years with an IHS diagnosis of migraine were enrolled in this randomized, multicenter, open-label, 5-way crossover trial. Current and previous triptan users and triptan-naïve migraine patients were eligible. Patients who had a history of non-response to a triptan were excluded. Patients were randomized to one of the 119 possible treatment sequences in which they treated one migraine attack with each study medication in sequence.

At the last visit patients assessed which medication they preferred.

Results The efficacy data were derived from the ITT population comprised of 372 patients who treated at least one attack. The majority of attacks treated (85%) were of moderate to severe intensity. The 2-h pain-free response rates were similar across sumatriptan 50 and 100 mg, rizatriptan 10 mg, and zolmitriptan 2.5 mg at 37%, 40%, 38%, and 36%, respectively. The 2-h pain-free response for naratriptan was 28%. A similar pattern in pain-free response was seen in patients who were not current triptan users, and in patients who were totally triptan naïve. Some 258 patients (69%) completed all 5 treatments and expressed a preference. The primary preference end point of this study was met with a greater number of patients preferring sumatriptan 100 mg. Additional results as well as design issues and potential biases involved with conducting preference trials will be presented.

Conclusions In this study where the majority of attacks treated were of moderate to severe intensity, sumatriptan 50 and 100 mg, rizatriptan 10 mg and zolmitriptan 2.5 mg demonstrate similar 2-h pain-free efficacy. In this open-label study, more patients preferred sumatriptan 100 mg. Design issues may have influenced the preference results.

P2-K13

Optimum-dose determination of the triptans
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Optimum-dose determination of the triptans is important for the practice of medicine as well as for the evaluation of comparative studies. It is important so that the physician knows what dose to prescribe when a triptan is available in more-than-one tablet strength and can be given in a range of doses. In comparative studies, a relevant picture can only be obtained when the medications are compared in their optimum dosages. Optimum-dose determination is based on the results of randomized, double-blind, placebo-controlled, dose-range studies. The two criteria that have been applied in the optimum-dose determination are: 1, The highest dose that is effective and is associated with a numerical occurrence of adverse events similar to placebo; and 2, The lowest dose that provides the maximum therapeutic benefit in cases where the effect levels off at a certain dosage point. For almotriptan and naratriptan, the optimum dose is the highest effective dose with placebo-level adverse events. For frovatriptan, rizatriptan, and zolmitriptan, the optimum dose is the lowest effective dose with maximum therapeutic benefit. Sumatriptan is the only triptan for which the optimum dose fulfills both criteria, that is, it is the highest effective dose with placebo-level adverse events as well as the lowest effective dose with maximum therapeutic benefit (Headache 1998; 38:184–90). When the above criteria used in optimum-dose determination are applied to eletriptan, the optimum dose of this triptan

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P2-K14

Migraine patients prefer Imitrex tablets 50 mg to their usual non-triptan prescription or over-the-counter therapy

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Objective Although standard clinical trial endpoints provide important information about the efficacy and safety of migraine medication, they should be supplemented with patient-based outcomes measures in order to gain a comprehensive assessment of the effects of therapy. This study (GlaxoSmithKline protocol SUM40260) assessed migraine patients’ preference for Imitrex® (sumatriptan) tablets 50 mg compared with their usual non-triptan prescription or over-the-counter therapy for the acute treatment of migraine.

Methods Triptan-naïve patients who prior to the study used a non-triptan prescription or over-the-counter therapy for their migraines treated up to 4 consecutive migraines with Imitrex tablets 50 mg in this open-label, observational study. At the end of the treatment period, patients indicated their preferred medication (Imitrex, usual therapy, or no preference) and the reason(s) for their preference. Patients provided information on treatment efficacy after each treated migraine via an interactive voice response system.

Results Some 402 patients who treated at least 1 migraine and submitted preference data at the final visit were included in these analyses. At the end of the treatment period, 73% of patients preferred Imitrex tablets 50 mg to their usual therapy (95% CI 69–78); only 18% preferred their usual therapy (most often, non-narcotic analgesics [79% of patients] or NSAIDs [61% of patients]). The most common reason for preferring Imitrex to usual therapy was effective pain relief (cited by 98% of patients) followed by restored ability to function or perform (93%), requirement for fewer doses (93%), relief of migraine-associated symptoms (89%), rapid onset of efficacy (86%), no tired feeling (85%), and fewer side-effects (81%). Relief of moderate or severe migraine 2 h after dosing was reported in 60% of all attacks. Pain-free response 2 h after dosing was reported in 63% of all mild headaches.

Conclusions Most triptan-naïve patients trying Imitrex tablets 50 mg for up to 4 migraines preferred it to their usual non-triptan prescription or over-the-counter therapy. Patients indicated that they preferred Imitrex tablets to their usual therapy because Imitrex tablets conferred effective pain relief that rapidly returned them to normal functioning with fewer doses.

P2-K15

Patient satisfaction with Imitrex tablets 50 mg compared with their usual non-triptan prescription or over-the-counter migraine therapy

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Objective Although the efficacy of Imitrex® (sumatriptan) tablets 50 mg has been firmly established with respect to standard clinical endpoints, patient satisfaction with Imitrex tablets relative to other migraine therapies has not been systematically assessed. This study (GlaxoSmithKline protocol SUM40260) assessed migraine patients’ satisfaction with Imitrex tablets 50 mg compared with their usual non-triptan prescription or over-the-counter therapy for the acute treatment of migraine.

Methods Triptan-naïve patients who prior to the study used a non-triptan prescription or over-the-counter therapy for their migraines treated up to 4 consecutive migraines with Imitrex tablets 50 mg in this open-label, observational study. At study visits occurring prior to and at the end of the treatment period, patients completed the Patient Perception of Migraine Questionnaire, which included questions on satisfaction with medication effectiveness and other attributes. Satisfaction was rated on a 7-point categorical scale ranging from very satisfied to very dissatisfied.

Results Some 402 patients who treated at least 1 migraine submitted satisfaction data at the initial visit, and recorded a medication preference at the final visit were included in these analyses. Usual therapy before study entry was most often non-narcotic analgesics (79% of patients) or NSAIDs (61% of patients). Significantly (P < 0.001) more patients were satisfied or very satisfied with Imitrex 50 mg tablets (rated at the end of the Imitrex treatment period) as compared with usual therapy (rated before the Imitrex treatment period) for each of the medication attributes measured: overall effectiveness (69% vs 19%), number of doses needed (71% vs 23%), no drowsiness (69% vs 33%), relieves migraine pain (66% vs 22%), lasting effect (67% vs 22%), relieves migraine-associated symptoms (60% vs 18%), speed of returning to usual activities (58% vs 18%), and speed of pain/symptom relief (57% vs 17%). Significantly (P < 0.001) more patients were also satisfied or very satisfied with their overall quality of medical care when it included Imitrex than when it included usual therapy (87% vs 35%).

Conclusions Triptan-naïve patients given the opportunity to try Imitrex tablets 50 mg for up to 4 migraines were significantly more satisfied with it than with their usual non-triptan or over-the-counter therapy on all 9 attributes measured in this study. These data suggest that Imitrex possesses the desired characteristics of a migraine medication that meets patients’ needs and that patients view Imitrex more favourably than their usual therapy.
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**Background** Numerous previous studies have validated the utility of triptan therapy in migraine management.

**Objectives** This study afforded migraineurs the opportunity to switch from non-specific therapy to sumatriptan 50 mg tablets. Resource utilization, patient satisfaction, and patient preference before and after access to sumatriptan and headache relief with sumatriptan were assessed.

**Study design and patient enrolment** This was an open-label, observational study conducted at two neurology offices in California. Study design utilized historical baseline data and a 3-month prospective treatment period. Thirty-one adults meeting IHS diagnostic criteria for migraine who were not using triptan medications as first-line therapy for migraines were enrolled.

**Intervention and outcome assessment** Subjects completed baseline and exit resource utilization and satisfaction questionnaires. Subjects were provided with sumatriptan 50 mg tablets and instructed to initiate treatment of migraine at the earliest onset of headache pain. Headache diaries, reviewed at an interim visit for completeness, captured time to meaningful relief, recurrence, and rescue medication use for each headache.

**Results** Twenty-nine evaluable patients treated 250 migraines. At baseline, subjects reported that the primary reason for not using migraine-specific triptan medications over conventional therapy was that a triptan was never prescribed (66%). At baseline, the most common non-triptans used to treat migraines included NSAIDs and other simple analgesics (69%), OTC or prescription combinations (28%), and narcotics (10%). At baseline, the majority of subjects reported dissatisfaction with current migraine therapy (76%). Summary of diary data showed that 164/250 (66%) of headaches was relieved with sumatriptan 50 mg tablets. 69% of patients preferred sumatriptan therapy over their previous non-triptan therapy, 16% preferred their previous therapy, and 14% had no preference. Primary reasons for preference for migraine-specific therapy included speed of relief (69%), effectiveness (30%) and lack of drowsiness (1%). Unscheduled MD visits went from 45 in the 3-month baseline period to 27 during the 3-month study period, ER visits went from 17 to 6, and hospitalizations went from 2 to 0.

**Conclusion** Most subjects preferred Sumatriptan 50 mg for first-line migraine therapy to previous non-triptan medications. Access to migraine-specific therapy enhances patients' satisfaction with managing their headaches.
P2-K18

Migraine headache exacerbation with sumatriptan injection: a sign of supratherapeutic dosing?

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Objective Description of the therapeutic outcomes of dose reduction in patients complaining of migraine headache exacerbation with sumatriptan injection.

Background Sumatriptan succinate has been available in injectable form since its introduction nearly 10 years ago. Despite the release of alternative sumatriptan formulations (tablet, nasal spray, rectal suppository) and the subsequent development and release of additional triptan products to treat acute migraine, the subcutaneous preparation remains the gold standard for speed and efficacy. Following the results of the pivotal dose-ranging studies, the 6-mg dose was selected for production in vial, prefilled syringe, and now syringe cartridge lines. Clinical experience has indicated a ‘therapeutic window’ for a subset of patients treated with dihydroergotamine mesylate. Individuals who report worsening headache or nausea with this product often enjoy limited or no benefit from the injection. Subsequent dose reduction frequently results not only in fewer adverse events, but greater efficacy. Occasional patients managed with subcutaneous sumatriptan describe an exacerbation of migraine headache following the dose. Similar to the experience with dihydroergotamine, this also seems to negatively impact the eventual efficacy of the drug.

Methods Single-centre, prospective, open-label study of a 3-mg rechallenge in patients reporting migraine headache exacerbation following 6-mg subcutaneous sumatriptan administration. 35 patients meeting IHS criteria for migraine were interviewed following headache exacerbation from an initial 6-mg dose and were asked to consider rechallenge with a 3-mg dose.

Results 29 of 35 patients agreed to and subsequently completed rechallenge with the 3-mg dose of sumatriptan. Of those 29 patients, 27 (93%) experienced successful treatment of the headache (reduction to mild or no pain) without any degree of initial exacerbation. Of the remaining 2 patients, one again experienced worsening headache and nausea without subsequent relief, while the other noted neither benefit nor penalty from the rechallenge.

Conclusions As is true for dihydroergotamine, sumatriptan injection may occasionally exacerbate migraine headache symptomatology. Such patients frequently respond to a 50% reduction in drug dose. These findings indicate a ‘therapeutic window’ may be present for at least a subpopulation of migraineurs treated with subcutaneous sumatriptan.

P2-K19

Naratriptan prevents migraine recurrence after initial relief with sumatriptan

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Introduction Triptans have become the mainstay of acute migraine therapy. Recurrent migraines require treatment with repeat doses, but limitations are placed on the number of doses that can be safely administered, with a warning to use not more than one triptan within 24 h. Triptans, as a class, differ in half-life, bioavailability, and ease of penetration through the blood–brain barrier.

Objective To evaluate if differing properties of triptan preparations could be exploited successfully for migraine patients who experience a high degree of recurrence of their migraine attacks, despite successful initial therapy with a triptan.

Methods Known adult migraineurs from two headache clinic populations were included in this study. All had recurrence of migraine more than 50% of the time, which was defined as the return of headache within 2–12 h after initial relief with one dose of sumatriptan. All migraineurs experienced 2–8 IHS-criteria migraines per month and each person treated up to 3 migraine attacks initially with sumatriptan (oral 50 mg, nasal spray 20 mg, or SC injection 6 mg). Severity of the initial migraine treated and subsequent satisfactory relief were recorded by study patients on a 0–10 visual analogue scale (VAS). If substantial relief was obtained after one dose of sumatriptan, naratriptan (oral 2.5 mg) was administered usually 2 h after initial treatment with sumatriptan. The end point was the presence or absence of recurrent migraine within 24 h of treatment with naratriptan. If migraine recurred after naratriptan treatment, the time to recurrence was recorded on headache diary cards, together with the VAS score.

Results 57 patients were enrolled (50 female and 7 male). A total of 170 migraine attacks were treated. 116 of 170 attacks (68%) did not recur by 24 h after treatment with naratriptan treatment. When migraine recurred after naratriptan, they recurred 14.5 h following treatment, as opposed to 4.2 h after treatment with sumatriptan alone. No patient dropped out of the study due to any adverse effects.

Conclusions The study results demonstrate a high efficacy of naratriptan in preventing recurrence of migraine headache up to 24 h after prior initial therapy with sumatriptan. This type of treatment is safe, and may be useful for treating migraines that have a high recurrence rate. Double-blind studies are warranted to replicate these findings.
P2-K20

**Naratriptan reduces rate of headache recurrence after initial relief with sumatriptan**

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**Objective** Some migraineurs experience recurrent headache despite adequate relief with an initial triptan. We evaluated whether naratriptan would prevent recurrence if administered at 2 h after an initial dose of sumatriptan in those patients whose headaches were relieved by the sumatriptan.

**Materials and methods** Open label study in adult migraineurs (IHS 1.1 or 1.2) who had headache recurrence within 2-24 h after initial relief for >50% of their headaches, based on history. At onset of migraine, subjects took sumatriptan oral tablet 50 mg (N=6) or nasal spray 20 mg (N=7). Subjects recorded symptoms at the time of sumatriptan administration, then at 30, 60, 90, and 120 min. If the initial dose of sumatriptan provided pain relief, subjects took naratriptan 2.5 mg at 2 h after the sumatriptan. Subjects then recorded the time and severity of any recurrence. Subjects were instructed to treat at least three migraineurs.

**Results** Thirteen adult migraineurs (2 men, 11 women; mean age 43.6 years) treated 43 headaches. In 33/43 (77%) headaches, relief was obtained after a single dose of sumatriptan. No recurrence occurred in 28/33 (85%) of these headaches following administration of naratriptan 2.5 mg. Historically, recurrence would have been anticipated in at least 17/33 headaches. In those headaches with recurrence despite naratriptan administration, the mean time to recurrence was 15.4 h. The combination of sumatriptan and naratriptan was well tolerated.

**Conclusion** Naratriptan reduces the rate of headache recurrence after initial relief with sumatriptan in migraineurs with a high frequency of recurrence.

P2-K21

**Factors predicting response to placebo in migraine attacks: results from the Sumatriptan Naratriptan Aggregate Patient (SNAP) database**

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**Objective** To determine the factors that predict alleviation of headache pain in patients treated for migraine in clinical trials of sumatriptan.

**Background** The Sumatriptan Naratriptan Aggregate Patient (SNAP) database consists of data from 128 sumatriptan and naratriptan clinical trials conducted from 1987 to 1998 that have been combined to provide an extensive data set for exploratory analysis.

**Methods** The data for patients taking placebo tablets (double-blinded for comparison to sumatriptan) for their first attack were extracted. Exploration and analysis of these data were performed using a variety of statistical techniques including recursive partitioning and logistic regression.

**Results** Among more than 900 patients treated with placebo as a double-blinded comparator to sumatriptan tablets, level of baseline pain and level of impairment at baseline (graded none, mild, severe or bed rest) were the most important predictors of headache response to placebo at 2 h postdose. (Headache response was defined as a shift from moderate or severe headache at baseline to mild or no pain.) Predictors of headache response to placebo at 4 h were age over or under 18 years and level of impairment at baseline. The rate of response for placebo patients overall was 28% at 2 h and 37% at 4 h. As with sumatriptan patients, placebo patients with less severe pain at baseline had a higher rate of response at both 2 and 4 h. Of the patients with moderate pain at baseline, 36% responded at 2 h and 41% responded at 4 h. At 2 and 4 h, 18% and 31%, respectively, of the patients with severe headache at baseline had mild or no pain. Adolescents (<18 years) had a placebo response rate of 42% at 2 h and 49% at 4 h. In comparison, adults had a placebo response rate of 25% at 2 h and 34% at 4 h. Patients requiring bed rest at baseline had a placebo response rate of 16% at 2 h and 27% at 4 h. Those not requiring bed rest had a response rate of 32% at 2 h and 39% at 4 h.

**Conclusions** This analysis shows that the major predictors for response in acute migraine attacks are the same for placebo as for sumatriptan. The higher placebo rate in adolescents shows that different end points might be needed in trials including this population.

P2-K22

**Factors predicting freedom from pain in migraine attacks: results from the Sumatriptan Naratriptan Aggregate Patient (SNAP) database**

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**Objective** To determine the factors that predict alleviation of headache pain in patients treated for migraine in clinical trials of sumatriptan.

**Background** The Sumatriptan Naratriptan Aggregate Patient (SNAP) database comprises data from 128 sumatriptan and naratriptan clinical trials conducted from 1987 to 1998 that have been combined to provide an extensive data set for exploratory analysis.

**Methods** Data for patients in double-blind trials taking placebo or sumatriptan 100 mg for their first attack were extracted. Analysis was performed using a variety of statistical techniques including recursive partitioning and logistic regression.

**Results** Among more than 2500 subjects in 19 studies who were treated for their first study attack with sumatriptan 100 mg tablets, level of baseline pain was the strongest predictive factor (adjusted P=4.31E-31) in determining whether a patient would be pain-free at 2 h. Fifty-eight percent (58%) of patients with mild pain at baseline (n=258, protocol violators) had no pain 2 h after taking sumatriptan. Of patients with moderate pain at baseline (n=1041) and severe pain at baseline (n=674), 32% and 18%, respectively,
Factors predicting headache response to therapy in migraine attacks: results from the Sumatriptan Naratriptan Aggregate Patient (SNAP) database

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Objective To determine retrospectively the factors that might predict headache response (moderate or severe pain reduced to mild or no pain) in patients treated for migraine in clinical trials of sumatriptan.

Background The Sumatriptan Naratriptan Aggregate Patient (SNAP) database consists of data from 128 sumatriptan and naratriptan clinical trials conducted from 1987 to 1998 that have been combined to provide an extensive data set for exploratory analysis.

Methods Data were extracted for patients in double-blind trials taking placebo or sumatriptan 100 mg for their first attack and for whom headache response data was available at 2 or 4 h post-treatment. Analysis was performed using a variety of statistical techniques including logistic regression and recursive partitioning.

Results Among more than 2300 patients treated with sumatriptan 100 mg tablets, baseline headache characteristics are among the most important factors in predicting response at 2 h. These characteristics include headache severity, presence of vomiting, aura associated with the headache, and level of impairment (graded as none, mild, severe, or bedrest) caused by the migraine. The less severe the initial pain and disability, the better the response at 2 h. For example, of patients with moderate pain at baseline, 66% (95% CI: 63%, 68%) had mild or no pain at 2 h, compared with 40% (95% CI: 37%, 43%) of those with severe pain at baseline. In terms of level of impairment, the response rates at 2 h after treating with sumatriptan were 72% for patients with mild or no impairment at baseline, 60% for those with severe impairment at baseline, and 43% for patients requiring bedrest at baseline. Response at 4 h appears to be affected by the same factors, with the exception of aura. The response rates at 4 h for patients with and without aura were not significantly different.

Conclusions Baseline headache severity proves to be a very strong predictor of response to acute migraine treatment with sumatriptan tablets. Patients treated for less severe migraines were more likely to have a good response.
P2-K25

The effect of migraine aura during an attack on treatment outcome: results from the Sumatriptan Naratriptan Aggregate Patient (SNAP) database

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Objective To determine the relationship between migraine characteristics and pain relief in patients treated for migraine, with and without aura during their attack.

Background The Sumatriptan Naratriptan Aggregate Patient (SNAP) database comprises data from 128 sumatriptan and naratriptan clinical trials conducted from 1987 to 1998 that have been combined to provide an extensive data set for exploratory analysis.

Methods Data were extracted for patients in double-blind trials taking oral sumatriptan 100 mg or placebo for their first attack and for whom pain-free or headache response data was available at 2 or 4 h post-treatment. Analysis was performed using a variety of statistical techniques including recursive partitioning and logistic regression.

Results The analysis data set included 3270 patients from 21 studies (sumatriptan 100 mg group = 2387; placebo = 899). Twenty-nine percent of the sumatriptan group and 21% of the placebo group had aura with their attack. The pain-free rate at 2 h after sumatriptan 100 mg was significantly higher in the absence of aura: 24% (95% CI: 21%, 27%) with aura and 32% (95% CI: 29%, 34%) without aura. In the placebo group, presence of aura did not influence outcome: 9% (95% CI: 5%, 14%) with aura and 9% (95% CI: 7%, 12%) without aura. The same pattern of higher 2-h pain-free rates following treatment with sumatriptan 100 mg in patients without aura was seen at mild, moderate, and severe baseline pain levels. Using recursive partitioning and logistic regression, treatment dose, baseline pain severity and baseline level of functioning were shown to be important predictors of pain-free response at 2 h and 4 h after dosing. Comparing patients with and without aura, it was found that patients with aura were more apt to suffer from nausea, vomiting, and light/sound sensitivity at baseline and tended to have more restricted functioning and more severe pain.

Conclusions In this analysis, the presence of an aura indicates that the following migraine headache will be both more severe and more resistant to treatment with sumatriptan 100 mg. Efficacy of placebo was not affected by aura at the time of the attack. This conclusion should be explored in prospective trials as it may represent an important confounding variable and offer insights into the relationship between migraine aura and headache.

P2-K26

Sumatriptan plus rofecoxib: reduction of headache recurrence in acute migraine

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Objectives Sumatriptan is highly effective and well tolerated in the treatment of migraine attacks. In clinical trials, however, roughly a third of all patients describe headache recurrence within 24 h. In this study it was investigated whether the combination of sumatriptan 100 mg with the COX-2 inhibitor rofecoxib 25 mg can reduce the rate of headache recurrence compared to sumatriptan alone. The half life of rofecoxib is 10–18 h, which is significantly higher than that of sumatriptan (2 h).

Materials and methods 50 patients fulfilling the IHS-criteria for migraine without aura or migraine with aura and a history of long-lasting attacks were asked to treat the next two migraine attacks in an open cross-over design either with oral sumatriptan 100 mg or sumatriptan 100 mg plus rofecoxib 25 mg. The sequence of treatment was randomized. Duration and intensity of migraine headache and accompanying symptoms were documented in a diary as were headache recurrence, adverse events and additional rescue medication. Efficacy was defined as a reduction of moderate or severe headache to mild or no headache 2 h post dose.

Results All 50 patients (39 women and 11 men; 47 with migraine without aura and 3 with migraine with aura; mean age 45 ± 13.2 years; 46 patients had a typical duration of attacks of 24–72 h) treated 2 attacks according to protocol. In 36 of 50 migraine attacks (72%) treated with sumatriptan, a significant headache reduction (as defined above) was documented after 2 h. The corresponding figure for the combination of sumatriptan 100 mg plus rofecoxib 25 mg was similar with 35 of 50 (70%). 16 of the 36 patients (44.4%) who first experienced headache relief within 2 h post dose reported headache recurrence within 24 h in the sumatriptan group compared to 9 of 35 patients (25.7%) in the sumatriptan plus rofecoxib group. The time until headache recurrence was significantly shorter in the sumatriptan group (10.3 h) than in the sumatriptan plus rofecoxib group (14.1 h). Adverse events were typical of sumatriptan (chest and throat tightness, paresthesia, tiredness), of mild intensity and did not require additional treatment. Patients with adverse events described them in both treatment groups.

Conclusions The combination of sumatriptan 100 mg plus rofecoxib 25 mg was not more effective in relieving headache than sumatriptan 100 mg alone. However, the rate of headache recurrence was lower and the time to headache recurrence was longer in the combination group. There was no difference in tolerability. These results show that the combination of sumatriptan 100 mg plus rofecoxib 25 mg
might be especially useful in patients suffering from long migraine attacks and therefore high headache recurrence rates.

P2-K27

Naratriptan plus naproxen: increase of efficacy and reduction of headache recurrence in acute migraine

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Objectives Triptans have been proved to be effective and well-tolerated drugs for the treatment of migraine attacks. Whereas the onset of action is rapid, however, headache recurrence is a common problem. In this study it was investigated whether the combination of naratriptan 2.5 mg with the non-steroidal anti-inflammatory drug naproxen 500 mg can reduce the rate of headache recurrence compared to naratriptan alone. The half life of naproxen is 12–24 h, which is significantly higher than that of naratriptan (6 h).

Materials and methods 50 patients fulfilling the IHS-criteria for migraine without aura or migraine with aura were asked to treat the next two migraine attacks in an open cross-over design either with naratriptan 2.5 mg or naratriptan 2.5 mg plus naproxen 500 mg. The sequence of treatment was randomised. Duration and intensity of migraine headache and accompanying symptoms were documented in a diary as were headache recurrence, adverse events and additional rescue medication. Efficacy was defined as reduction of moderate or severe headache to mild or no headache.

Results All 50 patients (37 women and 13 men; 46 with migraine without aura and 4 with migraine with aura; mean age 43 ± 12.1 years) treated 2 attacks according to protocol. In 20 of 50 migraine attacks (40%) treated with naratriptan, a significant headache reduction (as defined above) was documented after 2 h. The number increased to 29 of 50 attacks after 4 h (58%). The corresponding figures for the combination of naratriptan 2.5 mg plus naproxen 500 mg were higher with 27 of 50 after 2 h (54%) and 35 of 50 after 4 h (70%). 9 patients (31%) who first experienced headache relief reported headache recurrence within 24 h in the naratriptan group compared to 4 patients (11.4%) in the naratriptan plus naproxen group. The time until headache recurrence was shorter in the naratriptan group (14.2 h) than in the naratriptan plus naproxen group (18.4 h). Adverse events were mild and did not require additional treatment.

Conclusions The combination of naratriptan 2.5 mg plus naproxen 500 mg was found to be more effective than naratriptan 2.5 mg alone after 2 and 4 h. Furthermore, the rate of headache recurrence was lower and the time to headache recurrence longer in the combination group. There was no difference in tolerability. These results show that the combination of a triptan with a long-acting NSAID can increase the overall benefit patients may get from a triptan. The combination of naratriptan with naproxen is especially useful in patients suffering from long migraine attacks and therefore high headache recurrence rates.

P2-K28

The efficacy of sumatriptan plus metoclopramide in migraine patients who were triptan non-responsive

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Objective We evaluated the effectiveness of combination treatment using sumatriptan plus metoclopramide, or sumatriptan alone, for the treatment of migraine. The patients who were treated had failed to respond to triptans in the past, despite adequate doses and at least two separate trials of the same triptan or two different triptan attempts.

Materials and methods In this double-blind, randomized study, adult migraineurs meeting IHS criteria for migraine with or without aura (n = 16), who had failed to receive adequate relief from triptans, were randomized to either metoclopramide 10 mg plus sumatriptan 50 mg or placebo plus sumatriptan 50 mg to treat two migraineurs. Subjects took both sumatriptan 50 mg and metoclopramide or placebo at moderate to severe pain and recorded symptoms at 30, 60, 90 and 120 min

Results Thirteen women and three men (mean age, 40 years) treated two migraines (a total of 32 migraines). The combination of sumatriptan 50 mg plus metoclopramide 10 mg provided meaningful relief for 9 of 32 (28%) headaches compared with 5 of 32 (16%) headaches treated with sumatriptan 50 mg plus placebo. Headache response (moderate/severe to mild/none at 2 h) was seen in 6 of 32 (19%) headaches treated with Sumatriptan plus metoclopramide compared with 1 of 32 (3%) headaches of the sumatriptan 50 mg plus placebo group. The combination was well tolerated.

Conclusion Combining sumatriptan with metoclopramide provides relief in migraineurs who failed to achieve adequate relief with a triptan alone. It is not clear if initiating therapy when pain was mild, or using 100 mg of sumatriptan, would have provided additional benefit. Further studies are indicated.

P2-K29

Distribution and pharmacokinetics of zolmitriptan following administration by nasal spray

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Objectives To assess the distribution and pharmacokinetics of intranasally administered zolmitriptan.

Background Zolmitriptan tablets have well-established efficacy in the acute treatment of migraine. However, oral administration may not be appropriate for all migraine attacks. A nasal spray formulation of zolmitriptan has been developed to offer patients a convenient alternative to oral tablets.

Methods Nine volunteers were recruited to a single-centre, open, 2-phase trial. During phase 1, 2 volunteers received
intranasal 11C-zolmitriptan 2.5 mg and the most appropriate times for scanning were determined. In phase 2, 7 volunteers received 11C-zolmitriptan 2.5 mg and PET scanning of the nasopharynx, lungs or abdomen was performed for up to 2 h postdose. In a separate, randomized, crossover study, 12 volunteers received zolmitriptan 2.5 mg as an intranasal solution and as a tablet, on separate occasions to assess standard pharmacokinetic parameters of absorption.

**Results**

In the PET study, approximately 100% of the zolmitriptan dose was detected in the nasopharynx immediately after administration. The concentration in the nasopharynx then decreased as 11C-zolmitriptan appeared in the abdomen, such that at 20 and 80 min postdose, 30% and 35% of the administered dose, respectively, remained. Zolmitriptan was detectable in the plasma at the earliest assessment time (15 min postdose), when the majority of the administered dose was still within the nasopharynx. Radioactivity first appeared in the abdomen 20–60 min after dosing. Radioactivity was detected in the brain of all volunteers, although levels were very low (mean 0.54 ng/g), and was negligible in the lungs. The second study confirmed that zolmitriptan nasal spray is rapidly absorbed. Plasma levels of zolmitriptan were detectable in all subjects 5 min after administration of the nasal spray, compared with 20 min in 10 of 12 participants after the oral tablet. However, although absorption was more rapid following nasal spray, compared with 20 min postdose, 30% and 38% of Cmax was achieved following administration of zolmitriptan nasal spray at pH 7.4 and 5.0, respectively. All pharmacokinetic parameters were similar between the different pH formulations. Cmax values were 4.13 and 3.93 ng/mL following nasal spray at pH 7.4 and pH 5.0, respectively. Corresponding AUC values were 24.9 and 22.4 ng h/mL. In study 2, zolmitriptan nasal spray was rapidly absorbed following dosing and, on average, at least 50% of Cmax was achieved after 30 min in all dose groups. Dose proportionality was shown for AUC and Cmax following single and multiple dosing. After a single dose of zolmitriptan nasal spray 0.5, 1, 2.5 or 5 mg, mean AUC values were 5.30, 7.78, 22.10 and 42.10 ng h/mL, respectively, and mean Cmax values were 0.91, 0.99, 3.63 and 6.51 ng/mL, respectively. The proportionality coefficients for AUC were 0.97 and 0.98 following single and multiple dosing, respectively. Corresponding coefficients for Cmax were 0.94 and 0.98. Both studies showed zolmitriptan nasal spray to be well tolerated.

**Conclusions**

The results from these two pharmacokinetic studies demonstrate that zolmitriptan is more rapidly absorbed from the nasal spray than from the tablet, with detectable plasma levels 5 min postdose. PET analysis indicates that early plasma levels result from initial absorption directly across the nasal mucosa.

**P2-K30**

Zolmitriptan nasal spray exhibits rapid and dose-proportional absorption

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**Objectives**

To compare the absorption of zolmitriptan following administration by nasal spray at pH 7.4 and pH 5.0, and to investigate the mean plasma concentration–time profile and dose proportionality of zolmitriptan nasal spray.

**Background**

The conventional oral tablet formulation of zolmitriptan is highly effective in the acute treatment of migraine. The nasal spray formulation has since been developed to provide an alternative therapy for patients in circumstances where oral treatment may not be appropriate. However, at physiological pH (7.4), the nasal spray has limited stability at room temperature and a formulation of lower pH (5.0) was therefore developed to remove the need for refrigeration.

**Methods**

Study 1 involved 12 volunteers who were randomized to receive the zolmitriptan nasal spray 2.5 mg at pH 7.4 and at pH 5.0. Study 2 involved 30 volunteers who were randomized to receive a single dose of placebo or zolmitriptan nasal spray 0.5, 1, 2.5 or 5 mg on day 1 and two doses of each treatment, separated by 2 h, on days 2–4.

**Results**

In study 1, zolmitriptan was detectable in the plasma at 5 min postdose in all volunteers after nasal spray administration at both pH 7.4 and pH 5.0. At 10 min postdose, 30% and 38% of Cmax was achieved following administration of zolmitriptan nasal spray at pH 7.4 and 5.0, respectively. Zolmitriptan was detectable in the plasma at the earliest assessment time (15 min postdose), when the majority of the administered dose was still within the nasopharynx. Radioactivity first appeared in the abdomen 20–60 min after dosing. Radioactivity was detected in the brain of all volunteers, although levels were very low (mean 0.54 ng/g), and was negligible in the lungs. The second study confirmed that zolmitriptan nasal spray is rapidly absorbed. Plasma levels of zolmitriptan were detectable in all subjects 5 min after administration of the nasal spray, compared with 20 min in 10 of 12 participants after the oral tablet. However, although absorption was more rapid following nasal spray, compared with 20 min postdose, 30% and 38% of Cmax was achieved following administration of zolmitriptan nasal spray at pH 7.4 and 5.0, respectively. All pharmacokinetic parameters were similar between the different pH formulations. Cmax values were 4.13 and 3.93 ng/mL following nasal spray at pH 7.4 and pH 5.0, respectively. Corresponding AUC values were 24.9 and 22.4 ng h/mL. In study 2, zolmitriptan nasal spray was rapidly absorbed following dosing and, on average, at least 50% of Cmax was achieved after 30 min in all dose groups. Dose proportionality was shown for AUC and Cmax following single and multiple dosing. After a single dose of zolmitriptan nasal spray 0.5, 1, 2.5 or 5 mg, mean AUC values were 5.30, 7.78, 22.10 and 42.10 ng h/mL, respectively, and mean Cmax values were 0.91, 0.99, 3.63 and 6.51 ng/mL, respectively. The proportionality coefficients for AUC were 0.97 and 0.98 following single and multiple dosing, respectively. Corresponding coefficients for Cmax were 0.94 and 0.98. Both studies showed zolmitriptan nasal spray to be well tolerated.

**Conclusions**

There was no statistically significant difference in the absorption of zolmitriptan following nasal spray administration at pH 7.4 and pH 5.0. As the lower pH offers a more stable formulation, this was used for subsequent studies. Zolmitriptan nasal spray exhibits rapid, dose-proportional absorption. The early detection of zolmitriptan plasma levels following administration by nasal spray indicates that absorption occurs directly across the nasal mucosa. This rapid absorption of zolmitriptan may result in a faster onset of therapeutic effect for patients.

**P2-K31**

High efficacy and tolerability nasal spray extends to long-term treatment of migraine

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**Objectives**

The new nasal spray formulation of zolmitriptan may offer clinical benefits to migraine patients by providing a faster onset of relief. A dose-ranging clinical study investigated the efficacy of this formulation, and a follow-up study assessed the long-term efficacy and tolerability of zolmitriptan 5 mg nasal spray. Data for the primary endpoint (2-h headache response) have been presented elsewhere; secondary endpoints are presented.

© Blackwell Science Ltd *Cephalalgia*, 2001, 21, 405–432
Conclusions
Secondary endpoints confirm that zolmitriptan triptan was well tolerated. 

Results
Zolmitriptan nasal spray doses of 1, 2.5 and 5 mg were superior to placebo in achieving a pain-free response (reduction from moderate/severe pain at baseline to none) from 30 min \( (P<0.05 \text{ vs } \text{placebo at 30, 45 min, and 1, 2 and 4 h}. \) The 2 h pain-free response rates were 11\%, 25\%, 26\% and 36\% for nasal spray doses 0.5, 1, 2.5 and 5 mg, respectively, 36\% for oral zolmitriptan 2.5 mg \( \text{vs } 8\% \text{ for placebo}. \) A higher proportion of patients treated with zolmitriptan nasal spray had a satisfaction rating of excellent/good compared with placebo; satisfaction was highest in the zolmitriptan nasal spray 5 mg group (57\% vs 13\% for placebo recipients). The response to zolmitriptan nasal spray was consistent. Of patients treating 3 attacks, 74\% receiving nasal spray 5 mg had a 2-h headache response in >2/3 attacks compared with 25\% receiving placebo. Zolmitriptan nasal spray rapidly reduced pain (at least a 1-point decrease in intensity). From 15 min onwards, pain was reduced in a significantly greater proportion of attacks after zolmitriptan nasal spray 2.5 and 5 mg than after placebo. In the long term study, 783 patients took at least one dose of zolmitriptan 5 mg nasal spray to treat a total of 10505 attacks. In addition to consistent 2 h headache response rates over time, pain-free responses were consistent over each 3-month period (29-31\% and 52-57\% of attacks at 1 and 2 h postdose, respectively). Long-term use of zolmitriptan was well tolerated.

Conclusions
Secondary endpoints confirm that zolmitriptan nasal spray is highly effective in the acute treatment of migraine. This formulation shows consistent efficacy and is well tolerated in the long term. Zolmitriptan nasal spray offers patients a highly effective and convenient alternative to the conventional oral tablet.

P2-K32
Efficacy of zolmitriptan nasal spray in mild, moderate and severe migraine: relationship to timing of dosing
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Objective
Emerging data suggest that treating migraine attacks of mild intensity confers higher pain-free rates than treating attacks of moderate or severe intensity (Cady et al. Headache 2000; 40:792–7). However, it is unclear whether this is an effect of attack severity or of timing of treatment intervention; indeed the line between early and mild is blurred. A recent study with zolmitriptan nasal spray, in which patients could treat attacks of any severity, examines this issue.

Methods
In the dose-ranging study 1547 patients were randomised to zolmitriptan nasal spray 0.5, 1, 2.5 or 5 mg, zolmitriptan oral tablet 2.5 mg or placebo in a double-blind, double-dummy manner for the treatment of 3 moderate or severe migraine attacks. In the long term study, patients were initially randomized to zolmitriptan nasal spray 0.5, 1, 2.5 or 5 mg. Once the optimal dose had been determined from the dose-finding study, patients switched to the optimal 5 mg dose for the rest of the 1-year period.

Results
In a 2-phase, blinded study, 1146 patients were initially randomized across 4 dose groups (zolmitriptan 0.5, 1.0, 2.5 and 5 mg nasal spray) and subsequently were all assigned to 5 mg treatment. Prospective analysis of the 2-h pain-free response to zolmitriptan 5 mg nasal spray for the treatment of mild, moderate, and severe migraine was performed. Retrospective analysis of 2-h pain-free response rates was performed to assess the effect of time to treatment following onset of headache pain (0–15, 15–30, 30–45, 45–60, >60 min).

Results
Over the 1-year study, 10 505 attacks were treated with zolmitriptan 5 mg nasal spray. Nearly 50\% of all attacks (5126 attacks), irrespective of headache severity, were treated within the first 15 min of pain onset. Pain-free response rates were highest in patients treating mild headache. The 2-h pain-free response rates within each group of headache intensity (mild, moderate, severe) did not differ in relation to time of treatment following onset of pain.

Table 1 Percentage of attacks pain free at 2 h

<table>
<thead>
<tr>
<th>Time of treatment after headache onset (min)</th>
<th>Baseline intensity</th>
<th>Mild (n = 1476)</th>
<th>Moderate (n = 5906)</th>
<th>Severe (n = 2518)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>74.1%</td>
<td>81.8%</td>
<td>78.9%</td>
<td>56.6%</td>
</tr>
<tr>
<td>15–30</td>
<td>55.4%</td>
<td>60.6%</td>
<td>61.3%</td>
<td>56.6%</td>
</tr>
<tr>
<td>30–45</td>
<td>33.0%</td>
<td>38.1%</td>
<td>43.1%</td>
<td>27.8%</td>
</tr>
<tr>
<td>45–60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td></td>
<td></td>
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</tbody>
</table>

Conclusions
These data support previous reports that higher pain-free responses are achieved when treating mild headaches compared with moderate or severe headaches. However, these data show that within each category of headache intensity, 2-h pain-free response rates are unaffected by the time of treatment with zolmitriptan following onset of headache, thus giving patients confidence in achieving reliable relief. This suggests that baseline severity remains the key determinant in response to zolmitriptan and does not support the hypothesis that later intervention confers less clinical benefit. Additional studies are needed to address issues relating to the clinical benefits of early intervention vs Treatment of mild headache. Further prospective studies specifically looking at potential benefits of early intervention are needed, as is a definition for ‘early treatment’.
lives, and their treatment needs and preferences have been investigated. Respondents said highly effective and rapid pain relief were the most important benefits of migraine medication, and preferred treatments that were discreet, easy to carry around and that could be taken anywhere. When asked about possible formulations, 73% of patients expressed a preference for tablets that dissolve in the mouth without liquids. An orally disintegrating tablet (ODT) of zolmitriptan has been developed that dissolves on the tongue without needing additional fluids. This study evaluated the efficacy and tolerability of the ODT, and assessed patient preference for this formulation compared with conventional tablets.

**Methods** In this double-blind, multicentre study, patients were randomized to zolmitriptan 2.5 mg or placebo as an ODT for the treatment of a single moderate or severe migraine. The primary endpoint was 2 h headache response (reduction in headache intensity from moderate/severe at baseline to mild/no pain).

**Results** 470 patients were included in the ITT population (zolmitriptan n = 231, placebo n = 239). Headache response at 2 h was significantly higher in zolmitriptan ODT recipients compared with placebo recipients (63% vs 22%; P < 0.0001). A significant between-group difference in headache response was observed from 1 h (45% vs 19%; P < 0.0001). A statistically significant drop by ≥1 point in headache pain severity was reported for zolmitriptan recipients at 30 min postdose, indicating patients recognized early reduction in pain intensity following treatment (22% vs 15%; P = 0.0385). A significantly greater proportion of patients in the zolmitriptan group were pain free in the placebo group at 1 h (8% vs 3%; P = 0.0207) and 2 h (27% vs 7%; P < 0.0001). The majority of patients (70%) preferred the ODT formulation to a conventional tablet, and found it to be more convenient (78%). The presence of nausea at baseline had no effect on patient preference; 70% vs 69% with and without nausea preferred the ODT. The zolmitriptan ODT was well tolerated, with a profile of adverse events similar to that seen with the conventional zolmitriptan tablet.

**Conclusion** Patient preference is an important factor to consider in providing optimal migraine therapy. These studies show that the ODT formulation is well received by migraine sufferers. Zolmitriptan ODT is an effective acute treatment for migraine, and offers a convenient alternative for migraine sufferers. Zolmitriptan ODT is an effective acute treatment for migraine and offers a convenient alternative

**P2-K34**

**Zolmitriptan is effective in the treatment of menstrually associated migraine attacks**

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**Objectives** There is a perception that menstrually associated migraine attacks are more severe and more resistant to acute treatment than those unrelated to menstruation. However, few prospective clinical data exist to support this. Zolmitriptan is a selective 5-HT1B/1D receptor agonist that has demonstrated consistent efficacy in the acute treatment of migraine. This analysis collated prospectively recorded data from the zolmitriptan clinical trial programme to assess the efficacy of zolmitriptan in the treatment of menstrually associated migraine attacks.

**Methods** Female patients prospectively recorded details of their menstrual cycles in 7 zolmitriptan clinical trials were included in the analysis: 3 placebo-controlled trials (only 2.5 mg data included), 2 multiple-attack comparative trials with sumatriptan and 2 long-term open studies (all used zolmitriptan 2.5 or 5 mg, and data were combined where both dosages were used). Migraine attacks were defined as being menstrually associated if they occurred within 2 days before or 3 days after the onset of menstruation. Efficacy data were collected by the completion of diary cards.

**Results** A total of 4345 menstruating female patients were included in the analysis. The data confirmed that the incidence of migraine increased around the time of menstruation, but showed that menstrually associated attacks were no more severe than non-menstrually associated attacks. Attacks were classified as being severe in approximately 28% and 27% of menstrually and non-menstrually associated attacks, respectively. Zolmitriptan 2.5 mg was significantly more effective than placebo in the treatment of moderate/severe menstrually associated migraine. Two-hour headache response rates were 60% with zolmitriptan vs 39% with placebo (P = 0.0008). The efficacy of zolmitriptan was comparable in both menstrually and non-menstrually associated attacks. In the active comparator trials, zolmitriptan produced a 2-h headache response in 68% of menstrually associated attacks and 65% of non-menstrually associated attacks. The efficacy of zolmitriptan was consistently maintained, with 2-h response rates in the 2 long-term studies of 80% and 83% in menstrually associated migraine vs 81% and 82% in non-menstrually associated migraine. Furthermore, within individual patients, response rates were similar in both types of attacks irrespective of the percentage of attacks treated during menses.

**Conclusion** Collectively, these data demonstrate that zolmitriptan is a consistently effective treatment for menstrually associated migraine.

**P2-K35**

Zolmitriptan offers a range of formulations that provide consistent efficacy and increased treatment options

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**Objective** The characteristics of migraine are highly variable and a migraine treatment strategy should take into account both the clinical features of a patient’s attack and their treatment preferences. To address this need therefore, in addition to the conventional tablet, two new formulations of zolmitriptan have now been developed: an orally disintegrating tablet and a nasal spray. The orally disintegrating tablet is easy to handle and dissolves on the tongue without the need...
for additional fluid intake. This provides a convenient formulation that can be taken discreetly anytime a migraine strikes. The nasal spray formulation offers an alternative route of administration, which may be of particular benefit in attacks associated with nausea or if the patient is unwilling or unable to take a tablet.

Methods Review of clinical trial data to compare the efficacy of the 3 formulations of zolmitriptan.

Results An extensive clinical trial programme has already established the efficacy of the conventional zolmitriptan tablet in the acute treatment of migraine. Two-hour headache response rates with zolmitriptan 2.5 and 5 mg range from 59 to 67% and 61–67%, respectively, while 2-h pain-free rates are between 22% and 32% and 14% and 39%, respectively. The zolmitriptan 2.5 mg orally disintegrating tablet produced a 2-h headache response rate of 63% compared with 22% in placebo recipients (P<0.0001), a response rate consistent with those previously observed with the conventional tablet. Patient preference for the orally disintegrating tablet was high, with 70% of patients preferring this formulation to conventional tablets. In patients treated with the zolmitriptan 5 mg nasal spray, the 2-h headache response was 70% compared with 30% for placebo recipients, while the respective 2-h pain-free response rates were 36% and 8% (both P<0.001 vs placebo). Zolmitriptan nasal spray produces rapid relief, with a significant headache response within 15 min using the recommended 5 mg dose, compared with placebo (11% vs 5%; P<0.05). Headache response was consistent across attacks, with 74% of zolmitriptan nasal spray 5 mg recipients responding in at least 2/3 attacks. Zolmitriptan was well tolerated across all 3 formulations, and during long-term use.

Conclusion Zolmitriptan offers a range of formulations that demonstrate consistent efficacy, while also having unique benefits appropriate to varying migraine characteristics. Zolmitriptan therefore provides patients with a choice of formulations allowing the effective treatment of migraine anytime and anywhere a migraine strikes.

P2-K36

Serotonergic syndrome due to zolmitriptan: first two cases

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Introduction Zolmitriptan (Zomig®) is a new 5 HT1b/1d agonist available since April 1998 in France for acute treatment of migraine. Serotonergic syndrome has been described with many drugs but only with ergotamine and sumatriptan concerning migraine treatments. We report the first two cases of serotonergic syndrome associated with zolmitriptan intake.

First case A 25-year-old woman with a history of migraine since the age of 12 and depression for a few months, treated by indoramine (2/d) and paroxetine (2/d), received zolmitriptan (1 pill) for an acute treatment of migraine for the first time on 12 June in the morning. She was pain-free 1 h after. She presented a new migraine attack on 13 June in the afternoon and took zolmitriptan (1 pill) and paroxetine (1 pill) at the same time. She developed diffuse sweating, hypertonia and myoclonus of the forelimbs during the night. The symptoms disappeared in the morning. The patient then stopped indoramine but took another pill of paroxetine on 15 June. She experienced the same symptoms and also tachycardia, hyperreflexia, diarrhoea and agitation. She was then hospitalized. Her exam returned to completely normal in 3 days.

Second case A 43-year-old woman with a history of catamenial migraine since adolescence had been treated with zolmitriptan (one pill) since May 1998 with a good efficacy and tolerance. She was also treated with viloxazine for a mild depression. In November, she treated a migraine attack with zolmitriptan (3 pills in 6 h at 6, 9 and 00 p.m.). She presented the following morning with intense asthenia, abdominal pain, nausea, diarrhoea, and diffuse sweat alternating with diffuse heat. She had no myoclonus. All symptoms disappeared in 1 h. Physicians treating migraine must be aware of the serotonin syndrome and must be able to recognize its varying presentations.

P2-K37

Comparison of preference for rizatriptan 10 mg wafer vs sumatriptan 50 mg tablet in migraine

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Objective Preference is a patient-focused composite end point incorporating efficacy, tolerability and formulation of a medicine. MAXALT-RPD® is an orally disintegrating tablet formulation of rizatriptan, a selective 5-HT1B/1D receptor agonist with rapid onset of action in the acute treatment of migraine. The primary study end point was the assessment of preference for rizatriptan 10 mg RPD (wafer) to sumatriptan (IMIGRAN®) 50 mg tablet.

Methods This randomized, open-label, two-period crossover, multicentre study was conducted internationally in 481 patients treating a single migraine headache in each period. Patients treated one migraine with either rizatriptan 10 mg RPD or sumatriptan 50 mg tablet and then treated a second migraine with the alternate therapy. Patients completed a global preference question at the final visit, which included questions clarifying reasons for preference.

Results Almost twice as many patients preferred rizatriptan 10 mg RPD to sumatriptan 50 mg tablet (64.3% vs 35.7%, P<0.001). Only 44 patients did not express a preference. Faster relief of headache pain was the most important reason for preference, cited by 46.9% of patients preferring rizatriptan and 43.4% of patients preferring sumatriptan. Headache relief at 2 h was 75.9% for rizatriptan and 66.6% for
Conclusions and 6.7% respectively), dizziness (6.1 and 5.8%) and somnolence (7.4 and sumatriptan were nausea (6.6 and 6.9% of patients, P < 0.001). The most common side-effects with rizatriptan and sumatriptan were nausea (6.6 and 6.9% of patients, respectively), dizziness (6.1 and 5.8%) and somnolence (7.4 and 6.7%).

Conclusions Rizatriptan 10 mg RPD was preferred to sumatriptan 50 mg tablet. It was more effective in treating associated migraine symptoms and functional disability than sumatriptan, with headache relief and pain freedom occurring sooner than with sumatriptan.

P2-K38

Relationship between patient preference for either rizatriptan orally disintegrating tablet (ODT) 10 mg or sumatriptan tablet 50 mg and speed of pain relief

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Objective To evaluate the relationship between patient preference for either rizatriptan ODT 10 mg or sumatriptan 50 mg tablet and the speed of pain relief with these acute migraine treatments.

Background Migraineurs express treatment preference based on a variety of attributes including speed of pain relief and medication formulation. Rizatriptan ODT is an orally disintegrating tablet formulation of rizatriptan, a selective 5-HT1B/1D receptor agonist. Rizatriptan and sumatriptan have been shown to be effective and well tolerated acute migraine therapies.

Design and methods This was a multicentre, randomized, open-label, two-period crossover study in 524 enrolled patients. Patients treated a single moderate or severe migraine headache in each treatment period. Patients treated one migraine with either rizatriptan ODT 10 mg or sumatriptan 50 mg tablet, then treated a second migraine with the alternate therapy. Patients recorded headache severity at baseline, 30, 45, 60, 90 and 120 min post-dose. At the final study visit after treatment of their second migraine, patients expressed preference for one of the two study medications by completing an interviewer-administered Global Preference Question. A posthoc analysis was conducted to evaluate the relationship between patient preference for either rizatriptan ODT 10 mg or sumatriptan 50 mg tablet and the speed of pain relief with these acute migraine treatments.

Results Some 370 patients treated two migraine attacks, expressed a preference for either rizatriptan ODT or sumatriptan, and reported severity data. A large proportion of patients who experienced faster pain relief with rizatriptan ODT expressed a preference for rizatriptan ODT (78%). Similarly, a large proportion of patients who experienced faster pain relief with sumatriptan expressed a preference for sumatriptan (66%). For those patients who did not have one treatment provide faster pain relief than the other, there was no difference between whether the patient preferred rizatriptan ODT (50%) or sumatriptan (50%).

Conclusions Although a causal relationship cannot be concluded, based on results from this analysis, patients tended to prefer the acute migraine treatment which provided faster pain relief.

P2-K39

Are migraine patients who are pain free at 2 h after treatment also more likely to be free of nausea?

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Objective Nausea is a common accompanying symptom of migraine. Little is known about the relationship between nausea and pain in migraine. It is conceivable that nausea may arise as a response to pain. If this were so, it might be expected that those patients whose headaches were more effectively treated at 2 h would also have less nausea. We performed an analysis of data from rizatriptan clinical trials to investigate this.

Methods Data from 8 randomized, double-blind, placebo-controlled trials of rizatriptan 10 mg were included in the retrospective analysis. Headache severity (4-grade scale) and presence or absence of nausea were recorded at baseline and at 2 h after dosing. Patients were treated for a moderate or severe headache. Data from the subgroup of patients who had both headache and nausea at baseline were included in the analysis. We looked at the incidence of nausea at 2 h in 3 groups of patients with differing degrees of headache relief at 2 h: (1) pain free; (2) mild pain; (3) moderate or severe pain (i.e. no or little relief). A Cochran-Mantel-Haenszel statistic was calculated for each treatment group to assess the association between pain relief and nausea relief.

Results Approximately 60% of patients in the studies had both headache and nausea at baseline. In patients taking rizatriptan 10 mg (N=1165), 92% of those who were pain free at 2 h also had no nausea at 2 h, vs 71% of those with mild pain at 2 h and 30% of those with moderate or severe pain at 2 h. The P-value was 0.001, indicating a statistically significant association. A similar pattern was seen in patients...
taking placebo (N=750): 92% of those who were pain free at 2 h also had no nausea at 2 h, vs 70% of those with mild pain at 2 h and 28% of those with moderate or severe pain at 2 h (P=0.001 for the test of association).

**Conclusion** There was an association between headache relief and nausea relief in migraine attacks. These findings could indicate that in migraine nausea arises, at least in part, as a response to pain, or that headache and nausea share a common pathophysiological mechanism.

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**P2-K40**

**Triptan vs non-triptan treatment of migraine in long-term extension studies**

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**Objective** Previous long-term studies of rizatriptan have demonstrated that rizatriptan is more effective than ‘usual care’ (UC) medications in the acute treatment of migraine. In these studies, UC was determined by the physician and could consist of sumatriptan or any non-triptan analgesic (e.g. NSAIDs). We performed a retrospective analysis to compare efficacy in rizatriptan-treated attacks vs efficacy in attacks treated with different types of UC.

**Methods** Data from 4 open-label, long-term, extension studies, which followed on from double-blind, placebo-controlled studies, were analysed. Patients with IHS-diagnosed migraine were randomized to treatment with rizatriptan 10 mg, rizatriptan 5 mg, or UC. The UC medication(s) could be switched from 1 attack to another, and could consist of combinations of antimigraine or analgesic medications. Patients treated moderate or severe migraine attacks occurring over periods of up to 1 years. The percentage of attacks with pain relief at 2 h (reduction of pain to mild or none) and that were pain free at 2 h were calculated for rizatriptan 10 mg, sumatriptan UC, and non-triptan UC. Attacks that were treated with both sumatriptan UC and non-triptan UC were counted only in the sumatriptan UC group. The analysis was descriptive and no formal statistical testing was performed.

**Results** A total of 1000 patients treated 26434 attacks with rizatriptan 10 mg, 318 patients treated 6343 attacks with sumatriptan UC, and 230 patients treated 2819 attacks with non-triptan UC only. Non-triptan UC medications consisted mainly of NSAIDs, acetaminophen, barbiturates, or opiates. The percentages of attacks with pain relief at 2 h were 86% for rizatriptan 10 mg, vs 76% for sumatriptan UC and 55% for non-triptan UC. The percentages of pain free attacks were 55% for rizatriptan, vs 49% for sumatriptan UC and 23% for non-triptan UC.

**Conclusion** In these long-term extension studies of moderate of severe migraine attacks, there was a response in more attacks treated with rizatriptan or sumatriptan than attacks treated with non-triptan medications.

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**P2-K41**

**Long-term efficacy of rizatriptan wafers in menstrual migraine**

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**Objective** Menstrually associated migraine attacks (MAMAs) are commonly thought to be more difficult to treat than non-MAMAs. Previously, we showed that rizatriptan tablets were effective at relieving headache pain and other migraine symptoms during a single MAMA, defined as an attack occurring within 7 days of onset of menstruation. Here we describe the efficacy of rizatriptan wafers in MAMAs, using data from long-term studies and a stricter definition of menstrual association.

**Methods** Patients who completed a blinded, controlled study entered an open label extension where they treated moderate or severe migraine attacks over 6 months with rizatriptan 10 mg wafer. Attacks in women were classified as menstrual according to 2 definitions: (1) attack within 3 days of onset of menstruation (7-day window, onset=day 0; prospective definition); (2) attack within −1 to +2 days of onset of menstruation (4-day window; retrospective definition). The percentage of attacks with pain relief (reduction of pain to mild or none) or a pain-free response at 2 h following treatment with rizatriptan 10 mg were calculated for menstrual and non-menstrual attacks using the 2 definitions.

**Results** 95 women treated 1839 attacks with rizatriptan 10 mg; 31% of attacks occurred within 3 days of onset of menstruation while 21% occurred within −1 to +2 days of menstruation. Using the ‘±3 day’ definition of menstrual association, pain relief was observed at 2 h in 78% of MAMAs and 78% of non-MAMAs, while there was a pain-free response in 50% of MAMAs and 51% of non-MAMAs. Using the ‘−1 to +2 day’ definition, pain relief was observed at 2 h in 77% of MAMAs and 78% of non-MAMAs, while there was a pain-free response in 49% of MAMAs and 51% of non-MAMAs.

**Conclusion** Rizatriptan 10 mg wafers were as effective for treating MAMAs as non-MAMAs in long-term use, regardless of whether a ‘±3 day’ or a stricter ‘−1 to +2 day’ definition of menstrual association was employed.

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**P2-K42**

**Rizatriptan in the spectrum of headache**

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**Objective** Migraineurs may experience a spectrum of headache activity that includes International Headache Society-defined migraine with and without aura, migrainous
Studies on migraine headaches have shown that they can severely impair a patient's ability to function normally. Returning patients to their normal level of functioning is important because acute therapy should address not only the attack, but also allow the patient to resume normal social and family life. Triptan treatments are effective in treating migraine symptoms and in enabling patients to return to their normal level of functioning. Here, we compare the efficacy of rizatriptan vs other triptans on functional disability using data from direct head-to-head comparative trials.

**Methods**
Data from double-blind, placebo-controlled trials in which rizatriptan was compared with another triptan for the treatment of a migraine attack were included in the posthoc analysis. Rizatriptan 10 mg was compared with sumatriptan 100 mg in 1 parallel study (N=740), sumatriptan 50 mg in 2 crossover studies (N=1009), sumatriptan 25 mg in 2 crossover studies (N=1129), zolmitriptan 2.5 mg in 1 parallel study (N=314), and naratriptan 2.5 mg in 1 parallel study (N=409). Patients recorded their level of functional disability on a 4-grade scale (‘normal’; ‘daily activities mildly impaired’; ‘daily activities severely impaired’; ‘unable to do activities, requires bedrest’) at baseline and at 30-minute intervals up to 2 h after dosing. The analysis included only those patients who had some functional disability at baseline. Data were analysed in a pairwise fashion and methods of analysis were appropriate to the study design.

**Results**
The percentages of patients with pain relief (reduction of pain by at least 2 grades) at 2 h were 81% (95% CI: 75%, 86%) and 53% (95% CI: 43%, 63%) for placebo. Pain-free rates at 2 h were 52% (95% CI: 45%, 59%) for rizatriptan and 18% (95% CI: 11% and 27%) for placebo.

**Conclusion**
Rizatriptan appeared to have efficacy in treating headaches which, although they occurred in patients with a diagnosis of migraine, could be more accurately described as migrainous or possibly tension-type headaches.
sumatriptan 100 mg (P=0.768) (placebo=3%), and 8% for rizatriptan 10 mg vs 8% for sumatriptan 50 mg (P=1.000) (placebo=3%). The percentages of patients with drug-related drowsiness were 7% for rizatriptan 10 mg vs 6% for sumatriptan 100 mg (P=0.661) (placebo=3%), and 7% for rizatriptan 10 mg vs 6% for sumatriptan 50 mg (P=0.466) (placebo=3%). Most AEs were of mild or moderate severity and short lasting.

Conclusion in direct head-to-head comparative trials, there was no evidence that a 'brain-penetrant' triptan (rizatriptan) caused significantly more CNS AEs than a 'less brain-penetrant' triptan (sumatriptan). In fact, sumatriptan 100 mg was associated with slightly more CNS AEs than rizatriptan 10 mg.

P2-K45

Early intervention using rofecoxib alone, rizatriptan alone and combination of rizatriptan and rofecoxib in acute migraine

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Objective Early pain-free state and sustained pain-free without recurrence or need for rescue medications are the most desirable treatment outcomes in acute migraine. Objectives were to investigate the efficacy of 25 mg rofecoxib alone, 10 mg rizatriptan alone and combination of 10 mg rizatriptan and 25 mg rofecoxib in achieving pain-free state at 1 and 2 h, and sustained pain-free from 2 to 24 h when the medications were administered early in the attack.

Materials and methods Seventy-four patients with the diagnosis of migraine (IHS 1.1 and 1.2) between the ages of 20 and 64 were selected. A total of nine attacks of migraine were to be treated by each patient, rofecoxib alone for three consecutive attacks, rizatriptan alone for three and combination of rofecoxib and rizatriptan for three, randomly allotted and crossed-over. Patients were instructed to take medication as soon as possible at the onset of headache.

Results Sixty-one patients completed the study treating 549 attacks, 545 mild, 51 moderate and 4 severe. Thirteen patients discontinued the study because of intolerance to medications. A pain-free state for 1 h occurred in 14% of attacks with rofecoxib alone, 45% with rizatriptan and 48% with combination (P<0.01 rofecoxib vs rizatriptan and rofecoxib vs combination; NS for rizatriptan vs combination). 2 h pain-free was found in 35%, 69% and 72%, respectively (P<0.001 for rofecoxib vs rizatriptan and rofecoxib vs combination; NS for rizatriptan vs combination). Sustained pain-free periods of 2–24 h occurred in 26% with rofecoxib alone, 60% with rizatriptan alone and 67% with combination (P<0.001 for rofecoxib vs rizatriptan and rofecoxib vs combination; P<0.01 for rizatriptan vs combination). Adverse events for rofecoxib included skin rash, gastric irritation, nausea, oedema and drowsiness. Rizatriptan AEs included dizziness, lightheadedness, drowsiness and lethargy. Combination did not appear to increase AEs.

Conclusion (1) Early intervention during migraine attacks results in better pain-free state and sustained pain-free response compared to the response reported in conventional clinical trials. (2) Rofecoxib alone is efficacious in migraine, but pain-free efficacy and sustained pain-free of rizatriptan is significantly superior. (3) Combination of rofecoxib and rizatriptan yields better sustained pain-free response indicating continued effect and reduced recurrence of headaches with the combination.

P2-K46

Rizatriptan vs rizatriptan combined with rofecoxib for the acute treatment of migraine

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Background and objectives Rizatriptan is an effective and fast acting drug for the acute treatment of migraine. Some non-steroidal anti-inflammatory drugs (NSAID) have also demonstrated effectiveness to treat migraine attacks and the combination of a triptan and a NSAID seems to decrease recurrence. Rofecoxib is a new class of NSAID known as a selective inhibitor of the enzyme COX-2. The aim of this study is to compare rizatriptan and rizatriptan plus rofecoxib in the acute treatment of migraine.

Material and methods 56 triptan naive patients, 37 women and 19 men, ages 16–55 years (mean 35 years), from a tertiary private center, with migraine according to IHS criteria were prospectively studied. The patients were divided randomly into 2 groups. Group 1 (28 patients, 18 women and 10 men) had to treat 3 consecutive moderate or severe attacks with 10 mg rizatriptan. Group 2 (28 patients, 19 women and 9 men) had to treat 3 consecutive moderate or severe attacks with 10 mg rizatriptan plus 25 mg rofecoxib. The presence of headache and nausea after 1, 2 and 4 h, as well as side-effects, rescue medication consumption after 4 h and recurrence were compared.

Results Group 1 treated 76 attacks and group 2 treated 81 attacks. Nausea was present in 55 attacks of group 1 and in 53 attacks of group 2. Absence of headache after 1 h was obtained in 19 patients (25%) of group 1 and in 34 (42%) of group 2 (P=0.082); after 2 h in 60.5% of the patients in group 1 and in 76.5% of group 2 (P=0.115). After 4 h, 75% of the patients of group 1 and 87.6% of group 2 were pain free (P=0.122). With regard to nausea and after 1, 2 and 4 h, respectively, groups 1 and 2 were nausea free in 30.9% and 49.1% (P=0.091); 74.6% and 79.2% (P=0.736) and 81.8% and 90.6% (P=0.479) of the patients. Recurrence based on all attacks of those patients pain free after 4 h was observed in 52.6% of group 1 and in 19.7% of group 2 (P<0.001). There were no differences with regard to side-effects and rescue medication consumption after 4 h in between the groups.

Conclusions Even though there was a trend for the combination group to have a higher response rate, it was not statistically significant. The difference in recurrence rates,
however, was highly significant between the two groups but we have to recall the limitations of an open study. This study demonstrated that combining a fast acting triptan such as rizatriptan and rofecoxib reduces recurrence, is well tolerated and may be more effective than the single use of a triptan. Controlled studies are necessary to confirm these observations.

P2-K47
Migraine treatment with rizatriptan: effects on work loss in naturalistic setting
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Objective To evaluate the impact of migraine treatment with rizatriptan on work absenteeism and productivity in naturalistic settings.

Background Rizatriptan is a 5-HT1B/1D receptor agonist indicated for the acute treatment of migraine. The impact of treatment with rizatriptan on work loss and productivity has not been previously evaluated in a non-trial setting.

Design Migraineurs enrolled in a prospective study reported their rizatriptan treatment experiences (tablet or orally disintegrating tablet, both 10 mg) via an interactive voice response system within about 24 h post attack. Patients reported whether they missed a partial or whole workday during the last attack and whether they returned to usual activities 2 h post dose. They also indicated the level of difficulty in performing work-related tasks 2 h post-treatment. Similar information was collected at baseline regarding their most recent attack while patients were still using their previous medications. McNemar’s test was used to compare their work-related outcomes at follow-up vs their prior experiences reported at baseline.

Results A total of 687 migraineurs reported that their migraine attacks coincided with a scheduled workday both at the baseline and follow-up. Compared with prior experiences, employees treated with rizatriptan reported a significant reduction in missing a partial or whole workday from 54% to 32% ($P<0.01$) during the corresponding attacks. Moreover, a significant increase in return to their normal activities 2 h post-treatment was reported by patients after using rizatriptan (56%) vs their prior medications (37%; $P<0.01$). Similarly, patients reported a significant reduction in the level of difficulty in performing work-related tasks 2 h post-treatment compared with their experiences reported at baseline ($P<0.01$).

Conclusions Migraineurs treated with rizatriptan reported a significant reduction in migraine-related workday loss and less difficulty performing work-related tasks compared to their experiences with their previous medications.

P2-K48
Frovatriptan: preliminary efficacy in the early treatment of migraine attacks
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Background and objectives: Efficacy trials of triptans have concentrated on initiating treatment at the moderate or severe migraine headache stage. This has limitations in that it does not fully represent real life clinical practice where many patients take drug treatment at an earlier stage in the migraine attack when their headache pain is mild. Frovatriptan has been shown to be effective and have a long duration of action in the treatment of moderate or severe headache. Hence, it may also provide effective sustained relief of mild migraine headache.

Methods: In two long-term (6 and 12 months) open-label, safety studies of frovatriptan 2.5 mg, efficacy was assessed by patients recording time to meaningful relief (MR). This was a subjective assessment made when the patient felt that their entire migraine attack had resolved, including headache pain and all accompanying migraine symptoms. Kaplan Meier curves were constructed, and median time to MR was estimated by log rank analysis for mild, moderate and severe headache pain at time of first dose. Patients documented reasons for taking a second frovatriptan tablet at each attack. The percentage of attacks where the reason for taking a second tablet was ‘improved then worsened’ (i.e. recurrence) is presented in the table by initial headache severity.

Results: Approximately one quarter of attacks treated had initial mild headache pain. The majority of attacks treated had initial moderate headache pain. The results were consistent in each study and across multiple attacks. Median time to MR was related to initial headache severity but recurrence did not appear to be related to headache severity.

<table>
<thead>
<tr>
<th></th>
<th>Study 1 (12 months)</th>
<th>Study 2 (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of attacks*</td>
<td>13 882</td>
<td>4534</td>
</tr>
<tr>
<td>Mild</td>
<td>3655 (26%)</td>
<td>1046 (23%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7266 (52%)</td>
<td>2457 (54%)</td>
</tr>
<tr>
<td>Severe</td>
<td>2866 (21%)</td>
<td>993 (22%)</td>
</tr>
<tr>
<td>Median time to MR (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Mild</td>
<td>2.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Severe</td>
<td>6.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Recurrence rate (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Mild</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Moderate</td>
<td>15</td>
<td>19</td>
</tr>
<tr>
<td>Severe</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

*Includes attacks for which initial severity was recorded as none or missing.
Conclusion: Treatment of initial mild headache pain was associated with more rapid relief of migraine attacks. The low incidence of recurrence observed suggests that frovatriptan produced sustained headache relief irrespective of initial headache severity. These data support more formal study of the use of frovatriptan for the acute treatment of mild migraine headache.

P2-K49

Frovatriptan has no clinically significant interaction with fluvoxamine

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Objectives Frovatriptan is relatively resistant to metabolism, however, in vitro studies have shown that it is a substrate for (but not an inhibitor of) CYP1A2. Inhibitors of this isoenzyme could therefore reduce the metabolic clearance of frovatriptan in vivo. The potential for this to occur in clinical use was investigated in a study using the potent CYP1A2 inhibitor fluvoxamine and including females using the combined oral contraceptive pill (COC) which also inhibits CYP1A2.

Methods The study was conducted in 8 males/8 female COC users and 8 female non-COC users using a crossover design with wash-out where frovatriptan 2.5 mg was administered orally either alone or on Day 8 of an 11-day treatment with fluvoxamine 100 mg daily. The extent of CYP1A2 inhibition achieved by fluvoxamine treatment was assessed by measuring the urinary caffeine metabolite ratio after administration of caffeine 100 mg. Blood concentrations of frovatriptan were measured, and vital signs, ECG and adverse event data collected predose, during the study and at 7 days after the final phase.

Results Frovatriptan 2.5 mg was well tolerated, and there were no safety concerns when administered alone or with fluvoxamine. The caffeine metabolic probe confirmed that CYP1A2 had been strongly inhibited by fluvoxamine, and as expected, this resulted in an increased systemic exposure (AUC(0–24 h)) to coadministered frovatriptan. Increases in frovatriptan AUC(0–24 h) administered with fluvoxamine were 39%, 41% and 28% for male COC users, female COC users and female non-COC users, respectively; corresponding increases in Cmax were 28%, 49% and 27%. The apparent t1/2 of frovatriptan was similar for all subject groups but was shorter when frovatriptan was coadministered with fluvoxamine (mean t1/2 ≈ 17 h) than when administered alone (mean t1/2 ≈ 24 h). Exposure to frovatriptan, as expected, was highest for female COC users (because of the dual inhibition of CYP1A2 by fluvoxamine and COC) and lowest for male subjects. The gender difference in AUC(0–24 h) was about 10–30% and was similar for each administration of frovatriptan. Values of Cmax were highest for female COC users but were similar between males and female non-COC users. Even in female COC users values of Cmax (range 4.68–12.7 ng/mL) were well below those measured in previous studies where frovatriptan 40 mg was well tolerated (mean Cmax ≈ 60 ng/mL).

Conclusion Co-administration of frovatriptan with fluvoxamine, or any other potent inhibitor of CYP1A2, is not considered to present any safety concerns or warrant dose adjustment, particularly in view of the broad therapeutic index for frovatriptan.

P2-K50

Meta-analysis of the efficacy of almotriptan for the treatment of acute migraine attacks

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Objective To conduct a meta-analysis of the efficacy of oral almotriptan for the treatment of acute migraine attacks.

Methods Results from 4 double-blind, randomized, placebo-controlled trials of oral almotriptan. All studies used a similar design, which included patients aged 18–65 years who satisfied IHS criteria for acute migraine. Patients were assigned to treatment with placebo or almotriptan 6.25, 12.5, or 25 mg. Pain relief was defined as a decrease in pain severity from moderate or severe at baseline to mild or no pain at 2 h. Pain-free was defined as a decrease in pain severity from moderate or severe at the time of medication administration to no pain at 2 h after drug administration. Therapeutic gain was the difference between active drug and placebo in proportion of patients achieving pain relief or pain free status. Efficacy data were pooled using standard fixed-effects meta-analysis techniques, logistic regression was used to assess dose–response effects, and a random effects model was used to estimate therapeutic gain.

Results A total of 2294 patients were included in the analysis. Pain relief at 2 h was achieved in 35.1% of placebo patients and 56%, 64%, and 66% of patients on almotriptan 6.25, 12.5, and 25 mg, respectively (P < 0.001). At 2 h, 13.9% of placebo-treated patients were pain-free compared with 26.7%, 36.4%, and 43.4% of patients on almotriptan 6.25, 12.5, and 25 mg, respectively (P < 0.001). Therapeutic gain for pain relief ranged from 23.5% to 27.6%, and for pain-free ranged from 14.8% to 27.7% with almotriptan 6.25, 12.5, and 25 mg doses (P < 0.05). The incidence of adverse events was 10.9% with placebo and 9.9%, 12.3%, and 19.5% with almotriptan 6.25, 12.5, and 25 mg, respectively (P < 0.05 for 25 mg vs placebo).

Conclusions Almotriptan significantly reduces pain associated with acute migraine attacks, and the optimal dose is 12.5 mg.
P2-K51
Beneficial effects of early intervention with almotriptan during long-term treatment of migraine
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Objective To evaluate the efficacy of oral almotriptan 12.5 mg administered early in an acute migraine attack on response, relapse, and use of rescue medication during long-term treatment.

Methods This was a 1-year open-label trial of 762 adult patients aged 18–65 years who met IHS criteria for acute migraine. Patients were instructed to treat as many consecutive attacks as possible of any severity during the 1-year study period. Almotriptan 12.5 mg was administered; if after 2 h migraine pain had not decreased to mild or no pain, rescue medication was allowed. A second dose of almotriptan was allowed for treatment relapse between 2 and 24 h. For this analysis, patients who had experienced at least 3 mild and 3 moderate attacks during the 1-year follow-up were selected. Endpoints were the proportion of patients pain-free at 1 and 2 h, use of rescue medication, incidence of relapse, and incidence of adverse events. Data were analysed with paired t-tests.

Results 118 patients were included in this analysis. At 1 h, 48% of mild attacks and 14% of moderate attacks were pain-free ($P<0.001$). At 2 h, 84% of mild attacks and 61% of moderate attacks were pain-free ($P<0.001$). Rescue medication was used in 8% of mild attacks and 12% of moderate or severe attacks ($P<0.01$). Relapse occurred in 28% of mild attacks and 33% of moderate or severe attacks ($P=0.01$). The incidence of adverse events was 6% for those experiencing mild attacks and 7% in those with moderate or severe attacks.

Conclusion Almotriptan 12.5 mg administered early in an acute migraine attack induced a more rapid onset of action, a reduction in the use of rescue medication, and a lower incidence of relapse vs delayed therapy.

P2-K52
Almotriptan increases pain-free status in acute migraine patients treated in placebo-controlled clinical trials
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Objective To assess the efficacy of oral almotriptan in effecting a pain-free state following treatment of acute migraine attacks.

Methods The effect of almotriptan on the proportion of patients achieving a pain-free state was evaluated in two phase III, randomized, double-blind, placebo-controlled trials (CL12, CL14). Patients aged 18–65 years who meet IHS criteria for acute migraine were studied. Patients were provided two doses of assigned medication and instructed to take one dose at the onset of a moderate to severe migraine headache. The second dose was to be taken if a relapse occurred. Pain-free was defined as the decrease in pain severity from moderate or severe at the time of medication administration to no pain at 0.5, 1, 1.5, and 2 h after drug administration. The intent-to-treat population was analysed using the Fisher exact test for comparisons between treatment groups.

Results 1791 patients were included in the analysis. Treatment groups were comparable for baseline demographic and clinical characteristics. The majority of patients were women. In the first trial (CL12), 11.6% of patients treated with almotriptan (12.5 mg) vs 2.5% treated with placebo were pain-free at 1 h ($P=0.016$). At 1.5 h, 26.8% of patients treated with almotriptan (12.5 mg) vs 8.8% treated with placebo ($P=0.001$) were pain-free and at 2 h, 38.4% treated with almotriptan vs 11.3% treated with placebo were pain-free ($P<0.001$). In study CL14, 23.8% of patients using almotriptan therapy (12.5 mg) vs 10.2% using placebo therapy ($P<0.001$) were pain-free at 1.5 h, and 39.2% using almotriptan therapy vs 15.3% using placebo therapy were pain-free ($P<0.001$) at 2 h. The proportion of patients who were pain-free at 2 h was also significantly ($P<0.05$) greater with almotriptan treatment (6.25 mg) than with placebo treatment.

Conclusion Compared with placebo, almotriptan treatment (12.5 mg) significantly increases the proportion of patients who are pain-free as early as 1 h, and consistently within 1.5 h, after a dose is administered during an acute migraine attack.

P2-K53
Almotriptan is effective for multiple migraine attacks
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Objective To evaluate the effectiveness of almotriptan for the consistency of response across multiple attacks in patients with acute migraine.

Methods This analysis was from a double-blind, randomized, placebo-controlled trial of almotriptan 6.25 or 12.5 mg. Patients aged 18–65 years meeting IHS criteria for migraine were studied. Patients were provided two doses of assigned medication and instructed to take one dose at the onset of a moderate to severe migraine headache. The second dose was to be taken if a relapse occurred. Pain relief was defined as a decrease in pain severity from moderate or severe to mild or no pain at 2 h. Pain-free was defined as a decrease in pain severity from moderate or severe at the time of medication administration to no pain at 2 h after drug administration. Sustained pain-free was defined as pain-free at 2 h without subsequent relapse between 2 and 24 h and without the use of escape medication. These endpoints were assessed after three successive migraine attacks. Comparisons between treatment groups were analysed using the Fisher exact test.
Results 906 patients were included in the analysis; no significant differences were noted between groups at baseline. For pain relief, both doses of almotriptan were significantly (P < 0.001) superior to placebo for all three attacks. Similarly, for pain-free, both doses of almotriptan were significantly (P < 0.001) superior to placebo at all three attacks. A sustained pain-free state was achieved in significantly (P < 0.01) more patients with almotriptan 12.5 mg than with placebo for all three attacks and with almotriptan 6.25 mg (P < 0.05) at the first and third attacks. Overall, 21.6% of patients experienced an adverse event during any attack with placebo, 21.1% with almotriptan 6.25 mg, and 25.7% with almotriptan 12.5 mg. However, by the third attack, only 6.9% and 6.3% of patients on almotriptan 6.25 and 12.5 mg, respectively, vs 5.3% on placebo, experienced adverse events.

Conclusion Almotriptan 12.5 mg maintained a consistent response across multiple migraine attacks that was significantly greater than with placebo.

P2-K54

Almotriptan significantly increases sustained pain-free outcomes in acute migraine: results from placebo-controlled trials

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Objective Assess the efficacy of almotriptan for the treatment of acute migraine using the proportion of sustained pain-free patients as the outcome measure.

Methods The effect of almotriptan on the proportion of patients achieving a sustained pain-free state was evaluated from three randomized, double-blind, placebo-controlled trials. Two trials evaluated almotriptan 6.25 and 12.5 mg, and one trial evaluated almotriptan 12.5 mg and sumatriptan 100 mg. Patients aged 18–65 years meeting IHS criteria for migraine were studied. Patients were provided two doses of assigned medication and instructed to take one dose at the onset of a moderate to severe migraine headache. The second dose was to be taken if a relapse occurred. Sustained pain-free was defined as a decrease in pain severity from moderate or severe at the time of medication administration to no pain at 2 h after drug administration without subsequent relapse between 2 and 24 h and without the use of escape medication. Data were analysed using the Fisher exact test for comparisons between treatment groups.

Results Of 1781 patients included in the analysis, 1078 (60.5%) had moderate pain and 703 (39.5%) had severe pain at baseline. In two placebo-controlled trials, the proportion of patients achieving a sustained pain-free state was significantly (P < 0.01) higher in both almotriptan 6.25 and 12.5 mg groups than with placebo. When stratified by moderate or severe pain at baseline, a sustained pain-free state was observed in significantly (P < 0.05) more patients receiving almotriptan 12.5 mg than with placebo. Overall, almotriptan 12.5 mg was comparable to sumatriptan 100 mg for the proportion of patients achieving sustained pain-free status.

Conclusion Almotriptan 12.5 mg was significantly more effective than placebo and comparable to sumatriptan 100 mg for the proportion of patients achieving sustained pain-free status.

P2-K55

Almotriptan reduces the incidence of migraine-associated symptoms: results from phase III trials

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Objective To determine the incidence of migraine-associated symptoms occurring during the treatment of acute migraine attacks in placebo-controlled phase III trials with oral almotriptan.

Methods The effect of almotriptan on migraine-associated symptoms was evaluated in patients aged 18–65 years with migraine meeting IHS criteria who were enrolled in three randomized, double-blind, placebo-controlled trials. Two trials evaluated the effects of almotriptan doses of 6.25 and 12.5 mg, and one trial evaluated the effects of an almotriptan dose of 12.5 mg and a sumatriptan dose of 100 mg. Patients were provided two doses of assigned medication and instructed to take one dose at the onset of a moderate to severe migraine headache. The second dose was to be taken if a relapse occurred. Migraine-associated symptoms were nausea, vomiting, photophobia, and phonophobia occurring at 2 h after administration of study medication. Data for migraine-associated symptoms from the first attack were analysed using the Fisher exact test for comparisons between treatment groups.

Results A total of 1773 patients were included in this analysis. At baseline, treatment groups were comparable for demographic and clinical characteristics. Approximately 85% of patients were women, and the mean age ranged from 39 to 43 years. In the two studies of almotriptan administration of 6.25 and 12.5 mg, both doses provided significant (P < 0.05) relief from nausea, photophobia, and phonophobia compared with placebo. A significant (P < 0.05) reduction in the incidence of vomiting was observed with an almotriptan dose of 6.25 mg in one of the two studies. Significant (P < 0.05) reductions vs placebo were observed for vomiting and phonophobia with an almotriptan dose of 12.5 mg and for photophobia and phonophobia with a sumatriptan dose of 100 mg.

Conclusion Almotriptan provided significant relief from migraine-associated symptoms of nausea, photophobia, and phonophobia at 2 h, compared with placebo.
P2-K56
Almotriptan demonstrated a consistent response across multiple migraine attacks during a 1-year trial
S. J. Tepper
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Objective To assess the effectiveness and consistency of response with almotriptan 12.5 mg for the acute treatment of multiple migraine attacks over a 1-year treatment period.

Methods This was a 1-year open-label trial. Patients between 18 and 65 years of age with a history of migraine satisfying IHS criteria with or without aura were included. Almotriptan 12.5 mg was provided to patients with the instructions to take a dose at the onset of an attack; if after 2 h migraine pain had not decreased to mild or no pain, escape medication was allowed. A second dose of almotriptan was allowed for treatment relapse between 2 and 24 h. Patients were instructed to treat as many consecutive attacks as possible of any severity during the study period. Consistency of response was assessed by comparing the total number of attacks resolved (pain relief at 2 h) vs pain relief at 2 h for the first and last attacks. The proportion of patients achieving pain relief for the first, fifth, 15th, and 30th attacks was assessed.

Results 762 patients who experienced a mean of 18 attacks were included in the analysis. Overall, pain relief was achieved for 84.2% of attacks. For the first and last attacks, pain relief was achieved for 74.4% and 75.5% of attacks, respectively. Pain relief at 2 h was achieved in at least 80% of attacks by 61.8% of patients. In the overall population, pain relief was achieved in 74%, 80%, 86%, and 91% of patients for the first, fifth, 15th, and 30th attacks. Among patients who treated 30 or more attacks (n=97), pain relief for at least 60% of attacks was attained by 93.8% of patients.

Conclusion Almotriptan 12.5 mg demonstrated a consistent effectiveness for treating acute migraine across multiple attacks occurring during a 1-year trial.

P2-K57
Safety and tolerability of almotriptan for the treatment of acute migraine attacks: pooled analysis of clinical trials
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Objective To evaluate the safety and tolerability of oral almotriptan in the treatment of acute migraine from short-term, controlled phase II and III clinical studies.

Methods Data from 5 short-term, placebo- or active-controlled trials of oral almotriptan were pooled to assess safety and tolerability. Included in the analysis were extent of exposure, demographic and baseline characteristics, adverse events, laboratory assessments, vital signs, and ECG findings. For this analysis, data were included from studies using placebo, almotriptan 6.25, 12.5, and 25 mg, and sumatriptan 50 mg.

Results A total of 3195 patients were included in this analysis. Over 75% of patients received one dose of placebo or study medication, and the remainder received two doses. At baseline, the median age of patients was 41–42 years, over 85% were women, approximately 20% were using oral contraceptives, and approximately 20% were using migraine prophylaxis. No patient discontinued prematurely from these studies. The most common adverse events were of the digestive and nervous systems including diarrhea, nausea, dizziness, paresthesia, somnolence, and vertigo. At least 1 adverse event was experienced by 12.4% of patients on placebo; 14.0%, 15.4%, and 20.4% on almotriptan 6.25, 12.5, and 25 mg, respectively; and 19.4% on sumatriptan 50 mg. The incidence of drug-related adverse events was highest with almotriptan 25 mg (18.3%), followed by sumatriptan 50 mg (15.5%) as compared with 9.6% with placebo and 11.2% and 10.7% with almotriptan 6.25 and 12.5 mg, respectively. Severe adverse events occurred in 2.1% of patients on placebo; in 1.3%, 1.8%, and 2.1% of patients on almotriptan 6.25, 12.5, and 25 mg, respectively; and in 2.9% of patients on sumatriptan 50 mg. No clinically meaningful changes in laboratory assessments, vital signs, or ECGs were observed in any treatment group.

Conclusion This analysis indicates that oral almotriptan 6.25 and 12.5 mg and sumatriptan 50 mg are safe and well tolerated for the treatment of acute migraine, although the incidence of adverse events was higher with sumatriptan 50 mg.

P2-K58
Almotriptan reduces the use of rescue medication in acute migraine treatment: results from phase III, randomized, double-blind, placebo-controlled studies
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Objective To evaluate the effect of oral almotriptan on the use of rescue medication from phase III, randomized, double-blind, placebo-controlled studies of almotriptan for the treatment of acute migraine headache.

Methods The effect of almotriptan on the use of rescue medication was evaluated from three randomized, double-blind, placebo-controlled studies of almotriptan for the treatment of acute migraine headache. Two trials evaluated almotriptan 6.25 and 12.5 mg and one comparator study evaluated almotriptan 12.5 mg vs sumatriptan 100 mg. Patients aged 18–65 years with migraine with or without aura according to IHS criteria were enrolled in the studies. They were provided with two doses of study medication and instructed to take one dose for treatment of acute migraine headache of moderate or severe pain intensity. The second dose was to be taken if recurrence of moderate or severe pain occurred after reduction to mild or no pain at 2 h after treatment. The use of rescue medication was defined as intake...
of medication for relief of pain 2–24 h after taking study medication. The intent-to-treat population was analysed using the Fisher exact test for comparisons between treatments.

**Results** 1777 patients were included in the analysis. Overall, the use of rescue medication was significantly lower with both almotriptan 6.25 and 12.5 mg, as compared with placebo (P < 0.05). No significant differences were noted between the almotriptan 12.5 mg and sumatriptan 100 mg groups. When patients with moderate baseline pain intensity were considered, the use of rescue medication was significantly lower in the almotriptan 6.25 and 12.5 mg groups, as compared with placebo (P < 0.05), and equivalent to that of sumatriptan 100 mg. In the patients with severe baseline pain intensity, significant differences were observed for the almotriptan 6.25 and 12.5 mg groups vs placebo in two studies. In the third study, non-significant differences were observed between almotriptan 12.5 mg and sumatriptan 100 mg and placebo.

**Conclusion** Oral almotriptan 6.25 and 12.5 mg significantly reduce the use of rescue medication, as compared with placebo, in patients treating acute migraine headache of moderate or severe pain intensity.

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**P2-K59**

**Effects of almotriptan vs sumatriptan on satisfaction, functional status, and quality of life in patients with acute migraine**

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**Objective** To compare treatment satisfaction, functional status, and health-related quality of life (HRQoL) associated with almotriptan and sumatriptan use in a double-blind, randomized study of acute migraine treatment.

**Methods** Patients aged 18–65 years satisfying IHS criteria for acute migraine were randomly assigned to double-blind treatment with oral almotriptan 12.5 mg or sumatriptan 50 mg for moderate to severe headache. Treatment satisfaction and satisfaction with side-effects were evaluated at 48 h post onset of migraine. Functional status was assessed by analysing the change in the ability to perform normal activities during the acute migraine attack. HRQoL was assessed at 24 h with the Migraine Quality of Life Questionnaire (MqoLQ) domains of work functioning, social functioning, energy/vitality, feelings/concerns, and symptoms. All study endpoints were assessed with a 48-h migraine diary maintained by patients.

**Results** A total of 1255 patients were enrolled and 1173 were included in the analyses. The two treatment groups were comparable at baseline. Almotriptan and sumatriptan groups were comparable on satisfaction with pain relief. However, the almotriptan group was significantly (P = 0.016) less bothered by side-effects. Improvements in functional status at 24 h and HRQoL were comparable in almotriptan and sumatriptan groups.

**Conclusion** Almotriptan-treated patients were less bothered by side-effects and had similar improvements in functional status and HRQoL compared with sumatriptan-treated patients.

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**P2-K60**

**Concomitant eletriptan and selective serotonin reuptake inhibitor therapy for migraine patients: a review of seven clinical studies**

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**Objective** To evaluate the tolerability of eletriptan when given concomitantly with selective serotonin reuptake inhibitors (i.e. SSRIs; citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) through a retrospective review of seven clinical studies.

**Background** A review of seven double-blind, randomized, placebo-controlled eletriptan studies identified 253 patients who concomitantly received eletriptan and an SSRI, compared with 3908 patients who received eletriptan alone.

**Methods** Through the retrospective analysis, a comparison of the adverse events in the two subgroups (patients on eletriptan and an SSRI and patients on eletriptan alone) was made.

**Results** Treatment-related adverse events ≥5% for eletriptan with vs without SSRIs included asthenia (4% vs 6%), dizziness, and somnolence (6% vs 5%), for each. All-causality adverse events ≥5% for eletriptan with vs without SSRIs included asthenia (4% vs 8%), nausea (6% vs 7%), dizziness (7% vs 6%), and somnolence (8% vs 6%). None of the patients on eletriptan plus an SSRI or those on eletriptan alone had a treatment-related serious adverse event.

**Conclusion** The concomitant administration of eletriptan and SSRIs did not show any clinically significant differences with respect to the incidence of adverse events. The concomitant administration of eletriptan and SSRIs was well tolerated in these seven studies.

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**P2-K61**

**Improvement in migraine-specific quality of life with eletriptan (Relpax®) vs Cafergot®**

P. A. Funk Orsini & R. J. Miceli

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**Objective** Results from a previous study show that oral eletriptan was well tolerated and more effective than Cafergot (2 mg ergotamine tartrate, 200 mg caffeine) for the acute treatment of migraine (1). The current study was an analysis of health-related quality of life (QoL) data, collected as part of the previous study. The aim of this study was to compare the impact of eletriptan (40 mg and 80 mg) and Cafergot on migraine-specific QoL during an acute migraine attack.
**Methods** The analysis was based on patients who received eletriptan 40 mg ($n=194$), eletriptan 80 mg ($n=196$), or Cafergot ($n=185$) as the first dose to treat an acute migraine attack in a double-blind, randomized, placebo-controlled parallel group trial. Patients completed the 24-h Migraine Quality of Life Questionnaire© (24-h MQoLQ) 24 h after initiating treatment.

**Results** Compared with Cafergot, patients receiving eletriptan 80 mg had significantly better scores ($P<0.05$) on all five domains of the 24-h MQoLQ: energy, feelings/concerns, social functioning, symptoms, and work functioning. Patients receiving eletriptan 40 mg reported significantly better scores ($P<0.05$) than those receiving Cafergot on energy, social functioning, and symptoms, with a trend toward significance on feelings/concerns and work functioning ($P<0.10$).

**Conclusions** In this study, oral eletriptan showed statistically significant improvement in migraine-specific QoL compared with Cafergot. These findings reflect the superior efficacy of eletriptan, as well as its overall tolerability (1).

**Reference**

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**P2-K62**

**Comparison of the impact of eletriptan (Relpax®) and sumatriptan on migraine-specific quality of life**

P. A. Funk Orsini & R. J. Miceli

*Outcomes Research, Pfizer Pharmaceuticals Group, New York, NY, USA*

**Objective** In a previous study, oral eletriptan was well tolerated and superior to oral sumatriptan at relieving the symptoms of an acute migraine attack (1). The current study focused on health-related quality of life (QoL) data, collected as part of the former study. The aim of this study was to compare the impact of eletriptan, sumatriptan, and placebo on health-related QoL during an acute migraine attack.

**Methods** The analysis was based on patients who took placebo ($n=79$), eletriptan 40 mg ($n=163$), eletriptan 80 mg ($n=155$), sumatriptan 50 mg ($n=169$), or sumatriptan 100 mg ($n=152$) as their first dose to treat an acute migraine attack in a double-blind, randomized, placebo-controlled parallel group trial. Patients completed the 24-h Migraine Quality of Life Questionnaire© (24-h MQoLQ) 24 h after initiating treatment.

**Results** Patients taking either 40 mg or 80 mg of eletriptan had significantly better scores ($P<0.01$) than placebo on all five domains of the 24-h MQoLQ: energy, feelings/concerns, social functioning, symptoms, and work functioning. Although patients taking sumatriptan 50 mg also reported significantly better scores than placebo patients ($P<0.01$) across all domains, sumatriptan 100 mg patients reported significantly better scores ($P<0.05$) on three domains and trended toward significance ($P<0.10$) on the remaining two. In comparing active treatments, patients taking eletriptan 80 mg reported significantly better scores ($P<0.05$) across all domains than patients taking sumatriptan 100 mg. Similarly, patients taking eletriptan 40 mg had significantly better scores ($P<0.05$) than those taking sumatriptan 100 mg on all but one domain (feelings/concerns). There were no statistically significant differences between either dose of eletriptan and sumatriptan 50 mg. However, MQoLQ scores were more favorable across all domains with eletriptan (40 mg and 80 mg) than sumatriptan 50 mg, trending toward significance on two domains with eletriptan 80 mg ($P<0.10$).

**Conclusions** In this study, eletriptan was significantly superior to placebo in improving migraine-specific QoL. Moreover, the superiority of eletriptan over sumatriptan in terms of improving QoL is reflective of the significant advantage in efficacy provided by eletriptan (1).

**Reference**
POSTER SESSION II

L: Pharmacological and non-pharmacological migraine treatment

P2-L1

Intravenous valproate sodium in the treatment of intractable migraines in the headache clinic

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Objective
Valproate sodium is officially approved by the FDA for the prophylaxis treatment of migraine headaches. Recently, an intravenous form of this agent has been marketed and is primarily used for the acute treatment of seizures. As a treatment-intensive headache clinic, we use many intravenous agents to treat refractory migraines and other headaches. We decided to treat a cohort of patients with intractable migraines with intravenous valproate sodium, after they had failed other abortive therapy.

Background
Divalproex sodium is currently approved by the FDA for migraine prophylaxis. The availability of an intravenous preparation of the same medication might offer a rapid and unique treatment intervention for intractable migraines, particularly in a headache clinic setting.

Design/methods
78 patients were seen and treated in the clinic for refractory migraine that had not responded to the usual abortive therapies: 'triptans', DHE or opioids. After placement of an intravenous line, valproate sodium was given by IV push, 100 mg per 5 min. Patients self-rated their migraine severity on a 0–10 numeric rating scale (NRS).

Results
Our results in intractable migraine sufferers with intravenous valproate sodium showed a 86.6% decrease in migraine severity (patient-rated on a 0–10 NRS). The average dose of valproate sodium was 742 mg and the average time to best response was 50 min.

Conclusions
We conclude that intravenous valproate sodium is a highly effective abortive agent for intractable migraines treated in the setting of a headache clinic. Its use should expand our present armamentarium of rapidly acting agents for termination of ongoing migraine headaches. The exact mechanism of action by which valproate sodium achieves these dramatic results is not known, but may be via its agonist activity at GABA binding sites, via blockade of NMDA receptors or its ability to block sodium channels. Double-blind studies are warranted to replicate and extend the findings from this open-label study.

P2-L2

Comparison of intravenous valproate vs intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache

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Objective
This study was designed to investigate the use of intravenous sodium valproate (IV VPA) for the treatment of migraine headaches of significant duration.

Materials and methods
Patients (N=40) received either 500 mg IV VPA or 10 mg of intramuscular (IM) metoclopramide, followed by 1 mg IM dihydroergotamine (DHE). Patients rated severity of headache, and the presence or absence of nausea, photophobia, or phonophobia at baseline, 15, 30 and 45 min, and at 1, 2, and 4 h.

Results
IV VPA Group:
- 30% of patients reported headache relief (i.e. headache severity rating went from moderate or severe to none or mild) at 15 min, 45% at 30 min, 55% at 45 min, 50% at 1 h, 60% at 2 h, and 65% at 4 h.
- 75% had nausea at baseline, 40% at 15 min, 30% at 30 min, 25% at 45 min, 45% at 1 h, 40% at 2 h, and 45% at 4 h.
- 95% had phonophobia at baseline, 85% at 15 min, 80% at 30 min, 80% at 45 min, 75% at 1 h, 60% at 2 h, and 50% at 4 h.

DHE Group:
- 20% reported headache relief at 5 min, 40% at 30 min, 50% at 45 min, 50% at 1 h, 50% at 2 h, and 60% at 4 h.
- 60% had nausea at baseline, 60% at 15 min, 60% at 30 min, 60% at 45 min, 25% at 1 h, 30% at 2 h, and 30% at 4 h.
- 95% had phonophobia at 15 min, 90% at 30 min, 75% at 45 min, 55% at 1 h, 65% at 2 h, and 75% at 4 h.

In both groups, 100% had photophobia at baseline.

IV VPA Group:
- 85% had photophobia at 15 min, 90% at 30 min, 85% at 45 min, 70% at 1 h, 50% at 2 h, and 45% at 4 h.
- 95% had photophobia at 15 min, 90% at 30 min, 75% at 45 min, 75% at 1 h, 65% at 2 h, and 55% at 4 h.

DHE Group:
- 90% had photophobia at baseline, 80% at 15 min, 75% at 30 min, 80% at 45 min, 75% at 1 h, 50% at 2 h, and 50% at 4 h.

IV VPA-treated patients experienced drug-related side-effects, while 15% of DHE-treated patients experienced 1 or more episodes of nausea and diarrhea during the first 4 h of treatment.

Conclusions
IV VPA-treated patients showed a nearly 50% response rate at 30 min and displayed no side-effects. These results suggest IV VPA is a safe, effective, and well-tolerated treatment for patients with acute migraine headache.
P2-L3

Donepezil oral administration acutely relieves long lasting menstrual migraine attacks

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Introduction A relevance of central cholinergic system in controlling noiceptive pain has been already shown. We here suggest that acetylcholine pain controlling system might have a role also in primary pain, where also migraine (M) is included. Pain relieving action of donepezil, a second generation anticholinesterase, has been evaluated in M attacks without aura that occur during menstrual periods. M attacks have to last more than 1 day and need more than 1/day acute treatment. The study was performed on 29 females (mean age 34.8 ± 3.5SD) healthy except for 60%, mean 74.8%) with the single use

Design of the study Crossed comparison. After 1 month run-in, eligibility was determined according to: (i) duration of M attacks, (ii) M attacks during menses and the 3 days immediately following or preceding the event, (iii) more than 1 dose/day of drug for the acute treatment of M for more than 2 subsequent days. Volunteers have effectiveness of a triptan choice (1 tablet, oral route) with donepezil (15 mg, oral route). None of the volunteers was using prophylactic therapy for at least 6 months, and none was already known to be refractory to the chosen triptan or donepezil. Entry criteria Patients exempt from any systemic illness, normal vital parameters, no significant ECG abnormalities, no clinically relevant abnormality of routine blood and urine tests, no sign of psychiatric illness, no pregnant or lactating women. Because of the chosen oral route, we excluded patients with attacks associated with vomiting or severe nausea. Treatment period was 2 months to allow a retest of both the types of drugs. Both the triptan and donepezil had to be taken at the very onset of the M pain. Rescue treatment intake was free and was to be indicated in the diary patients had to fill in during the entire period of the comparison, which led to the following results: donepezil and triptans were similar in providing relief of pain. Time to relief was quicker for triptans ($P < 0.0001$). Relapse in the same or following days was significantly minor ($P < 0.0001$) following donepezil. Rescue treatments were significantly minor ($P < 0.0001$) following donepezil administration. Note-worthy donepezil, at the dose of 15 mg, oral route, was well tolerated, when acutely given during M attacks. In fact, it gave rise to mild nausea only in 1 female (21 years). Adverse experience or changes in vital signs or examinations were never reported. The exception was a transitory decrease in heart beat frequency (from 75 to 68 and from 80 to 74 beat/min) in 2 patients having a basal frequency over 70. The data support the crucial role of acetylcholine in analgesia even in case of primary pain.

P2-L4

A randomized double-blind crossover placebo-controlled study of nimesulide in the treatment of migraine attacks

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Aim of the study The evaluation of the efficacy and safety of nimesulide in the treatment of migraine attacks.

Patients and methods Thirty-five migraineurs with or without aura according the I.H.S. criteria, with previous headache history at least 1 year before and 1 attack in the last 3 months, were enrolled in the study. Informed consent was obtained from each patient. Exclusion criteria were medical history of peptic ulcer, bleeding, anticoagulant treatment, hypertension, cardiac disease and chronic abuse headache. The study is a randomized double-blind comparative of nimesulide 100 mg crossover placebo. The primary endpoint was the frequency and severity of headache and secondary endpoints were the associated symptoms, the all day living activity, as well as the possible adverse events of the treatment. All patients have managed 4 attacks with nimesulide or placebo.

Results Thirty-one migraineurs completed the study. Four patients dropped out due to severe epigastric pain and nausea. The percentage of response to the treatment differed between nimesulide and placebo group and was higher in nimesulide group. The headache intensity and duration were significantly reduced with nimesulide compared to placebo. There was a good tolerability of nimesulide supporting the use of this drug for the migraine attack.

P2-L5

Dexamethasone decreases migraine recurrence after treatment with a triptan combined with a non-steroidal anti-inflammatory drug

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Background and objectives Triptans are effective drugs for acute treatment of migraine. However, an average 30–40% of treated patients present recurrence, requiring a further dose. Non-steroidal anti-inflammatory drugs (NSAID) combined with sumatriptan have demonstrated efficacy in reducing recurrence rate observed with the use of this drug alone. Steroids, specifically dexamethasone also have been suggested to treat refractory migraine and Status migrainosus. The aim of this study was to evaluate whether patients presenting frequent recurrence even with the combination triptan plus NSAID would have a lower recurrence rate with the addition of 4 mg PO of dexamethasone.

Patients and methods 23 patients, 17 women and 6 men with migraine were prospectively studied. All patients presented frequent recurrence ($\geq 60\%$, mean 74.8%) with the single use.
Recurrence may occur with all acute treatments.

Conclusions

Attacks (mean 23.2%). Eminent recurrence in 3 out of the 6 attacks (50%) while the study, 11 took rizatriptan plus rofecoxib, 4 rizatriptan plus tolfenamic acid, and the 20 patients taking single tablet of 4 mg of dexamethasone. All patients took oral formulations and none did not fill out the diary properly and 1 woman took the drug who were completely helpless when confronted with it. A similar development has now appeared in publications about the daily use of naratriptan, where its providers appear to be equally helpless. We conclude that (1) the use of ergotamine drugs cannot be completely discontinued since a sizeable minority of migraine patients do not respond to triptans but respond to ergotamines, often to the extent that they remain headache free for years; and (2) that simplifications of current clinical observations are dangerous since the predominant underestimation of ergot misuse and abuse has its revival with the triptans.

P2-L6

On the limited survival of ergotamines after the triptan revolution, with inferences concerning the use, the misuse and abuse of triptans

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After the advent of the triptans with their numerous advantages when compared to the ergot preparations used in migraine attacks, the ergot drugs were often considered as obsolete or antediluvian, from before the flood (of triptans). Some authors explicitly declined to mention positive results concerning ergot drugs gained from triptan–ergot–placebo studies, and older placebo controlled studies on ergotamines were rejected since they had been done before the publication of the 1988 IHS classification, and were therefore considered worthless, despite the fact that ergotamine was the first headache drug, and one of the first drugs at all, to be systematically compared with placebo (Traube, 1926). There were some attempts to insist on the use of parenteral dihydroergotamine but leading opinions increasingly rejected the use of ergotamines altogether. However, patients often insisted on the ergot drugs they had been using for decades, and not rarely, misusing for daily prophylaxis. This paper describes a group of patients from the Zurich Migraine Clinic who insisted on their ergot drug despite our offers to replace them by triptans. A minority had been taking an ergot preparation as a daily prophylactic. One subgroup needed increasing doses of ergot, and had to switch to triptan overuse or decide to undergo withdrawal without replacement by triptans. Another subgroup had succeeded to avoid headache and migraine attacks for several to many years by using less than 1 mg ergotamine tartrate per day. This development had not been foreseen by the providers of the drug who were completely helpless when confronted with it. A similar development has now appeared in publications about the daily use of naratriptan, where its providers appear to be equally helpless. We conclude that (1) the use of ergotamine drugs cannot be completely discontinued since a sizeable minority of migraine patients do not respond to triptans but respond to ergotamines, often to the extent that they remain headache free for years; and (2) that simplifications of current clinical observations are dangerous since the predominant underestimation of ergot misuse and abuse has its revival with the triptans.

P2-L7

The effect of flumazenil and oxygen on migraine with prolonged aura

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Background and objective

GABAergic mechanisms have been implicated in the pathogenesis of migraine. The benzodiazepine (BZ) receptor is a site at the GABAa receptor–chloride channel complex. Moreover O2 administration is effective in some primary headache forms. The aim of this study was to assess the efficacy of flumazenil, a BZ antagonist, and O2 for the acute treatment of an attack of migraine with prolonged aura under EEG monitoring.

Material and methods

We studied a 52-year-old female suffering from migraine with prolonged aura since the age of 11 years. Attacks are characterized by right or left hemiparesis and hemiparesthesias, also involving the hemiface and hemitongue, and usually lasting 1–3 days. Occasionally she reported dysphasia and altered mental state. A throbbing headache, with photophobia, nausea and vomiting, developed together with the aura symptoms. Intercital neurological examination and cerebral MR were normal. We monitored, by means of scalp EEG, a spontaneous migraine attack with right hemiparesis, aphasia and depressed mental state. A 33% glucose i.v. infusion was given to the patient and after 30 min a first dose of 0.2 mg of flumazenil i.v. was infused. A second and a third dose of 0.1 mg were administered at 4 and 6 min from the first, respectively. Finally, 2 min after the last dose, O2 was administered for 5 min via a non-rebreathing mask at a flow rate of 8–10 L/min.
P2-L8

Non-pharmacological therapy in the treatment of tension-type headache (TTHA) and coexisting migraine with TTHA

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Non-pharmacological therapy in the form of a home video was tested on 70 patients, meeting the International Headache Society criteria to TTHA or coexisting migraine with TTHA. Patients completed initial questionnaires relating to their headache severity, frequency, duration and consumption of over-the-counter (OTC) medications. Patients were asked to follow the 25-min home video that included relaxation techniques, diaphragmatic breathing, stretching, cervical range of motion and self-massage, once a day for a 30-day period. Patients then completed follow-up questionnaires and subjective evaluations. A paired t-test was used to determine if there was a significant decrease in the mean scores in the variables measured at baseline and one month after therapy. Results of the statistical data revealed a 26.7% reduction in the severity of headache pain and a 33.4% reduction in headache frequency. There was a 37% reduction in headache duration and a 43.8% reduction in the consumption of OTC medications. All statistical data were significant with a P-value of < 0.0001 and 95% confidence interval for the mean difference. Subjectively, 16 patients rated the video ‘very effective’ (22.9%) and 45 patients rated the video ‘moderately effective’ (64.3%). 7 patients felt the video was ‘not effective’ (10%), and 2 patients could ‘not tolerate’ the video (2.9%). We conclude that non-pharmacological therapy in the form of a home video is an effective adjunctive therapy in the treatment of TTHA and coexisting migraine with TTHA.

P2-L9

Pharmacokinetics of liquid forms of ibuprofen, and their efficacy in the acute treatment of migraines in adults and children

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Objectives (1) To compare the pharmacokinetics of ibuprofen liquigels, suspension, and tablets; and (2) to evaluate the efficacy and safety of ibuprofen liquigels and suspension in the acute treatment of migraines.

Methods Pharmacokinetic study: Randomized, open-label, single-dose, crossover design. Following a 10-h fast, 29 subjects ≥ 18 years of age received a single 400 mg dose of the assigned dose form. Blood was drawn up to 16 h later, and plasma samples were assayed for racemic ibuprofen using HPLC. Efficacy studies: All studies were randomized, double-blind, placebo-controlled, and parallel in design, and evaluated migraines with moderate to severe pain. The primary end point was cumulative percentage of responders (pain reduced from moderate/severe to none/mild) at 2 h. 'Adult' trials: In two pooled trials, a total of 1118 subjects 12–72 years of age with migraines according to IHS criteria received a single 400 or 600 mg dose of ibuprofen liquigels or matching placebo. Pain intensity and relief were rated over 8 h. Paediatric trial: A total of 84 subjects 6–12 years of age with paediatric migraines (IHS-R criteria) received a single 7.5 mg/kg dose of ibuprofen suspension or matching placebo. Pain intensity was rated over 4 h.

Results Results for the different forms of ibuprofen are summarized in the table. Statistical significance (P = 0.05) is indicated by an asterisk (*). In the ‘adult’ migraine trials, adverse events (AEs) were comparable across all treatments. No AEs were reported in the paediatric study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liquigel (n = 29)</th>
<th>Suspension (n = 29)</th>
<th>Tablet (n = 29)</th>
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<tr>
<td>AUCinf (µg h/mL)</td>
<td>136</td>
<td>137</td>
<td>141</td>
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<tr>
<td>Cmax (µg/mL)</td>
<td>48*</td>
<td>43*</td>
<td>38</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>0.70*</td>
<td>0.81*</td>
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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liquigel 600 mg (n = 413)</th>
<th>Liquigel 400 mg (n = 399)</th>
<th>Placebo (n = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative % responders, 2 h</td>
<td>65*</td>
<td>64*</td>
<td>47</td>
</tr>
<tr>
<td>% sustained responders, 2–8 h</td>
<td>53*</td>
<td>52*</td>
<td>34</td>
</tr>
<tr>
<td>Cumulative % with no pain, 2 h</td>
<td>23*</td>
<td>21*</td>
<td>12</td>
</tr>
<tr>
<td>% with recurrence, 8–24 h</td>
<td>23</td>
<td>26</td>
<td>24</td>
</tr>
</tbody>
</table>
Conclusions These results demonstrate that liquid forms of ibuprofen are absorbed faster than a solid tablet, and that ibuprofen liquid gels and suspension are effective and well tolerated in the treatment of migraines in adults and children, respectively. The faster absorption of a liquid form is particularly desirable during a migraine, since gastric stasis occurs, further delaying the disintegration and absorption of a solid tablet.

P2-L10
A comparative study of acetaminophen, aspirin, and caffeine vs ibuprofen in the acute treatment of migraine
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Background This study compared acetaminophen 500 mg, aspirin 500 mg, and caffeine 130 mg (AAC) with ibuprofen tablets 400 mg (IB) and placebo in the acute treatment of migraine.

Methods This was a multicenter, double-blind, randomized, single-dose, double-dummy, parallel group design. The primary efficacy endpoint was sum of pain relief (TOTPAR) at 2 h; other endpoints included TOTPAR at 4 h, sum of pain intensity difference from baseline (SPID), headache response (HR), pain free (PF), and onset of meaningful relief. Subjects met International Headache Society diagnostic criteria for migraine with or without aura and had 1–6 attacks monthly over the previous year; patients with disability and vomiting were not excluded.

Eligible subjects were randomized in a 3:3:1 ratio to treat a moderate or severe attack with a two-tablet dose of AAC (n = 665), IB (n = 665), or placebo (n = 224). Subjects rated pain intensity, pain relief, and functional disability, as well as nausea, vomiting, photophobia, and phonophobia at baseline, 15, 30, 45, 60, 90, 120, 180, and 240 min. Time to onset of meaningful relief was assessed with a stopwatch.

Results Demographic, migraine history, and baseline characteristics of the treated headache were similar in the AAC, IB, and placebo groups. For TOTPAR, AAC was significantly better than IB (P < 0.03) and placebo (P < 0.01) at 2 h and remained significantly superior to IB (P < 0.01) and placebo (P < 0.004) through 4 h. For SPID, AAC was significantly better than IB and placebo at 2 and 4 h. At 3 h significantly more AAC subjects were PF than IB or placebo subjects. HR rates were numerically superior for AAC subjects over IB subjects at all timepoints but they did not reach statistical significance; AAC significantly separated from placebo at 2, 3, and 4 h. Median time to onset of meaningful relief was 20 min earlier for AAC than IB subjects; both were significantly faster than placebo. Significantly fewer AAC subjects required rescue medication than IB and placebo subjects. Although more AAC subjects than IB subjects reported gastrointestinal and nervous system adverse experiences, both active treatments were well tolerated.

Conclusion AAC provided significantly superior overall analgesic efficacy and faster onset of meaningful pain relief than IB tablets or placebo in the relief of acute migraine attacks.

P2-L11
Examining family and marital issues in recurrent headache syndromes
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Introduction There is increasing interest in family factors related to chronic pain including both the impact of the family environment on the behaviour of the patient and the impact of pain on the family. The chronic pain literature indicates that family factors can contribute to the maintenance or remediation of pain disorders, and that the impact of pain on the family can be significant. This study examined the impact of headache on the family, as well as the relationship of family context factors and spouse responses on the psychological status, headache, and physical symptoms of patients with recurrent headache.

Method Subjects were 49 headache patients who presented for treatment of migraine or tension-type headache and their spouses (patients: 83% female, M age 41.3 years, range 22–60; spouses M age 42.8 years, range 25–67; 90% Caucasian, 10% African American). 75% of patients and 68% of spouses received education beyond high school, and annual income was > US$20,000 for 78% of the families. Patients and spouses completed the Family Environment Scale (FES), the Wabler Physical Symptoms Inventory, the Beck Depression Inventory, and the Spielberger State-Trait Personality Inventory (anger/anxiety). Spouses also provided ratings of their characteristic responses to the patient’s pain behaviours in 3 categories: Solicitous, Avoidant, and Angry.

Results Unlike findings with other chronic pain populations, few spouses of headache patients experienced significant
psychological or physical symptoms (e.g. only 17% of spouses in the mild and 2% in the moderate depression range). Spouses' symptoms were uncorrelated with patients' symptoms. Reportedly family adjustment (FES scores) more closely resembled normal than distressed families. Family context variables were significantly associated with patient psychological and physical symptoms. Spouse reports of their responses to patient headaches were strongly correlated with the level of patient headache symptoms – less frequent solicitous responses and more frequent anger and avoidance from spouses were associated with more severe patient headaches. The latter finding appears contrary to research with other chronic pain patient populations demonstrating that more 'solicitous' and less 'punishing' spouse responses are associated with greater pain intensity and pain behaviour. 

Conclusions These results suggest family context and spousal responses to pain were significantly associated with patient symptoms. Furthermore, the effects of social factors on the behaviour of persons with headache are dissimilar from the effect of these factors on the behaviour of persons with other pain disorders.

P2-L12

Treatment of vascular headache by stellate ganglion irradiation with super laser and its effect on transcranial Doppler

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Objective To observe the results of treatment of vascular headache by stellate ganglion irradiation with Super Laser (SL) and its effect on intracranial arterial blood flow assessed by transcranial Doppler (TCD) examination.

Methods 40 cases of vascular headache were treated by bilateral stellate ganglion irradiation with SL and 11 intracranial major arteries were detected with TCD before and after radiation.

Results There was a significant effect of SL irradiation on the symptom of headache (complete relief 60%, effective 92.5%) and slowdown of blood flow in 9 out of 11 major arteries. Suppression on intracranial vasospasm lowered vascular resistance and the velocity of blood flow returned to normal. The change was significant or very significant \((P < 0.05-0.01)\) compared with that before treatment.

Conclusion The headache can be cured or relieved by stellate ganglion irradiation with SL. The therapy was especially effective for plexiform aggregation headache and menstrual vascular headache.

P2-L13

May local cold application rival usual acute anti-migraine drug care?

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Objectives According to patients’ desires, efficient acute migraine treatment should abort pain and other symptoms quickly and completely. Subjects try to reduce discomfort in many ways, and local cold application is one of the most popular procedures in this context. Nevertheless, there are as yet comparatively few studies on local cold for migraine treatment. The objective of this study is to evaluate the effect of a cold bandage in the forehead as compared to usual drug care in acute migraine treatment.

Subjects and methods Sixteen IHS migraine with and without aura female patients (38.6 ± 10.8-year-old, min 19, max 60) were divided in two groups. Group A treated the first two consecutive attacks with usual remedies not influenced by the investigators and the following two with a cold bandage (CB) applied in the frontal and temporal regions. Group B treated also four consecutive migraine attacks, but cold was applied in the first two. Subjects recorded data immediately before treatment and at the following 30, 60 and 120 min. The parameters recorded were pain intensity (4 point scale), capacity to function and work (4 point scale), nausea, vomiting, photo- and phonophobia. Values are presented as percentage of treated attacks.

Results As usual care (UC) subjects took ergotamine, triptans, and common analgesics alone or in various combinations. Among attacks with pain intensity 2 or 3 just prior to treatment pain reduction to levels 1 or 0 occurred at time points 30, 60 and 120 min, respectively, 11.5, 26.9 and 50% of attacks treated with UC as compared to 24, 36 and 40% of attacks treated with CB. For the pain-free end point values were 0, 7.6 and 19% (UC); and 0, 12 and 20% (CB). Concerning improvement of work capacity (reduction to levels 1 or 0) and reestablishment of full functioning (reduction to level 0), values were virtually the same at 30 and 60 min, but usual care tended to be better at the 120 point. Nausea also tended to be reduced quicker in the UC group, as photo and phonophobia were equally affected. All but one subject considered using cold for acute treatment in the future. However 15 out of 16 patients took drugs as escape medications after the cold application. No adverse event was recorded during this study.

Conclusions Low temperature seems to act faster than usual treatment, especially within the first hour. Cold application for migraine control, a comparatively cheaper and friendly approach, may be used either alone or together with an effective drug to speed up the response and improve quality of life.

Acknowledgement The authors acknowledge CRYOMED for cold bandage supply.

© Blackwell Science Ltd Cephalalgia, 2001, 21, 433–439
Effectiveness of biofeedback in the treatment of migraine and tension-type headache

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Objective To assess the effectiveness of biofeedback in the treatment of migraine and tension-type headache.

Background Biofeedback is a technique that assists patients in developing an awareness of the manner in which they respond subjectively to external stimuli. Patients become directly involved in their treatment and learn to acquire a degree of voluntary control over physiologic functions that have a demonstrable effect on the genesis of a particular problem. Multiple published studies have suggested that biofeedback techniques are effective in reducing the frequency and intensity of headaches and often allow patients to decrease their dependence on medication. With ever increasing limitation of funds available for medical care it is imperative that treatment modalities have proven efficacy in scientific studies to ensure that money is not needlessly wasted.

Design and methods Sixty-four patients were entered into our single-blind study. Patients were over the age of 18, suffered from migraine and/or tension-type headache and were referred to the Harvard Vanguard Pain Program, a modified day treatment programme for chronic pain of non-neoplastic origin. The programme emphasizes education and training in pain theory. Pain management methods include group therapy encounters, movement therapy, relaxation training and individual sessions with a pain clinician. From the Pain Program patients were chosen at random to receive biofeedback in addition to the basic Pain Program. Biofeedback training consisted of 10 sessions utilizing standard EMG and temperature control techniques under the direction of a psychologist. Thirty-three patients were entered into the biofeedback plus Pain Program group, 21 into the Pain Program alone and 11 patients served as controls having completed neither biofeedback nor the Pain Program. All patients answered periodic questionnaires for 36 months.

Results Patients who completed the Pain Program alone showed a statistically significant decrease in the frequency and severity of the headaches in the first 12 months that continued to 36 months. Biofeedback provided no additional benefit. Patients reported a subjective improvement in their condition after completing biofeedback training, however, there was no objective data to substantiate their perception. The number of medications used by patients and utilization of medical care decreased in all groups over 36 months suggesting a regression to the mean.

Conclusions Biofeedback is an extremely costly and time consuming treatment modality that provides no objective benefit in the treatment of migraine and tension-type headache in adults.
P3-M1

Influence of study design on placebo or verum response in migraine trials

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Objectives The aim of this analysis was to investigate whether the design of a clinical trial had any influence on placebo response or the efficacy of the tested drug in migraine trials. One hypothesis was that poorly designed studies would have a higher placebo rate and a high efficacy of the drug being tested, while studies being conducted in accordance with the IHS recommendations of clinical trials in migraine would result in low placebo and verum numbers.

Materials and methods Some 200 hundred studies (100 each in prophylactic and acute treatment of migraine) were published between 1976 and 1998 in major journals in the headache field, such as Cephalalgia and Headache, as well as journals of anaesthesiology and general medicine. The studies were given a score depending on their quality. Criteria which influenced the score were double-blind, prospective, placebo-controlled, multicentre, n > 50, and quality of centre). Studies which used IHS criteria as endpoints of efficacy got a higher score than studies which used Glaxo criteria or other criteria such as patient preference or rescue medication. The highest possible score was 18 points. We also observed whether the route of administration had any influence on the outcome.

Results The quality of the study design had no influence on either placebo or verum response. The route of application had no influence either. Looking at verum response of Triptans, Ergots and Analgesics in acute trials Triptans showed a higher efficacy than other medication but the same placebo response occurred.

Conclusion Migraine is a disease with a high intra individual and interindividual course which influences the outcome of clinical studies. Placebo response can be seen in every single trial in migraine and pain studies and tends to be around 30–40%. Tfelt-Hansen published his concept of net gain (Verum-placebo) in 1997; our analysis showed that study design has no influence on net gain either. Maybe the concept of a single score does not fully integrate all different factors which influence both verum and placebo rates in a special disease like migraine. Further work is necessary to investigate the influence of design in migraine trials.
Reference

P3-M3
Placebo prohibition: a crucial criterion for future studies design
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During September 1998–September 2000, we performed assays in samples of general population (age 18–59). Subjects were asked their opinion about the use of placebos in studies for the evaluation of new drugs’ potency. Self-administered questionnaires were filled out by 1043 general population subjects. The sample included representative subgroup of 4 population bands: Band A = 287 subjects who are well off; Band B = 251 subjects who live in dignified way; Band C = 302 subjects who are near to misery threshold; Band D = 203 subjects who are under the misery threshold. Subjects included in a single band were matched for sex. Bands were matched for sex and age. Indicated subjects fill the following questionnaire that was preceded by a clear description of what placebo is and what its role is in therapeutic gain.

**First question** ‘Do you think you gave your consent to a placebo controlled study?’ Allowed answers were: (1) Yes, I think I will participate; (2) I think I will participate in case I suffer a specific disease that I can herein indicate (for instance cancer or metabolism problems or something now am unable to indicate below); (3) I think I will never participate; (4) I do not know. The questionnaire also included a second group of questions with two possible answers: yes or no. (a) I will participate in a comparison between two drugs which are considered to be active in my disease. (b) I will never participate in any study comparing different drugs because, certainly, one is known to be better for me.

**First question** All the subjects aged 21–48 answered ‘No’, independently of the band they appertain to (n = 591). ‘Yes I think I will participate’ was the answer of 135 subjects all included in Bands C and D, independently of age and sex. The remaining subjects answered ‘I do not know’. Less than half of the investigated subjects agreed to the hypothesis of participating in a comparison with the exception of 502 subjects (aged 27–49) equitably distributed in the first 3 bands. No significant difference was found regarding sex distribution. These subjects hypothesize that one of the administered compounds is previously clearly known to be more effective than the other. Thus, they only have been eligible for open studies. Finally, new generations seem not to agree in defining a placebo comparison ethical or acceptable. Moreover, the outcome is that a placebo controlled study will include only a part of the population. That can affect either results regarding actual ‘pharmacological gain’ or adverse effects. Thus, the results will not mirror what would happen in general practice. To better consider problems of placebo administration seems mandatory for future study designs.

P3-M4
Comparison of triptan efficacy: examination of response ratios and therapeutic gain
P. Winner
*Director, Palm Beach Headache Center, West Palm Beach, FL, USA*

**Objective** Review of triptan efficacy to establish (a) whether the response ratio (RR) is a useful measure of triptan effect, and (b) its relationship to therapeutic gain (TG).

**Background** Comparisons of triptan efficacy are complicated by differences in study design and patient populations. As the efficacy end points are subjective, assessing active response (AR) is highly dependent on placebo response (PR). TG (= AR−PR) has been used to offset placebo variability in attempts to compare triptans. However, TG is additive and is directly affected by both AR and PR. In order to address this problem, a factorial approach can be used, finding RR (= AR/PR).

**Methods** The placebo-controlled pivotal studies of triptans either on the market, or for which draft labelling is available, were used to provide the standard regulatory parameter

<table>
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<tr>
<th>Drug</th>
<th>2 h response</th>
<th>4 h response</th>
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<tbody>
<tr>
<td>Sumatriptan 50 mg</td>
<td>27 (22–37)</td>
<td>34 (30–38)</td>
</tr>
<tr>
<td>Sumatriptan 100 mg</td>
<td>32 (24–40)</td>
<td>43 (33–55)</td>
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<tr>
<td>Rizatriptan 10 mg</td>
<td>32 (23–37)</td>
<td>26 (11–38)</td>
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<tr>
<td>Zolmitriptan 2.5 mg</td>
<td>29 (24–35)</td>
<td>38 (33–43)</td>
</tr>
<tr>
<td>Naratriptan 2.5 mg</td>
<td>22 (10–32)</td>
<td>34 (33–46)</td>
</tr>
<tr>
<td>Frovatriptan 2.5 mg</td>
<td>17 (13–19)</td>
<td>29 (26–35)</td>
</tr>
</tbody>
</table>

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(pain score 3.2–0.1) at 2 and 4 h postdose. The mean and range of TG and RR for each drug were calculated.

**Results** Mean RR showed an overlap between triptans for both the 2 and 4 h timepoints, with typical magnitude about 2-fold higher than placebo (see table on previous page). In general, the range for TG was broader than for RR. Mean TG correlated with mean RR (R=0.9 and 0.71 for 2-h and 4-h data, respectively).

**Conclusion** Triptans have an approximate 2-fold magnitude of effect on headache response compared to placebo. There was a reasonable correlation between RR and TG. RR provides another useful measure of effect when attempting to compare triptans.

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### P3-M5

**The pharmaceutical presentation and its preference by the patient as a variable in drug treatment of migraine**

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**Objective** To investigate which pharmaceutical presentation is preferred by the migraine patient and why.

**Material and methods** A representative sample (N=101) of migraine patients treating with drugs, stratified by age and sex. A standardised questionnaire was used. Interviews were conducted via telephone by experienced interviewers. The following items were investigated: (1) preference of solid or liquid forms; (2) evaluation of different pharmaceutical presentations (tablet, capsule, drops, syrup/suspension, effervescent tablet, effervescent granules, injection, suppository) on a 6 grade scale (1 = excellent, 6 = unsatisfactory); and (3) reasons on judgement.


**Discussion** Overall tablets are the preferred form of migraine drugs. However, all presentations have users which rank them highest. Migraine drugs should therefore be offered in a broad range of different presentations to cover individual preferences. Oral solid forms should always be part of such a range. If, for clinical or pharmaceutical reasons, no oral solid form can be offered, an accompanying patient education program to stress the advantages of the chosen form should be planned.

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### P3-M6

**The aggregation and analysis of the Sumatriptan Naratriptan Aggregate Patient (SNAP) database**

C. Barrows, W. Saunders, S. R. Austin, G. Putnam & H. Mansbach

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**Objective** Aggregate and analyse data from GlaxoSmithKline sumatriptan and naratriptan clinical trials.

**Background** The Sumatriptan Naratriptan Aggregate Patient (SNAP) database consists of data from 128 sumatriptan and naratriptan clinical trials conducted from 1987 to 1998 that have been combined to provide an extensive data set for exploratory analysis. We present the tasks and challenges involved in aggregating, validating, and analysing these data.

**Methods** SAS® programs were written to collect data into a standard structure in one location. Independent reviewers performed validation of the aggregation. To explore these data, recursive partitioning and regression analysis procedures were used. Recursive partitioning (using data mining software) was used to identify important variables and significant splits in the observed aggregate data. Regression analysis was used to model the response rates based on multiple independent variables, including patient characteristics and baseline attack characteristics. An advisory team, the SNAP Database Study Group (H-C Diener, M Ferrari, P Goadsby, RB Lipton, KMA Welch, SR Austin, C Barrows, H Mansbach, G Putnam and W Saunders), provided critical clinical and statistical input to the project.

**Results** The final database consists of data from more than 49,000 patients, including components for demographics, study treatment, baseline attack characteristics, efficacy, adverse events, concurrent and rescue medications, premature study withdrawals, and vital signs. Studies of the efficacy and safety of sumatriptan and naratriptan taken for acute migraine account for the majority of the data. Challenges in the aggregation phase included the following: retrieving the data from various computer platforms, finding the necessary documentation, determining a standard structure for the aggregate database, standardizing data from a variety of designs and collection methods, and maintaining quality control. Exploratory analyses have been performed for
Therapeutic gain and therapeutic ratio for estimating triptan efficacy in the acute treatment of migraine

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²President, EBD Group, Carlsbad, CA, USA

Objective Comparison of therapeutic gain (TG) and therapeutic ratio (TR) in pivotal clinical trials of triptans when used for acute therapy of migraine.

Background Head-to-head clinical trials are the optimum way to compare active therapies. Nonetheless, meta-analyses are often performed across different clinical trials due to the practical impossibility of comparing all therapeutic permutations of drug and dose size in a scientifically perfect manner. Meta-analyses can use active treatment response rates (ARR). However, this is an era of fluctuating placebo response rate (PRR), and adjustments to ARR are usually needed. Therapeutic gain (TG = ARR – PRR) is the increment of patients who benefit because therapy was active rather than placebo. Since ARR and PRR are themselves fractions, this subtraction requires an assumption that their denominators are the same. In crossover studies, the patient population is the same for each treatment, and this is a valid subtraction (1). In parallel-group studies, the denominators represent different patient subsets. The therapeutic ratio (TR = ARR/PRR) is the increment in probability that a patient will benefit from active rather than placebo therapy. The division of one fraction by another does not require shared denominators.

Methods Data from all pivotal studies in US product labelling (approved or draft) were tabulated. TG and TR were found using the standard headache response rates (pain score 2 or 3 at dosing, positive end point being a score of 1 or 0 at 2 h) in each study; all were parallel-group, placebo-controlled designs. Active drugs were (number of clinical trials) almotriptan (n = 2), naratriptan (n = 2), rizatriptan (n = 6), sumatriptan (all formulations, n = 24), and zolmitriptan (n = 8).

Results TG and TR were correlated (R = 0.85, t = 10.4, P < 0.001; for 1 and 43 degrees of freedom, F = 108, P < 0.001). The largest deviations from the correlation were clinical trials with relatively high values of TG and TR (i.e. relatively high ARR or low PRR).

Conclusions For comparisons across multiple parallel-group studies, and when there is a need to correct for PRR, there is no advantage of using TG over TR. Since the latter is mathematically sound in both crossover and parallel-group studies, it is to be preferred.

Reference

are consistent in 345 of 500 cases examined (69%). In the same patients in the 10 centres participating in the study.

Results
The diagnoses carried out using the computerized chart were also analysed. Given by the computerized case chart for the same patients discrepancies between the diagnoses of clinicians and those given by the computerized case chart and those reported by clinical chart information. Errors in the diagnosis or the use of diagnostic categories not included in IHS. Diagnoses could not be given using the computerized chart in 103 cases (20.6%) due to the lack of one or more data needed for formulating a correct diagnosis according to IHS criteria. Moreover, the diagnoses carried out using the computerized chart were not in agreement with those made by the clinicians in 41 cases (8.2%) due to the incorrect interpretation by the clinicians of the patients’ clinical charts. Only in 2.2% of cases (n=11) were the misdiagnoses due to program errors, which were promptly corrected.

Conclusions
The present study shows an incorrect application of IHS criteria for the diagnosis of primary headaches in almost one-third of patients attending headache centres. This can be easily overcome using a computerized case chart based exclusively on the current IHS criteria even if the diagnosis remains to be done by the clinician. The use of this computerized tool need not be limited to improving clinical accuracy in daily practice, but can also be extended to studies investigating the effectiveness of symptomatic and prophylactic drugs for primary headaches, to be sure that patients are selected according to the above criteria.

References

P3-M9
Application of IHS classification in headache centres in Italy: results using a computerized IHS-based diagnostic chart
V. Gallai, P. Sarchielli, A. Alberti, C. Rossi, E. Cittadini & Italian Collaborative Group for the Application of IHS Criteria

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Background
Although current IHS Criteria have been widely accepted for clinical practice and research, their real application in specialized headache structures has been poorly investigated.

Materials and methods
We developed a computerized structured chart based exclusively on the requirements needed for the diagnosis of primary headaches according to the operational IHS classification system. We applied the computerized IHS-based chart for testing the diagnosis of 500 patients attending 10 headache centres in Italy (50 randomly chosen patients from each centre) who were judged by the clinicians as being affected by primary headaches based on clinical chart information. The concordance among diagnoses given by the computerized case chart and those reported by clinicians in the clinical charts was calculated. The causes of discrepancies between the diagnoses of clinicians and those given by the computerized case chart for the same patients were also analysed.

Results
The diagnoses carried out using the computerized case chart and those reported in the clinical charts of the same patients in the 10 centres participating in the study are consistent in 345 of 500 cases examined (69%). In the remaining 155 cases, the diagnoses made with the computerized case chart and those reported in the clinical charts were discordant. In 144 cases (28.8%) this was due to missing information, errors in the diagnosis or the use of diagnostic categories not included in IHS. Diagnoses could not be given using the computerized chart in 103 cases (20.6%) due to the lack of one or more data needed for formulating a correct diagnosis according to IHS criteria. Moreover, the diagnoses carried out using the computerized chart were not in agreement with those made by the clinicians in 41 cases (8.2%) due to the incorrect interpretation by the clinicians of the patients’ clinical charts. Only in 2.2% of cases (n=11) were the misdiagnoses due to program errors, which were promptly corrected.

Conclusions
The present study shows an incorrect application of IHS criteria for the diagnosis of primary headaches in almost one-third of patients attending headache centres. This can be easily overcome using a computerized case chart based exclusively on the current IHS criteria even if the diagnosis remains to be done by the clinician. The use of this computerized tool need not be limited to improving clinical accuracy in daily practice, but can also be extended to studies investigating the effectiveness of symptomatic and prophylactic drugs for primary headaches, to be sure that patients are selected according to the above criteria.

P3-M10
A hand-held computer headache diary: an innovative method for the collection of data in a clinical trial of a migraine treatment intervention
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Objective
To evaluate the convenience and user-friendliness of the hand-held (Palm) computer headache diary for use in a randomized clinical trial.

Background
Hand-held computer technology offers the potential to improve the validity and reliability of headache information obtained via diary and provides a novel and interactive methodology for delivering adherence-related and other disease-management interventions. Advantages to data collection afforded by Palm computer technology include a reduced burden on the participant, collection of superior data quality, and the ability to monitor accurate time of all diary entries. These advantages suggest that this assessment methodology may be an optimal alternative to other assessment strategies. However, participants’ amenability to and level of comfort with this technology is largely unknown.

Methods
A pilot study was conducted to assess the user-friendliness of the palm diary and patient’s amenability to this mode of record-keeping. The study sample consisted of men and women attending a tertiary healthcare clinic for headache treatment. Participants who consented to participation were asked to maintain a daily record of their headache using the palm diary computer. Patients were provided personal training on the operation of the palm dairy prior to
beginning the palm diary trial. The average trial period of data collection using the palm diary was 3 weeks. After 3 weeks, participants completed a questionnaire eliciting both qualitative and quantitative feedback regarding their experiences with the palm diary.

**Results** Pilot testing of the palm diary revealed that participants took, on average, 1.7 min to complete the diary on days with no headache. On days with headache, the average completion time increased to M=3.8 min. Despite this increase, most participants indicated that they could complete the diaries in 'very little time.' Participants also completed a multi-item measure that used a 5-point Likert scale (1 = 'Very easy' to 5 = 'Difficult') to assess the user-friendliness of the palm diary (sample items: 'Using the stylus/pen' and 'Understanding error messages'). The mean rating on this user-friendliness scale was M=1.3 (range = 1.7–3.0). In general, participants indicated that most diary entries were fairly easy to complete; only one diary entry (i.e. 'impaired of activities') was perceived to be more difficult to accomplish.

**Conclusion** Pilot study findings suggest that, overall, participants had a positive experience with the palm diary and judged the diary program to be very convenient and easy to use.

**P3-M11**

Do we understand the migraine sufferer's perception of mild, moderate, and severe pain?

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**Objectives** Migraine patients are typically treated based on the level of pain they report. Thus, it is important that health care providers accurately interpret migraine sufferers’ descriptions of various levels of headache pain. The primary purpose of this study was to determine if health care professionals could accurately interpret the levels of pain reported by migraine sufferers based on their descriptions of mild, moderate, and severe pain. A secondary objective was to determine if health care professionals could more accurately identify pain intensity levels than those outside the healthcare field.

**Methods** Migraine sufferers (N=31) provided written descriptions of mild, moderate and severe pain associated with migraine. These responses were randomly arranged to create an 84-item questionnaire. Fifteen health care professionals and 25 non-health care providers were asked to rate each description based on the following scale: '1' if the statement describes mild pain; '2' if the statement describes moderate pain; and '3' if the statement describes severe pain. Ratings among the groups were compared using percentage agreement and independent samples t-tests.

**Results** The average percentage agreement between the 31 migraine sufferers and the sample was 60.28% (SD=12.63%) across all three pain levels. Males and females had equivalent levels of agreement (M = 58.39%, F = 61.08%) across all three pain levels. However, men did significantly better than females in identifying descriptions of mild pain (M = 66.37%, F = 54.51%, P < 0.05) and women did significantly better than men in identifying descriptions of severe pain (M = 58.33%, F = 76.06%, P < 0.1). Individuals that reported having migraines were not any better at rating the pain descriptions (55.48%) than those individuals who did not experience migraines (62.33%). Overall, non-health care providers were better at rating migraine sufferers’ pain (61.79%) than health care professionals (57.75%), although this difference was not significant. Health care professionals were significantly worse at identifying migraine sufferers’ descriptions of severe pain (61.43%) than non-health care providers (76.33%, P < 0.1).

**Conclusions** Health care professionals appear to have difficulty accurately interpreting migraine sufferers’ descriptions of various levels of headache pain, especially at the severe pain level. Males appear better able to recognize descriptions of mild pain whereas females appear better able to recognize descriptions of severe pain. Future studies are needed to identify whether such misinterpretations contribute to the under-treatment of migraine pain.

**P3-M12**

Comparison of visual analogue scale and categorical ratings of headache pain in a large clinical trial

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**Objective** The 4-grade scale (4GS; ‘no headache’, ‘mild pain’, ‘moderate pain’, ‘severe pain’) is the standard instrument for evaluating treatment effects in clinical trials of new antimigraine drugs. A visual analogue scale (VAS) has also been used in some trials and intuitively would appear to allow for greater sensitivity for determining treatment effects, due to the greater range of possible scores (0–100 for a 100-mm VAS). We compared the 4GS and VAS in a clinical trial of the efficacy of rizatriptan 5 mg vs sumatriptan 50 mg.

**Methods** The 4GS and VAS were both administered at baseline and at 2 h after dosing in a randomized, double-blind, clinical trial involving 792 treated migraine patients who took oral rizatriptan 5 mg, sumatriptan 50 mg, or placebo for a moderate or severe headache. The VAS consisted of a 100-mm horizontal line with the words ‘No pain’ at the left end and ‘Unbearable pain’ at the right end; patients made a mark along the continuum corresponding to their current level of pain. The 4GS measure analysed was the percentage of patients with pain relief (reduction of pain to mild or none) at 2 h; this is typically the primary outcome measure in most treatment trials. Data were analysed using a logistic regression model. The VAS measure analysed was the change from baseline in VAS score (mm) at 2 h for each patient. Data were analysed by means of an ANOVA model.

**Results** More patients on rizatriptan 5 mg and sumatriptan 50 mg had pain relief at 2 h on the 4GS compared with
The 4GS may be the preferred assessment instrument in aVAS was associated with additional administrative burdens, for assessing treatment effects in clinical trials. Given that theConclusion

The 4GS and VAS appeared to be equally useful (was no significant difference between active treatments & placebo (63% and 67% vs 23%, P-values <0.001). There was no significant difference between active treatments (P=0.329). The mean changes from baseline in headache pain on the VAS were greater in the rizatriptan 5 mg and sumatriptan 50 mg groups compared with placebo (–29 mm and –31 mm vs –3 mm, P-values <0.001), and again there was no significant difference between active treatments (P=0.439).

Conclusion The 4GS and VAS appeared to be equally useful for assessing treatment effects in clinical trials. Given that the VAS was associated with additional administrative burdens, the 4GS may be the preferred assessment instrument in a clinical trial setting.

P3-M13

When does a difference make a difference in preference trials?

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Background When several drugs of one therapeutic class are available with comparable efficacy and tolerability data, a patient preference study can provide useful guidelines for drug selection. A preference study is a randomized crossover study comparing two or more treatments with patient preference as the primary outcome measure. Patients value treatments according to their expectations and life circumstances and when selecting a drug they will take efficacy, tolerability, formulation, and many other (unknown) factors into account. Patient preference is a balance of many factors including all traditional outcome measures. With the increasing availability of triptans for the acute treatment of migraine, there is a growing interest in preference studies. However, will the results of such a study really influence clinical decision making? Do doctors believe that patient preference does make a difference? If so, what is the minimal difference in patient preference between treatment A and B required to influence physicians in deciding which treatment to prescribe? When planning the sample size in a clinical trial it is necessary to know which difference is generally considered to be clinically relevant. We conducted a study among neurologists and general practitioners to identify the smallest clinically relevant difference.

Objective To identify the smallest clinically relevant difference in patient preference between two drugs for the acute treatment of migraine.

Methods We asked 100 general practitioners and 50 neurologists the following question:

Which minimal difference in preference in favour of drug A would you consider sufficiently clinically relevant to prescribe drug A first in a ‘new’ migraine patient rather than drug B? The clinicians could choose one of 5 options; (a) at least 10% in favour of drug A (e.g. 45% vs 35%), (b) at least 20%, (c) at least 30%, (d) at least 40%, or (e) a preference trial would not influence my choice.

Results Preliminary results among 49 neurologists are: (a) 16 (33%), (b) 13 (27%), (c) 11 (22%), (d) 4 (8%) and (e) 5 (10%). The study among 100 GPs will be completed by the end of March.

Conclusions The majority of the neurologists consider a difference of at least 20% to be clinically relevant and one-third even think that a difference of 10% is worth detecting in a patient preference study. The results of the completed study will be presented at the meeting.

P3-M14

Evaluation of headache intensity in migrainous patients with visual handicap through the tactile analogue scale (TAS)


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The tactile analogue scale (TAS) was elaborated to be used in blind subjects or those who cannot utilize vision during their crises. The objective of this study was to characterize from TAS the architecture of migraine attacks in subjects with visual disability. In this study, 11 migrainous subjects with visual disturbances (MVD) that started before the age of 14 years were studied, and 22 normal migrainous subjects (with normal vision) were used as a control group. All patients in the group studied showed visual acuity less than 20/200. The MVD study group was subdivided into two subgroups, according to their visual acuity: subgroup A (subnormal vision), and subgroup B (amaurotic individuals). In subgroup A, we evaluated 46 attacks with average intensity of 56.50 mm; in subgroup B, 45 attacks with average intensity of 59.58 mm; and in the control group, 92 attacks with average intensity of 49.88 mm. When subgroup B and the control group were compared, there was a significant statistical difference (P=0.022). Through these outcomes, we can observe that the migrainous subjects with no visual afferents show a higher pain intensity during the migraine crises compared with those subjects with no visual handicap. The study suggests that, as with other senses, total visual loss, before 14 years of age, can also interfere with the nociceptive control of pain.
POSTER SESSION III

N: Women’s issues

P3-N1

Prevalence of menstrually related migraine and non-migraine headaches in female students of Belgrade university

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Objectives To determine prevalence and characteristics of menstrually related migraine and non-migraine headaches in female students of Belgrade University.

Method The questionnaire was administered to female students at randomly selected classes of the School of Medicine and the School of Pharmacy. Migraine diagnosis was assigned using diagnostic criteria of the International Headache Society and MacGregor’s stricter definition of ‘menstrual migraine’.

Results Of 1943 female students (18–28 years old), 1298 (66.8%) had primary headaches. Among 1298 students with headache, 245 (12.6%) had migraine and 1053 (54.2%) had non-migraine headache. The prevalence rates of migraine and non-migraine headaches in defined relation to menstrual cycle as premenstrual, menstrual, menstrually associated, menstrually unchanged, menstrually unrelated were: 0.9%, 1.5%, 6.1%, 2.7% and 1.4%, respectively, for migraine, and 4.4%, 1.5%, 10.1%, 19.2% and 18.9%, respectively, for non-migraine headache. Female students with migraine had menstrually related attacks more frequently (67.7%) than students with non-migraine headaches (29.5%). The difference was the most prominent, approximately 4.5:1, among students with menstrual migraine (12.2%) compared to students with menstrual non-migraine headaches (2.7%). The exacerbation of migraine during menstruation was slightly more severe and more complex than exacerbation of non-migraine headaches. Female students with various migraines and non-migraine headaches did not differ significantly either in their average age or in average age of onset of menstruation and onset of migraine and non-migraine headaches. Female students with migraine significantly more frequently reported: positive family history for migraine (54.1%) and menstrual migraine (31.0%), severe attacks (35.9%), reduced working activity (95.1%) and aura (15.5%) compared to students with non-migraine headaches (23.8%, 18.7%, 9.2%, 78.4% and 2.2%, respectively). All associated symptoms were significantly more frequent in students with migraine than in those with non-migraine headaches. Various types of migraine did not differ by majority of symptoms. The associated symptoms were more frequently present in menstrually related than in menstrually unrelated non-migraine headaches.

Conclusion The results obtained suggest that women with migraine are more susceptible to the effects of fluctuations of female sex hormones than women with non-migraine headaches.

P3-N2

Abstract withdrawn

P3-N3

Heredity in menstrual migraine

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Background Menstrual migraine is defined as a migraine headache occurring regularly between days −2 to +3 of the menstrual cycle and at no other time. Women having an increased number of attacks around menstruation in addition to other attacks during the month, are defined as...
having menstrual-associated migraine. The primary trigger for migraine associated with the menstrual cycle is not known but appears to be hormonal changes, especially oestrogen withdrawal. The genetics of menstrual migraine have not been elucidated yet. Review of the literature revealed no data about the mode of inheritance in this subgroup of migraine patients. Specific mutations leading to an increased risk of rare forms of migraine have been identified in both mitochondrial DNA and a calcium channel gene. Migraine susceptibility locus was recently linked to the X chromosome. This study focuses on the hereditary patterns of menstrual migraine patients.

**Objective** To evaluate the hereditary patterns in women with menstrual-associated migraine.

**Methods** Records of female migraine patients from a tertiary headache clinic were reviewed and data related to their family history and perimenstrual headache occurrence was collected. The study population included 12 women with pure menstrual migraine, 19% women with menstrual-associated migraine (208 patients with menstrual-associated migraine overall), and, as the control group, 153 women without menstrual associated migraine.

**Results** Family history of migraine was more prevalent in family members of women with menstrual associated migraine – 84.1% vs. 65.4% in family members of patients without menstrual associated migraine ($P < 0.0001$). Maternal inheritance of migraine was found in 54.8% of menstrual associated migraine patients vs. 22.9% of the patients without menstrual-associated migraine ($P < 0.0001$). Paternal inheritance of migraine headaches was found in 13.5% of patients with menstrual-associated migraine compared with 34.6% of patients without menstrual-associated migraine ($P < 0.0001$). In the pure menstrual migraine group, maternal inheritance was found in 58%, whereas paternal inheritance was found only in 8% – a pattern similar to the group of patients with menstrual associated migraine.

**Conclusions** This study provides for the first time evidence that menstrual migraine might have a unique hereditary pattern. Our data implies that there is a maternal genetic component in menstrual migraine. Further research of the genetic basis of this subgroup of patients may help unravel the pathophysiology of menstrual migraine and development of novel therapeutic approaches.

**P3-N4**

Gynaecological health history of women with migraine or chronic tension-type headache compared with controls: more alike than different


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**Objective** To compare gynaecological health in women with migraine or chronic tension-type headache with controls.

**Background** Epidemiological and empirical research has linked migraine with hormonal changes associated with menarche, menstruation, pregnancy, and oral contraceptives. Hormonal fluctuations might play a role in chronic tension-type headache. Migraine and chronic headaches have been linked to gynaecological problems.

**Methods** Patients were 95 consecutive headache sufferers who presented to a neurologist’s office for headache management. Patients received IHS diagnoses of migraine ($n = 46$) or chronic tension-type headache ($n = 49$). Demographics and medical, gynaecological, and headache history were obtained from headache patients and a comparison group of women without headache problems ($n = 39$).

**Results** Participants ranged in age from 17 to 62 ($M = 36$ years). 88% were Caucasian, 6% were African American, and 6% were Other (4 Asian, 2 Hispanic, 1 Native American). Except for the premenstrual symptom of headache, every premenstrual symptom (e.g. breast tenderness, menstrual cramps, irritability, moodiness) was endorsed by a majority of women in each group, and there were no statistically significant differences between groups. Headaches occurred premenstrually in 91% of migraine patients, but in only 63% of CITH patients, and in only 7% of the controls. No statistically significant differences were found between groups in the occurrence of gynaecological problems, such as cervical dysplasia, endometriosis, ovarian cysts, or hysterectomy. Worsening of headaches at menarche was reported by patients in both headache groups, but not controls. There were no statistically significant differences between CTT patients and migraine groups with this variable. There were no statistically significant differences in any reported changes in headache activity associated with the use of oral contraceptives between groups. Migraine patients reported improvement in headache activity associated with pregnancy compared to controls, but there were no differences in changes in headache activity associated with pregnancy between CTT patients when compared to controls, or between CTT patients and migraine patients.

**Conclusions** Except for the association of headaches with menarche and menses among patients with migraine or chronic tension-type headache, and improvement in headaches during pregnancy reported by women with migraine, the gynaecological histories were more alike than different in this sample of 95 headache patients and 39 controls.

**P3-N5**

Adjusting oestradiol concentrations reduces headache frequency and severity in female migraineurs

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**Objective** To determine if hormonal strategies that reduce drops in endogenous or exogenous oestradiol can reduce headache frequency and severity.
Methods Twenty-seven consecutive adult women presenting with IHS migraine between January and June 2000 were considered. Exclusion criteria included pregnancy, lactation, and postmenopausal women already receiving steady (or no) hormonal therapy. One patient refused the protocol and is not included in the data. Sixteen (61.5%) of the 26 women had migraine plus chronic daily headache (CDHA defined as equal to or greater than 15 days of headache/month). Headache frequency and severity were assessed at baseline and 2–4 months later. A weighted headache score for the preceding 30 days was tabulated with days of mild headache pain scored as ‘1’, moderate as ‘2’, and severe ‘3’. Patients with CDHA received naratriptan 2.5 mg daily for 7 days and then 2.5 mg every other day for 3 doses, while all analgesics and decongestants were stopped. Hormonal strategies were tailored to comorbidities, and a variety were employed to minimize drops in oestriadiol.

Results With improvement arbitrarily defined as equal to or greater than a 50% decrease from baseline in weighted headache score, 20 (76.9%) of the women improved. Their average improvement was 80.8%. Among the subset of CDHA patients, 12 (75%) improved; their average improvement was 88.5%. Ten of the 11 women not receiving hormonal therapy. One patient refused the protocol and is not included in the data. Sixteen (61.5%) of the 26 women had migraine plus chronic daily headache (CDHA defined as equal to or greater than 15 days of headache/month). Headache frequency and severity were assessed at baseline and 2–4 months later. A weighted headache score for the preceding 30 days was tabulated with days of mild headache pain scored as ‘1’, moderate as ‘2’, and severe ‘3’. Patients with CDHA received naratriptan 2.5 mg daily for 7 days and then 2.5 mg every other day for 3 doses, while all analgesics and decongestants were stopped. Hormonal strategies were tailored to comorbidities, and a variety were employed to minimize drops in oestriadiol.

Conclusions Hormonal strategies that reduce drops in oestradiol are associated with improved migraine management and benefit the female migraineur.

P3-N6
Prevention of migraine in the pill-free week of combined oral contraceptives using natural oestrogen supplements: a double-blind placebo-controlled study

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Objectives The aim of this study was to determine whether migraine occurring during the pill-free interval of combined oral contraceptives could be prevented by the use of natural oestrogen supplements during the pill-free interval.

Materials and methods Fourteen women completed the double-blind placebo-controlled randomized crossover study for four pill cycles (two using placebo and two using active 50 µg oestradiol patches [Evorel®]).

Results Complete data were available for 12 women and data were available for two cycles for one woman. One woman withdrew consent before treatment. With respect to the number of days where the women had migraine during the pill-free interval, there was a suggestion that when the women were using 50 µg oestrogen patches, they had fewer days of migraine than when they were using placebo (median difference −0.5 days, 95% confidence interval −2.0, 1.5), but the results were not statistically significantly different (P=0.55). The overall severity of migraine was assessed using a weighted difference score which suggested that women using oestrogen tended to have less severe migraine but the difference was not statistically significantly different (mean score −1.0, P=0.67, median score −1.0, P=0.53).

Conclusions Because so few women were recruited to the study, no firm conclusions can be based on the results since no associations were statistically significant. However, the suggestions that come from the analysis of the results are that use of 50 µg oestrogen patches during the pill-free week of combined oral contraceptives reduce the frequency and severity of migraine at that time. This study should be repeated with larger numbers of women and a higher dose of oestrogen.

P3-N7
The role of gonadotropin-releasing hormone (GnRH) agonists with oestrogen add-back therapy in migraine prevention

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Objectives (1) To determine if the administration of a GnRH agonist with or without oestrogen add-back therapy will reduce the severity or disability of headache in female migraineurs when compared to a placebo run-in phase. (2) To ascertain whether the addition of oestrogen to GnRH therapy will lead to an improvement or worsening of headache severity and disability.

Methods Consecutive female patients evaluated at the Cincinnati Headache Center were eligible if they (1) were 21–45 years of age, (2) had a diagnosis of migraine with or without aura, (3) had regular menstrual periods, and (4) reported moderate to severe headaches on three or more days during the non-perimenstrual period. Subjects recorded headache severity on a 0–10 visual analogue scale and disability scores on a 0–5 scale three times per day in a headache diary throughout the length of the study. After a placebo run-in period of 2.5 months, a medical menopause was induced for the remaining 3 months of the study by administration of goserelin, a GnRH agonist. 1 month after administration of the goserelin, patients were randomized into either a GnRH/oestriadiol group or a GnRH/placebo group. The GnRH/oestriadiol group received a 100-µg oestriadiol patch and the GnRH/placebo group received a matching placebo patch. The primary efficacy measures were the mean daily severity score (MDSS) and the mean daily disability score (MDDS). A general linear model analysis of variance was used for the statistical analysis.

Results Twenty-one patients completed the study; nine in the GnRH/oestriadiol group and 12 in the GnRH/placebo group. There was a significant treatment group/study period interaction noted in both the severity and disability analyses (P=0.001 for both severity and disability). After adjustment for pretreatment (placebo run-in) scores, the average daily severity and disability were significantly lower in the GnRH/oestriadiol group compared to placebo (P=0.04 and P=0.03, respectively). The overall severity and disability scores were 38% and 42% lower in the GnRH/oestriadiol group compared to placebo, respectively. The results were not significantly different when comparing the GnRH/placebo group to placebo.
Conclusions (1) The GnRH/oestradiol group demonstrated improvement in their severity and disability scores in the treatment phase when compared with the placebo run-in phase while the GnRH/placebo group demonstrated no improvement. (2) Daily headache severity and disability scores were found to be significantly lower in the GnRH/oestradiol group as compared to the GnRH/placebo group suggesting a preventative role for oestrogen replacement therapy in this study.

P3-N8

Brain infarction after postcoital contraception in a migraine patient

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Objective A temporal relationship between migrainous stroke and emergency postcoital contraception has not been described. We report on the case of a young female suffering from an ischaemic stroke 2 days after taking the postcoital contraception.

Clinical case This 22-year-old woman with a personal history of menstrual migraine with and without aura was admitted due to right pulsating headache and vomiting associated with dysarthria and left body weakness. She had taken emergency contraception (levonorgestrel 1 mg plus ethinylloestradiol 0.20 mg) 2 days earlier. Laboratory determinations were normal, including specific hypercoagulation studies. ECG, echocardiogram, carotid Doppler and angioMRI showed no abnormalities. Cranial CT on admission was normal. SPECT showed hypoperfusion over the right posterior temporal lobe, while a cranial MRI performed 3 days after admission disclosed an ischaemic stroke in the right middle cerebral artery territory. Headache disappeared 12 h after admission. She was discharged with a slight weakness in her left upper extremity.

Conclusion This case suggests that postcoital contraception with a high dose of oestrogens can be a risk factor for ischaemic stroke in migraine patients.
Migraine and eating disorders

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Objectives The rather high prevalence of both migraine (>10%) and the eating disorders anorexia nervosa (AN; 0.5–1%) and bulimia nervosa (BN; 1–3%) in young women makes it quite probable that these will co-occur in some individuals, even if there is no aetiological connection between the two. Yet the issue of comorbidity of migraine and eating disorders has received little attention to date in either field. Since the presence of unrecognized eating disorders may have serious implications for the treatment of migraine, the purpose of this presentation is to provide an introduction to AN and BN with the goal of increasing awareness of these disorders among those treating migraine, particularly in female adolescent and young adult patient populations.

Discussion We will provide an overview of AN and BN, focusing on the demographic characteristics and psychological profile of the groups at greatest risk. Behaviours characteristic of these disorders (e.g., skipping meals, excessive exercise) which may also act as migraine triggers in individuals prone to migraine will be emphasized. Current pharmacological approaches to treatment will be summarized with particular emphasis on selective serotonin reuptake inhibitors (SSRIs) which have been used successfully in treatment of BN, suggesting the involvement of serotonergic mechanisms in AN as in migraine. Medical complications of eating disorders will be summarized, as will the risks introduced by excessive laxative and emetic use in BN. From the perspective of migraine treatment, cardiac abnormalities are of particular concern. Signs that may alert the physician to the possible presence of an eating disorder will be considered.

Conclusions Since individuals with untreated eating disorders may not disclose this fact unless directly questioned and even then may deny or be unaware of their condition, it is important for those treating migraine to recognize the possible risks associated with these disorders and to consider the possibility of co-occurrence. There is a great need for scientific evaluation of the comorbidity of migraine and eating disorders, and for investigation of possible common underlying etiological factors.

Chronic or recurrent headache in systemic lupus erythematosus

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Objective To analyse and compare the prevalence of chronic or recurrent headache in systemic lupus erythematosus (SLE). We also studied the relationship of such headaches with other manifestations of the disease.

Materials and methods Fifty-six patients (49 women and 7 men) with a mean age of 42 ± 7 years (range 24–74 years) were included.

Results Thirty-four patients (61%) presented headache, 27 (49%) being vascular and 29 (51%) muscle-contraction type. In general, headache was more frequent after the onset of SLE (P < 0.001). The prevalence of muscle contraction headache, in particular, was greater following manifestations of SLE. A family history of migraine was recorded in 51% of the patients with vascular headache. This antecedent was more common in patients in whom migraine started before the onset of SLE (P = 0.05). A greater number of neuropsychiatric symptoms were observed in the patients with vascular headache and a family history (P < 0.02). Patients with thrombocytopenia presented headache less frequently (P < 0.05).

Conclusions Our results showed headache, of both vascular- and muscle-contraction types, to be frequent in SLE. We note that there is an increased frequency of muscle contraction headache after the onset of SLE and that there is a migraine-like headache directly related to SLE. Finally, it is suggested that severity of SLE is not related to the presence of headache.

Menstrual migraine in teenaged girls suffering from the Chernobyl disaster

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Introduction 70% of the radioactive substances released during the Chernobyl disaster fell on Belarus (population 10 million) and many individuals were subjected to low doses of prolonged external and internal radiation. Some experiments showed that deviations of neuromediator interrelations in brain cortex, hypothalamus and brain stem were due to the lowering of basic biogenic amines (catecholamines, 5-hydroxytryptamine).

Objective Investigation of clinical and functional peculiarities of menstrual migraine in 18 teenaged girls suffering from the Chernobyl disaster (basic group).

Methods Blood concentrations of hormones were measured every 4 h at the luteal, follicular and periovulatory phase by radioimmune assay.
Results Some deviations of the clinical course of migraine were revealed in the teenaged girls in the basic group. First of all, the disease was diagnosed in the basic group more often than in controls. Second, the menstrual migraine became the most prevalent form. Third, 75% of all attacks were at night and were always accompanied by vomiting. No reliable differences were found during evaluation of average daily hormone levels in blood serum of teenaged girls suffering from the Chernobyl disaster and in the control group. The concentration of sex steroid hormones was normal. However, a tendency to increased testosterone concentration was noted during our research in the basic group (0.49 ± 0.12 nmol/L and 0.78 ± 0.20 nmol/L). Then we investigated blood ability to transport oestradiol and noticed that free oestradiol concentration was increased in the basic group (5.9 ± 0.3% and 21.7 ± 1.9%). This fact was experimentally confirmed in animals (11.6 ± 1.7% and 35.9 ± 7.5%). We have investigated the circadian rhythm of oestradiol, testosterone, progesterone and prolactin secretion. Analysing these data we have found normal circadian rhythm in secretion of progesterone and testosterone, while so-called ‘oestrogens rhythm’ was in the stage of stabilising. Changes of serum prolactin at the periovulatory period level were chaotic, although the average level at night was a little higher than the morning or in the evening.

Conclusion Increased incidence of menstrual migraine in teenaged girls, who were victims of the Chernobyl disaster can be explained by a modification of the system of neuroendocrine regulation.

P3-N13
Effects of hormone replacement treatment (HRT) in postmenopausal women with migraine
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Background and objectives Only retrospective reports exist on the relationship between hormone replacement treatment (HRT) and migraine course in postmenopausal women. This longitudinal study compares the effect of different regimens of HRT in postmenopausal migraineurs.

Methods 56 postmenopausal women (mean age 51.0 ± 2.5 years) requiring HRT affected by migraine without aura (with 1–6 attacks/month in the previous 6 months) were enrolled. They had had their last menstrual period 14.5 ± 12.4 months before. Women submitted to surgical menopause, on prophylactic therapy for migraine or previously exposed to HRT were excluded. A daily headache diary was filled in for 7 months: 1 before and 6 during HRT. HRT regimen was chosen at two Menopause Clinics by physicians unaware of the study aims. Three main regimens were administered: a continuous, sequential, transdermal (CST) treatment, by using 17b-oestradiol (50 µg/day) + medroxyprogesterone-acetate (10 mg/day) in the last 12 days of a 28-day cycle; a continuous, sequential, oral (CSO) treatment, by using conjugated oestrogens (0.625 mg) + medroxyprogesterone-acetate (10 mg/day) in the last 14 days of a 28-day cycle; an intermittent, sequential, oral (ISO) treatment, by using oestradiol-valerate (2 mg/day) + ciproterone-acetate (1 mg/day) in the last 10 days of a 21-day cycle, with 7 days of withdrawal. Non-parametric tests were used for data analysis.

Results Fifty-four patients concluded the study. Overall, at the 6th month of treatment, attack frequency increased from 2.7 ± 2 to 3.8 ± 2 per month (P < 0.0001), while attack duration decreased from 14.8 ± 8.9–11.3 ± 5.4 h (P = 0.002). Analgesics consumption increased from 4.0 ± 3.9 to 5.2 ± 3.8 per month (P = 0.001). Twenty-five women received CST, 12 received CSO and 11 ISO; the remaining 8 women received other HRT regimens according to their clinical needs. Both CSO and ISO increased attack frequency, respectively, by 140% and 71% at the sixth month, while CST did not influence it. Accordingly, analgesics consumption increased by 83% and 42% with CSO and ISO, respectively, while it remained unchanged with CST. On the contrary both CST (−27%) and CSO (−37%) reduced the attack duration, which remained unchanged with ISO. Attack severity was unaffected by all the regimens.

Conclusions HRT worsens migraine course in postmenopausal women, increasing attack frequency and analgesics consumption. The transdermal route of oestradiol delivery seems to be neutral in this respect. Specific HRT regimens for migraine women should be studied.

P3-N14
Livedo reticularis and migraine: a marker for stroke risk?
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Background and purpose Livedo reticularis (LR) is an ischemic dermatopathy characterized by an irregular, violaceous net-like pattern, usually sparing the face. Associated with a variety of conditions, it is secondary to narrowing of small- and medium-sized arteries at the dermis–subcutis border. Sneddon’s syndrome refers to the idiopathic coupling of LR and stroke, in the absence of other vascular risk factors. Our recent review of reported cases of Sneddon’s syndrome revealed history of headache or migraine in 60% of patients. In a survey of patients in a general dermatology clinic, we found LR in 25% of those with migraine, with an OR of 2.3 for the association in women. Only 12% of the patients without migraine had livedo. We undertook this study to determine the frequency of livedo reticularis in our headache clinic.

Methods We performed a retrospective chart review of consecutive patients with migraine (IHS classification 1.1, 1.2) attending a headache clinic over a period of 6 months. The patients had all been seen by one MD (GET) who noted the presence or absence of livedo reticularis. The charts were reviewed for age, sex, and vascular risk factors, including history of smoking, current use of oral contraceptives,
coronary artery disease, hypertension, diabetes mellitus, stroke, and arthritis.

**Results** Charts from 133 patients with migraine were reviewed (24 men [18%], 109 women [82%], average age 42 ± 13 year). Livedo reticularis was observed in 29 patients (22%), in a similar proportion of male (25%) and female (21%). When we stratified the migraine population by presence or absence of livedo, we found no significant difference in age (44.5 vs. 41.7 year, $P = 0.16$). There was a higher frequency of stroke diagnosis in the cohort with livedo reticularis (28% [8/29] vs. 7% [7/104], $P = 0.005$), but no significant differences in frequency of hypertension, OCP use, diabetes mellitus, coronary artery disease, arthritis, or cigarette smoking.

**Conclusions** In our headache clinic population, LR is present in more than one-fifth of the patients with migraine. History of stroke is more frequent in this subset of migraineurs. This raises the possibility that LR can be used as a clinical marker to identify those migraineurs with an increased risk of stroke.
**POSTER SESSION III**

**O: Headache in children**

**P3-O1**

Agreement between questionnaire, interview and diary data in the assessment of headache frequency in schoolchildren

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**Objectives** In epidemiological research on childhood headache several important methodological problems exist. In the majority of previous prevalence studies questionnaire data have been used. The reliability of information on children’s headaches based on a questionnaire has been debated. To increase the validity the use of other methods such as interview and headache diary has been advocated. The results of a previous study have shown good agreement between interview information and recordings in a diary regarding headache frequency in school children. However, in a clinical study the estimates were higher in interviews as compared to diary recordings. The aim of the present study was to examine the concordance between different sources of information in the assessment of headache frequency in schoolchildren.

**Materials and methods** From a prevalence study of headaches among 1850 schoolchildren aged 7–16 years, a stratified, randomly selected sample of 131 children participated in a semistructured interview. Before the interview the children were asked to fill in a headache questionnaire at home together with a parent. The interviews were performed by one of the authors (KL) and questions were asked directly to the children. For younger children the parent supplemented the interview information. The children were then asked to keep a headache diary during 3 weeks and 64% returned completed diaries. The final sample comprised 84 children, 45 girls and 39 boys.

**Results** In the questionnaire 13% reported headaches occurring at least once a week. No headaches during the previous year was reported by 43%. The corresponding figures as revealed from the interview were 17% and 37%, respectively. However, the diary data showed that 46% had headaches weekly or more often. The agreement between the questionnaire data and the interview was good (κ=0.71) and the discrepancies in the ratings showed no distinct pattern. The agreement between the headache diary information and the two other assessment methods was poor (κ=0.12–0.26). Overall, the children reported much more frequent headaches in the headache diary than with the two other methods. Of those who reported no headaches during the previous year in the questionnaire and the interview, almost one third reported headaches at least once a month in the diary.

**Conclusion** Good agreement regarding frequency of children’s headaches was found between questionnaire and interview data. However, much lower concordance was found between information based on a headache diary and the two other assessment methods.

**P3-O2**

The aetiology and prognosis of chronic daily headache in children and adolescents

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Chronic daily headache, defined as headache recurring on more than three days each week, is the headache symptom which causes the greatest disruption of quality of life. Aetiology of this symptom and its prognosis have been little studied in children and adolescents. From 70 children and adolescents presenting as outpatients to a general paediatric unit over 1 year with a presenting complaint of headache, we identified 17 patients with chronic daily headache. The symptom was more common in teenagers than in younger children and many had symptoms for more than 1 year before presenting. The most common diagnosis found in over half our cases was analgesic misuse headache and this often followed intermittent migraine episodes. Other diagnoses were cervicogenic headache, headache associated with constipation and chronic fatigue syndrome. With appropriate management, 15 of the 17 patients became headache free or had less than 2 headaches per month. One patient moved to another district and one was lost to follow-up. The prognosis of chronic daily headache in children and adolescents is therefore excellent.

**P3-O3**

Vascular malformations and headache in children

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In recent years we frequently found vascular malformations of carotids in young headache sufferers (YHS). Now we tried to evaluate the real extent of the problem: the incidence, its effect on headache, the higher presence in children compared to adults. The study was conducted on 259 subjects who were hospitalized in our centre the last 3 years. It was performed by echocolour Doppler of extracranial vessels.

Approximately 26% of YHS, evaluated outside the pain crisis, showed alterations of the velocimetric profile as an increase of the diastolic component of the continuous flow, a sign of encephalic vascular resistances, whereas 18.2% of the
Neural network, LUMC, Leiden, The Netherlands, 2Neurosurgery, & M. D. Ferrari

L. A. Laan 1, J. A. van Vliet 1, J. H. Voormolen 2

P3-O4
An unusual cause of headache attacks in a 1-year-old child
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A 3-year-old girl presented with a history of extremely painful headache attacks since the age of 1 year old. During these attacks she had severe pain in her right ear associated with an ipsilateral tearing eye, eyelid oedema, rhinorrhea, and intense crying. These episodes lasted 12–24 h and occurred every week. In between attacks she was free of symptoms. Sometimes she would wake up during an attack at night. Aspirin was not effective. Family history was negative for migraine or cluster headache. Neurological examination revealed no abnormalities. An atypical form of cluster headache was considered. Video-recording of an attack, however, showed a crying 3-year-old girl in severe continuous pain with superimposed attacks of a few seconds of very intense pain during which she would rock back and forth. The clinical presentation with very short-lasting attacks, suggested trigeminal neuralgia. Because of the young age of onset and the atypical presentation, an MRI of the brain was performed, which revealed an unexpected finding. For educational reasons we will reveal the findings and clinical follow-up in detail at the congress.

P3-O5
Familial neck–tongue syndrome
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Neck–tongue syndrome (NTS) is an uncommon clinical condition characterized by brief attacks (seconds to 1 min) of intense stabbing pain on one side in the upper neck or occipital region on sudden rotation of the head, accompanied by transient paresthesias or numbness of the tongue ipsilateral to the pain. Since the original descriptions by Cyriax (1962) and Lance and Anthony (1980), the clinical phenomenology of neck–tongue syndrome has expanded from ipsilateral tongue numbness to include lingual pseudo-athetosis, dysarthria, and lingual paralysis. The mechanism of neck–tongue syndrome was proposed by Bogduk in 1981. He demonstrated, by cadaveric dissection, that the C2 ganglion and spinal nerve lie dorsal to the lateral atlanto-axial joint, the joint innervated by the C2 ventral ramus. Temporary, abnormal subluxation of the lateral atlanto-axial joint on rotation of the head causes the pain by straining the joint capsule. The unilateral and ipsilateral tongue symptoms occur as a result of compression of proprioceptive afferent impulses traveling from the lingual nerve via hypoglossal nerve to C2 root. Anatomical anomalies of the cervical spine have been found in the majority (65%) of adult patients with neck–tongue syndrome including congenital anomalies of the cervical spine, ankylosing spondylitis, degenerative spondylosis, and tuberculous atlanto-axoid osteoarthrits. The syndrome has also resulted following head or neck trauma during water skiing, spinal manipulation, motor vehicle accident or motor cycle accident. From review of the literature, the majority of children and adolescents (79%) with NTS have had no identifiable anatomical defects. We report 8 patients, 5 adolescents and 3 adults with NTS. The adolescents were 12–16 years of age and there were 2 boys and 3 girls. All 5 had normal neurological examinations and no evident anatomical defects following neuro-imaging. The
3 adult patients, all currently asymptomatic and healthy, were the parents of three of the NTS children and described having transient symptoms consistent with neck–tongue syndrome during their adolescence, indicating a familial (autosomal dominant) form of NTS.

P3-O6

Age-specific health-related quality of life (HRQL) measurement in childhood headaches

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Background

Headaches can be disabling and negatively affect quality of life (QL). For children this has primarily been assessed by school absences. A HRQL measure has been used for some chronic childhood illnesses and would be a useful tool for childhood headaches. Specific paediatric domains would also assist with determining areas of disability and their response to treatment.

Objective

To assess the validity of an HRQL for childhood headaches and investigate the impact of recurrent headaches on children’s functioning and disability.

Methods

221 patients with migraines (49% female, mean age 11.3 ± 3.4) were evaluated with an HRQL (PedsQL® 4.0 Generic Core Scales). This measures general paediatric HRQL divided into 4 age groups (ages 2–4, 5–7, 8–12 and 13–18-year-old) and 4 domains (physical, emotional, social and school). The HRQL was completed by 216 children and 220 parents interpreting their child’s headaches. The parents and children completed their forms independently.

Results

For the 221 patients, the mean frequency was 13.3 ± 10.6 headaches per month; the mean severity was 6.7 ± 1.8 (10-point scale); and the mean duration was 9.5 ± 13.9 h. 91% of the patients indicated that activity worsened their headache. School functioning was reduced to 40 ± 27% effectiveness. Home functioning was reduced to 36 ± 28% effectiveness. 4.6 ± 9.8 days of school were missed due to headaches per semester. For the children the mean total score was 23.4 ± 13.1 and four domain scores were 6.9 ± 5.7, 6.4 ± 4.1, 3.2 ± 3.4 and 6.9 ± 3.9 for physical, emotional, social and school, respectively. For the parents the total score was 24.1 ± 13.2, while for the 4 domains the scores were 7.1 ± 5.7, 6.7 ± 4.1, 3.5 ± 3.6, and 6.8 ± 3.9. A comparison with established norms for a healthy paediatric population, variations amongst ages, differences between parents and children scoring and response to treatment will be presented.

Discussion

Paediatric headaches negatively affect many aspects of a child’s life. An accurate measure of these effects would be a useful tool in assessing the impact of headaches on a child’s life. Using such a measure, studies will be able to investigate the effectiveness of multidisciplinary care in improving headache symptomology and functional outcomes.

P3-O7

Psychosocial impact of headache and other pain in Swedish adolescents

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To examine the prevalence of frequency and troubles with various pains in a school sample of adolescents, i.e. headache, abdominal pain, muscle pain, joint pain, and their psychosocial impact on functional disability, anxiety, depressive symptoms and illness behaviour encouragement from the parents. n = 793 subjects, 49% girls (n = 385) and 51% boys (n = 407) between 13 and 19 years of age (M = 15.8; SD = 1.6) participated. The response rate was 86%. A questionnaire was administered to the students during one hour at class. The participants rated frequency and troubles with pain. The participants also answered questions regarding functional disability (Functional Disability Inventory, Walker, 1991) in their everyday life, anxiety (Revised Child Manifest Scale, Reynolds, 1997) and depressive symptoms (Center of Epidemiologic Studies: Depression Child) as well as parents’ illness behaviour (Illness Behavior Encouragement Scale, Walker and Zeman, 1992). The most common pain (at least once a week) among girls was headache, which 42% reported. For boys the most common pain was muscle pain, reported by 32%. Headache was reported by 24% of boys and was the second most common pain while muscle pain was the second most common problem for girls, reported by 24%. Back pain, joint pain and abdominal pain were the 3rd, 4th and 5th most common pains for all subjects. Girls had a significantly higher number of pains than boys (P < 0.001). Subjects with headache had an overall higher rating of functional disability, anxiety, and depressive symptoms than those without headache (P < 0.05). Girls with headache experienced more psychosocial impact than boys with headache regarding disability, anxiety, and depressive symptoms (P < 0.005). There was no difference regarding parents’ illness behaviour for subjects with or without pain. The most common areas of functional limitations for those with headache were in concentrating in the classroom, participating in sports at school, being in school all day and running. Subjects with headache had similar ratings as those with back pain and abdominal pain; however, subjects with abdominal pain had the highest ratings of psychosocial measures. Headache and abdominal pain were positively correlated to anxiety and depressive symptoms, and both pains correlated positively to each other. Of subjects with headache, 32% also had muscle pain, 32% had a back pain and 25% had abdominal pain. Of those with headache at least once a week, 23% took medication for pain at least once a week; for the whole sample, this was 9%. Adolescents commonly report various types of pain. Subjects with headache, back pain and abdominal pain experience a large psychosocial impact from pain. Systematic recordings of various pains and psychosocial functioning in, for example, diaries, should be emphasized in future studies.

P3-O8

Paediatric-specific migraine disability assessment (PedMIDAS) for childhood headaches
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Background Recurrent headaches are common in children and adolescents. A tool has been developed to assess headache disability for adults (MIDAS). A corresponding tool has not been developed for children to account for paediatric specific activities (school, home and peer interaction), as well as differences by age groups.

Objective To develop and test the validity of PedMIDAS and investigate the improvement in disability with treatment.

Methods 350 PedMIDAS scores were obtained from 273 patients with migraines (81 patients with multiple scores due to return visits). Six questions were used including school attendance and function, home function and social activities.

Results 113 patients completed PedMIDAS at their initial visit, 88 at their first return visit, 51 at their second return visit, and 104 at subsequent visits. 30% of the initial patients have been followed longitudinally. The overall score of the 350 PedMIDAS was 23.9 ± 38.9. At the initial visit the mean of the total score was 41.9 ± 52.8, while for the first return visit the mean was 20.3 ± 34.5 and for the second return visit the mean was 12.6 ± 20.9. The improvement from the initial visit to each of the return visits was significant (P<0.001). For the longitudinal group the mean of the initial scores was 41.4 ± 47.8, which improved to 18.3 ± 32.4 (P=0.0098) at the first return visit. For patients with chronic daily headaches (CDH) the mean score was 63.5 ± 64.9, while for non-CDH the mean was 13.3 ± 16.6 (P<0.0001). Validation of PedMIDAS, analysis of the individual questions, comparison of different ages and further correlation with frequency and severity will be presented.

Discussion PedMIDAS shows potential as a useful tool in assessing disability for children with migraines. Correlation with severity and frequency as well as comparison to alternative quality of life instruments will further demonstrate its potential. Longitudinal studies will also verify its usefulness as a measurement of treatment response to a wide variety of management techniques.

P3-O9

Paediatric migraine disability assessment
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Objective To evaluate a Paediatric Migraine Disability Assessment tool in clinical practice.

Background A recent meta-analysis of 1932 adolescents with IHS Migraine reported the associated symptom of pain aggravated by activity-85% (1). What is the associated disability attributed to adolescent migraine?

Method The Paediatric Migraine Disability Assessment Questionnaire (PMDAQ) was administered to 45 adolescent migraine patients. The PMDAQ is patterned after the Adult Migraine Disability Assessment Questionnaire; altered to address childhood and adolescent issues (school, homework, computers, TV, stereos, sports, social issues, or school clubs).

Results 51% of the adolescents reported severe disability, 11% moderate disability, 15% mild disability and 22% little or no disability. The number of headache days reported over the last three months ranged from 0 to 90, with a mean of 31 days.

Conclusion A grade resulting in mild disability or greater identifies the child or adolescent who may benefit by further evaluation. The PMDAQ is under continued study and promises to be a useful tool in clinical practice.

References

P3-O10

Caffeine-containing products intake among children attending a headache centre
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Background and objectives Although caffeine abuse has been well studied in adults presenting with headache, the role of caffeine intake among children is less investigated. The aim of this study is to evaluate sources and frequency of caffeine intake among children referred to a tertiary headache centre.

Material and methods 118 children (62 girls and 56 boys), aged 4–12 years, attending a tertiary headache center in two different states, and diagnosed as suffering from primary headache (episodic migraine with or without aura, episodic tension-type headache and chronic daily headache), were retrospectively studied. During the first visit, one of the parents or the person responsible for the patient’s care was given a questionnaire about the patient’s nutritional habits. A particular section had to be completed about caffeine containing products taken by the patient. Specific questions had to be answered: Is the product taken on a daily or frequent basis? How much (per day or week)? How long (more/less than 6 months)? For the analysis, patients were grouped by age and diagnosis.

Results The majority of answered questionnaires provided complete information about specific kinds of nutritional items. 12 questionnaires were excluded due to the lack of information. 72 patients (67.9%) had daily intake of at least...
one source of caffeine, for more than six months. In this group, 34 (47.2%) presented chronic daily or near daily headache. Among those who did not take caffeine daily, only 3 patients (6.3%) presented chronic daily or near daily headache. The main sources of caffeine intake were chocolate, followed by the soft drinks guaraná (a typical Brazilian seed) and cola (Coke). Surprisingly, coffee was taken in high daily doses (as high as 120 mg/daily) even in the group of younger patients. Caffeine-containing teas were used less frequently.

Conclusions This study shows that caffeine is frequently present in children’s diets. The results suggest that caffeine may be associated with an increase in frequency of headache attacks. Avoiding children’s excessive intake of caffeinated products may be an important preventive measure to be discussed with parents. Further studies are necessary to confirm these initial observations.

P3-O12

Headache and epileptic photosensitivity in children

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Objectives Migraine and epilepsy are two different syndromes which often show an overlapping of symptoms in childhood. A relationship between epilepsy and migraine has been postulated. There is comorbidity in both conditions. In 1984, Wilkins found an association between headache and the tendency to report illusions of a colour, shape and motion when looking at black and white striped patterns known to be most epileptogenic in patients with photo- and pattern-sensitive epilepsy. The aim of the present study is the follow up of children suffering from headaches in order to verify if headache can be the only symptom of epileptic photosensitivity.

Materials and methods 21 children (14 males and 7 females) aged 5–16 years affected by headache are the sample. They were screened on the basis of photosensitivity showed on the EEG. According to the criteria of International Headache Society (IHS) of 1988, 13 patients suffered from migraine without aura (MwoA), 6 from tension-type headache (TTH) and 2 from migraine with aura (MWA). According to the criteria of the International League Against Epilepsy, 8 children showed seizures (3 partial seizures and 5 generalized seizures); 2 girls showed recurrent syncope.

Results The features of sample were as follows: always familiarity with migraine and/or epilepsy; normal neuroimaging (NMR); EEG with sharp waves, spikes, spikes and waves, polyspikes and waves generalized and/or occipital; association of MWA and occipital epilepsy (of Panayotopoulos) in 1 female with celiac disease and comorbidity of celiac disease in 2 females. The seizures were evoked by television in 4 children and by videogames in 4 children. All the children were followed during 10 years. In the study, clinical and EEG features were examined. Antiepileptic drugs (VPA, CBZ, CZM) improved seizures and headaches. In the other patients, therapy of migraine improved the epileptic photosensitivity on the EEG.

Conclusions Headache can be only the symptom of epileptic photosensitivity. Migraine and photosensitive epilepsy in childhood are of particular interest because of...
In recent years, the finding of cytokine modifications in the various forms of essential headache, led researchers to believe that these play the role of common mediator in headaches (1). Starting from the above hypothesis, we looked for an answer by evaluating a few cytokines in a population of young headache sufferers. The study was performed on children chosen at random, who from January 1999 to December 2000, were hospitalized in our centre and on two control groups: one group was chosen from among young patients hospitalized for inflammatory pathologies and another group was chosen from primary schools. Sample under examination: ETTH – 50 (28F/22M); average age, 9.2 ± 1.8; range, 5/15 years. Controls: 38 (22F/16M); average age, 8.9 ± 1.7; range, 6/14 years. MwoA – 46 (27F/19M); average age, 9.9 ± 2.3; range, 5/13 years. Inflam. path – 44 (24F/20M); average age, 9.7 ± 1.8; range, 5/15 years. Controls: 38 (22F/18M); average age, 8.9 ± 1.7; range, 6/14 years. Basal values of IL-1β, TNF-α and the antibody of the sIL-R2 were evaluated. All the children had taken no drugs in the preceding 4 days, and the sample was taken always at the same time. All the cytokines were dosed by an immunologic technique with amplified sensibility solid enzyme (EASIA) Biosource Belgium 1998 (2). The data were compared with analysis of variance and Bonferroni T-test.

<table>
<thead>
<tr>
<th></th>
<th>sIL-R2 (U/mL)</th>
<th>IL-1β (pg/mL)</th>
<th>TNF-α (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETTH</td>
<td>748.4 ± 24*</td>
<td>5.8 ± 10*</td>
<td>19.7 ± 5.6**</td>
</tr>
<tr>
<td>MwoA</td>
<td>935.6 ± 37**</td>
<td>4.3 ± 9.6</td>
<td>19.2 ± 6.7**</td>
</tr>
<tr>
<td>Inflammatory patholy</td>
<td>1119 ± 52**</td>
<td>15.5 ± 17.7**</td>
<td>26.4 ± 14**</td>
</tr>
<tr>
<td>Controls</td>
<td>637 ± 95</td>
<td>4 ± 2</td>
<td>10.4 ± 2</td>
</tr>
</tbody>
</table>

* n.s.  **P < 0.05.

All the cytokines were found altered in subjects with inflammatory pathology. The TNF-α was found higher both in ETTH and MwoA. The IL-1β was found similar to controls, whereas sIL-R2 was found significantly altered (P < 0.05) in MwoA. Our results are different from those coming from the literature; this may depend on the characteristics of childhood headache, or on the fact that in recent years methods have become more accurate. Having found all the cytokines altered in subjects affected by an inflammatory pathology is a confirmation in the field of cytokines activation in these forms. Certainly the cytokines may play some sort of role in headache genesis and also in childhood a certain ‘sterile inflammation’ may exist; this is proved by an increase in the two forms of TNF-α. For migraine, conversely the high level of the antibody sIL-R2, if confirmed, may be a specific marker.
dramatically. However, a subset of patients develop disabling headaches which interfere with school, work and social function. Although rarely due to a shunt obstruction, the headaches have been perceived as abnormalities of ICP. Treatment is oriented to altering ICP by shunt revision or surgical decompression. The results of these surgical interventions have been disappointing. There is occasional temporary relief, but the headaches return.

**Methods and discussion** We looked at 8 hydrocephalic patients disabled by headaches, ranging in age from 7 to 31 years. All had numerous hospital admissions for headaches. We noted 2 types of headaches. (1) Throbbing, frontal headaches with all the associated symptoms of migraine except the criteria excluding underlying cause. We called these headaches Hydrocephalus Associated Vascular Headaches (HAVH). (2) Chronic Daily Headaches (CDH) defined as more than 15 headaches monthly. These headaches are non-throbbing and vary in severity with no associated symptoms. 3 of 8 patients had only HAVH, 4 had mixed HAVH-CDH and 1 had CDH. The average age of patients with HAVH was 10 years. The average age of patients with HAVH-CDH was 22. The CDH patient was 20. We managed the HAVH as migraine patients and used a comprehensive approach including triptans for the actual headaches. The HAVH-CDH patients were managed by treating rebound when present, and preventive medications and triptans were used for the HAVH. To evaluate our results, patients filled out a questionnaire before and after treatment. In 5 of 8 patients, both the severity and frequency of the headaches decreased. Duration decreased in 3 of 8. Associated symptoms improved in 4 of 7 patients. Only 2 patients were evaluated for shunt malfunction and both were negative. 4 of 8 patients missed less school or work as a result of treatment.

**Conclusion** The subset of patients with hydrocephalus and disabling headaches should be approached as headache patients rather than shunt malfunction patients. These headaches can be broken down into 2 types – HAVH and CDH. The patients with HAVH are significantly younger and despite the small number in our series, it appears that HAVH may evolve into HAVH-CDH over time. Early treatment of HAVH may prevent the development of HAVH-CDH which is more disabling and more difficult to treat successfully. This approach significantly decreases the number of imaging studies, hospital admissions and surgical procedures as well as lessening the disabling features of the headaches.

### Table for abstract P3-O16

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of the structure has been considered to be improved. We underline the utility of working to improve attention to communication and the doctor-patient relationship. It allows the stress of the importance of framing the patients’ instances both on medical and psychological (‘human’) perspective.

P3-O17
Headache disorders in children: change of indication for migraine prophylaxis by triptan use
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Objectives Indication for prophylactic therapy in childhood is given in frequent, long lasting and severe migraine attacks. Improvement in attack treatment with triptans during the last 1–2 years seems to reduce pharmacological prophylaxis and may profoundly change the long-term strategy.

Material During the last year about 150 children with headache have been screened in our outpatient neuropediatric department, about half of them diagnosed migraine with or without aura. A group of about 30 children fulfilled the IHS criteria for prophylactic treatment.

Results 4/5 of them did not need or accept a long-term regime because of effective attack treatment, mostly with nasal sumatriptan. Only very few patients responded well to different substances like a beta-blocker or calcium antagonist for 3–4 months given once in the evening in common dosage.

Conclusion First experiences show a new trend away from prophylactic therapy in migraine because of sufficient attack treatment with triptans. Quality of life seems to be responsible for the individual decisions. Cost–benefit analysis and long-term tolerance of repetitive triptan intake must be observed systematically in order to preserve the important resource of this substance for the attack therapy in children.

P3-O18
Preventive treatment for childhood and adolescent headache: role of once-daily montelukast sodium
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Background Frequent migraine, migrainous, or chronic daily headaches are not uncommon in children and adolescents. Adult patients with frequent headaches are generally managed with preventive therapies. Parents and physicians are hesitant to use daily preventive medications in children because of concerns about adverse reactions. Leukotrienes have been implicated in the inflammatory cascade believed to be associated with the pathophysiology of migraine. Therefore, treatment with a medication that may inhibit this inflammatory process may offer therapeutic benefits for patients with migraine. Montelukast sodium is a leukotriene antagonist currently licensed for treatment of asthma in children over 2 years of age. There is clinical evidence that montelukast sodium prevents headaches in adults (1). Montelukast sodium is well tolerated in children as young as age 2 years. This study reviews a small cohort of children who were treated with montelukast sodium as preventive therapy for frequent migraine, migrainous, or chronic daily headaches (IHS criteria).

Methods Restrospective chart review of 17 adolescent and paediatric headache patients (aged 5.5–16.5 year; 9 females, 8 males) with a mean age of 10.3 years and a mean age of onset of headaches of 7.9 year. Patients were treated with montelukast sodium 5 mg or 10 mg, once daily as preventive therapy. Patients returned to the clinic for 1 or more follow-up visits between 1 and 6 months.

Results At the time of first consultation, the baseline frequency was 16.2 headaches/month (range 6–30). Follow-up was available for 11 of 17 patients (one patient failed to take medication; 5 had no follow-up available to date). Ten of 17 patients also reported allergy symptoms. The average time of treatment was 2.8 months (range 1–6). All 11 evaluable patients showed a greater than 50% reduction in headache frequency with the average headache frequency post-treatment being 2.8 headaches/month (range 0–4). No patient discontinued medication due to side effects, and no adverse reactions were reported.

Conclusions This preliminary observation of a small group of adolescent and paediatric headache patients suggests that montelukast sodium may offer a clinical benefit as preventive treatment for children with migraine, migrainous, or chronic daily headaches. Prospective, longer-term, placebo-controlled studies are needed to further assess the efficacy and safety of montelukast sodium as preventive therapy in children with frequent headache. Additional studies are also needed to assess the possible confounding role of other conditions such as allergies in relation to frequent headaches in children.

Reference

P3-O19
Efficacy and tolerability of the marketed doses of rizatriptan in children and adolescents: a retrospective review
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Purpose To assess the response and adverse experiences of children and adolescents treated with rizatriptan (Maxalt, Merck) for migraine headaches.

Methods Medical records and headache diaries of 64 children below the age of 18 who were treated with rizatriptan in a tertiary headache centre between July 1998 and July 2000 were reviewed retrospectively. Adequate response to
medication administration was determined from diary entries, progress notes, and patient willingness to use the medication for subsequent headache attacks.

**Results**

64 children were given rizatriptan to be self-administered for acute abortive care of migraine attacks. All patients suffered from IHS migraine with or without aura. The average age was 13 years (range 6–17 years) and the average body weight was 117 lb (range 51–271 lb). There were 43 females and 21 males. Of the 64 patients, 16 received 5 mg and 48 were treated with 10-mg doses of rizatriptan. Acceptable or good efficacy was reported in 6 of the 16 (37.5%) treated with 5 mg and 38 of the 48 (79%) treated with 10-mg tablets. Of the 10 patients who did not respond to a 5-mg dose, 6 were subsequently treated with 10 mg, 4 of these (67%) reported good efficacy with 10 mg. There were only 3 adverse events reported, all of which occurred in patients treated with 10 mg rizatriptan (6.25%). The three AEs included 2 patients who experienced drowsiness and one who experienced a warm sensation. There were no reports of chest pain, palpitations, or gastrointestinal symptoms such as nausea in this series of patients.

**Discussion**

The efficacy in the patients treated with 5-mg tablets (37.5%) was lower than one would expect from the published data. The response and patient satisfaction with the 10-mg dose on the other hand was quite robust (79%) and is commensurate with previously published data from controlled trials in adults. Pharmacokinetic studies suggest that the 5-mg dose of rizatriptan in an adolescent population achieves similar blood concentrations to the 10-mg dose in adults. However, in a recently conducted controlled efficacy trial with 5 mg in an adolescent population, a clear separation from placebo was difficult to prove. The data from our chart review suggests that attaining rizatriptan blood concentrations known to be effective in adults may not induce an acceptable clinical response in children and adolescents and that controlled trials using the 10 mg dose in this population are warranted.

**P3-O20**

**Behavioural treatment of recurrent headaches among school children and adolescents: results from a replication series**

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During the past two decades various forms of behavioural treatments administered within clinical or school settings have been shown to be effective for children and adolescents suffering from frequent recurrent headaches. Relaxation and biofeedback training have been shown to be effective in reducing migraine and tension-type headaches primarily in adolescents. A further step is the development of various cost-effective treatment formats, for example, self-help, largely home-based relaxation or biofeedback training procedures or treatment delivered by school health personnel.

The results of our own intervention research by now including 244 adolescents (age 10–19 years; 85% girls and 15% boys) having participated in seven controlled outcome studies, have shown that relaxation training administered within a school setting can reduce their headaches effectively. The majority (73%) of the subjects suffered from tension-type headaches (TTH), 24% from combined TTH and migraine, and a small group had migraine only (4%). Those with TTH or combined headaches had more severe headaches than those with migraine only. Overall, the results showed that adolescents treated with relaxation improved significantly more than those treated with attention-control strategies (ATCO) or self-monitoring their headaches only (SM). Therapist-assisted relaxation (administered twice a week during 8–10 sessions) was somewhat more powerful than a self-help format or relaxation without application training. School-nurse administered relaxation based on audiotapes emerged as a powerful treatment alternative. Overall, approximately 50% of those treated with relaxation training achieved a 50% headache reduction or more after treatment and the effects were well maintained at a 6–8 month follow-up. However, no differential outcomes in regard to sex, age or headache diagnosis were obtained. It is suggested that various forms of behavioural training approaches are the treatment of choice for children and adolescents with frequent (more than once a week) tension-type or migraine headaches. Relaxation training procedures can also be administered to students by a trained school nurse in regular school health care. Although outcomes of behavioural interventions for recurrent headaches in children and adolescents are satisfactory, optimizing treatments and further identification of predictors of outcome are important issues that should be addressed in future research. Treatments that have proven to be effective in research trials should also be evaluated in field studies conducted in various settings by different therapists.

**P3-O21**

**Biofeedback, CTTH and adolescence**

D. Moscato

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In an adolescent suffering from ETTH, when his lifestyle worsens and the boy no longer succeeds in keeping school, family, the relationships with his peers, under control, the headache has a tendency to increase and show up daily, thus preventing him from leading a normal life. A therapeutic choice may be biofeedback, whereby not only a mechanism of conditional reflex is involved that replaces the tension from relaxation, but also the awareness of acquiring a self-control ability, like a manner of transferring elsewhere tensions and rage of being and other mechanisms not yet clarified (1). This study involved 43 subjects suffering from CTTH, 20 males aged 12–18, 23 females aged 11–19; the headache was at the beginning ETTH 58%, migraine without aura 12%, initially chronic 30%; the onset from 6 months to 4 years; the most
common causes for becoming chronic: altered relationship in the family environment 43.6%; problems in the school 53.8%; tensions in the group of friends 29.8%; relationship with brothers and sisters 25.3%. Our therapeutic scheme: 10–12 sessions twice a week of BFB EMG, each session 5 min of baseline and 5 periods of 5 min of BFB after 1 min rest. At the 5 session home exercises of relaxation by a 30-min tape (2) daily and 3 follow-up visits (2, 4, 8 months). EMG values (µV/s) were used as improvement indexes together with the Total Pain Index. Student–Newman–Keuls test was employed for statistical evaluation. The EMG values decreased constantly during the therapeutic cycle, at the follow ups this reduction decreased a lot, the TPI conversely continued to decrease constantly (1sed/3fup 48.5–33.7, P < 0.05). We confirm therefore also for adolescents that the BFB is the first choice intervention for chronic tension headache, since it also improves his ability to cope with social suffering.

References

P3-O22
Nutritional treatment of children with migraine and tension-type headache: a controlled research-study of 117 children
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Objectives Because of the still increasing number of headaches in children, we tried to find some of the reasons. By starting with a special diet, it is easy to see that many of the children improve by changing their daily food.

Material 117 children with headache and migraine were examined and put into two different groups. All children fulfilled IHS criteria. Children with a permanent headache were not included. One group received a booklet with information regarding the diet and the other group received personal counselling in how to change their nutrition. The personal counselling and the booklet were directed to the children as well as to their parents.

Results 3/4 of the children who changed their diet had a more than 50% relief or no headaches anymore. Children with migraine had greater benefits than children with tension-type headache. Children in the booklet group were not as successful as the children in the personal counselling group, but were also in a 50% range of improvement. The follow-up for long-term effect of the treatment is ongoing.

Conclusions We see that children with headaches have good results and relief from headache by improving their diet. Even though counselling takes quite a bit of time, this can be compensated with the booklet. Diet is an effective low-cost method to cure headache, showing children as young as 6 how to help themselves by their own participation. Children who do not react (enough) from the dietary treatment receive pharmacological treatment and/or relaxation training.

P3-O23
Responsiveness to a multidisciplinary headache centre at 1 and 2 years after initial visit
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Background Headaches are a common problem for children and adolescents. However, outcome research for paediatric headaches is limited. This restricts our ability to determine effectiveness of long-term management and overall responsiveness of childhood headaches.

Objective To assess long-term effectiveness by comparing baseline headache features vs. 1-year and 2-year follow-up. To contrast differences in those who did or did not return for follow-up.

Methods Headache characteristics were obtained at the initial visit and were re-evaluated 1 or 2 years later. Outcome was determined by changes in these characteristics. Patients that returned were compared to patients who did not after their initial consultation.

Results 96 patients were assessed at 1 year (59% females, presenting mean age 11.0 ± 3.4) and 71 patients at 2 years (49% females, presenting mean age 10.6 ± 3.4). 94% of the 1-year sample and 96% of the 2-year sample clinically had migraines, while 74% and 71% met the IHS criteria, respectively. For these two groups, the initial mean frequency was 12.4 ± 1.2 and 11.9 ± 10.8 headaches per month; the mean duration was 12.3 ± 18.6 and 9.7 ± 15.1 h; and the mean severity was 7.3 ± 2.0 and 7.1 ± 2.0 on a 10-point scale. 77% of the 1-year patients and 68% of the 2-year patients reported that their headaches were better. For the 1-year patients, the frequency, duration and severity were reduced to 4.9 ± 7.0, 5.2 ± 9.7 and 5.2 ± 2.4, while they were reduced to 4.7 ± 7.6, 4.8 ± 7.6 and 5.0 ± 2.4 for the 2-year patients. These values compared with the initial visit were significantly lower for all values (P < 0.01). 21 of the 1-year patients and 12 of the 2-year children were only seen at their initial visit. These patients initially had less significant headaches that remained under good control. Sustained improvements in patients’ functional ability were also noted.

Discussion Children’s headaches improved from baseline assessment to follow-up. Children’s ability to maintain effective headache control over time should allow for continued improved quality of life and global functioning. Assessment over additional years should aid with further defining this observation.
P3-O24
Clinical efficacy of nimesulide against paracetamol and ibuprofen for the treatment of headache in children with upper respiratory tract infections
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Headache is a common symptom in children. The signs and symptoms such as headache, overall pain and fever are the leading features, observed in children with acute upper respiratory tract infection. To evaluate the clinical efficacy of nimesulide (2.5 mg/kg, twice times daily, max. 200 mg/day) against paracetamol (10 mg/kg, four times daily, max. 1500 mg/day) and ibuprofen (10 mg/kg, four times daily, max. 600 mg/day); two hundred and sixteen paediatric patients, aged 6–14 years, with acute upper respiratory tract infection were included into the scope of the study. Each agent was administered to 72 children, and three groups were simultaneously treated with azitromycin (10 mg/kg, once a day for 3 days). Statistically significant differences between nimesulide and paracetamol ($P < 0.05$), and nimesulide and ibuprofen ($P < 0.01$) were evident for relieving the headache. 91%, 82% and 75% of the patients treated with nimesulide, paracetamol and ibuprofen, respectively, were reported by physician to have a good or a very good response to therapy. There were no reported side-effects. In conclusion, nimesulide was more effective than paracetamol and ibuprofen in reducing headache and other symptoms.

P3-O25
Chronic daily headache in children and adolescents presenting to tertiary headache clinics
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Objective This study describes the clinical features of Chronic Daily Headache (CDH) in children and adolescents and evaluates the efficacy of headache classification criteria.

In addition, the features of coexistent daily and episodic headaches are compared to better determine whether they represent separate syndromes or a stage in the transformation process.

Background Adults with CDH often describe a transformation from episodic migraine with partial retention of migrainous features. Although poorly described in a pediatric population, one study showed a predominance of coexisting daily headache and episodic migraine without a clear history of transformation.

Design We surveyed 189 consecutive patients, under age 18, who presented for initial evaluation of daily or near-daily headache at one of 9 tertiary headache clinics. Data were collected in semistructured interviews based on a standard questionnaire and analysed using SAS and STATA.

Results Of the patients enrolled, 70% were female and 87% white with a mean age of 13.0 ± 3.1 years. Male sex was associated with a higher degree of reported disability. A family history of headache was described in 79%, most of which was migraine. Use of non-steroidal anti-inflammatory drugs 5 days per week or more was reported in 44%. The International Headache Society (IHS) criteria and Silberstein’s 1996 criteria failed to classify 64% and 31% of patients, respectively. Participating physicians misclassified patients according to IHS and Silberstein’s criteria one-third of the time. Nearly one-quarter of patients reported 2 separate headache types with distinguishing characteristics. The baseline headache occurred 27.3 ± 4.1 days per month with a mean pain intensity of 5.9 ± 2.1 on a 10-point scale. The superimposed episodic headache occurred 4.7 ± 3.8 days per month with a mean pain intensity of 8.4 ± 1.4 and was more often associated with migrainous symptoms. After logistic regression to control for pain intensity, the only statistically significant difference between the two headache types was a lower prevalence of tension pain in the superimposed headache.

Conclusions These data suggest that, rather than having 2 coexistent headache types, children and adolescents with CDH have a syndrome that, in many cases, periodically worsens and gathers migrainous features. Longitudinal data will help clarify whether the reported coexistence of 2 headache types represents an intermediate stage in the transformation of episodic to daily headache.
P3-P1

American Headache Society members' view of diagnostic criteria for primary headache, analgesic rebound, and daily headache conditions

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Objective To survey members of the American Headache Society (AHS) to ask respondents to rate the importance of IHS diagnostic criteria and diagnostic criteria not included in the IHS system for migraine and tension-type headache as well as for analgesic abuse headache. To determine the use of the proposed transformed or chronic migraine diagnosis.

Background The International Headache Society (1988) classification system was adopted immediately in epidemiological studies and in clinical trials around the world. Adoption of the IHS criteria by clinicians, particularly in the US, is proceeding more slowly. US clinicians may continue to rely on diagnostic criteria not included in the IHS system.

Methods 856 individuals listed as active members in the 1997–98 AHS member directory and listed as residing in the US were surveyed. 363 surveys were returned; 35 were not codable, leaving a sample of 301.

Results Only 67.5% (N=203) of the respondents reported using the IHS classification system. Primary headaches. Almost all of the IHS criteria were deemed more important for making a diagnosis than non-IHS criteria for both migraine and tension-type headache. For migraine and tension-type headache, IHS criteria grouped together in separate factor analyses to form statistically coherent constructs. Analgesic rebound headache: 42% of respondents preferred to diagnose medication-rebound headache based on number of days of analgesic medication used monthly, compared to only 12% of respondents who preferred to base the diagnosis primarily on quantity of analgesic medication used monthly, a key criterion set by IHS. Respondents also were apt to diagnose rebound based on medication levels lower than stipulated in the IHS classification. Respondents considered between 14 and 18 days of monthly analgesic use to be sufficient to cause rebound headache. Chronic daily headache: Almost two-thirds (63%) of the respondents reported using the diagnosis of transformed migraine, and assigned this diagnosis to 23% of their patients.

Conclusion This study provides valuable information about the views of AHS respondents on the diagnostic criteria for the most commonly occurring (migraine and tension-type) and currently controversial (analgesic-rebound and transformed migraine) headache diagnoses.

P3-P2

Three questions identify migraine, chronic daily headache, and medication overuse

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Objectives Migraine and drug rebound headache represent the most important primary headache disorders, and both are underdiagnosed and undertreated. Although a variety of screening tools for headache have been developed, none screen for both of these disorders, and none are in common clinical use. The Brief Headache Screen generates diagnoses based on the frequency of severe and mild headache, and the frequency of use of symptomatic medication. The Brief Headache Screen was found to be sensitive for the diagnoses of migraine and drug rebound in an Emergency Department population. Evaluation of this tool in a general medical population is important to support its use in a primary care setting.

Methods The sample was composed of patients who presented for an appointment to the family practice department in a suburban health maintenance organization. Patients who chose to participate completed the Brief Headache Screen, and were later contacted for a telephone interview. Diagnoses generated by the Brief Headache Screen were compared to diagnoses of the trained clinical interviewer.

Results At an interim analysis, 115 patients have completed the Screen and 66 were interviewed. The single question, ‘How often do you experience severe headaches?’ identified 33/33 (100%) of cases of migraine, although 14/33 (42%) were also categorized as transformed migraine. Transformed migraine was correctly recognized in 15/20 (75%) patients, with 4 others labelled as chronic daily headache and 1 as migraine. Of 6 cases of episodic or chronic tension-type headache, 1 was labelled as migraine. Medication overuse was correctly recognized in 18/20 (90%) but not confirmed by clinical interview in an additional 20.

Conclusion In a primary care population, the frequency of severe and mild headache, and use of symptomatic medication, are highly sensitive questions for the recognition of migraine and drug rebound headache. Populations with higher prevalence of tension-type headache will have higher false positive rates for migraine. Replies to written frequency questions, especially of medication use, require confirmation by a clinical interviewer. Incorporating questions regarding the frequency of severe and mild headache, and symptomatic medication use, may improve primary care recognition of migraine and drug rebound headache.
P3-P3

Chronic daily headache with drug abuse prevalence in a population attending a general health centre
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Introduction and objectives Our aim was to know the prevalence of chronic daily headache with drug abuse (CDH+DA) in a population attending a general health centre in two semiurban cities: Gandía and Tavernes de la Valldigna with 43,216 and 16,706 inhabitants, respectively. Sex and age of the sufferers were also considered.

Methods We used a previously validated questionnaire with 6 items (yes/no answers), which was offered to all the people attending both general health centres during 2 months. The questionnaire makes a diagnosis of CDH+DA when 5 or more items are answered yes, according the previous validation phase. A descriptive statistical analysis is made.

Results A total of 2507 users were interviewed from 59,922 inhabitants: 759 males (30.28%) and 1748 females (69.72%). 8.38% of them (210) have CDH+DA, according to the questionnaire: 91.4% are females (192) and 8.6% are males (18) with a mean age of 50.33 for females and 46.69 for males. In 11% of the cases, the reason for consultation was headache.

Discussion and conclusions The prevalence observed in our study was higher than previously reported and probably was related to the fact that people attending the general health centres have greater prevalence because one of the main reasons to attend was to demand prescriptions. The higher proportion of females attending the general health centres (2.31/1 females/males) can explain the higher percentage of females. In only a minority of cases the reason to attend the health centre was headache. This simple questionnaire is a good instrument to detect and offer treatment to patients with headache and drug abuse.

References

P3-P4

Evidence supporting the headache continuum
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Clinically, tension-type headache and migraine seem to fall on a continuum. On the continuum, episodic tension-type headache stands on one side and (episodic) migraine on the other. In between, there are the (almost) daily headache conditions, chronic tension-type headache and ‘tension-type vascular headache.’ The latter is referred to in the IHS classification as chronic tension-type headache coexistent with migraine. In most patients, however, it is one single condition rather than two, as suggested by the terminology used in the classification. The term continuum is used here because of the number of intermediary stages that can be seen clinically between the headaches on it. The principle of the headache continuum is confirmed by a study of more than 250 patients with ‘chronic daily headache’ (1, 2). In the study, the presentation and development as well as the outcome of this particular headache condition was determined. Of the patients, 63% gradually developed the (almost) daily headaches out of initially intermittent headaches. The remaining 37% developed the daily headaches more or less abruptly, with one-fifth of them having a prior history of severe headaches, which is also the prevalence of severe headaches in the USA (3). The transition from initially intermittent to (almost) daily headaches took an average of 10.7 years. Of the patient with ‘gradual-onset chronic daily headache’, 33% initially had mild headaches and 67% severe ones. The severe headaches were significantly more frequently associated with nausea than the mild ones. This suggests that the initial, intermittent mild headaches were episodic tension-type headache and the initial, severe headaches were migraine headaches. However, the (almost) daily headaches that these patients ultimately developed were the same, whether their initial headaches were tension-type or migraine. Of the patients who went back to having intermittent headaches, 77% of those who initially had migraine, presented with migraine at follow-up. Of the patients who initially had episodic tension-type headache, 43% had episodic tension-type headache at follow-up.

References
1. Sheehan & Lecrubier, 1998. IHS and Silberstein criteria by a senior psychiatrist through administration of the MINI International Neuro-Psychiatric Interview

P3-P5

Nosological problems in assessing abuse in migraine patients: preliminary results of a neuro-psycho-physiological study
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Objectives This study examined if patients diagnosed as analgesic abusers using IHS and Silberstein criteria also fulfil DSM-IV criteria for substance abuse or dependence.

Methods 22 transformed migraine patients (Silberstein, 1996) with analgesic abuse (IHS criteria, or Silberstein criteria, or triptan >18/month) were compared to 20 simple migraine patients (IHS criteria) seeking care in a French pain clinic. Patients were assessed using IHS and Silberstein criteria by a senior neurologist. They were then assessed using DSM-IV criteria by a senior psychiatrist through administration of the MINI International Neuro-Psychiatric Interview (Sheehan & Lecrubier, 1998). IHS and Silberstein diagnosis
Results None of the patients with analgesic abuse defined by IHS or Silberstein criteria fulfilled DSM-IV substance abuse diagnosis, whereas most of them (75%) met DSM-IV criteria of dependence. There was no statistical difference between an IHS analgesic abuse diagnosis and a DSM-IV dependence diagnosis. Similarly, we did not find any statistical difference between analgesic abuse defined by Silberstein criteria and DSM-IV dependence criteria. By contrast, 10 patients fulfilled DSM-IV dependence criteria but did not fulfill IHS analgesic abuse criteria due to the fact that they did not overuse medication in quantities required to receive the IHS diagnosis. Nevertheless the behavioural disturbances observed met the DSM-IV diagnosis of dependence. Four patients fulfilled IHS analgesic abuse criteria but not DSM-IV dependence criteria: substances were medically prescribed and these patients were not aware of the behavioural and medical consequences of their overuse. Conclusion We conclude that IHS criteria for analgesic abuse is correlated with DSM-IV criteria for substance dependence. However, patients defined as abusers according to neurological criteria (IHS and Silberstein) cannot be diagnosed as abusers if we apply the DSM-IV psychiatric diagnosis. This discrepancy can be explained by a conceptual difference in that, for neurologists, the term ‘abuse’ is a matter of quantity (how much substance is used) and of pharmacological dependence. For psychiatrists, however, it is more a matter of behavioural and psycho-social disturbance. Nevertheless, IHS and Silberstein criteria defined abusers who also met DSM-IV dependence criteria, a diagnosis which implies serious impairment beyond a simple pharmaco dependence. More research is required to extend this conclusion to community-drawn samples.

P3-P7

Demographic and clinical characteristics of chronic daily headache in Turkish patients


Background The existence of ‘chronic daily headache’ (CDH) as a separate headache form is still controversial. There have been several attempts to classify it as a distinct type, and currently there is a tendency to accept it as such. Methods and material CDH was diagnosed in patients whose headache frequency was more than 16 days a month; who had an initial history of migraine or tension type headache (TTH) that evolved into a more chronic form over time and developed features of both migraine and TTH (but not fulfilling the IHS criteria for either one) and who are likely to overuse medication. The baseline demographic and clinical characteristics of 158 such patients, with a diagnosis of...
CDH, who were enrolled for a national treatment trial in 11 centres were evaluated.

Results

The mean age was $38.9 \pm 10.1$ (SD), 86% were women, duration of CDH was 1–3 years in 38%, 4–5 years in 12.7%, and >5 years in the remaining. The initial headache was migraine in 55.6%, and TTH in 33.5%. 59.5% described daily headaches, while in others the frequency was 4–6 days/week. The prominent feature of the pain was throbbing in 44.6%; pressure in 25.3%, and a combination of various forms in others. It was described as mild in 4.4%, of moderate intensity in 70.9%, and severe in others. Nausea was reported to accompany most headaches by 41.1%, vomiting by 20.9%, photophobia by 51.9% and phonophobia by 62%. 68.4% used 1–3 tablets of analgesics per day, 17.4% more than 4 tablets a day, and 11.4% used more than 4 mg/week of ergotamine. A psychiatric battery was also carried in these patients.

Conclusion

CDH has some distinct features to be considered as a subgroup of primary headaches, that develop only in a limited number of people with migraine or TTH.

P3-P8

Prevalence and description of chronic daily headache in the general population in France in 2000


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Objectives

Surveys based on patient registries in headache clinics have concluded that a significant proportion of headache sufferers have chronic daily headaches (CDH). However, there is as yet no information on both the exact prevalence and description of CDH in the general population. To address this shortcoming, we have conducted this study.

Methods

We have exploiting the data obtained in a recent large, nationwide study of the clinical epidemiology of headache disorders performed in France (GRIM 2000, Abstract, Henry et al.). This study screened 10 585 subjects, representative of the total French population, and involved face-to-face interview with 1486 subjects identified as suffering from headaches. A positive reply to the question 'Do you suffer from headaches every day?' led to a diagnosis of CDH. As well as collecting epidemiological data, this study also assessed data on the clinical presentation, quality of life (QVM disease-specific measure), disability (MIDAS scale) and healthcare consumption. Individuals with CDH were compared to subjects with migraine as diagnosed according to IHS criteria.

Results

In the sample interview, 151 individuals responded positively to the question ‘Do you suffer from headaches every day?’ This provided an estimate of the crude prevalence of CDH in the French general population of 2.96%. Adjusted for age and sex, a value of 2.95% was obtained. Prevalence was significantly higher in females than in males. The CDH individuals were older than migraine sufferers (mean age: 43.2 years vs 38.1 years), although this difference was not statistically significant. Approximately two-thirds of CDH patients had typical migraine symptomatology (pulsatility, nausea, photo- and/or phonophobia). The values obtained with the MIDAS score confirmed a significant degree of disability in CDH individuals who scored worse than migraine sufferers. Individuals with CDH also scored worse than individuals with migraine on the QVM measure of quality of life. Concerning the consumption of healthcare resources, main results were that: (i) the number of visits to GPs was significantly greater in CDH individuals than in migraine sufferers, (ii) psychiatrists were the medical specialty most often consulted, (iii) drug consumption was over six times higher in the CDH group than in the migraine group.

Conclusions

With a prevalence of 2.95%, this study confirms that CDH is an important problem in the general population. Two-thirds of these cases present migraine-like features and may correspond to transformed migraine. Subjects with CDH have poorer functional status and quality of life than migraine sufferers. Data about the consumption of healthcare resources indicate that CDH in the general population are associated with drug overuse and psychiatric morbidity. Finally, this study indicates that CDH is associated with an important burden of suffering in the general population and with considerable expenditure in the health service.

P3-P9

Snoring as a risk factor for chronic daily headache: results from the frequent headache epidemiology study (FRHE)

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Objective

To estimate the effect of sleep-disordered breathing on the risk of chronic daily headache (CDH) in a community sample.

Background

Chronic daily headache (CDH) occurs in 4–5% of the population. Sleep disturbances and sleep-disordered breathing have been noted in episodic headache sufferers, both in clinic patients and in cross-sectional population surveys. In this study, we evaluated the risk of chronic daily headache associated with snoring in a community sample.

Design and methods Cases (180 + HA days per year) and controls (2–104 HA days per year) were identified from a community sample of adults that had completed a telephone interview on general health. Follow-up interviews were completed on cases (n = 206) and controls (n = 507) to determine headache type and to assess many risk factors for the development of CDH. Snoring was assessed with the following question: ‘How often do you snore: never/rarely, less than half the time, more than half the time, or always?’ Snoring was considered present for those answering ‘always’ and all other answers were considered non-snoring.

Results Of the demographic factors considered (age, gender, race, educational level, marital status), snoring was more likely with increasing age and tended to be less common with increasing educational level. Snoring was also positively associated with a history of psychiatric dx (P = 0.037), dx hypertension (P = 0.006), current PRIME-MD depression (including depression without sleep disturbances) (P = 0.020), body mass index (BMI) (P = 0.000), and, for the controls only, higher dietary caffeine consumption (P = 0.033). Snoring was more common in cases than controls (24% vs 14%, P < 0.004), with a similar effect for males and females. Snoring was a greater risk factor for the tension-type group (25% vs 11%) than either the migraine (19% vs 14%) or unclassified group (27% vs 18%). After adjustment for demographic factors, the following odds ratios (ORs) for CDH were found for snoring vs non-snoring overall and by primary headache type: Overall: OR = 2.4 (1.4–4.0), attributable risk = 11%; tension-type HA: OR = 4.6 (1.8–11.8), attributable risk = 16%; non-tension type headache: OR = 1.8 (1.0–3.4), attributable risk = 9%. Further adjustment for dx high blood pressure, psychiatric dx, BMI, alcohol use, caffeine use, and current use of narcotics for pain resulted in an overall OR of 2.5 (1.2–5.5).

Conclusions Current habitual snoring was independently associated with CDH in this community sample, particularly for chronic tension-type headache.

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P3-P10

Painkiller usage for headache in Brazil

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Background Analgesic drug prescription varies between countries in accordance with differences in official rules. In the United States, dipyrone (a pyrazolon derivative) use has been banned because of the putative increased risk of aplastic anemia among its users. In Brazil, the Ministry of Health permits the use of dipyrone and its derivatives as over-the-counter painkillers. Recently, a case-controlled study with nationwide sampling revealed that dipyrone was not associated with aplastic anemia. The consumer price of dipyrone is greater than aspirin and acetaminophen.

Objective To assess painkiller usage in relation to headaches or other complaints among individuals who sought an initial medical consultation at a tertiary-care hospital.

Methods A simple questionnaire about headache symptoms, according to the International Headache Society (IHS) criteria, was applied to 90 randomly selected patients who sought medical assistance at an outpatient service for other chronic complaints that did not necessarily include headache symptoms. Subjects answered a question regarding the drug they most frequently used when they had headaches of any type. After this, patients were seen by a headache specialist physician, who classified the present or past headache using IHS criteria. We compared painkiller usage in migraine and tension-type headaches using stratified analysis (Mantel-Haentzel test).

Results In this sample, 50% of the diagnoses were of migraine without aura. Migraine with aura (14.4%), episodic tension-type (25.6%), and chronic tension-type headache (2.2%) were the other frequent headaches. The most-used headache medicine was dipyrone, regularly used by 55.5% of the subjects. This was followed by aspirin (16.7%), acetaminophen (8.9%) and ergot derivatives (8.9%) (especially tartarate). Non-steroidal anti-inflammatory drugs (NSAIDs) were the first choice for only 2.2% of the subjects. There were no differences regarding the drug profile used, comparing migraine with tension-type headache patients. Conclusion In spite of its higher cost, dipyrone is widely used as the first-choice painkiller among headache sufferers in Brazil. More than 50% of this sample of patients at a tertiary-care facility regularly used dipyrone as an analgesic drug. The use of NSAIDs was rare. It is possible to speculate that the efficacy of dipyrone as a painkiller is greater than other analgesic drugs.
EMG activity in pericranial muscles in healthy volunteers, patients with chronic daily headache and patients with anxiety and/or depression

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**Objectives** To study the role of muscular and psychological factors in headache pathophysiology.

**Materials and methods** 32 chronic daily headache patients with anxiety and/or depression (CDH w. A-D), 21 chronic daily headache patients without any psychological disorder (CDH wo. A-D), 30 anxiety and/or depression patients without any kind of headache (A-D) and 26 healthy controls were examined. The presence of anxiety and/or depression was determined by Mini International Neuropsychiatric Interview. Electromyography measurements were carried out at the level of Frontalis muscles. We performed two-way ANOVA with EMG as dependent variable and CTH and A-D as grouping variables ($F = 5.157$, $P = 0.002$). *Post hoc* comparisons were performed in order to identify the responsible intergroup differences.

**Results** (1). Normal subjects present significantly less EMG activity than (A-D) and (CDH w. A-D) patients ($P = 0.006$ and $P = 0.0003$, respectively). Also, less EMG activity was recorded from (CDH wo. A-D) patients in comparison to (CDH w. A-D) patients ($P = 0.02$). (2). Normal subjects present less EMG activity than (CDH wo. A-D) patients but not significant ($P = 0.055$). However, three patients in the CDH wo. A-D group had EMG values beyond normal range (mean $\pm 2.5$ SD).

**Conclusions** Although IHS recognizes anxiety and/or depression as a cause of tension-type headache, no study has yet been published regarding the pericranial EMG activity in these psychological disorders. Our results (increased EMG activity in A-D patients without any headache) indicate that psychological factors play a role in pericranial muscle function. Furthermore, normal EMG activity in CDH wo. A-D patients suggested that the increased pericranial EMG activity reported in chronic tension type headache could be a result of one of the pathophysiological changes of the coexisting psychological disorders.

**P3-P13**

**Plasticity of the serotonin system and mechanism of analgesic-abuse headache**

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The present series of experiments have been conducted to determine the role of serotonin (5-HT) in the pathogenesis of analgesic-abuse headache. The measured parameters in humans consisted of platelet 5-HT content, 5-HT2 serotonin receptors on platelet membrane and platelet ultrastructure. Those of animal experiments included platelet 5-HT, 5-HT2 receptors and 5-HT transporters in frontal cortex, noiception-evoked Fos-like immunoreactivity (FLI) in dorsal horn neurons and behavioural nociceptive measures. The results showed that platelets obtained from patients with analgesic-abuse headache had a decrease in 5-HT content, an increase in maximum number of 5-HT2 binding sites, fewer 5-HT storage granules, and vacuolization of intraplatelet canalici. The process of 5-HT2 receptor up-regulation became normalized after analgesic withdrawal. These observations imply that the patients with analgesic-abuse headache have an altered 5-HT system, which is characterized by 5-HT depletion and 5-HT2 receptor up-regulation. The effect of simple analgesics on the 5-HT system was also confirmed by experiments in animals. Acute administration of paracetamol led to a decrease in maximum number of 5-HT2 binding sites and an increase in the maximum number of 5-HT transporter binding sites in rat frontal area as well as a rise in platelet 5-HT content. The degree of receptor down-regulation and transporter up-regulation became less evident after prolonged drug administration. This re-adaptation of 5-HT receptors and transporters coincided with the decrease in the analgesic efficacy of paracetamol as well as a fall in platelet 5-HT level. Effect of 5-HT2 receptor activation on the process of thermal and chemical noiception was measured using tail flick and formalin methods and noiception-evoked FLI in dorsal horn neuron. The results showed that rats pretreated with 5-HT2 agonist were more sensitive to both thermal and chemical noxious stimuli than controls. The number of noiception-evoked FLI neurons was also greater in the 5-HT2 agonist-treated group than those in the control. We suggest that chronic analgesic exposure can alter the central nociceptive system by interfering with the 5-HT-dependent antinociceptive mechanism. The up-regulation of noiception-facilitating 5-HT2 receptor may increase the...
sensitivity of central nociceptive neurons and lead to analgesic-related painful syndrome, especially analgesic-abuse headache.

P3-P14

Hypothesis: trigeminal myofascial system (TGM): hypothesis for the relationship between tension-type headache and migraine

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Migraine and tension-type headache (TTH) are common disorders. While it is likely that their high prevalence can produce comorbidity, their relationship is highly controversial: Are they related or separate disorders? Moreover, is TTH a central or peripheral disorder? We propose a pathophysiological model that may help to conceptualize the issues and perhaps reconcile some aspects of the controversy. Our hypothesis is an extension, to some degree, of work by Olesen in regard to integration of vascular, supraspinal and myofascial inputs to the Trigeminal Nucleus Caudalis (TNC). Addition of Moskowitz’s concept of the trigeminal vascular system (TVS) may help to clarify the issues even further. Just as the TNC receives input from sensory afferents of meningeal vessels, it also receives input from myofascial receptors in the distribution of the Vth nerve. Once afferent impulses enter V, and, subsequently, the TNC, the brain does not differentiate vascular from myofascial afferent impulses and processes them rostrally in a similar fashion. If this is correct, then in patients with a biologic predisposition for migraine, excitable cortex, etc., we submit that myofascial input could potentially ‘trigger’ typical attacks, or even potentially gain access to vascular innervations in the periphery, a ‘trigeminomyofascial’ (TGM) system. Can central sensitization secondary to myofascial input lower the threshold for firing of trigemino-vascular neurons? This model could help explain results of the SPECTRUM study and efficacy of triptans in TTH in patients with migraine and not in patients with no history of migraine. The neuroanatomy of sensory afferents from the upper cervical segments and their spillover effects on trigeminal afferents could lead to referral of cervical pain to the distribution of V1 and vice-versa. It would thus appear that if TTH is indeed a separate disorder from migraine, in patients with increased myofascial firing and central sensitization with a migraineous biology the two may be related if one accepts this TGM model of TTH and its similarities to the traditional TGV model. The next steps will include developing both animal and human models to test our hypothesis.

P3-P15

Intractable migraine triggered by brachial plexopathy (thoracic outlet syndrome) displayed by MRI and MRA

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Background and objectives Patients with thoracic outlet syndrome (TOS) present with pain, tingling and numbness of the upper extremity and headache. Over 150 patients referred for intractable migraine had symptoms and signs of TOS. Abduction/external rotation of the upper extremities rotates the clavicles and subclavius muscles and the coracoid processes of the scapulae which compresses the draining veins of the upper extremity and neck, and the neurovascular bundle within the supraclavicular fossa and scalene triangle (costoclavicular compression). This maneuver triggers patients’ complaints of numbness, tingling, pain, and headache. Monitored bilateral magnetic resonance imaging (MRI) and angiography (MRA) display sites of neurovascular compromise. Abduction external rotation MRI sequence triggers these symptoms in the MRI gantry.

Materials and methods A 1.5 T G.E. Sigma Unit, was used, with 5.7 software, 4.0 thickness and saline water bags alongside the neck to enhance signal-to-noise ratio. A body coil was used for full field of view (44 cm) of the neck and the thorax to image both supraclavicular fossae. Contiguous (4.0 mm) coronal, transverse (axial), transverse oblique and sagittal T1-weighted images were obtained. For arm abduction external rotation MRI sequence, the patient was removed from the gantry and, without changing body position, the arms were abducted and extended (arm overhead), and the patient was reintroduced into the gantry.

Results Pain and paresthesias of the hands and arms preceded the migraine. Patients also complained of pain and/or paresthesias of the face, ear, chest, leg, foot, and back. Whooshing sounds and ringing in the ears, syncope and near-syncope, spasms and tremors, and hypertension also occurred. Structural abnormalities included cervical ribs, aberrant right subclavian arteries, hypertrophic scalene and sternocleidomastoid muscles, clavicle fractures, and cancers. Precipitating factors for TOS included trauma, shoulder girdle muscle laxity from fatigue, aging or immobilization, repetitive hand/arm movements and arm abduction and external rotation. The arm abduction-external rotation MRI sequence demonstrated costoclavicular compression and decreased venous return. Surgery confirmed the compromising abnormalities displayed by MRI/MRA. All patients had resolution of the intractable migraine symptoms after scalenectomy and rib resection.

Conclusions Monitored bilateral MRI and MRA display compression abnormalities of the neurovascular bundle and impaired venous drainage of the upper extremities and neck in patients with intractable migraine and TOS. The relationship of neurovascular compression and venous obstruction to migraine trigger will be discussed.
P3-P16

Nerve growth factor in the cerebrospinal fluid of patients affected by chronic daily headache

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Background The biochemical bases of chronic daily headache (CDH) have been poorly investigated. An alteration of serotonin concentration as well as an increased nitric oxide synthase activity and an up-regulation of 5-HT2 receptors have been demonstrated in platelets of patients with CDH, particularly in those with analgesic abuse. The involvement of neurotrophins in this pathological condition has never been studied.

Patients and methods The levels of the nerve growth factor (NGF) were measured in the cerebrospinal fluid (CSF) of patients with CDH which evolved from a previous history of migraine. These levels were compared with those of age-matched control individuals. The sensory neuropeptide calcitonin-gene related peptide (CGRP) and substance P (SP)-like immunoreactivity (LI) was also measured in CSF of both patient and control groups by the RIA method. The ANOVA with least significance difference (LSD) test as well as Pearson correlation were used for statistical analysis.

Results Patients with CDH showed significantly higher NGF levels in CSF compared to the control subjects (P<0.0001). Significantly higher CSF levels of SP and CGRP were also found (P<0.002 and P<0.0001, respectively). A significant positive correlation emerged between NGF and both SP and CGRP values in the CSF and duration of chronic headache and number of days with headache/month (for SP: R=0.78, P<0.006 and R=0.74, P<0.03, respectively; for CGRP: R=0.81, P<0.001 and R=0.68, P<0.008, respectively). This can reflect the association found between values of NGF and values of sensory neuropeptides LI in CSF of CDH. In the patient group, no significant correlation was found between the NGF, SP and CGRP levels and VAS values and pain intensity.

Conclusions These findings support the involvement of NGF in CDH by enhancing the production of the neuropeptides from sensory neurons of the trigemino-vascular system. This may, at least in part, account for the long-lasting sensitization and activation of this system which could contribute to maintaining head pain (1, 2).

References

P3-P17

Quantitative sensory tests in transformed migraine before and after analgesic drug withdrawal

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Objectives The physiopathology of drug-induced headache is still unclear. This preliminary study aims to compare warm and heat-pain thresholds in transformed migraine (Silberstein, 1996) with analgesic abuse before and after medication withdrawal, and in migraineurs without any history of analgesic abuse (IHS criteria).

Methods 27 female subjects were include: 9 volunteers without headache, without analgesic consumption (C group); 9 migraineurs with no analgesic abuse (6 without aura, 3 with aura [SM group]); and 9 patients with a transformed migraine (8 without aura, 1 with aura [TM group]). In the later group, investigations were performed before (TM0) and 8 days after total drugs withdrawal (TM8). A thermostest device (Somedic®, Sweden), operating on the Peltier principle, was used to assess on the warm and heat-pain thresholds on the face and the neck, according to the method of limits. A paired T-test was performed between TM0 and TM8, non-paired T-test between the 4 groups.

Results The warm threshold increased after drug withdrawal particularly on the trigeminal dermatom (34.5±2.2°C to 35.3±2.5°C, P=0.04), but this increase was not significant on the cervical area (P=0.07). The heat-pain threshold increased after drug withdrawal, particularly on the cervical area (44.2°C±2.2–45.5°C±1.9; P=0.04), but not on the face (P=0.16). No differences were evidenced between each group for warm thresholds. Trigeminal heat-pain thresholds seemed greater in patients after withdrawal (46.3°C±1.7) than in control (43.1°C±3.5) or in migrainous group (43.9°C±2.9) (P=0.02 and 0.04, respectively).

Discussion The increase of warm and heat-pain thresholds after withdrawal might reflect an attenuation of a hyperalgesia related to the analgesic abuse and/or to the chronic daily headache state. But this initial hyperalgesia could not be evidenced here, because we did not find any difference between TM0 group and SM nor control group. Increasing the sample size should be necessary to confirm this hypothesis. The fact that patients with medication withdrawal were all headache-free at the end of the withdrawal could explain the decrease of pain sensitivity observed in TM8 group. However, control and migrainous patients were also headache free during the investigations. So the disappearance of headache was not sufficient to explain the lesser pain sensitivity observed after withdrawal. A direct effect of the medical care could not be excluded.
Glutamate and nitric oxide in chronic daily headache: mediators of central sensitization?
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Background Experimental findings using the nitroglycerin model and NO inhibitors evidenced the involvement of NO in migraine patients. Recent research from our group demonstrated an increase in L-arginine/nitric oxide (NO) pathway activity in platelets of patients with chronic daily headache (CDH) with a previous history of migraine (1).

Patients and Methods In the present study we investigated the levels of NO metabolites, nitrites, and glutamate, both measured by HPLC, and those of cyclic guanylate monophosphate (cGMP), measured by the RIA method in the cerebrospinal fluid (CSF) of 20 patients affected by CDH with a previous history of migraine without aura. The above parameters were compared with those determined in the CSF of 15 age-matched control individuals.

Results An increase in the levels of nitrites and cGMP levels emerged in CSF of CDH patients compared with the same levels determined in CSF of control subjects (P < 0.0001 and P < 0.001, respectively). No statistical difference was evident between CSF nitrites and cGMP levels of patients with and without analgesic abuse. Significantly higher glutamate values were also detected in CSF of CDH patients with and without analgesic abuse with respect to controls (P < 0.002). A significant positive correlation was found between glutamate and nitrites and cGMP levels in CDH patients (R = 0.56, P < 0.01 and R = 0.49, P < 0.02).

Conclusions It can be hypothesized that the increased levels of nitrites in the CSF of CDH patients reflects an analogous central up-regulation of NOS activity in the spinal horn/trigeminal nucleus and supraspinal structures involved in the modulation of nociceptive input from cranial structures contributing to central sensitization. On the other hand, the increase in glutamate content in the same patients suggests the implication of this excitatory amino acid in spinal and supraspinal sites involved in head pain induction and maintenance in the same patients. NMDA and NMDA activation by glutamate in these sites could be responsible for NO and cGMP increase as well as sensory neuropeptide release contributing not only in developing hyperalgesia but also in mediating central sensitization in CDH patients. Due to their critical role in this regard, NO and glutamate could be the target of novel therapeutic strategies in these patients.

Reference
P3-P20

Perpetuation of rebound headache in patients who are using analgesics only 1–2 days/week

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Most articles on rebound headache associate daily or almost daily prolonged headaches and daily or almost daily pain relief medications. At our tertiary centre, we have seen occasional patients with proven rebound headaches who initiated the problem by using daily or almost daily medications and noted continuation of the condition for a year or so after they reduced their medications to one or two days each week. Histories of three such patients will be presented. If a physician treating the patient with almost daily headaches inquires only about the recent use of analgesics and fails to ask about the use of pain relief medications at the onset of the daily headache, the diagnosis might be missed.

P3-P21

Rebound headache presenting as frequent migraine without a tension-type headache component

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The typical pain of rebound headache is described by the patient as daily or almost daily prolonged tension-type headache which is noted as the patient awakens or shortly after arising each day. This dull, non-throbbing pain persists all day, dulled by using over-the-counter analgesics or similar medications. In addition, 80% of these patients note super-imposed migraine-like attacks which occur 2–3 times a week or as infrequently as once every 3 months. The latter disabling headache may last for hours or days. The patient is often placed on narcotics, triptans, etc. to reduce the pain and multiple agents to prevent the pain; these treatments sometimes prove ineffective. This pain pattern may persist for months or years. Approximately 0.5–4% of patients with rebound headache describe only frequent, prolonged migraine attacks and deny having the tension-type headache pain. Prior descriptions of rebound headache have not stressed this phenomena. Three illustrative case histories will be presented. The first patient had frequent but not daily migraine. The next had daily migraine and the last had frequent episodes of Status migrainosus. The usual patient with migraine notes 1–2 headaches each month lasting 1–3 days and is headache free on most of the days of the month. Whenever a patient presents with migraine-like pain more than 15 days per month, the possibility of rebound headache should be considered. This diagnosis can be established only by noting improvement after the patient is prohibited from taking all pain relief medications other than prn injections of dihydroergotamine. There have been no reports of dihydroergotamine perpetuating rebound headache when this particular serotonin agonist is used as a single agent.

P3-P22

Analgesic overuse in chronic migraine

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Background Chronic daily headache (CDH) accounts for a high percentage of the people who seek help in headache clinic. Transformed migraine (TM) is the most common CDH. Most patients with CDH used excessive amounts of analgesics or other abortive medications on a daily basis. The use of daily symptomatic medication was more common in patients with TM than those with other CDHs. Frequent use of symptomatic medications was considered to be a major factor to influence and perpetuate migraine into CDH. However, there was some debate that drug overuse might be a consequence of the worsening of the illness.

Method Patients with the chief complaint of headache were consecutively registered in our headache clinic. We followed the operational diagnostic criteria proposed by the IHS. The proposed revision to the IHS criteria for classification of daily and near-daily headaches by Silberstein et al. was used as the basis for the diagnosis of CDH. Patients with CDH other than TM were excluded. We analysed the headache characteristics in a semistructured questionnaire through interview with the patient. All patients underwent detailed neurological and physical examinations. Electroencephalographic and neuroimaging studies were done in patients with suspected organic disorders. Patients with secondary causes of headache were excluded.

Results Of the 1965 cases of headache, 1088 (55.4%) were migraines. 536 cases were included in this analysis. Among them MO was diagnosed in 471 patients, and MA in 65. The ratio of female to male was 5:3. The average age was 40.6 ± 13.9 (5–81). The duration of their headache history was 10.3 ± 8.6 (0–40). There were 217 (38.8%) patients with the diagnosis of TM. Most patients with TM (69.1%) were found to have analgesic overuse. However, 43.3% of those patients with episodic migraine were also found to have analgesic overuse. We divided the patients by duration of headache history into 6 groups. The ratio of TM was 25.5% in the shortest history group, gradually increased to 50.9% in the longest group. In the meantime, the patients with drug overuse were increased from 25.0% to 85.7% in TM patients and from 20.0% to 59.3% in those with episodic migraine. The percentage of drug overuse was higher in patients with TM than in those without TM with a ratio of 1.2–1.6 in each group with migraine history.

Conclusion Analgesic overuse is not only a common problem in transformed migraine, it is also frequently seen in those with episodic migraine. Actually, there is an incremental trend of analgesic overuse as migraine progressed into chronic stage. Nevertheless, over the years, the
patients with TM tended to overuse abortive medication more than those without TM with by a steady ratio.

P3-P23
Personality abnormalities in chronic daily headache: a general population study
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Objective The prevalence and profile of the personality abnormalities in unselected subjects with chronic daily headache (CDH) are unknown. Our aim was to assess the personality profile in a group of subjects meeting Silberstein et al.’s CDH criteria taken from the general population.

Methods Eighty-nine CDH subjects were detected in a sample of 1883 unselected subjects (aged >14) from the general population. They were asked to fill in the EPQ-A personality questionnaire. We considered a questionnaire as abnormal when scores were under the 75% percentile.

Results Some 60% of CDH subjects showed an abnormal questionnaire, mainly neuroticism (52%) and/or psychotism (36%). There were no significant differences in the percentages of abnormal questionnaires for transformed migraine (TM) (64%) vs chronic tension-type headache (CTH) (60%) subjects. The proportion of abnormal questionnaires for subjects with analgesic abuse was significantly higher than for those without abuse (52 vs 36%). There were no significant differences in the personality profiles between TM (56% showing abnormal questionnaires for neuroticism and 47% for psychotism) and CTH (47% and 32%). By contrast, there were clear differences in this regard between subjects with analgesic abuse (68 and 50%) as compared with those without abuse (47 and 32%).

Conclusions Almost two-thirds of CDH subjects from the general population show personality abnormalities, mainly neuroticism but also psychotism. These abnormalities are more patent in subjects meeting criteria for analgesic abuse.

P3-P24
Lifestyle factors in clinic-based headache sufferers
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Objective To examine the meal schedule, sleep length, and caffeine consumption of clinic-based headache sufferers and the relationship between these lifestyle factors and headache, disability, and quality of life.

Background Certain lifestyle factors are widely assumed to contribute to headache. However, little is known about the actual lifestyle pattern of headache sufferers. In addition, little is known empirically about whether these lifestyle factors are related to headaches, disability, and quality of life.

Methods Eighty-six (n = 86) individuals seeking treatment at a hospital-based outpatient headache clinic participated.

Four-fifths (81.6%) were female and the average age was 40.5. They suffered from headaches an average of 17.5 years and averaged 21 headache days per month. Also, 19% were classified as having tension-type headache, 37% as having migraine, and 44% as having both. Participants completed instruments assessing quality of life (MOS SF-36), depression (BDI), and headache-related disability (Chronic Pain Grade). Participants then completed one month of daily monitoring of headaches and lifestyle factors, including delayed/meals, skipped meals, length of sleep, and consumption of caffeinated beverages.

Results Nearly half of this clinic-based sample (45.3%) delayed at least one meal and 38% skipped at least one meal a week. One quarter (25%) of individuals drank 2 or more caffeinated beverages at least half the days in a month. About the same number (24.4%) slept less than 6 h a night or one or more times in a week. Pearson product-moment correlations were conducted to determine the relationship between these lifestyle factors and headaches, disability, and quality of life. Results indicated that delaying meals was significantly correlated with disability days (r = 0.64), depression (r = 0.36), headache severity (r = 0.34), headache frequency (r = 0.29), and mental health functioning (r = 0.29). Total number of daily meals was correlated with disability days (r = -0.45), level of disability (r = -0.38), and characteristic pain level (r = -0.26). Sleep length was correlated with disability days over the past six months (r = 0.45) and headache severity (r = -0.33). Caffeine consumption did not correlate with any headache, disability, or quality of life measures.

Conclusion The majority of headache sufferers in this clinic-based sample do not report a frequent pattern of problems with meal schedules, deprived sleep, or caffeine consumption. There is some evidence of a pattern emerging with delayed/skipped meals and increased levels of pain and disability. There was no evidence of any pattern with caffeine consumption and headache, disability, or quality of life. Further investigation can evaluate whether lifestyle factors in combination are more likely to affect headaches and functioning.

P3-P25
Overuse of zolmitriptan and naratriptan: clinical features
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Objectives Recently, patients who developed drug-induced headache associated with naratriptan (N) or zolmitriptan (Z), overuse were reported. This study was conducted in order to precise clinical features observed in migraine patients with overuse of these new 5-HT agonists.

Methods The specific clinical features of 29 consecutive migraine patients with overuse of N or Z, are given. All patients had a past history of migraine according to the IHS criteria. N or Z overuse was defined according to the two following criteria: daily intake for longer than 1 month, and
more than 37.5 mg a month. Analysis was focused on prior overuse with others drugs, time and importance of overuse, associated overuse with other abortive drugs, headache pattern, psychiatric comorbidity (HAD Scale), overuse-induced adverse events (clinical examination, standard blood tests, ECG), and efficacy of withdrawal.

Results The sex ratio was 3:14:1 and the mean age 48.7 years. 19 patients overused Z and 10 overused N. Twenty seven patients (93%) had a former history of drug overuse (caffeine: 16 and ergotamine: 14). The mean monthly dosage was 70 mg in 22 patients. The mean time of overuse was 6 months (2–27). Seventeen patients (58%) described a pure overuse (PO) involving N or Z alone whereas 12 patients (42%) described a complex overuse (CO) involving N or Z and other abortive drugs. PO patients (16/17) reported a non-disabling headache-free period between two triptan intakes. CO patients (11/12) reported a constant headache between two headache-free period between two triptan intakes. CO abortive drugs. PO patients (16/17) reported a non-disabling headache-free period between two triptan intakes and significant elevation of depression score (but not of anxiety score). Detoxification was more effective in triptan intakes and PO patients (15/17) than CO patients (4/12). Only one patient (but not of anxiety score). Detoxification was more effective in treatment of triptan intakes and significant elevation of depression score (but not of anxiety score). Detoxification was more effective in treatment of triptan intakes and significant elevation of depression score (but not of anxiety score). Detoxification was more effective in treatment of triptan intakes and significant elevation of depression score (but not of anxiety score). Detoxification was more effective in treatment of triptan intakes and significant elevation of depression score (but not of anxiety score). Detoxification was more effective in treatment of triptan intakes and significant elevation of depression score (but not of anxiety score).

Conclusions All members of the ‘triptan family’ can be involved in drug overuse. Both former history of drug overuse and complex overuse show that patient-dependent factors are largely involved in occurrence of N or Z overuse. Pure N or Z overuse is characterized by a frequent absence of the constant disabling headache usually reported in drug-induced headache, a lower level of psychiatry comorbidity and an easier management.

P3-P26

MMPI profiles in transformed migraine patients with drug overuse

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Introduction MMPI was used in evaluating the relationship between recurrent headache syndromes and the presence of specific psychological traits and personality characteristics. Among the various forms of chronic daily headache (CDH), Transformed Migraine (TM) defines a daily or almost daily headache developing from a previous episodic migraine which is very often associated with overuse of symptomatic drugs. Although TM is common in clinical practice, little is known about its psychological correlates and underpinnings. Aim The purpose of our study was to administer the MMPI test in a group of patients suffering from TM with drug overuse before they undertook a withdrawal program. This was performed in order to verify if there is a specific psychological pattern in these patients, if this psychological pattern may be a predictor of clinical improvement, and if improvements in personality characteristics correspond with clinical improvement.

Materials and methods A sample of 123 patients suffering from TM with drug overuse (according to criteria by Silberstein et al., 1993, 1995) was studied: 103 females and 20 males, aged between 20 and 65; mean duration of illness was 25 years. All of the patients were hospitalized to facilitate withdrawal of the overused drugs. Detoxification was followed by a preventive therapy. Before beginning the treatment program, all patients were tested to define their psychological profiles by MMPI.

Results Examination of the validity and clinical scales revealed significant elevations on 3 scales: Depression (M = 72.0), Hysteria (M = 71.4), and Hypochondriasis (M = 75.1). In analyses now ongoing, we are examining other, specially derived scales (select content scales, Harris/ Linges subscales, subtle–obvious, and critical items), 2 point codes and other configural patterns and comparing these results to comparison groups from other investigations.

Discussion Although the lack of a control group is a limiting factor in this study, the focus on a carefully selected and homogeneous sample of an understudied patient group can be helpful to provide some preliminary and cautious conclusions. Our results confirm other data of the recent literature on patients with CDH. The patients in our study will be followed for a period of one year after withdrawal of the overused drug for observing the clinical improvement, and the behaviour of the psychological variables as demonstrated by repeating the MMPI. This study may be helpful to confirm the value of psychological testing in predicting outcome and also to verify if the clinical improvement corresponds to an improvement in psychopathological characteristics in TM patients with drug overuse.

P3-P27

Transformed migraine: the role of psychopathological factors and of drug-abuse

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Background and objectives The transformation of episodic migraine into chronic daily headache is an important and frequent problem. Understanding the causative factors of this transformation would lead to better prevention and treatment of this pathological condition. Previous studies have emphasized the role of psychopathological factors and of drug-abuse.

Methods Three groups of patients were evaluated: mild migraine (less than 4 attacks per month, n = 22), severe migraine (attacks > 4, n = 22) and transformed migraine (more than 15 days with headache per month, n = 22). The following semistructured questionnaires were used: Quality of Life score, MIDAS score, MINI scale, MADRS scale, HAMA score and a questionnaire of daily life events (Amiel-Lebigre). For drug-abuse, a composite index elaborated from IHS criteria, Silberstein and Limmroth criteria was used. Statistical analysis was performed with the EPI-INFo system. The 3 groups did not differ with respect to sex-ratio and mean age.
Results Results are shown in the table.

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Comments This study showed 2 main results: (1) a progressive quality of life impairment and socio-professional handicap across the 3 groups (mild, severe and transformed migraine), without clear-cut distinctions between groups; (2) a clear difference between mild migraine in one hand and both severe and transformed migraine in the other hand with respect to anxiodepressive comorbidity and daily events scores. Regarding drug-abuse, only one patient was found in the mild migraine group. Drug-abuse was more frequent and severe in transformed migraine than in severe migraine and was correlated with the number of headache days per month.

Conclusion This study emphasizes the pre-eminent role of psychopathological factors, mainly anxiodepressive condition in the transformation of episodic migraine into chronic daily headache. Drug-abuse seems to be more a consequence than a causative factor of this transformation.

P3-P28

New daily persistent headache due to lithium carbonate intoxication

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Objectives To present the first case of new daily persistent headache as the main clinical manifestation of lithium intoxication reported to literature.

Case report The patient (62-year-old female) had suffered from bipolar disorder for 12 years and had been treated with lithium carbonate (1200 mg daily), diazepam (5 mg) and thioridazine (25 mg) for 3 years. She presented good control of the symptomatology. Two weeks before the new case, she started to have daily bilateral, intense holoacranial headache, described as being of a heavy nature, without photophobia but with phonophobia and nausea. The patient often awoke with headache already present and was occasionally awakened during the night by headache. She did not remember any previous need for headache medication but had been taking analgesics several times a day since the beginning of the symptoms. Her family reported no alterations in her mood or behaviour. Examination showed parkinsonian and mild cerebellar syndromes. The eye fundus was normal. Magnetic nuclear resonance and a cerebrospinal fluid tap (suboccipital puncture) including pressure measurement were also normal. Laboratory exams only revealed a serum lithium concentration of 2.5 mEq/L (normal reference value – up to 1.5 mEq/L). The lithium carbonate concentration was then reduced. One week later, the patient was free of headache (lithium concentration of 1.4 mEq/L) and showed partial improvement of the extrapyramidal and cerebellar signs and symptoms. She was followed-up for nine months showing no recurrence of headache (last lithium concentration of 1.3 mEq/L) and a normal neurological exam.

Discussion It should be pointed out that even though the neurological examination of the patient was altered, her visit was motivated by the onset of a new and persistent headache. Since cerebrospinal fluid pressure was normal, the following three hypotheses were raised to explain the headache: (1) new and persistent chronic daily headache triggered by intoxication with lithium, (2) headache due to the chronic use of lithium, and (3) headache related to Parkinson’s disease. In our opinion, the signs and symptoms described satisfy better the first hypothesis since the patient’s headache only started in the presence of intoxication with lithium. This hypothesis is supported by the fact that the headache disappeared when lithemia stabilized at therapeutic non-toxic levels.

Conclusions There are no references in the literature to new and persistent chronic daily headache associated with lithium intoxication as the main clinical manifestation. More attention should therefore be paid to patients receiving a chronic therapeutic lithium regimen who report headache.

P3-P29

Outpatient intravenous dihydroergotamine is effective in chronic daily headache

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Introduction Chronic daily or near-daily headache (CDH) affects 4–5% of the general population and 30–70% of patients in primary care and headache specialty centres. Despite its wide prevalence, the management of CDH is quite variable. Many case series have demonstrated the benefit of in-hospital dihydroergotamine (DHE) for patients with CDH. The restrictions against the hospitalization of patients with headache led us to evaluate the role of outpatient therapy. Accordingly, we conducted a retrospective chart review of patients with this condition who were evaluated at a tertiary Headache Referral Center.

Methods We retrospectively reviewed medical charts of 36 consecutive patients who received a 2–3 day outpatient course of intravenous DHE for CDH between 1998 and 2000. Measures of DHE home infusion efficacy were as follows: change in headache severity using a scale from 1 to 10, with 10 being the worst headache; change in use of abortive therapies; and physicians’ impression of improvement.
Conclusions

Better delineate the potential of outpatient DHE for CDH. Call for a larger, double-blind, placebo-controlled trial to regimen. The encouraging results of this observational study of the patient's condition and payers are likely to endorse this visiting nurses are able to assess the psychosocial components of the patient's condition and payers are likely to endorse this regimen. The encouraging results of this observational study call for a larger, double-blind, placebo-controlled trial to better delineate the potential of outpatient DHE for CDH.

P3-P30

Placebo response in chronic daily headache

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Introduction and objectives Different mechanisms are involved in the development of Chronic Daily Headache (CDH) and some of them are related to drug abuse. We present the case of a patient with a long history of CDH and ergotamine abuse who stopped the ergotamine abuse and became dependent on placebo. We discuss the possible mechanisms contributing to this dependency. A 78-year-old man with history of migraine without aura from his puberty. At 50 years, the frequency of his headaches increased, and he started the ergotamine consumption. At 55, he became ergotamine-dependent with daily consumption of 1–2 mg of ergotamine tartrate. He was attended in our department when he was 74-year-old. The headache fulfilled the IHS criteria for migraine. After several trials and failures to stop ergotamine overuse, we decided to substitute ergotamine with placebo capsules (lactose). For 42 months, the patient had a very good response to the placebo. 14 months ago the patient suffered a trauma over the shoulder and experienced continuous pain over his left arm. He was treated by the Pain Unit and they prescribed transcutaneous morphine. After 1 year of receiving transcutaneous morphine, the response of the arm pain is still very good. The headache did not respond in any degree to morphine in all this period, but the placebo capsules are still very effective and completely eliminate his headache. During the period of placebo ‘abuse’, the headache fulfilled the IHS criteria of tension-type headache.

Discussion and conclusions The mechanisms involved in the development of CDH are multiple and some of them are related to the drug abuse. A down-regulation or suppression of an already abnormal antinociceptive system through excessive use of symptomatic medication, analgesic psychotropic side effects such as sedation or euphoria or vascular mechanisms in the ergotamine abusers can contribute to drug dependency. Psychological factors are also very important and are related to positive conditioning. This case report illustrates very well the large role of psychological factors in drug dependency and the influence of the drug overuse on the clinical characteristics of headache.

P3-P31

Use of a phenobarbital loading protocol for rapid detoxification in butalbital overuse

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In the USA, butalbital-containing combination analgesics are commonly used for symptomatic treatment of acute headache. The development of overuse syndromes with physical and/or psychological dependence and analgesic rebound headache are common problems among headache patients in both the primary care and specialty setting. Successful management requires withdrawal from the butalbital-containing medications. Despite the frequency of this problem in clinical practice, a literature search revealed only one article outlining a standard tapering method of drug discontinuation. Attempts at butalbital withdrawal using standard tapering methods require slow discontinuation over a number of days and are subject to patient non-compliance. If the patient does not accurately report butalbital intake or the taper is too rapid, withdrawal seizures can occur. Unsuccessful attempts to withdraw from daily use of butalbital-containing medications are a common source of frustration for headache patients and physicians alike. We describe the application of a phenobarbital-loading protocol in 13 headache patients hospitalized for withdrawal from daily use of 8 and 34 butalbital-containing pills. The protocol features predetermined interval dosing with phenobarbital, a quantitative rating system to determine physiologic tolerance and loading endpoint, and standardized nursing assessments. It allows rapid detoxification from the use of butalbital-containing medications. Compared with traditional tapering schedules for butalbital withdrawal, the phenobarbital loading protocol provides for (1) more rapid and efficient medication withdrawal; (2) reduced opportunities for patient non-compliance and medication ‘bargaining’ behaviour; and (3) superior safety since the quantitative determination of loading endpoints ensures loading to physiologic tolerance. This makes knowledge of actual daily intake prior to detoxification unnecessary and minimizes risk of withdrawal seizures.
P3-P32

Pilot study of continuous subcutaneous infusion of dHE (CSQI-DHE) in the treatment of transformed migraines

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Objective To describe our initial experience with continuous subcutaneous infusions of dihydroergotamine (CSQI-DHE) in the treatment of the type of chronic daily headaches (CDH) known as transformed migraines.

Background Repetitive intravenous (IV) DHE has been used to treat refractory headaches and facilitate the detoxification from analgesics felt to be their inciting cause. DHE has been used not only by intermittent IV bolus, but also by intramuscular injection, subcutaneous injection, and continuous IV infusion. Utilizing a programmable, portable, computerized infusion pump attached to a subcutaneous line, we administered DHE to a group of patients with transformed migraines by continuous subcutaneous infusion (CSQI). We attempted to correlate outcomes of CSQI-DHE with previous responses to IV bolus DHE.

Design and methods After obtaining informed consent, we treated 15 consecutive CDH/transformed migraine patients, in a non-randomized and unblinded fashion, with an IV bolus of 0.5–1.0 mg of DHE. Response was measured with a 4-point pain scale, pain relief scale, and scales for photophobia, phonophobia, nausea and side effects. The IV trial was then followed by a CSQI-DHE, the 8-hourly dose calculated to equal to the initial IV bolus, during which time patients were detoxified from immediate relief analgesics and started on prophylactic agents. Response to treatment was measured using a daily headache diary and the above mentioned study variables. The CSQI-DHE was continued for 7 days or until the patient was 24 h headache-free, whichever came first. A positive response to IV DHE was defined as the reduction of a headache rated moderate (#2) or severe (#3), to a headache rated as mild (#1) or none (#0) by 2 h. A positive response to CSQI-DHE was defined as headache-freedom.

Results Twelve patients responded to IV DHE and 9/12 became headache-free with CSQI-DHE (75%). Of the 3 who did not respond to IV DHE, 1 responded to CSQI-DHE (33%). While the correlation between IV and CSQI-DHE was statistically better than chance ($P = 0.02$), the large difference in percentage response was not statistically significant, due to the small numbers.

Conclusions This study, which utilizes CSQI-DHE, demonstrates the feasibility of detoxifying and treating transformed migraines on an outpatient basis at a significant cost savings compared to inpatient hospitalization. While not reaching statistical significance, due to the small number of patients involved, a positive response to IV DHE suggests a beneficial response to CSQI-DHE.

the first failed, and discontinuation of the opioid if there was no change in headache or if side effects occurred. We assessed their headache diary, side effects of treatment, affect on number of rescue medications, number of headache complaints, and their self-reported performance in daily activities including number of days missed at work or home.

Results There were 24 patients who were placed on low-dose long-acting time-contingent opioids. Three patients discontinued use due to lack of efficacy and two discontinued due to the side effect of peripheral edema. Of the remaining 19 patients, all have been on opioids for at least 6 months. These 19 patients (79%) experienced self-reported stabilization of headache severity, reduction of rescue medications, and reduced number of days missed at work or home activities. All of the 19 patients reported that the time-contingent opioids enhanced the quality of their lives.

Discussion Practitioners have shied away from opioid use in chronic headache due to the fear of addiction, escalating dosages, leading to further morbidity and worsened quality of life with chronic daily headache. Our experience would suggest that in certain carefully studied and defined patients, escalation in dose does not routinely occur. Increased number of headaches (rebound) did not occur.

Conclusion There may be a role for time-contingent opioids in the treatment of certain individuals with chronic daily headaches. This treatment modality deserves more careful, prospective evaluation.

P3-P36
Botulinum Toxin A for refractory chronic daily headache
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This prospective study of 79 patients was designed to evaluate the efficacy of low-dose Botulinum Toxin A for chronic daily headache (CDH) sufferers who have not responded to the usual daily preventive medications. Several previous studies have demonstrated the value of Botulinum Toxin A for the prevention of migraine headache. However, previous studies have varied as to the value of Botulinum for CDH. Preventive medications are only effective for approximately 50% of CDH sufferers. 79 patients with moderate to severe refractory CDH were evaluated. Using a visual analogue scale, one month pretreatment was assessed, followed by 3 months post-therapy. This was a non-blinded, non-placebo-controlled study. Each patient received a total of 24 units (a low dose) of Botulinum Toxin A, 12 injections of 2 units each. The injections, 6 on each side, were done with 2 in the temporal muscles and 4 frontally. To be considered a responder, the patient must have had at least a 2-point decrease in severity, utilizing a 10-point visual analogue scale. 36 of 79 patients (46%) did not respond to the injections. 43 of 79 (54%) were considered positive responders. Among these responders, in the first month, 44% were mild responders, 47% moderate, and only 9% had an excellent response. Among the mild responders, during the second month, 16% had no response, 63% continued to have a mild response, and 21% did well for at least 6 months. Advantages: Increased energy, lack of sedation or weight gain. Disadvantages: Cost, necessity of repeated injections every 3–4 months, possible tolerance over time.
response, and 10.5% had a moderate response. 10.5% improved to an excellent response during the second month. During the third month, 13 (68%) of these mild responders reported no response, with 2 patients continuing mild, 2 moderate, and 2 actually having an excellent response. Among moderate responders \( n=20 \), during the second month, 15% had no response, 15% lessened to a mild response, and 70% continued with a moderate response. None went on to have an excellent response. Among these moderate responders, during the third month, 50% had no response, 10% had a mild response and 40% continued with a moderate response. Among the few initial excellent responders \( n=4 \) of 79, during month 2, all four of these remained excellent. During month 3, 2 went down to mild, one moderate, and one continued with an excellent response. The side effects were mild and the medication well tolerated. Six patients reported a unilateral lid lag for up to 3 weeks, and 2 experienced mild bilateral edema of the eyelids, which resolved over weeks. 2 patients experienced a dramatic increase in headaches. 30% (24 of 79) of patients experienced a moderate or excellent response to the injections. For these patients the injections were felt to be worthwhile. However, for 70% of the patients enrolled, the response was either none or only mild.

**P3-P37**

A retrospective analysis of piroxicam with an antidepressant for the treatment of chronic daily headache

M. Maizels, V. Saenz & J. Wirjo

**Objectives** Chronic daily headache afflicts up to 5% of the adult population, and 1–2% may have drug rebound headache (DRH). There is no consensus as to the best treatment for these conditions. The effect of piroxicam – with or without a tricyclic antidepressant – for these diagnoses, is evaluated.

**Methods** Pharmacy records were reviewed to identify patients who had been given a prescription for piroxicam by headache clinic personnel. A retrospective analysis of charts was performed. Patients were included if the diagnosis was chronic daily headache with or without medication overuse. Treatment effect was estimated as complete relief (fewer than 3 mild headache days/month), greater than 50% relief, less than 50% relief, or no relief.

**Results** Sixty patients had received piroxicam, and 34 (57%) had results which could be evaluated. Eight (24%) received piroxicam alone and 26 (76%) combined with a tricyclic antidepressant. Overall, 24/34 (71%) of patients reported a 50% or greater decrease in daily headache; 19/24 (79%) of patients with medication overuse, and 5/10 (50%) of patients without. Headache frequency was reduced in 19/26 (73%) patients who received both piroxicam and tricyclic, and in 5/8 (63%) who received piroxicam alone. Frequency of migraines decreased by 50% or greater for 17/22 (77%) patients with transformed migraine with medication overuse, and 5/8 (63%) patients without medication overuse. Three out of six (50%) patients treated without a TCA had fewer migraines.

**Conclusions** The combination of piroxicam with a tricyclic antidepressant reduced the frequency of daily headache and migraine, although sample size and study design prevent any conclusions of efficacy. Double-blind trials of treatment regimens, including the current combination, would be useful for the development of treatment guidelines for chronic daily headache syndromes.

**P3-P38**

Prednisolone alleviates and shortens withdrawal phase in drug-induced headache

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**Kiel Pain Clinic, Kiel, Germany**

**Objectives** Drug-induced headache unfortunately is still a common complication in migraine sufferers. Furthermore, it is one of the most frequent headache syndromes that require inpatient pain therapy. In this open study it was investigated whether prednisolone can ease and shorten the withdrawal necessary for the treatment of drug-induced headache.

**Materials and methods** 20 inpatients of the Kiel Pain Clinic fulfilling the IHS-criteria for drug-induced headache were included in the study. All patients primarily had suffered from migraine without aura or migraine with aura and not from chronic tension-type headache. Before treatment all patients complained about daily headache. All patients received the tricyclic antidepressant amitriptyline 25 mg intravenously and 25–50 mg orally during the withdrawal period. 10 of 20 patients in addition were randomized to openly receive prednisolone 100 mg for 3 days, then 50 mg for 3 days and finally 25 mg for 3 days. The time to occurrence of the first headache-free day was recorded as was the frequency of rescue medication use (metoclopramide as an antiemetic or the neuroleptic drug melperone for severe withdrawal headache).

**Results** Both treatment groups were comparable. In the prednisolone group the average age was 45.6 years; patients were suffering from migraine for an average of 23.4 years and from drug-induced headache for an average of 3.7 years; 6 patients were overusing triptans, 1 patient an ergot and 3 patients combination analgesics. The average age in the control group was 49.2 years; patients were suffering from migraine for an average of 24.7 years and from drug-induced headache for 3.2 years; 5 patients were taking triptans and 5 patients combination analgesics. In the prednisolone group headache-free days occurred after 8.6 ± 2.1 days compared to 12.7 ± 3.2 days without prednisolone. The days on which rescue medication (either metoclopramide or melperone) was needed was 2.8 ± 1.8 days with prednisolone and 6.7 ± 3.2 days without prednisolone. The tolerability of prednisolone was good. No patient withdrew because of adverse events.

**Conclusions** In all 20 patients with drug-induced headache, withdrawal of acute migraine medication led to
headache-free days. However, patients taking prednisolone during the withdrawal phase experienced headache-free days earlier. Furthermore, withdrawal symptoms including nausea and headache were milder and patients needed less rescue medication. Prednisolone was well tolerated. These results show that prednisolone can be helpful to alleviate and shorten the withdrawal period necessary for the treatment of drug-induced headache.

P3-P39
Another look at tizanidine: mechanism of action and wide spectrum of clinical usage
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Objective Tizanidine HCl (Zanaflex®) is an aminoimidazoline derivative with structural similarities to clonidine. As a centrally acting \( \alpha_2 \)-adrenergic agonist, it is currently indicated as a skeletal muscle relaxant for spasticity. Several small, open-label studies have shown efficacy across a wider spectrum of painful conditions, including chronic daily headache (CDH). The objective of this study was to better understand the diverse roles of tizanidine and whether or not the \( \alpha_2 \)-agonist mode of action is responsible for all of them.

Materials and methods A review of the literature involving the assessment of tizanidine’s efficacy within potential indications was conducted. The majority of the literature focused on various forms of CDH and its comorbid disorders, including analgesic rebound headache (ARH), chronic tension-type headache (CTTH), myofascial pain, and fibromyalgia.

Results Positive results with tizanidine in patients suffering from ARH have been reported. In a 12-week study, 46 subjects (66%) responded to tizanidine, and many were able to discontinue their non-steroidal anti-inflammatory drug (NSAID) use. Another study among 150 patients with CTTH, showed a 72.5% reduction in headache frequency with tizanidine use. Norepinephrine (NE) may play a role in CDH patterns. Tizanidine may be able to decrease NE output in the central nervous system. Another avenue for tizanidine appears to be in the treatment of myofascial pain; a chart review study reported a 70% improvement in pain symptoms. Because stimulation of nociceptors in muscle results in pain, the possible antinociceptive properties of tizanidine may help alleviate myofascial pain. Tizanidine has been linked to positive results within fibromyalgia patients as well, with a 46% improvement on global assessment scores. The ability of tizanidine to decrease muscle spasticity, its central action, and sedative qualities may attribute to this effect.

Conclusions Tizanidine appears to affect antinociception from the brain stem and spinal cord via regulation of NE systems. Small, open-label studies have shown promising results but do not unequivocally demonstrate efficacy. Additional prospective, randomized, double-blind evaluations are needed. Future studies to investigate the clinical uses of tizanidine and its mechanisms of action are warranted.

P3-P40
Treatment of refractory chronic daily headache with zonisamide: a case series
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Objective Zonisamide (Zonegran\textsuperscript{®}, ZNS) is a novel anticonvulsant, with a broad mechanistic profile, including sodium and calcium channel blocking activities. This study was designed to assess the effectiveness of the use of ZNS in the treatment of refractory chronic daily headache (CDH).

Materials and methods This study included 16 patients who received ZNS for prophylaxis of CDH (i.e. >15 headache days/month) for at least 3 months. All patients had previously failed at least 2 prophylactic medications (mean = 5.9, range = 2–10). Patients were initiated on 100 mg/day of ZNS, and 6 were titrated to a dosage of 200 mg/day after 2 weeks. Patients kept headache diaries, which included headache frequency, duration, severity, and disability ratings. Headache severity and disability were rated using a 4-point scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). Using headache diaries and clinic records, mean headache duration, frequency, severity, and disability were determined for each patient 1 month prior to initiation of ZNS therapy and again 3 months after establishment of a stable ZNS dosage.

Results All 16 patients were female (mean age = 37.3, range = 20–57). Prior to initiation of ZNS, patients experienced a mean of 22 headache days/month, and average headache duration was 8.46 h. After 3 months of ZNS treatment (mean dosage = 137.5 mg/day), the mean number of headache days/month was reduced by 34% to 14.5 days, and the average headache duration was reduced by 24% to 6.41 h. Total headache time was reduced by 50% (from 186 to 93 h/month). Mean headache rating decreased by 23% (from 1.84 to 1.41), and mean disability rating decreased by 24% (from 1.48 to 1.12). Reports of adverse events included mild diarrhoea in 2 patients and weight loss in 9 patients (mean = 11 lb).

Conclusions The results of this study suggest that ZNS is clinically useful in patients with CDH who have been refractory to numerous prophylactic medications. Notably total headache time was reduced by 50%, and ZNS treatment was well tolerated. Controlled trials to investigate the use of ZNS in CDH prophylaxis are warranted.
P3-P41

The effectiveness of fluoxetine on treatment of chronic daily headache

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Background Chronic daily headache (CDH) patients represent a challenge to the neurologist and to the headache specialist. Patients with CDH are difficult to classify, biologically as well as phenomenologically and difficult to treat. SSRIs represent an alternative on treating CDH. The objective of our study was to evaluate the efficacy of fluoxetine on treatment of CDH patients.

Setting Headache Center, Clinic of Neurology.

Method We report an open-label 6-month study on efficacy of fluoxetine on treatment of CDH. 24 patients (18 females, 6 males) entered the study. We considered as CDH all the primary headache disorders that occurred more frequently than 15 days a month and had a duration 4 h or longer. Drug abused patients were excluded from the study. All the patients had been resistant to previous multiple standard therapy. The doses prescribed were 20–40 mg per day. All the patients kept records of the severity and the duration of their headache in a standardized chart.

Results 16 patients (66.6%) had a significant improvement of their headache 2–4 weeks after the initiation of therapy. 3 patients had a moderate improvement and 5 patients did not experience any change of their headache. We did not observe any important side effect of the drug in our patients to discontinue therapy.

Conclusion Fluoxetine is effective and well tolerated and represents an attractive alternative for treatment of CDH.

P3-P42

Peripheral neurostimulation for control of intractable occipital headaches

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Objective To present a novel, safe, and effective surgical approach for treatment of intractable occipital headaches utilizing percutaneous peripheral nerve neurostimulation techniques.

Introduction Occipital neuralgia is a relatively rare headache syndrome characterized by intermittent, paroxysmal, lancinating pain in the distribution of one or more greater and/or lesser occipital nerves. A much broader presentation of occipital headache can occur in up to 50% of migraine headache patients under a variety of diagnosis categories including cervicogenic headache, C2-mediated headache, and transformed migraine headaches. Treatment options initially include medication regimens and nerve blocks. Surgical intervention for intractable headaches in the form of neurectomy or ganglionectomy procedures are significantly invasive with marginal long-term relief and risk development of postoperative deafferentiation pain syndromes. Neurostimulation of the subcutaneous tissues overlying the occipital nerve trunk at the level of C1 can effectively block a variety of occipital headache presentations.

Methods From 1993 through mid-2000, 57 patients underwent permanent implantation of neurostimulation electrode and generator devices in the subcutaneous space at the level of C1 posteriorly after successful percutaneous stimulation trial. Periodic follow-up evaluations over the past 7 years have been performed to measure the effectiveness of the therapy.

Results Follow-up of 1–7 years (mean 3 years). Age range 26–72 years (mean 49). Males 25%, females 75%. Excellent (>75% pain relief) = 26 pts (46%); Good (>50% pain relief) = 21 pts (36%); Fair (>25% pain relief) = 5 pts (9%); Poor ≤ 5 pts (9%). Overall effective pain control 82% (>50% relief).

Conclusions Subcutaneous peripheral nerve stimulation of one or more occipital nerves at the level of C1 can effectively control medically refractory C2-mediated occipital headaches. This application of reversible neuromodulation is a relatively safe and simple surgical technique which should be considered prior to more invasive or destructive surgical intervention for intractable occipital headache pain.


P3-P43

The outcome of treating patients with suspected rebound headaches

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Introduction Previous articles on rebound headache (RH) have usually implied that the patients improved but failed to specify the percent of improvement, the pattern of improvement, or the end point which is achieved. This is a prospective outcome evaluation of 50 consecutive patients who were suspected of having RH based on the history of prolonged headaches of 2 months or longer duration which occurred at least 5 days each week. For inclusion there had to be absence of myocardial disease or stroke which prevented the use of dihydroergotamine as a rescue medication. After careful explanation of the likely cause of their headaches, each patient was given a written list of agents to discontinue (aspirin, acetaminophen, any NSAID, all opiates, ergotamine, all triptans and caffeine). They were instructed how to self-administer subcutaneous dihydroergotamine for excruciating headache and asked to keep a headache log. They were told that the goal was six consecutive headache-free days.

Subjects 34 females, 16 males, age 15–66 (mean 37 years), duration of headaches 2 months, 35 years (mean 50 months); outcome information was obtained from every patient.

Results 11 patients did not follow the instructions to completely omit the analgesics and when last contacted were still having daily headaches. 30 patients achieved the goal of six consecutive headache-free days. The time required
to reach this goal varied from 3–323 days (mean 84 days). Less than half of these patients used DHE. 8 patients showed varying degrees of ‘improvement’ ranging from less intense daily headaches to five consecutive headache-free days. 1 patient had no improvement after omitting the forbidden medications for one year. Comment: These results were similar in those patients with headache of 2–5 months duration, unilateral headaches, post-traumatic headaches, and those who at the time of their initial visit were using analgesics 4 days or less each week. There was no apparent way to predict those who made a rapid recovery or required over 4 months to reach the 6-day goal.

Conclusion 30 of the 39 patients (77%) who stopped the pain relief medications reached the six consecutive headache-free days.

P3-P44

Quality of life measures for headache: a comparison and evaluation

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Objective To describe and comparatively evaluate the characteristics of 19 measures used to assess the impact of recurrent headache disorders on functioning or quality of life. Background It is widely recognized that assessing pain severity alone imperfectly captures the impact of a recurrent headache disorder on an individual’s life. For example, pain severity provides an imprecise measure of the impact of headaches on work productivity, mood, and activities of daily living. Consequently, there is a keen interest in more precisely assessing the impact of headaches on functioning and quality of life. A burgeoning number of measures that differ in their purpose, design, and psychometric characteristics are being used to do this. This paper will provide a description and evaluation of 19 measures that have been used to assess the impact of headaches on functioning or quality of life.

Methods The characteristics of 19 measures will be summarized including a general description of each measure, the method of measure development, type and number of subscales, and the designated population for assessment. Each measure will also be compared on relevant psychometric properties including internal consistency, test-retest reliability, convergent validity, discriminative validity, and sensitivity. The measures that will be described and evaluated include 11 headache-specific quality of life measures (e.g. Headache Impact Test-6, the Migraine Disability Assessment, and Migraine Quality of Life Questionnaire) and 8 general quality of life measures that have been applied to headache populations (e.g. Medical Outcomes Study SF-36, the Minor Symptom Evaluation Profile, and the Psychological General Well-Being Scale).

Conclusion Considerable variability was evident in the dimensions assessed by these measures and in their psychometric strengths and weaknesses. Tables summarizing the characteristics and the psychometric properties of each measure will be provided to assist clinicians or researcher in selecting appropriate measures.

P3-P45

A comparison of disability and psychological factors in migraine and transformed migraine

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Objective The classification of patients with migraine who develop chronic daily headache is controversial, with some classifying such patients as ‘transformed migraine’. The purpose of the present study was therefore to determine the similarities and/or differences between these two headache groups.

Methods We compared patients with intermittent migraine attacks and patients with transformed migraine in terms of mean headache intensity on days with headache, depression (using the Beck Depression Inventory; BDI), pain-related anxiety (using the Pain Anxiety Symptom scale; PASS), and headache-related disability (using the Headache Disability Inventory; HDI). Patients classified clinically as also having significant tension-type headache were excluded.

Results The two patient groups were very similar on all these parameters, with the exception that patients with transformed migraine tended to show more depressive symptoms than migraine patients as measured by the BDI (P < 0.05). This difference in mean BDI scores was small. Aside from the number of days with headache per month, patients with intermittent migraine attacks and patients with transformed migraine were very similar in terms of all parameters studied.

Conclusion Our results support the concept that migraine and transformed migraine headaches are closely related.

P3-P46

Quality of life and disability in transformed migraine with drug overuse

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Introduction Transformed migraine (TM) is a particular form of daily chronic headache, which refers to daily or almost daily headache developing from a previous episodic migraine and/or characterized by the presence of superimposed migraine attacks. Patients with TM very often overuse symptomatic medications. Little is known of functional impact of chronic headache associated to regular intakes of symptomatic drugs on patients’ lives.

Objective To investigate disability and health-related quality of life in a population of Italian patients with TM and drug overuse.

Materials and methods 123 consecutive patients with TM (diagnosis according to Silberstein et al. 1995) and with drug use were included.

Comment: These results were similar...
overuse (defined according to Silberstein et al. 1993) were studied. They were 103 females and 20 males, mean age was 45.7 years, mean illness duration was 25.4 years. All patients were invited to complete two well reported instruments to assess their disability and health-related quality of life: the Migraine Disability Assessment (MIDAS) questionnaire, and the Short Form-36 (SF-36). For both questionnaires the validated Italian versions were used.

**Results** The mean MIDAS score found in our patients was 77.5. 86% of them had higher disability grades (i.e. MIDAS grades III-IV). For all the SF-36 scales but one (Vitality) the mean scores were statistically and clinically lower in the studied sample than those reported in the general population: \( P < 0.000 \) at Student's \( t \)-test; >10-point difference. Similar differences were found for the two summary scores (physical and mental) of SF-36.

**Conclusions** Our results suggest that Transformed Migraine with drug overuse is characterized by a severe functional impairment. The prevalence of highly disabled subjects among the studied patients was more than 80%, and a significant reduction in quality of life scores was also evident.
POSTER SESSION III

Q: Tension-type headache

P3-Q1

Experimental tenderness in episodic tension-type headache

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Objectives The majority of patients with tension-type headache (TTH) have increased tenderness of their pericranial muscles. The pathophysiology is largely unknown but tenderness might be a result of peripheral excitation and/or sensitization of sensory afferents in myofascial tissue. The primary aim of this study was to examine the effect of intramuscular administration of a combination of endogenous substances into healthy subjects. The secondary aim was to compare the experimentally provoked tenderness after infusion of this combination in patients with episodic TTH (ETTH) to healthy subjects.

Materials In study I five healthy subjects (3m, 2f) with a median age of 26 years were included. In study II 15 patients with ETTH associated with increased tenderness of pericranial muscles (5m, 10f) and 15 age matched healthy controls (5m, 10f) participated. The diagnosis of ETTH was in accordance with the IHS-criteria.

Methods In a randomized, double-blinded and placebo-controlled design, infusions of 1 mL of a combination of bradykinin, serotonin (5-hydroxytryptamine), histamine, and prostaglandine E2 was given into the trapezius muscle over 10 min. Tenderness was registered by a palpmeter and scored on a 100-mm visual analogue scale (VAS) throughout the observation period of 24 h.

Results In study I the infused combination produced a local mild tenderness (19 mm on VAS) persisting for >50 min ($P<0.04$) compared to placebo. In study II a local, mild to moderate tenderness persisting for >1 h ($P<0.01$) was produced both in patients and in controls. The increase in tenderness tended to be more pronounced in patients compared to controls ($P=0.08$) and the duration of tenderness was longer in patients compared to controls ($P=0.04$).

Conclusion The infusion model using a combination of endogenous substances can produce a local, moderate and relative long-lasting tenderness in humans and might represent a reliable human model of myofascial pain. Perception of applied stimuli tended to be different in patients with ETTH compared to controls, indicating a possible peripheral sensitization in these patients.

P3-Q2

A new experimental human model of myofascial pain. Pain perception in patients with episodic tension-type headache

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Objectives Most patients with tension-type headache (TTH) have increased tenderness of their pericranial muscles, which may precede the headache. The mechanisms behind this tenderness are unknown but endogenous substances can excite and/or sensitize sensory afferents in animals. The primary aim of the present study was to examine the effect of a combination of endogenous substances infused into the trapezius muscle of healthy subjects. The secondary aim was to compare the pain perception after infusion of this combination in patients with episodic tension-type headache (ETTH) to healthy subjects.

Materials In study I five healthy subjects (3m, 2f) with a median age of 26 years were included. In study II 15 ETTH patients with associated pericranial myofascial tenderness (5m, 10f) and 15 age matched healthy controls (5m, 10f) participated. The diagnosis of ETTH was in accordance with the IHS-criteria.

Methods In a randomized, double-blinded and placebo-controlled design, infusions of 1 mL of a combination of bradykinin, serotonin (5-hydroxytryptamine), histamine, and prostaglandine E2 was given into the trapezius muscle over 10 min. Pain was assessed by means of a 100-mm visual analogue scale (VAS), McGill pain score, and a 24-h diary.

Results In study I the infused combination produced a moderate pain (37 mm on VAS) persisting for >50 min ($P=0.04$) compared to placebo. The pain quality was described using sensitive words and with a PRI(R) higher after the combination ($P=0.04$) but still slightly lower compared to spontaneous pain conditions. In study II the combination produced a moderate pain persisting for >20 min ($P<0.01$) compared to placebo in both patients and controls. Pain quality was described using sensitive words and PRI(R) was higher after the combination compared to placebo in both groups ($P<0.01$). The pain intensity tended to be stronger in patients compared to controls ($P=0.08$) and pain description and distribution was different in patients and controls.

Conclusion The present human model of myofascial pain using intramuscular infusions of a combination of endogenous substances might be a reliable human model that can produce a moderate and prolonged pain. The trend of variations in pain perception between patients and healthy
controls might indicate that sensitization also plays a role in ETTH.

**P3-Q3**

**Can we predict coping with pain? Coping with laboratory stressors in individuals with tension-type headache**

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Coping is an important element in the experience of recurrent headache. Many studies have investigated how coping responses relate to health outcomes. Frequently these studies rely on coping measures that ask the individual how they cope in general or the individual is asked to describe how they cope with a specific event. However, little evidence exists to support the underlying assumption that these reports of general coping strategies are related to coping efforts in specific situations. In the present study, coping was assessed twice, once as part of a screening process and once during the experience of laboratory stressors. The participants in the study were 24 women who suffered from episodic tension-type headache and 22 control participants who reported infrequent headache (2 or fewer per month). As part of the screening process the participants completed a shortened version of the Cognitive Coping Strategies Inventory (CCSI; Butler et al. 1989). This scale asks individuals how they cope with pain. The short version contained 20 items assessing coping (use of distraction, etc.) and 10 items measuring catastrophizing (I imagine the pain getting worse, etc.). The participants were subsequently asked to participate in two experimental tasks involving pain and discomfort, the cold pressor and a blood pressure cuff task in which the cuff was inflated to 80 mmHg. The shortened version of the CCSI was completed in which participants reported how they coped with each task. Headache sufferers reported more discomfort during each task. Headache sufferers also reported greater levels of catastrophizing at all points of assessment. Controls reported greater use of coping at the screening assessment, but headache sufferers reported more coping efforts during the laboratory tasks. Control participants’ coping scores at the screening were uncorrelated with actual coping efforts reported during the laboratory tasks. However, there were several positive correlations (ranging from 0.46 to 0.54) between screening and task measures for the headache sufferers. The results suggest that headache sufferers are consistent in their reports of pain-related coping strategies and that a general coping assessment might have utility in predicting how individuals with episodic tension-type headache cope with pain. This means that this type of coping assessment would be useful in tailoring a cognitive-behavioural treatment program for headache sufferers.

**P3-Q4**

**Implicit models of headache: a comparison of beliefs about headache in headache sufferers and headache-free individuals**

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Implicit models are the beliefs individuals possess about the causes, consequences, and long-term course of an illness. Implicit models have been found to predict compliance with medical and behavioural treatments of disorders such as hypertension and cancer. Given the subjective nature of pain, it is logical to expect that implicit models of headache would impact the experience and behaviour of headache sufferers. A small number of studies have explored the beliefs headache sufferers have about the causes of headache, however, headache sufferers have not been compared to a headache-free population to determine if they have different beliefs about headache. Previous research has also not attempted to determine whether these beliefs have an impact upon headache-related behaviour. We have surveyed 240 individuals who fall on a continuum from infrequent to frequent headache. Participants were asked questions that would allow for a provisional diagnosis of headache type. They were also asked questions about the causes and impact of headache, methods for controlling headaches, the personality qualities of headache sufferers, the amount of control people had over preventing headaches and the coping strategies they had utilized to deal with headache. 57% of our population reported having headaches more than once per month, the majority of these individuals meet criteria for tension-type headaches. Frequent headache sufferers are more likely to have identified events that cause headache and they report that a typical headache is more likely to impact functioning. Interestingly, frequent headache sufferers also feel they have more control over preventing future headaches. The two groups did not differ in their beliefs about the efficacy of many headache treatment approaches, however, individuals who had received a physician’s diagnosis regarding their headache were less likely to believe that prescription medications or seeing a physician were an effective approach to controlling headache pain. The implications of these results for treating headache will be discussed.

**P3-Q5**

**Evolution of pain perception in tension-type headache. A 10-year follow-up study**

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**Objectives** Cross sectional and experimental studies have reported decreased mechanical and thermal thresholds in patients with chronic tension-type headache (CTTH) compared to healthy subjects. Moreover, thresholds are lower in
younger subjects compared to the elderly. The aim of the present study was to examine the evolution of thresholds in a 10-year follow-up study of patients with tension-type headache (TTH).

**Materials** 31 patients with an IHS diagnosis of episodic TTH (ETTH) (n = 14) or CTH (n = 17) and 11 healthy controls first examined in the period from 1989 to 1992 participated.

**Methods** Patients and controls were re-examined median 9 years (range: 8–11 years) after the first examination. Actual headache diagnosis and frequency were recorded by means of a headache diary and a structured interview. Pressure pain detection and tolerance thresholds (PPDT, PPTO) and thermal heat detection, pain, and tolerance thresholds (THDT, THPT, THTO) were re-examined on the index finger (fing) and in the temporal region (temp) on the non-dominant side using the same standardized methods.

**Results** In former patients the present median age was 54 years (range: 31–72) and in controls 41 years (range: 35–68). Among patients the median frequency of TTH decreased from 15 to 7 days/4 weeks (P = 0.005). All thresholds but the PPTOfing and the THDTs had increased. However, only the PPDTtemp (P = 0.041), the PPTOfing (P = 0.910), the THPTtemp (P < 0.001) and the THDTs (finger: P = 0.020; temp: P < 0.001) increased significantly. In contrast, the THDTs were significantly decreased (finger: P = <0.001; temp: P = 0.030) compared to prior tests. Among controls the frequency of headache was unchanged, 0 days/4 weeks (P = 0.783). All pain thresholds but the PPDTtemp and the THDTs had increased. However, only the THPTtemp (P = 0.026) and the THTOs (finger: P = 0.008; temp: P = 0.005) increased significantly. No significant changes were found comparing changes in thresholds or tenderness in patients to controls after this 10-year period.

**Conclusion** In line with previous cross sectional reports, this study supports the hypothesis that depression increases vulnerability to experience headaches following a stressful laboratory task, and the increased vulnerability to experience headaches following stress was associated with elevated levels of pericranial muscle tenderness.

**P3-Q6**

Depression increases vulnerability to tension-type headaches following stress in a laboratory paradigm

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**Objective** To determine if depression increases vulnerability to tension-type headaches (TTHs) following a stressful laboratory task and to examine psychophysiological variables that might be associated with any increase in vulnerability.

**Background** Correlational data have established a relationship between depression and recurrent and chronic pain disorders but the nature of this relationship remains unclear.

**Methods** Screening (N = 852) and structured diagnostic interviews (Prime MD and IHS Diagnostic Structured Interviews) identified three groups of undergraduate females (median age, 18.5 year): depressed (Prime MD Mood Disorder diagnosis) and headache prone (> 8 TTHs per month; N = 13), headache prone but not depressed (N = 22) and healthy controls (N = 13). (All subjects who met screening criteria for depression or received a Prime MD Mood Disorder diagnosis also experienced regular headaches, so a fourth depressed but relatively headache free group could not be formed.) Beck Depression Inventory scores were significantly higher in depressed/headache prone subjects (M = 21.6) than in either headache prone (M = 4.6) or healthy controls (M = 5.5). When subjects were headache free they began an approximately hour-long stressful math task previously found to induce TTHs in some individuals. Blind evaluations of pericranial muscle tenderness (PMT) using a standardized protocol and a dolorimeter (500 g/cm2) to standardize the pressure applied at 12 bilateral muscle sites were completed immediately before, immediately after, and 24 h after the one-hour math stressor task. Subjects also recorded headache activity before, during, and immediately after the stress task and during the 24 h post-task.

**Results** Subjects in all three groups reported equally high levels of stress during the laboratory stressor. However, depressed/headache prone subjects were significantly more likely to record headache pain (P < 0.05) 30 min into the math task and immediately following the laboratory stressor than were either headache prone subjects or healthy controls (P < 0.05). Depressed/headache prone subjects also exhibited significantly higher PMT total tenderness scores (TTS) than other subjects (P < 0.05) both before and after the laboratory stressor.

**Conclusion** Depression increased vulnerability to developing TTH following a stressful laboratory task, and the increased vulnerability to experience headaches following stress was associated with elevated levels of pericranial muscle tenderness.

**P3-Q7**

Paroxetine for chronic tension-type headache: effectiveness in tricyclic non-responders


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**Objectives** Evaluate the effectiveness of paroxetine HCL in two groups of chronic tension-type headache (CTTH) sufferers, tricyclic antidepressant medication non-responders, and placebo non-responders.

**Materials** A daily diary was utilized to record headache activity, analgesic medication, and compliance with study medication.

**Methods** Subjects were patients treated with tricyclic antidepressant medication (amitriptyline to 100 mg/day and if not tolerated, nortriptyline to 75 mg/day) or matched
Tension type headache

P3-Q8

Treatment of frontal tension headaches with Botulinum Toxin A

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Objectives The majority of chronic headaches are classified as tension, or muscle contraction, headaches (TH). The pathogenic mechanism of TH is unknown. Treatment of patients with TH, especially chronic daily headache, can be challenging. Intramuscular injections of Botulinum Toxin A (Botox) produce a localized chemical denervation muscle paralysis. The aim of this study was to determine the efficacy of frontalis, corrugator, and procerus muscle paralysis in the treatment of episodic or chronic frontal TH.

Materials and methods All patients ages 18 years or older with episodic or chronic frontal TH (as defined by IHS) were eligible for inclusion in the study. Patients with a history of stroke, migraine alone (i.e. un mixed headache), previous Botox injections, or forehead muscle surgery were excluded. 41 patients were enrolled in this prospective, double-blind, randomized controlled study. The age of the patients ranged from 19 to 80 years, with a mean age of 46 years. There were 32 female and 9 male participants. Each patient had a complete history and neurological examination, which was done by a neurologist. Subjects completed daily headache and analgesic logs. After collection of a baseline daily headache and analgesic log for 30 days, the subjects were randomized for injection of either 50 U of Botox or an equal volume of sterile saline into the glabella and forehead region. Daily headache and analgesic logs were collected for up to 6 months postinjection. Frequency of headaches before and after injection was compared using Student’s t-test. Intensity of headaches before and after injection for Botox-treated and control groups was tested using a fixed effects model to account for the repeated measures design.

Results Botox-treated patients experienced an average of 5.4 headaches per week before injection and 3.9 headaches per week after injection. Control patients experienced an average of 5.3 headaches per week before injection and 4.2 headaches per week after injection. The net difference in the average number of headaches per week (−1.5 vs −1.1) was not statistically significant (P=0.72). The average intensity of headaches for control patients was not significantly reduced after injection (5.4 pre vs 5.3 post, P=0.07). However the intensity of headaches in the Botox group fell significantly from an average 5.2–4.6 (P<0.0001).

Conclusions Although Botox did not significantly reduce the frequency of tension headaches, it did significantly reduce the intensity of the headaches. This supports the hypothesis that muscle contraction contributes in part to tension headaches.

P3-Q9

Abstract withdrawn
The effect of mianserin on quality of life survey in tension type headache patients

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Tension type headache is the most common primary headache type, which diminish the quality of life survey of the suffering patients. This study addresses the question: how effective is the mianserin therapy, a tetracyclic antidepressant (2×10 mg) combined with non-steroidal anti-inflammatory drug for one month on quality of life in tension type headache patients? 19 tension type headache patients evaluated according to IHS criteria, were enrolled in this study (16 F, 3 M, mean age: 29 ± 1.7). Mianserin was combined with a non-steroidal anti-inflammatory drug (naproxen sodium 2×275 mg [n=9] or nimesulid 2×100 mg [n=10]) and used for approximately 1 month. Quality of life was assessed using Medical Outcome Study (MOS) Short Form Health Survey (SF-36). The SF-36 Health Survey is an instrument used for the assessment of the health-related quality of life of patients. The survey was constructed for self-administration by people 18 years of age and older. Evaluated parameters are physical functioning, limitations due to physical health, limitations due to emotional problems, energy-fatigue, emotional well being, social functioning, pain and general health. Mianserin therapy combined with non-steroidal anti-inflammatory...
drug, in tension type headache patients for one month improves significantly all the parameters assessed and related to quality of life. As it is well known that tension type headache diminishes quality of life, the management of tension type headache should also be addressed to the effect of the therapy on quality of life. In this study we present the beneficial effect of mianserin (2×10 mg) on quality of life in tension type headache patients.
R: Cluster headache

P3-R1
Characteristics of cluster headache sufferers from a tertiary headache centre
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Background and objectives A cluster headache is a relatively rare disorder, marked by excruciating bouts of head pain with associated autonomic features. This condition is difficult to study due to spontaneous remissions and its low prevalence in the population. The objective of the study was to compare characteristics of cluster headache sufferers seen at a headache specialty centre to characteristics described in the published literature.

Methods Eighty-eight charts from all episodic and chronic cluster headache sufferers seen at an ambulatory headache specialty centre over a 10-year period were reviewed retrospectively. Diagnoses were made by 1988 International Headache Society criteria.

Results Seventy-two men and 16 women with cluster headaches (74 episodic and 14 chronic) were identified. The mean age of first onset of cluster headache was 27 years (ranging from 11 to 50-year-old). The average duration of episodic cluster cycles was 8 weeks and mean remission periods were 27 months. Review of social histories revealed that 66% were smokers, 16.5% used greater than 6 alcoholic beverages weekly and 21% used greater than 4 caffeinated beverages daily. Comorbid self-reported and physician-reported anxiety or depression was infrequent with 4.6% reporting anxiety and 4.6% depression. Twenty-seven percent (27%) had other comorbid headache conditions; 19% had tension-type headaches and 12% had migraines. Sixty percent (60%) had a family history of headaches; 51% reported at least one family member with migraine and 8% cluster headache. 58% noted alcohol was a headache trigger while 25% noted no identifiable triggers. Review of responsiveness to oxygen abortive therapy revealed that 61% had found relief with oxygen therapy. A review of laboratory data revealed comorbid hypercholesterolaemia in 24% of patients with total cholesterol levels greater than or equal to 250. Eleven percent (11%) had levels above 300 and 5% had levels above 350.

Conclusions This retrospective study revealed great variability in headache characteristics of episodic and chronic cluster sufferers presenting to a tertiary treatment centre. Self-reported or physician-reported anxiety and depressive disorders were lower than previously reported. Comorbid hyperlipidaemia has not been previously reported. Age of first cluster presentation, average cycle duration and headache remissions were consistent with previously reported data. Social history of greater tobacco, alcohol and caffeine use of the general population was also consistent with reported data. Family history of headache and response to oxygen therapy was consistent with response rates noted in prior studies.

P3-R2
Female cluster headache in Argentina: an epidemiological study
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Objectives Cluster headache is a form of primary headache that prevails among men, but this male predominance of the disease has decreased progressively from decade to decade. We usually find that this group of patients have a male phenotype, are heavy smokers and sometimes alcohol abusers. Kudrow, Ekborn, Lance and Manzoni have made large epidemiological studies. Cluster headache prevalence was 0.09% and incidence was about 0.4%.

Male:female ratio was 5:1 in these studies, and symptoms usually begin at 30 years approximately. We will describe our epidemiological findings of 114 cluster headache patients in two neurology centres in Buenos Aires, Argentina.

Materials and methods We have followed 114 patients in two neurology reference centres in Argentina. We have searched epidemiological data retrospectively in our archives for a period of 4 years. If there was a missing value, we have made a telephonic update.

Results We analysed 114 patients (84 males and 30 females; ratio 2.8:1). The mean age was 47.2 years (range 18–82). The symptoms have begun on average at 33 years of age. 18% of the men had chronic type cluster headache, whereas 43% of women suffered chronic headache. 76% of the male group were smokers, whereas only 41% of the women were smokers. On average, the female group presented 16.1 attacks per week while men had a mean value of 10.5. The concomitance of other types of headache is much more common in women (53%) than in men (22%).

Conclusions This study shows some particularly interesting data about female cluster headache: Gender ratio is closer than in other studies (M:F = 2.8:1). This may be due to significant changes in lifestyle over the last decades especially regarding employment. Chronic type headache is more frequent in women, but the frequency of attacks is less. Even in the episodic type, we have seen more irregular patterns in this group. The presence of other concomitant primary headaches in the female group makes the diagnosis more difficult, especially in patients who suffer severe migraine. Men are heavier smokers than women in our group of study. The clinical picture was similar in both groups of study. It is hard to analyse the pharmacological
response in a retrospective study because a lot of drugs are used without a proper response control, but in our experience SC sumatriptan is almost always effective. On the contrary, the oxygen response is generally poor.

P3-R3

Prodromal, premonitory and aura complaints in episodic cluster headache patients

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Several reports have described different symptoms that may occur before the pain starts in episodic cluster headache sufferers. However these clinical manifestations were not discussed by other researchers. Detailed information concerning these subjects may help us in the understanding of this painful entity. Thirty-nine episodic cluster headache patients in accordance with HIS criteria (30 males, aged 26–73 and 9 females, aged 24–58) with premonitory and/or prodromal symptoms were studied. They reported spontaneous symptoms one day to several weeks before the ‘cluster bouts’ onset (premonitory) or revealed symptoms minutes before the beginning of the attack (prodromes). A group of patients related spontaneous premonitory symptoms such as stiffness, tiredness, neck discomfort, oppressive sensation, paresthesias, hypersensitivity and ice-pick-like pain over the area subsequently affected. Blurred vision and sleep disturbances were also reported. Other patients commented on the presence of prodromal symptoms. The most frequent prodromal symptoms described were osmophobia, palatal hypoestesia, yawning, neck stiffness, abdominal pain, limb paresthesias, impaired taste, bleeding from the nose, tiredness, hunger, somnolence, pressure, tension or icy pain in the affected areas of subsequent pain. Moreover in four patients an ‘aura phenomenon’ was described before the episode or during the attack. In three of them visual aura appeared; only one patient had visual aura and hemisensory changes. This picture has been documented in patients with longer periods of evolution or severe attacks. The different clinical manifestations of the patients seems to reflect a complex pathophysiological abnormality. Improving our understanding of cluster headache may provide a more rational, specific and early treatment.

P3-R4

Episodic cluster headache: clinical phases

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Background and objectives A still undetermined percentage of patients suffering from episodic cluster headache have non-painful symptoms preceding the onset of a cluster headache period (premonitory symptoms) and/or at the start of a painful attack (prodromal symptoms). The presence of these symptoms in some patients can make possible the detection of physiopathological variants and the early institution of a therapy to prevent the painful attack. In order to emphasize the existence of premonitory and prodromal symptoms and the importance of identifying them, a clinical subdivision of episodic cluster headache into phases is proposed.

Methods A structured questionnaire was given to patients with episodic cluster headache or filled in during a visit.

Results The questionnaire was completed by 38 patients. 13.15% of them said they had had premonitory symptoms, 36.85% stated they had had prodromal symptoms and 5.25% reported they had had both symptoms. Of the patients with prodromal symptoms, 71.4% had them 20–30 min before the onset of pain, and such symptoms were paresthesia sensations, heaviness or discomfort in the side that would be later affected by the pain attack. As for the remaining 28.6%, prodromal symptoms began up to 12 h before the onset of pain, and these symptoms included not only paresthesias but also euphoria, great energy and eye discomfort. Post-headache symptoms – discomfort, pressure, listless – were reported by 11 patients (29%).

Conclusions In our view, prodromal symptoms preceding the onset of the pain attack for a short period of time – 30 min – should be considered as part of the attack itself – the significance or origin of earlier symptoms are yet to be clarified. In order to have a better study, understanding and detection of all the clinical symptoms, the following phases in episodic cluster headache are proposed: 1- previous symptoms phase: (a) premonitory symptoms; (b) prodromal symptoms. 2- headache and autonomic symptoms phase; 3- postheadache phase. Studies with a greater number of patients are needed in order to validate these interpretations and pave the way for better knowledge and the early introduction of a treatment for this illness.

P3-R5

Episodic cluster headache and illumination of lunar disc

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Since ancient times, the moon has been associated with several human pathologies, such as epilepsy or mental disorders. Furthermore, it has been related to other aspects of human life. Indeed, despite contemporary scepticism, the possible effects of the moon on humans continue to obtain popular support by the layman and to stimulate research among scientists. Thus, the possible relationship between lunar phases and human behaviour has been considered in a number of recent works, mainly on the issues on emergency activity; car accidents; violent behaviour (Thakur 1984). Episodic cluster headache (CH) is characterized by a typical pattern of the attacks, which may present with regular
Cluster headache: clinical features and habits in La Plata

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Objective The purpose of our study is to show the clinical features of a sample of cluster headache in La Plata, Argentina.

Materials and method Our study included 108 cluster headache patients, referred to the Headache Unit of Hospital Rossi of La Plata between 1995 and 2000. Cluster headache diagnosis was made according to the International Headache Society criteria. We reviewed the clinical records used at our centre and we analysed the following parameters: clinical type, sex and age at onset, annual and daily distribution of attacks, accompanying symptoms during the attacks and patients' habits.

Results Female 15/male 93, ratio 1/6.2. Average of age at onset: 30.2 years. Average of age at first consulting: 42 years. Clinical type: Episodic form: 85 patient (91.8%). Chronic form: unremitting from onset: 4 patient (3.70%). Periodicity undetermined: 9 (8.33%). Average daily attacks: 1.9. Duration of attacks: 34.30 min (15–120 min). Time of cluster attacks: Patient asleep (only): 25.5%, patient awake (only): 10.5%, both: 64%. Past medical history: Hypertension and coronary heart disease: 47 patients (43.51%). Peptic ulcer and gastritis: 49 (45.37%). Head trauma: 30 (27.77%). Diabetes mellitus: 9 (8.33%). Accompanying symptoms during attacks: Horner Sd. 81 patients (75%). Conjunctival injection: 92 patients (85.18%). Eyelid swelling: 60 patients (55.55%). Forehead sweating: 43 patients (39.81%). Nausea: 52 patients (48.14%). Nasal stenosis: 79 patients (73.14%). Rhinorrhea: 85 patients (78.70%). Photophobia: 83 patients (76.85%). Phonomphobia: 76 patients (70.37%). Diarrhoea: 22 patients (20.37%). Habits: Cigarette smoking: 99 patients (91.66%). Alcohol intake: 58 patients (53.70%). Coffee intake: 99 patients (91.66%).

Conclusions The most important observation of this study suggests that these patients are severely affected with high percentage of accompanying symptoms during the attacks, have several associated diseases and are very heavy cigarette and caffeine consumers.

P3-R7

Blood pressure in cluster headache

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Although the relationship between cluster headache and the autonomic nervous system is well known, details are still few. In the present study, we examined the systolic blood pressure in cluster headaches in 248 patients (193 male and 55 female cases). Their age ranged from 17 to 65-year-old with the mean of 37.2 ± 10.3. The onset initially occurred between 14 and 57 years. The controls were 193 cases of cervical spondylosis without neurological symptoms. The average blood pressure was 117.1 ± 10.4 mmHg in non-headache attacks in the cluster period, and 117.8 ± 9.5 mmHg in the non-cluster period and 122.2 ± 12.8 mmHg in control cases. The statistical difference was negative. We divided patients into seven groups according to their blood pressure: <100, 101–110, 111–120, 121–130, 131–140, 141–150 and >151 mmHg. The case numbers and frequency in each group was 8 cases (3.2%), 71 (28.6%), 92 (37.1%), 55 (22.2%), 15 (6.0%), 6 (2.4%) and 1 (0.4%) in that order during the cluster period, and 4 (2.0%), 38 (19.7%), 46 (23.8%), 49 (25.4%), 41 (21.2%), 13 (6.7%), and 2 (1.0%) in the control cases. The results for the non-cluster period and by sex were also similar. One of general findings in cluster headaches is that the systolic blood pressure tends to be lower, and the autonomic nervous system was presumed to be a contributing factor in this result.
Precipitating factors in cluster headache patients: a nationwide study in 1844 Dutch patients

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Background The identification of factors that precipitate cluster headache (CH) periods and attacks is important as it may influence treatment. Recognizing these factors may help patients to avoid these triggers.

Objectives In order to assess precipitating factors in cluster headache patients, we conducted a questionnaire study in a large Dutch population of CH patients, focusing on trigger factors for CH periods and attacks.

Methods Patients with CH or CH-like syndromes were identified by means of public announcements and by direct mailings to all neurologists (n = 5800) in The Netherlands. All patients were sent two questionnaires: one screening questionnaire which included the IHS criteria and one more extensive questionnaire.

Results From 04/01/98 until 01/03/2001, 1844 patients returned the screening questionnaire. The second, more extensive questionnaire was obtained from 1406 patients. Of these, 1076 (77%) were IHS-CH and 289 (21%) were non-IHS-CH patients. Of these 1076 IHS-CH patients the precipitating factors will be reported. This study included 844 male (78%) and 232 female (22%) IHS-CH patients (M/F ratio 3.6:1). (1) Precipitating factors preceding the cluster period were reported by 439 patients (41%). Stress was reported in 247 patients (56%), change in weather condition in 180 (41%) various illnesses in 160 (36%), alcohol consumption in 57 (13%), and flying in 28 (6%). (2) Precipitating factors triggering the actual CH attack were reported by 840 patients (78%). All of these 840 patients noticed a circadian timing of their attacks. The majority of the attacks were between 1 and 3a.m. Exclusively during the cluster period, drinking alcohol provoked a CH attack in 483 patients (82%), lying down or taking a nap during the day in 204 (35%), flying in 97 (16%), high altitude in 58 (10%), change in weather condition in 157 (27%), and exercise in 128 (22%). Smoking was reported in 748 patients (70%) and an additional 221 patients (20%) had smoked heavily in the past. Of 935 patients, 856 (91%) smoked before the CH started. Stopping smoking did not have any effect on the CH.

Conclusion There are many precipitating factors of CH periods and attacks. CH is self-reported to be triggered by stress, change in weather condition, alcohol consumption, lying down, flying, high altitude and exercise. 968 patients (90%) were current smokers or had smoked heavily in the past. Quitting smoking did not influence the course of CH. The role of smoking has still not been elucidated.

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Epidemiology and clinical spectrum of cluster headache (CH) and CH-like syndromes in The Netherlands: a nationwide study in 1844 patients

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Objectives To estimate the prevalence and assess the clinical spectrum and diagnostic trajecory of CH and CH-like patients in The Netherlands.

Methods Patients with CH or resembling syndromes were identified by public announcements (Internet, patients’ society) and by direct mailings to all neurologists (n = 5800) in The Netherlands. All patients filled in two questionnaires: one short, screening questionnaire to establish an IHS diagnosis, and another, more extensive questionnaire, analysing a variety of clinical features.

Results Between April 1998 and January 2001, 1844 patients returned the screening questionnaire. So far 1719 of those were analysed: 1320 (72%) patients fulfilled the IHS criteria for CH (IHS-CH) and 376 (20%) fulfilled all but 1 or 2 criteria, but had either restlessness during attacks, or response to oxygen or verapamil (non-IHS-CH). Of the remaining 136 patients (7%), 22 had chronic paroxysmal hemicrania (CPH) and 1 SUNCT. Based on a population of 16 500 000 in the Netherlands, the prevalence of CH was estimated at 0.1 per million. This prevalence was the same in all 12 provinces in the Netherlands, supporting the reliability of our epidemiological methods. The second, more extensive questionnaire was returned by 1406 patients (1076 IHS-CH, 289 non-IHS-CH). Important results include the following: (1) 66% of the non-IHS patients had attacks exceeding 3 h (median: 4 h, 17% > 6 h, 5% > 24 h). (2) The male: female ratio in the IHS-CH group was 3.6:1 and in the non-IHS group 1.5:1. In CPH the ratio was 1:4.5. (3) The median time between first attack and diagnosis was 3 years (range: 0–48) in IHS-CH and non-IHS-CH. CH, migraine and sinustis were equally often mentioned as first diagnoses (22%, 19% and 22%, respectively). Patients visited a mean of 3 physicians (SD 1.5) prior to diagnosis, mostly otorhinolarngologists (37%) and dentists (34%). (4) Of all IHS-CH patients 72% had episodic CH, 10% had primary chronic CH and 11% had secondary chronic CH. Continuous headache in between attacks was reported by 16% of patients (29% of chronic and 14% of episodic patients).

Conclusion The estimated prevalence of CH in the Netherlands is 0.1 per million. There is a remarkable delay in the diagnosis of IHS-CH and non-IHS-CH (median 3 years). The results suggest that CH attacks may be substantially longer than 3 h, even up to 48 h. A substantial part of CH patients had interictal headache. These features may both have hampered the diagnosis.

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P3-R10

Triptan response is maintained in cluster headache after trigeminal sensory root section

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Introduction Cluster headache is a strictly unilateral headache that occurs in association with autonomic features. We report a patient who presents an opportunity to reconsider both the vascular and peripheral neuronal hypotheses.

Case report A 59-year-old man described a 14-year history of strictly left-sided episodes of excruciating, sharp pain centred on the retro-orbital and orbital regions, forehead and temple. These episodes lasted 1–4 h, recurring 2–3 times daily. They were associated with ipsilateral ptosis, conjunctival injection, lacrimation, rhinorrhoea and facial flushing. Alcohol triggered an attack within half an hour. From 1986 to 1988 he had trials of propranolol, amitryptiline, lithium, methysergide and ergotamine without any benefit. In February 1988 he had complete surgical section of the left trigeminal sensory root which shortened the attacks in length for one month without change in their frequency or character. In April 1988 he had further surgical exploration of the left trigeminal sensory root which was found to be completely excised; postoperatively there was no change in the symptoms. From 1988 to 1999 he had a number of medications, including verapamil, indomethacin, oxygen, lidocaine nasal drops and zolmitriptan, all of which were ineffective. Prednisolone 30 mg od rendered the patient completely pain free. Sumatriptan 100 mg orally and 6 mg subcutaneously aborted the attack after about 45 and 15 min, respectively. He was completely anaesthetic over the entire left trigeminal distribution. Left corneal reflex was absent. Motor function of the left trigeminal nerve was preserved. Neurological and physical examination was otherwise normal. Magnetic resonance imaging (MRI) scan showed a marked reduction in the calibre of the left trigeminal nerve from the nerve root exit zone in the pons to Meckel’s cave.

Methods An ECG-gated 3D-multislab MRI inflow angiogram (MRA) using a 2T Siemens MAGNETOM Vision scanner was performed. MRA was performed using a transverse section through the internal carotid artery (ICA) just distal to the carotid bifurcation at rest and during a nitroglycerin-induced cluster attack. Using the Siemens integrated software, regions of interest were drawn around the ICAs, and vessel diameter, blood flow and mean velocity were calculated.

Results No dilatation was observed in the left ICA during the cluster attack.

Discussion Lack of ipsilateral vessel dilatation makes the role of vascular factors in the initiation of cluster attacks questionable. With complete section of left trigeminal sensory root the brain would perceive neither vasodilatation nor a peripheral neural inflammatory process but the patient continued to have an excellent response to sumatriptan. This case illustrates the primacy of the brain in cluster headache.

P3-R11

Neurophysiological assessment of cluster headache

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Background and objectives The intense pain in cluster headache (CH) is thought likely to be mediated by the trigeminal nerve and its central pathways. Neurophysiological assessment of the functional integrity of peripheral and central afferent pathways of the trigeminal system can therefore contribute to the knowledge of the pathophysiology of CH.

Methods Trigeminal somatosensory evoked potentials (TSEP) and blink reflex (BR) were investigated in 22 healthy controls, and in 26 episodic CH patients during an active bout. Eleven patients were measured both in and outside of a cluster period. Patients had strictly one-sided CH and did not use prophylactic treatment. P1 latencies of TSEP, R1 and R2 latencies, and areas of the blink reflex were assessed. Differences between controls and patients, between the affected and non-affected side, and during and outside a cluster period were investigated. Limits of agreement and non-parametric tests were used for statistical analyses.

Results Mean age was 40 ± 12 years for healthy controls and 47 ± 10 years for patients. TSEP measurements in healthy controls were reproducible: limits of agreement for repeatability for contralateral P1 were −3.4 to 3.6 (right stimulation) and −3.6 to 3.4 (left stimulation). There were no relevant side-to-side-differences: limits of agreement were −1.9 to 2.1 (1st measurement) and −1.7 to 1.5 (2nd measurement). Means ± SD for TSEP P1 were 18.8 ± 2.7 ms (1st measurement) and 18.8 ± 2.5 ms (2nd measurement). TSEP P1 latencies tended to be longer in patients in the cluster period as compared to controls: 20.5 ± 2.5 ms vs 18.8 ± 2.7 ms, P = 0.052 (mean ± SD). Latencies between the affected and non-affected side did not significantly differ in patients (20.5 ± 2.5 ms vs 20.2 ± 2.8 ms, P = 0.70). In patients outside a cluster period (n = 11) and patients inside a cluster period (n = 26), P1 latencies did not differ significantly on both sides (19.1 ± 2.3 vs 20.3 ± 2.5 (affected side, P = 0.8) and 19.9 ± 2.3 vs 20.2 ± 2.8 (non-affected side, P = 0.9)). No correlation was found between P1 latencies of the affected side and the time since the last attack (R = 0.3) or the time to the first attack after measurements (R = 0.1). Significant differences could not be detected between latencies or areas of the BR.

Conclusions Our study suggests a changed function of the trigeminal nociceptive system in CH patients during a cluster period, unrelated to the side of the attacks. The bilateral changes in CH patients seemed to not normalize outside the cluster period. However, not all patients were yet investigated both in and outside of the active period.

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MR angiography of intracranial arteries before and during alcohol-induced cluster headache

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Objective Recently we had the opportunity to examine, by conventional MR imaging and MR angiography, a cluster headache patient before and during an attack induced by alcohol.

Patient and methods A 30-year-old male patient had an 18-year history of headache bouts at roughly the same time each year (spring and autumn). Each bout would last about 20 days, and during these periods he experienced very severe right-sided retro-orbital and supraorbital headaches 1–2 times every 24 h, which often occurred in the morning. Each acute attack of headache was accompanied by watering and reddening of the right eye and nasal blockage, but not by ptosis. The average duration of each acute attack was about 30 min. He had found that drinking about 100 mL beer (4% alcohol) or 10 mL liquor (53% alcohol) would precipitate his headaches; hence, he would avoid alcohol. Treatment with oral acetaminophen had little improvement. He was studied during an active headache phase after he had been free from headache for 36 h. A right-side cluster headache was suddenly induced 40 min after he drank 5 mL liquor (53% alcohol). Conventional MR imaging and MR angiography using a GE 1.5 T superconducting MR scanner was carried out immediately after drinking liquor, using 3d TOF sequence with the scan time of 5 min and 11 s. MRA was repeated 15 min after the onset of headache.

Results The diameter of the ophthalmic artery on the headache (right) side was significantly smaller than that of the opposite ophthalmic artery before onset of headache. Fifteen minutes after onset of headache, the diameter of the ophthalmic artery on the headache side was significantly larger than that before onset of headache, and there was no significant change of the ophthalmic artery on the non-headache side. The diameters of anterior cerebral arteries, middle cerebral arteries, terminal portions of internal carotid arteries, posterior cerebral arteries on both headache and non-headache sides, the ophthalmic arteries on the sides of the non-headache and basilar artery showed no visible changes before and after onset of headache.

Conclusion Our findings showed the spasm of ophthalmic artery on the symptomatic side before onset of headache, and then followed by dilatation during the acute attack of cluster headache. The result suggested the importance of haemodynamic changes in ophthalmic artery in the induction of attacks of cluster headache.

CACNA1A gene polymorphisms in cluster headache

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Objective Cluster headache (CH) is a primary headache disorder where the etiological and pathophysiological mechanisms are still largely unknown. An increased risk of CH in first- and second-degree relatives suggests the importance of genetic factors. Mutations of the brain specific CACNA1A gene on chromosome 19p13 have been shown to be involved in a few, mainly episodic, neurological disorders with a wide clinical spectrum (FHM, SCA6 and EA2). Sib-pair analysis has indicated that there might be an involvement of the CACNA1A gene even in the more common forms of migraine. P-type neuronal calcium channels mediate serotonin (5-HT) release. Verapamil, an L-calcium channel blocker, is effective as prophylactic treatment in CH and may act by interacting with calcium channels. The CACNA1A gene is thus a promising candidate for conferring susceptibility to CH.

Materials and methods We performed an association analysis of an intragenic highly polymorphic (CA)n-repeat with marker D19S1150 and a (CAG)n-repeat in the 3’UTR region. Blood samples were collected from 75 Caucasian patients with sporadic CH (6 patients with chronic CH and 69 patients with episodic CH) according to IHS criteria and 108 matched controls. DNA isolation and PCR was performed. Electrophoresis of amplified DNA-fragments was performed on polyacrylamide gels and analysed by GENESCAN/GENOTYPER software. Statistical analysis was performed by Fischer’s exact test by comparisons between allele and phenotype frequencies in patients and controls. Monte Carlo simulation test was performed to assess the likelihood of our data. Linkage disequilibrium (LD) was accessed by Fischer’s exact test and chi-square analysis between allele and phenotype frequencies in patients and controls. Monte Carlo simulation test was performed to assess the likelihood of our data. Linkage disequilibrium (LD) was assessed by Fischer’s exact test and allele frequency was calculated by the Monte Carlo simulation test.

Results Genotypes and allele frequencies for both the (CA) repeat marker D19S1150 and the coding (CAG)n expansion polymorphism were similarly distributed in patients and controls. A few slight differences were observed, and they fall well inside what would be expected by chance. We analysed the extent of LD between specific alleles of the two markers, and the distribution of genotypes was similar in patients and controls. Two alleles occurred more often together, indicating a slight LD between the two markers that appeared to be similar in both groups.

Conclusions This study offers no support for an association between sporadic CH and two polymorphic markers of the CACNA1A gene. Based on the power estimations performed, we conclude that it is unlikely that genetic variation within this gene contributes greatly to the susceptibility to CH.
P3-R14

Helicobacter pylori infection and cluster headache

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Objectives The purpose of this study was to evaluate whether chronic Helicobacter pylori (H. pylori) infection is a risk factor for cluster headache (CH). Several studies have reported a significant association between H. pylori chronic gastric infection and different vascular diseases as coronary heart disease, primary Raynaud phenomenon and stroke. Several mechanisms could link chronic H. pylori infection and vascular diseases including a low-grade acute phase response, free radical formation, and immune-mediated mechanisms. However, the precise mechanism by which chronic H. pylori infection mediates these vascular effects remains unclear. Previous studies on seropositivity for H. pylori in patients with migraine showed contradictory results.

Material and methods 15 CH patients (2 females and 13 males; age range 20–59 year; mean age ±SD: 41.6 ±10.6 year) attending the Headache Center of the University of Turin were involved in the study. CH was diagnosed according to the International Headache Society criteria. H. pylori gastric infection was diagnosed by means of both 13-carbon urea breath test and presence of blood H. pylori antibodies. In accordance with previous published research guidelines, only patients with positive results for both tests were defined as infected by H. pylori. A group of 15 healthy subjects matched for age, sex, and socioeconomic status served as controls.

Results Helicobacter pylori positivity was present in 53.3% of CH patients and 46.6% of controls (P=n.s.).

Conclusions Our preliminary data suggest that chronic H. pylori infection is as frequent in patients with CH as in controls. Further prospective studies are needed in order to exclude any relationship between H. pylori infection and cluster headache.

P3-R15

Altered nocturnal lipolysis in cluster headache. A sign of central autonomic dysfunction?

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Background Hypothalamic dysfunction has been proposed to be closely related to the pathogenesis of cluster headache (CH) if not its cause. Ipsilateral, ocular autonomic symptoms and effects on heart and blood pressure during CH attacks, may either be manifestations of central dysautonomia, a local sympathetic or parasympathetic disturbance or pain. However, a metabolic change in CH – like altered lipolysis – would reflect generalized autonomic dysregulation. With microdialysis, it is possible to continuously measure glycerol concentrations as an estimate of generalized sympathetic activity. Increased sympathetic tone increases glycerol concentrations, the end-product of lipolysis. Preliminary data have suggested a nocturnal decrease of glycerol concentrations in CH patients rather than the expected physiological increase. One aim of this study was to compare nocturnal lipolysis in CH and healthy controls. Since most of the CH patients are smokers, a second aim was to study the effect of tobacco smoking on lipolysis in healthy smokers and non-smokers.

Methods Two microdialysis probes were implanted in the abdominal adipose tissue and perfused with a Ringer solution. Microdialysis samples were collected continuously at hourly intervals between 10 p.m. and 6 a.m. The glycerol data were evaluated by use of non-parametric statistics. Results are presented for the periods 1–2 a.m., 3–4 a.m. and 5–6 a.m.

Results Patients in an active period had significantly lower glycerol concentrations (27–39%; P<0.05) during all 3 periods compared with controls and no significant nocturnal increase. In remission the lipolysis rate did not differ at 1–2 a.m. but was lower (32–37%; P<0.05) at 3–4 a.m. and 5–6 a.m. when compared with controls. The lipolysis rate did not differ between active period and remission. The glycerol concentrations did not differ between healthy smokers and non-smokers and for that reason these data were pooled. In controls there was a significant increase (P<0.05) of lipolysis during the night.

Conclusion In contrast to the findings in healthy controls, there was no significant nocturnal increase of lipolysis in CH. Habitual smoking did not influence the lipolysis rate. Our results indicate dysregulation of lipolysis in CH possibly secondary to hypothalamic dysfunction affecting sympathetic activity and/or circadian rhythmicity. Effects of catecholamines, insulin, insulin sensitivity and GH on lipolysis should also be considered in future studies.

P3-R16

Metabolic alteration during cluster headache attacks: what is the significance?

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Many aspects of cluster headache are still obscure, despite the bulk of reports about it. Various stimuli are capable of inducing the pain crises and some medications are able to ameliorate them. Breathing CO₂ induces and breathing O₂ (normo- or hyperbaric) ameliorates the attacks. Also, rare
Chronic cluster headache accounts for 5–10% of all patients with cluster headache. Traditionally, this disorder is resistant to medical management.

Objectives To determine the outcome and morbidity of trigeminal nerve section in patients with intractable chronic cluster headache.

Patients and methods Seventeen patients aged between 27 and 67 (mean 38) underwent trigeminal nerve section for chronic cluster headache between 1981 and 1997. All were male patients. All attacks were classic of cluster headache. At the time of surgery, patients had been suffering from the disorder for an average of 8.8 years. The mean attack frequency was 11 per week. Mean attack duration was 1.5 h. On average, each patient tried 8 prophylactic and abortive medications prior to surgery. Half of the patients tried radiofrequency ablation at least once prior to surgery. Surgery was performed via the suboccipital route.

Results 12 patients (70%) underwent complete nerve section, 5 patients (30%) underwent partial nerve section. Vascular compression was found in two patients at the time of surgery. Follow up period ranged between a few months to 19 years (mean 5 years). In general, 88% had complete or near complete relief of their symptoms. Of the 12 patients who had complete nerve section, 9 had complete relief, 2 near complete relief and one had incomplete relief. Of the 5 patients who had partial root section, 2 had complete relief, 2 had near complete relief and one had incomplete relief. One patient developed meningitis following surgery with no long-term effects. One patient developed a CSF leak that resolved with no complications. One patient developed mild anaesthesia dolorosa. 82% of the patients had mild persistent eye complaints and 70% had clinically insignificant motor weakness. One of the patients in the complete section group and another in the partial section group had recurrence of their cluster headache on the same side after initial complete relief. Both patients underwent a second surgery, one died after the second surgery and the other had incomplete relief of his symptoms. Two patients with no previous history of contralateral headache developed cluster headaches on the other side. None of the patients with complete relief were on medications at the time of this study. All the patients with complete relief indicated satisfaction with the procedure.

Conclusion Trigeminal nerve section is an effective treatment with acceptable morbidity for patients with medically refractory chronic cluster headache. Total nerve section is associated with a better surgical outcome. The benefits appear to be sustained with long-term follow-up.

R: Cluster headache

Botulinum Toxin A (Botox) for cluster headache: 6 cases

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The purpose of this study was to evaluate the efficacy of Botox for cluster headache patients who had been refractory to preventive therapy. All of the patients in this study were male, with 4 suffering from chronic clusters, and 2 with episodic clusters. Each patient kept a headache diary, using a visual analogue scale, for 4 months postinjection. 12 injections of 2 units each (24 units per patient = a low dose) were utilized. 8 injections were given frontally and temporally ipsilateral to the pain, and 4 in the contralateral frontal area. Each patient had failed multiple preventive medications. The case summaries are as follows: There were 4 chronic cluster patients, and 2 episodic cluster patients. Chronic Cluster Patients (4): 1. A 59-year-old man with chronic clusters, in a severe exacerbation (2–3 per day). Botox was not effective.

PO2 and PCO2 as well as acid-base balance profiles (pH and HCO3 concentration), in 7 patients affected by cluster headache (5 men and 2 women mean age 43.12 ± 6.72). Blood samples were taken during a cluster period: then out of the attack, at the beginning, at the peak and at the end. A group of 10 healthy subjects was used as a control (mean age 35.45 ± 3.45). The values out of the crisis (arterial: pH 7.41 ± 0.67, pO2 91.56 ± 5.63 mmHg, pCO2 41.23 ± 3.45 mmHg, HCO3 24.78 mEq/L; venous: pH 7.39 ± 0.45, pO2 38.91 ± 3.27, pCO2 42.85 ± 3.45 mmHg, HCO3 27.78 ± 6.46 mEq/L) were not significantly different from the controls (arterial: pH 7.44 ± 0.53, pO2 95.76 ± 4.21, pCO2 40.92 ± 4.78 mmHg, HCO3 23.61 mEq/L; venous: pH 7.40 ± 0.89, pO2 39.16 ± 5.14, pCO2 41.04 ± 6.72 mmHg, HCO3 25.12 ± 8.71 mEq/L). They were considered as basal values. The pO2 values measured during the crisis were not different from the basal values (data not shown). Significant variation (P < 0.05) was found in the pH, pCO2 and HCO3 at the beginning and at the peak of the attacks. Value at the beginning: arterial pH 7.21 ± 0.42, pCO2 26.43 ± 2.51, HCO3 14.43 ± 7.56 mEq/L; venous: pH 7.19 ± 0.89, pCO2 33.77 ± 5.34, HCO3 17.63 ± 4.35. Values at the peak of the attack: arterial pH 7.25 ± 0.46, pCO2 29.43 ± 2.01, HCO3 17.43 ± 5.16 mEq/L; venous: pH 7.24 ± 0.54, pCO2 35.77 ± 5.16, HCO3 20.14 ± 2.22. All parameters at the end of the crisis did not differ significantly from basal values (data not shown). We show that acidosis, hypocapnia and loss of bicarbonate is present during the attacks of cluster headache. This indicates a condition of metabolic acidosis with respiratory compensation. The occurrence at the beginning of the crisis indicates that it is a primary alteration and not a consequence. The meaning of this alteration still needs to be clarified.

R: Cluster headache
2. A 63-year-old man with chronic clusters, in a severe exacerbation (4–5 per day). Botox was moderately effective. The clusters decreased to one daily. This relief lasted 4 months. He had been scheduled to have a surgical procedure for the clusters, but cancelled it due to the relief from the Botox. 3. A 53-year-old man with chronic clusters, in a moderate exacerbation. No relief from the Botox. 4. A 38-year-old man with chronic clusters in a severe exacerbation. There was dramatic, immediate relief after the injections, with no headache for 3 months. Episodic Cluster Patients (2): 1. A 62-year-old man with episodic clusters, 2 per day. Complete relief after Botox (the injections immediately stopped the cycle). 2. A 43-year-old man with severe episodic clusters. He received 2 sets of injections, one year apart. After the first Botox injections there was immediate, complete relief. The second time there was only moderate improvement. After the second set, the clusters diminished from 4 per day, lasting 1–2 h each, to 1 headache daily lasting less than 1 h. In summary, 4 patients had chronic cluster headache, refractory to preventive medications. The Botox was administered during a flare-up of the headaches. In 2 of these 4, no relief was obtained. One patient had moderate relief, with one experiencing excellent (complete) relief. Two patients suffered from episodic clusters. Both patients reported excellent (complete) relief postinjections. In one of the 2 patients, a 2nd set of injections (one year later) resulted in moderate relief. Side effects were few; 2 patients experienced a temporary mild droop of one eye. Botulinum Toxin is a safe therapy that, although expensive, is relatively easy to administer. This small study demonstrated that, for some refractory cluster patients, Botulinum Toxin may be an effective treatment. It is possible that larger doses (low doses were used in this study) would be more effective.

P3-R19
Preventive treatment of nocturnal cluster headache (CH) attacks with the hypnotic agent Imovane
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Background It is well known that the majority of CH attacks occur during nocturnal sleep. In a previous study in which 20 patients were observed during the cluster period before and after the CH attack, significant disturbances in sleep structure were revealed by means of night polysomnography, including difficulties in going to sleep, a large percent or superficial sleep stages, a decrease in delta sleep, and a complete absence of the REM stage.

Aim In this study we tested the hypothesis that the hypnotic agent Imovane (Zopiclone), which normalizes the structure of nocturnal sleep, could be useful in preventing nocturnal CH attacks. Imovane was shown to promote the increase of slow sleep stages, delta-sleep in particular.

Results Six patients with episodic CH who had 2–3 attacks per night and 1–2 daytime attacks were studied during the cluster period by using headache and sleep diaries. All patients had sleep disturbances only during the cluster period. The mean subjective quality of sleep was reduced to the sum ball of 18 (normal value 25). Patients took Imovane in a dose of 7.5–15 mg/day (1–2 tablets) 15–30 min before going to sleep for 15 days. At the end of the treatment course 3 patients had no nocturnal attacks. In 2 patients the occurrence of the attacks shifted from 2–3 a.m. to 7–8 a.m. 1 patient has stopped taking the drug and the attacks have manifested again. In all patients there was a clear trend toward a decrease in the intensity and duration of daytime attacks as well. The quality of sleep improved in all subjects (the mean sum ball of 23).

Conclusion By improving the structure of nocturnal sleep and by increasing the percentage of delta sleep, in particular, Imovane effectively promotes nocturnal sleep and prevents nocturnal CH attacks during the cluster period. It could be suggested that delta sleep is an important antinociceptive factor with increased brain metabolism. Improvement of delta sleep could prevent the beginning of CH attacks.

P3-R20
Topiramate in the prophylactic treatment of cluster headache
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Introduction and objectives The efficacy of the preventive treatment of the cluster headache is limited, especially in the chronic forms. The aim of this work is to present our open-label experience demonstrating the efficacy of topiramate as preventive treatment of cluster headache.

Methods 21 patients with a diagnosis of episodic and chronic cluster headache according to the International Headache Society (IHS) were treated with topiramate as preventive drug. The results were collected prospectively. The treatment was started with 25 mg at bedtime and the dose was increased every 3–7 days until a maximum of 200 mg.

Results 11 patients fulfilling the criteria for chronic and 10 for episodic cluster headache (IHS). 4 were women and 17 men. The mean age of cluster onset was 34.4 years (range: 17–60) and the mean age of the patients at the start of treatment was 42.1 years (range: 19–65). The mean duration of the cluster period at the time of topiramate treatment was initiated was 18.4 months (range: 13–33) in the chronic forms and 23.7 days (range: 1–47) in the episodic cases. All the chronic cases were previously treated with other drugs with poor or no response. In 11 patients, topiramate induced cluster remission in 1–27 days (mean: 14 days). In 5 patients the remission was obtained in the first week with doses between 25 and 75 mg. In another 5 patients topiramate reduced the number of attacks more than 50%. Two patients with episodic cluster had a good response in two successive
cluster headache. For abortive treatment, the most effective treatments are sumatriptan injection, oxygen inhalation, and sublingual ergotamine; for the preventive treatment, most effective are verapamil, prednisone, and lithium. Naratriptan is an effective and well-tolerated abortive antimigraine medication; it has been used preventively in transformed migraine (Headache 1999; 39: 506–510). It is a cranial vasoconstrictor, more selective than the ergots and therefore safer from a cardiovascular perspective. The ergots, in particular ergotamine, are sometimes used as adjunct in the preventive treatment of cluster headache. Here, we describe the preventive use of naratriptan with good tolerability and promising results in terms of efficacy. Seven patients were treated consecutively in the period from August 1999 through August 2000. All but one were male and their ages ranged from 43 to 71 years. Four of them suffered from episodic and three from chronic cluster headache; all were taking verapamil 480–960 mg SR/day with incomplete relief of their headaches, which continued to occur from one to six times per 24 h. Naratriptan was added to the treatment in a dose of 2.5 mg once or twice daily and was tolerated well without side effects by all patients. Six of the seven patients responded to the addition of the naratriptan with a reduction in frequency of their headaches to once every 1–7 days (three patients) or (almost) zero (four patients). Two of the six patients who responded to the adjunct treatment suffered from chronic cluster headache, making it unlikely that the observed effect was due to spontaneous remission of the headaches. However, the above observation is based on an open-label study only and needs confirmation in a randomized, double-blind, placebo- or comparator-controlled study.

P3-R23
Characterizing the response factors of IV histamine as adjunctive therapy in chronic cluster headache with comparison to IV DHE as adjunctive therapy or medical therapy alone

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Background The use of histamine as a treatment for cluster headache was developed by Bayard Horton, MD, at the Mayo Clinic. Because of criticism, his work fell into disrepute for many years. We have previously described its successful use in several papers.

Study objective and methodology An observational study was conducted over 5 years to compare the efficacy and patient characteristics of standard medical therapy (SMT) for cluster headache, SMT plus IV DHE (SMT+DHE), or IV Histamine (SMT+IVH) as adjunctive therapy in patients with chronic cluster headache (CCH) as defined by the IHS criteria. Patients Twelve females and 106 males participated, all but 5 of whom had secondary CCH.

Patient characteristics and results See table for results. Headache indices (HAI) were calculated as HAI = number of headaches × severity/days evaluated. There was no statistical difference in patients’ ages, years with CCH, or pretreatment HAI. SMT patients were generally younger and treated with less previous medications than the other groups. SMT efficacy declined in a statistically significant fashion...
with increasing previous treatments. SMT and SMT+IVH produced statistically significant improvements compared to SMT + DHE. SMT + IVH gave statistically significant improvement compared to SMT alone. Patients treated with SMT alone or SMT + IVH were equally likely to revert to episodic cluster headache (ECH). SMT + IVH approached a statistically significant likelihood of SMT maintaining cluster remission compared to other treatments. SMT + IVH non-responders (SMT + IVH –) had pretreatment HAI nearly twice than of SMT + IVH responders (SMT + IVH +).

### Table 1

<table>
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### Conclusions

SMT is suitable for younger patients without a history of multiple drug failures for CCH preventative care. Both SMT + DHE and SMT + IVH are successful in treating patients who have failed SMT alone. SMT + IVH is significantly more likely than SMT + DHE to produce a positive outcome even in SMT + DHE failures and patients who have had CCH surgery. SMT + IVH is as likely as SMT alone to lead to reversion to ECH and statistically more likely to produce a SMT maintained remission of CCH.

### P3-R24

**Greater occipital nerve block for intractable cluster headache**

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**Background**

Cluster headache that fails to respond to oral corticosteroids or other pharmacological interventions is an infrequent but very disabling condition.

**Objectives**

To evaluate the effectiveness of greater occipital nerve steroid block (GON-B) in patients with intractable episodic cluster headache.

**Methods**

Retrospective review of records of patients evaluated at the outpatient headache clinic of a tertiary care institution in 1993–2000. Inclusion criteria: (1) episodic cluster headache, by IHS criteria; (2) cluster headache bouts failed to respond to p.o. corticosteroids, calcium channel blocking agents or other regular pharmacological treatment modalities; (3) cluster headache bout resolved completely within 7 days after GON-B, with or without other concomitant medication use.

**Results**

12 patients (male/female: 11/1) were identified. The age was 40.1 ± 14.8 (24–79). 24 GON-B we performed for 24 bouts. 23 (96%) were successful in completely stopping the bout within 7 days. One patient showed no response. Concomitantly used medications were: ergotamine (n = 4, 17%), naratriptan (n = 15, 62%), sumatriptan (n = 12, 4%), no medication (n = 4, 17%). There were no complications of the GON-B.

**Conclusions**

Greater occipital nerve steroid block, especially in combination with a long-acting triptan, is a safe and very effective treatment for intractable episodic cluster headache bouts.

### P3-R25

**Intractable cluster headache responding to amitriptyline: a case report**

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We report a 36-year-old male patient suffering from episodic cluster headache. The patient’s history began in 1984 with cluster periods occurring twice a year and lasting 2–3 months with spontaneous remission without any treatment (because the patient had not been diagnosed as having cluster headache before). Typically, the attacks were unilateral, of periorbital localization, stabbing and of extremely severe intensity with sudden onset and remission. Concomitant symptoms were conjunctival injection, tearing, rhinorrhea, miosis and ptosis on the ipsilateral side and motor hyperactivity. The attacks occurred 1–4 times a day and lasted 20–60 min. In March 1999 he first came to our outpatient department and cluster headache was diagnosed. Clinical and MRI findings were normal. He received corticosteroids i.v. and verapamil p.o. The acute attacks were treated with sumatriptan s.c. or dihydroergotamine intranasally. The period lasted 2 months. A new cluster period started in February 2000 with 1–2 attacks per day. He received verapamil up to 360 mg daily and methylprednisolone beginning with 500 mg/day i.v., over 7 days tapering to 125 mg/day i.v., continuing with a tapering regime p.o. for 4 weeks. Despite this therapy, he still had 2–3 attacks/day. Therefore, in addition to verapamil, he was put on a lithium therapy up to 1125 mg/day, but this had to be stopped because of gastrointestinal side effects after 4 weeks. A therapeutic trial with topiramate 50 mg/day had to be discontinued due to severe paraesthesias after 2 weeks. Alternative trials with gabapentine in a maximum dose of 1200 mg/day for 4 weeks and afterwards lamotrigine in a maximum dose of 200 mg/day for 12 weeks did not decrease the attack frequency. The patient still was on verapamil until lamotrigine was started. In December 2000, with unchanged...
attack frequency, the patient was put on a monotherapy with amitriptyline up to 95 mg/day which was well tolerated. During the following 5 weeks he was suffering from only 5 mild cluster attacks and he has been pain free until today. To our knowledge this is the first published patient receiving amitriptyline in cluster headache. Although a spontaneous remission cannot be excluded, we suggest that the remission could be connected to the amitriptyline therapy, particularly, because the cluster attacks could not be influenced substantially by standard therapies.

P3-R26

Intractable chronic cluster headache relieved by electrode implant to posterior inferior hypothalamus

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The posterior inferior hypothalamus homolateral to the pain is activated during nitroglycerine-induced cluster headache (CH) attacks (May et al. 1998). This finding, which appears specific for CH, suggests that the cluster headache generator is located at this site. We present a 39-year-old male who suffered with severe intractable chronic bilateral CH for 5 years, diagnosed in accordance with International Headache Society criteria. Brain and orbital MRI, CT-angiography, and other examinations were unremarkable. Percutaneous thermal rhizotomy to the right Gasserian ganglion (most attacks on the right) reduced the pain but also resulted in complete loss of sensation in all three districts of the nerve. Soon after more than once daily drug-refractory crises began presenting on the left. The patient had previously become blind in the right eye so intervention on the left trigeminal nerve was absolutely contraindicated. We therefore proposed the absolutely novel treatment of electrostimulation of the homolateral (left) hypothalamus, in the same area shown to be activated during CH attacks. After informed consent a quadripolar electrode connected to an ITREL II pulse generator (both supplied by Medtronic, Minneapolis, USA) was implanted stereotactically. No changes in arterial blood pressure, heart rate or skin temperature were observed during intraoperative stimulation or during the postoperative course. More than 6 months after the implant, the patient is completely free of left-side headaches, except on 2 occasions when the stimulator was turned off and the left-side headaches reappeared. When the stimulator was switched on again these crises disappeared. No sensitivity disturbances in the left trigeminal distribution developed after the implant. By contrast 8 months after the last right trigeminal rhizotomy, the right-side crises gradually reappeared, with the same characteristics as the preoperative headaches. This is the first case of intractable chronic CH to be successfully treated by stereotactic electrode implant to the homolateral hypothalamus; the result should therefore be interpreted cautiously. Nevertheless the disappearance of the crises after the electrode was switched on shows that the stimulation site plays a primary role in the pathophysiology of CH, and indeed strongly suggests that the cluster headache generator is located at this site, as also suggested by May et al. (2000). If this is confirmed, stereotactic positioning of electrodes in the hypothalamus could become an important therapeutic option for chronic drug-resistant CH, not least because it avoids the risk of anaesthesia dolorosa and corneal ulcer that are common sequelae of trigeminal nerve surgery.
POSTER SESSION III

S: Rare primary headaches

P3-S1
Periodic idiopathic stabbing headache
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Introduction  Idiopathic stabbing headache (ISH) was first reported in 1964 by Lansche, who observed a new painful syndrome that he called ‘Ophthalmodynia periodica’. The condition has since been variously described. Currently, it is coded as ISH to Group 4 of the International Headache Society classification. We describe four patients with IHS attacks characterized by periodic recurrence over time.

Case 1  A 29-year-old woman. Since the age of 22, she had suffered from cyclic migraine. Since age 18, she had experienced very short-lived, sharp stabs of pain in the vertex and sometimes in the frontal region. The stabs occurred spontaneously every day with 10–20 stabs a day, often spaced by only a few minutes from each other. The stabs always had a periodic pattern, recurring for about one month, 2–4 times a year, with symptom-free intervals in between. Since age 18, the patient had also suffered from cyclic migraine.

Case 2  A 23-year-old woman. Since the age of 19, she had complained of very sharp stabs of pain in the right parietal region, lasting about 1 s and not associated with other symptoms. The pain occurred spontaneously every day with 2- or 3-month periods in which the symptoms occurred daily alternated with longer periods in which the patient was completely symptom free. In some periods she also experienced similar painful symptoms in the left hip. Since age 9, the patient had also suffered from tension-type headache.

Case 3  A 79-year-old woman. Since the age of 71, she had complained of very severe, excruciating stabs of pain in the right parietal region, lasting only a fraction of a second and recurring several times a day every 10–15 min. The pain occurred spontaneously and was accompanied by hyperalgiesia of the scalp. The periodic recurrence and the frequency of the stabs has changed over time: initially, the active periods lasted 20–30 days, were followed by long symptom-free intervals and the attacks were less frequent; currently, the periods appear to last for about 6 months.

Case 4  A 67-year-old woman. Since the age of 65, she had reported three periods of about 45–100 days each in which she experienced very short-lived, sharp stabs of pain in the vertex and sometimes in the frontal region. The stabs occurred spontaneously several times a day (eight to 10) and were not accompanied by any other symptoms. The painful periods alternated with completely symptom-free intervals lasting for 2–5 months. In none of these cases was remission of headache induced by preventive therapy, nor did any of the patients have neurological signs. To our knowledge, this is the first description of IHS cases with attacks distributed over active periods alternating with completely symptom-free intervals, closely resembling the pattern of episodic cluster headache.

P3-S2
Trigeminal neuralgia: time to diagnosis – differences between medical and dental practitioners
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Objectives  The aim of this paper is to evaluate clinicians’ ability to properly diagnose trigeminal neuralgia. As a measurement of diagnostic skill, this paper examines the mean ‘time to diagnosis’ of trigeminal neuralgia by physicians and dentists. ‘Time to diagnosis’ refers to the time a patient reports the onset of symptoms to the time a clinician provides a diagnosis of trigeminal neuralgia.

Methods  149 patients were included in this study. Patients were divided into two categories: patients whom upon entry into the healthcare system elected to seek a dental specialist consultation and patients whom upon entry into the healthcare system elected to seek a medical specialist consultation. Time to diagnosis between physicians and dentists was analysed for three different subgroups (six comparisons): patients with trigeminal neuralgia regardless of the division of the trigeminal nerve afflicted, patients with trigeminal neuralgia afflicting the second division, and patients with trigeminal neuralgia afflicting the third division. Regardless of the type of clinician first encountered, time to diagnosis was compared between patients diagnosed with trigeminal neuralgia afflicting the second division and those diagnosed with trigeminal neuralgia afflicting the third division. A t-test was used to find the difference between the means for each comparison. A survival analysis utilizing the Log Rank of Equality/Strata measurement analysed differences in patterns in time to diagnosis.

Results  The mean time to diagnosis for physicians was 17.7 months. The mean time to diagnosis for dentists was 25.3 months. A comparison of Log Rank of Equality/Strata found a significant difference in patterns of time to diagnosis between physicians and dentists regardless of nerve division ($P = 0.03$). A t-test and a Survival Analysis utilizing the Log Rank of Equality/Strata found a significant difference in the mean time to diagnosis between physicians and dentists when trigeminal neuralgia limits itself to the third division ($P = 0.04$).
Conclusions ‘Time to diagnosis’ is dependent upon the type of healthcare professional a patient elects to visit. Time to diagnosis is also dependent upon, and limited to, practitioner background and the point of view of his or her training.

P3-S3

Two cases of medically and surgically intractable SUNCT - a reason for caution and an argument for a central mechanism

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Introduction Since Sjaastad first described short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) in 1989, less than 100 cases have been published and the underlying pathophysiology remains unclear. Although two patients have been reported to respond to microvascular decompression surgery and a third to balloon compression, no long-term data are available on the feasibility or durability of these invasive procedures.

Objective To report two cases of SUNCT which demonstrate the medically and surgically refractory nature of this primary headache disorder. To use these cases as examples to support the hypothesis that SUNCT is a disorder which originates and is capable of being maintained from within the central nervous system.

Methods We report two patients whose symptoms met the IHS criteria for SUNCT. The first was a 39-year-old man with a 2-year history of 60–400 episodes per day of stabbing right retro-orbital pain lasting about 20 s associated each time with rhinorrhoea, lacrimation, and ipsilateral conjunctival injection. The second patient was a 28-year-old man with a 10-year history of \(\sim\)100 episodes per day of lancinating right retro-orbital pain lasting 20–30 s with associated rhinorrhoea, lacrimation, and conjunctival injection. Each patient had failed medical therapy with medications typically effective when used for the treatment of trigeminal neuralgia, cluster headache, and migraine headache.

Results The first patient failed to respond to either a glycerol rhizotomy of the gasserian ganglion or gammaknife radiosurgery of trigeminal nerve at the root exit zone. The second patient derived absolutely no benefit from gammaknife radiosurgery of the root exit zone, microvascular decompression of the trigeminal nerve in the posterior fossa, or finally a microvascular decompression of the nerve internum. Both patients continue to be disabled with recurrent attacks of SUNCT. In addition, the first patient suffers from anaesthesia dolorosa and the second patient from unilateral deafness, chronic vertigo and dysequilibrium as a result of surgical trauma.

Conclusion These cases demonstrate the treatment refractory nature of SUNCT. They also highlight the uncertainty regarding the role for surgery in these patients and the caution which must be exercised before invasive procedures with significant potential for morbidity are undertaken. We believe these cases also strongly suggest that SUNCT originates and may be maintained from within the CNS. This central locus explains why SUNCT is not typically amenable to interventions aimed at the peripheral portion of the trigeminal nerve.

P3-S4

Hypnic headache: a new Italian case with a good response to pizotifene and melatonin

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Hypnic headache is a rare form of idiopathic headache that wakes elderly patients from sleep; it generally lasts half an hour to two hours; most of the patients complain of a moderately severe pressured type pain affecting the anterior aspect of the head or the whole head; associated autonomic symptoms are rare. Case report: A 72-year-old man suffering from hemicrania since his childhood. This case came to us in September 2000 because almost every night, for over 8 months, he began to wake up at 3–4 a.m. with a dull pressure pain, rarely throbbing, located at the forehead and at the frontal parietal regions bilaterally. Even naturally, the headache reverts after an hour and a half and sometimes even before. The patient notices that two situations help him a lot: (a) to drink a cup of milk and coffee and after to defecate; (b) to sit in an armchair with his back at a right angle and to keep still, especially the head; when the patient does either a or b his headache generally reverts in 30 min. He is a very active man. Except for two episodes of atrial paroxysmal fibrillation reverted in less than 24 h (5 years ago and then again 2 years later), he has always been well. He generally does not take drugs. I suggested that he take pizotifene 0.5 mg sugarcoated pills t.i.d. plus a 3-mg melatonin tablet at bedtime. The headache disappeared completely after 6 weeks. His therapy with pizotifene lasted 9 weeks. After 5 weeks from the interruption of the therapy, the patient noticed some light reappearance of hypnic headache; this time the pain was lighter and, ‘by keeping his head still and raised by two pillows’, it quickly reverted. His general medical and neurological examinations, along with complete blood count and blood chemistries, EEG, CT, and MRI were all normal. This case has some interesting aspects: (a) above all, the rarity of hypnic headache; (b) the presence of an autonomic induced feature: the defecation, even if helped by milk and coffee; (c) the beneficial effect of coffee (already reported by many other authors); (d) the beneficial effect of the sitting position; (e) the positive effect of the therapy with pizotifene plus melatonin. Many drugs have been recommended: lithium or a cup of coffee at bedtime, indomethacin, ergotamine tartrate with phenobarbital and belladonna, atenolol, aspirin with caffeine, flunarizine, cyclobenzaprine, verapamil, and metisergide. In our case another classic prophylactic agent, the pizotifene, was found to be effective on this rare headache. This drug is well tolerated by the elderly. This is an important aspect because many drugs
listed above have remarkable side effects especially among the elderly.

P3-S5

Botulinum Toxin A in the treatment of chronic paroxysmal hemicrania – a case report

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Objectives Controlled studies have demonstrated the efficacy of Botulinum Toxin A in the prophylactic treatment of migraine and tension-type headache. Also, case reports have been published reporting positive results in the treatment of cluster headache. However, it is difficult to assess the efficacy of Botulinum Toxin A for this predominantly episodic headache disorder as spontaneous improvement after a cluster period is the rule. In the following case report for the first time the use of Botulinum Toxin A in a patient with chronic paroxysmal hemicrania (CPH) is documented, a headache disorder with similarities to cluster headache, yet without spontaneous improvement.

Case report A 52-year-old male was admitted with a 3-year history of paroxysmal headaches. The severe attacks were strictly unilateral (left side) with a temporal pain maximum. The attacks usually lasted about 10 min and occurred about 15 times every day. The pain was associated with conjunctival injection, lacrimation and eyelid oedema on the painful side. The physical examination and an MRI-scan did not reveal any underlying disorder. The patient was diagnosed as suffering from chronic paroxysmal hemicrania and was consequently treated with indomethacin 3 × 50 mg. For the first weeks the number of attacks dropped to one mild attack every 6–7 days confirming the diagnosis. Then, however, despite an adjusted indomethacin medication of up to 3 × 100 mg, the number of attacks increased again. Methylprednisolone (1 g i.v.) and verapamil (up to 720 mg) given on a trial basis were ineffective. At this point the patient was offered a treatment with Botulinum Toxin A. After consenting to the therapy the patient received 30 MU Botox® divided over 3 injection sites in the painful left temporal muscle. With a latency of 6 days the CPH attacks disappeared for the following 14 weeks. The patient reported no side effects. When the CPH attacks reappeared, the treatment was successfully repeated.

Conclusions In the last few years Botulinum Toxin A has been demonstrated to be helpful in the treatment of the major primary headache disorders migraine and tension-type headache. Recently, cluster headache has reportedly been treated effectively with Botulinum Toxin A and now for the first time a patient suffering from the rarest primary headache disorder – chronic paroxysmal hemicrania – has gained from the treatment. Thus, further controlled clinical studies and at least as important research on possible mechanisms of Botulinum Toxin A in primary headache disorders are justified.

P3-S6

Evaluation of pharmacological therapy for the treatment of neurogenic facial pain

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Introduction Trigeminal neuralgia (TN) and atypical facial pain (AFP) are neurogenic/neuropathic facial pain syndromes (NFP) that are complex, debilitating and often of unknown aetiology. While pharmacotherapy is effective for many patients, it may not relieve the pain in others and can produce intolerable side effects with significant medical and functional morbidity. This study will focus on pharmacological treatment of TN and AFP.

Objectives To evaluate the effectiveness of a variety of pharmacological agents used in the treatment of TN and AFP.

Methods Eighty patients who were undergoing treatment for TN and AFP at the Center for Oral, Facial and Head Pain at CPMC and Craniofacial Pain Center at MGH were recruited and retrospectively evaluated. Each patient was given a questionnaire which evaluated the following: type of pain, division of the trigeminal system affected by the disease, as well as their response to drug therapy. These patients were followed over time to evaluate the long-term response to pharmacological treatment.

Results Carbamazepine and Gabapentin, the most commonly prescribed medications for the treatment of NFP were compared. Carbamazepine was found to be somewhat more effective in relieving pain. Average pain relief was 60% with Carbamazepine vs 47% for Gabapentin. However, Carbamazepine had a much higher incidence of serious side effects, which made patients stop taking the medication (31%) vs 12% for Gabapentin. The most common side effects from both medications were drowsiness (57%) and inability to concentrate (21%). 47% of the patients in this study reported to have numbness in addition to pain.

Conclusions Carbamazepine and Gabapentin are both effective for NFP; however, Gabapentin caused less intolerable side effects. Combination therapy had similar responses resulting in pain relief with surprisingly few side effects that were no more significant.
P3-S7
The syndrome of long-lasting autonomic symptoms with hemicrania (LASH): three cases
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Chronic paroxysmal hemicrania (CPH) and hemicrania continua (HC) are trigeminal autonomic cephalgias that are defined by their responsiveness to indomethacin. The LASH syndrome (Rozen 2000) is a new type of indomethacin-responsive headache in which the autonomic symptoms overshadow the head pain, which can be absent in some attacks. Three patients presented with stereotypical headache disorder marked by long-lasting autonomic symptoms. One patient experienced isolated autonomic symptoms without a headache in the first attacks.

<table>
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<tr>
<th>Female</th>
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<td>51 years</td>
<td>41 years</td>
<td>65 years</td>
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<tr>
<td>Episodic</td>
<td>Chronic</td>
<td>Episodic</td>
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<tr>
<td>Attacks without headache</td>
<td>Attacks with moderate headache</td>
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<td>Menses</td>
<td>No trigger mechanisms</td>
<td>Wind</td>
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<td>Cerebral MRI</td>
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<td>Indomethacin +++</td>
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Neuroradiological investigations were non-diagnostic for all patients. Indomethacin controlled both headache and autonomic symptoms in two patients. CPH and HC are distinct but closed disorders that cause only mild autonomic symptoms. LASH syndrome could be defined as an intermediate syndrome between these two entities.

P3-S8
Hemicrania continua with aura
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Introduction Hemicrania continua (HC) is a primary headache disorder that is characterized by a continuous unilateral headache of moderate severity, exacerbations of severe pain, and complete responsiveness to indomethacin. We report four patients with a unique variant of HC: visual auras that precede or accompany the pain exacerbations.

Case 1 A 44-year-old man with a 25-year history of episodic headaches started to have daily headaches two years prior to evaluation. The headaches were strictly right-sided. He experienced unilateral tearing, conjunctival injection, photophobia, phonophobia, and nausea. He also complained of seeing light flashes in his left peripheral visual field that lasted 5 min, and accompanied the headaches about 5% of the time. The patient had complete headache and aura resolution with indomethacin, 150 mg a day.

Case 2 A 44-year-old woman with a 20-year history of a continuous left-sided headache located in the orbital temporal region. She had nausea, diarrhoea, photophobia, and phonophobia associated with the headache. She also complained of bright white flashes, which she described as sparkles, that lasted 5–10 min. These white flashes usually preceded pain exacerbations but could accompany them. The visual phenomena was located in her entire visual field (more central than peripheral) and occurred in 10% of her headache exacerbations. Indomethacin 75 mg per day gave her complete pain and visual symptom relief.

Case 3 A 44-year-old woman with a 25-year history of unilateral, continuous, right-sided ocular headaches. She had pain exacerbations and accompanying symptoms of right eye ptosis, nausea, vomiting, phonophobia, and photophobia. Preceding 20% of the headache exacerbations, she reported seeing 10–20 bean-shaped black spots in her right visual field, lasting 5 min. The spots were centrally located for the first few minutes and would then travel to the right peripheral visual field. The headache and visual symptoms completely responded to indomethacin 50 mg a day.

Case 4 A 58-year-old woman with a four-year history of a continuous right-sided headache in her frontal/orbital region. Her baseline headache was mild to moderate in intensity. She had exacerbations of more severe pain that lasted two hours and occurred every day. She had associated ptosis, photophobia, and phonophobia. She also complained of seeing bright, round-shaped flashes, in 20% of her pain exacerbations, lasting 15 min, always preceding the pain spikes. Visual symptoms were located in the right upper quadrant of her visual field. Her headaches and auras responded to indomethacin, 75 mg per day.

Concluding remarks Auras do not appear to be a migraine-dependent phenomenon. Auras have been shown to occur with cluster headaches, and now we report aura with HC. This appears to be the first description of aura with HC.

P3-S9
Dose and efficacy of long-term indomethacin treatment of chronic paroxysmal hemicrania and hemicrania continua
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Background and objective Indomethacin is the only proven drug that consistently provides complete and sustained relief of symptoms of Hemicrania Continua (HC) and Chronic Paroxysmal Hemicrania (CPH), but unfortunately is not devoid of side effects. The risk of reappearance of symptoms due to discontinuation of the drug requires continuing
indomethacin for an undetermined period of time. The goal of this retrospective study is to assess the dose and side effects of prolonged indomethacin treatment of both disorders. **Material and methods** Twenty-six patients suffering from either HC or CPH were followed during a period of 3.8 years after onset of treatment with indomethacin. Diagnosis was made according to the criteria of Sjaastad et al. for HC patients, and IHS diagnostic criteria for CPH. The initial dose used for statistical analysis was defined as the daily dose of indomethacin needed for a complete and sustained relief of symptoms for approximately one month. The current dose was defined as the daily effective dose taken within the last three months at the time of the most recent follow-up visit and resulting in the patient being pain free. **Results and conclusions** All patients presented relief of symptoms within 3 days of treatment with a dose of 84 ± 32 mg/day of indomethacin. With time, 42% of patients experienced a mean decrease of 56% (CPH of −52%; HC of −60%) in the dose required to maintain a pain-free state (41 ± 19 mg/day). Eight patients (50%) in the HC group and six (60%) in the CPH did not show any significant change in the dose. Only one HC patient required an increase from 75 to 100 mg/day of indomethacin over 16 months. Although 27% of patients suffered mostly from gastric discomfort, no major side effects were observed. In conclusion, patients suffering from HC or CPH may expect sustained efficacy of indomethacin treatment with smaller doses without developing tachyphylaxis.

**P3-S10**

Relief of continuous hemicrania by gabapentin: a case report

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**Objective** Report a case of continuous hemicrania non-responsive to indomethacin but with a benefit response to gabapentin.

**Design and methods** Case report.

**Results** A 40-year-old single man was referred to the Hospital das Clinicas at Ribeirão Preto suffering from headache for 17 years. The pain was non-pulsatile (pressing quality), left-sided, frontotemporal located, moderate, and it was continuous. The pain started suddenly without any trigger, was severe, and lasted 3 days, was not related to physical exercise and was associated with nausea and vomiting. Since then, the intensity has been diminishing but with periods of pain exacerbation during which the patient presents bilateral conjunctival hyperaemia, mild unilateral ptosis and vomits. Both general physical and neurological examinations were normal. The patient underwent extensive investigation; cerebrospinal fluid examination, brain magnetic resonance imaging, cerebral angiography and magnetic resonance angiography were unremarkable. Until that moment, the patient had used non-steroidal anti-inflammatory drugs, corticosteroids, indomethacin, benzodiazepines, tricyclic antidepressants, lamotrigine, barbiturates, ergotamine and dihydroergotamine, opiates, zolmitriptan and sumatriptan. During the period of hospitalization, indomethacin was prescribed in doses up to 200 mg a day for 1 week long, without improvement. Then the following regimen was initiated: chlorpromazine, 50 mg a day; promethazine, 50 mg a day; and, dexamethazone, 13 mg a day at day four, with a mild improvement. Great occipital nerve block was performed but no improvement was obtained. One day after the use of gabapentin, 1200 mg a day, there was pain relief.

**Conclusion** The headache presented by this patient leads to a clinical diagnosis of Hemicrania Continua. Subsidiary exams excluded secondary headache. There was no improvement with the indomethacin use. The good response to gabapentin is unpublished.
Conclusion The severe headache attacks in hemicrania continua meet migraine diagnostic criteria in many patients and are easily confused with episodic migraine when daily background headache is not identified. SHA are unilateral and typically pulsatile and associated with photophobia, phonophobia, nausea and vomiting. Additionally, many patients experienced episodic migraine before hemicrania continua ever developed. These features are in favour of hemicrania continua being a migraine variant, yet it is a trigeminal autonomic cephalalgia and probably represents a primary headache syndrome that overlaps these disorders.

P3-S12

A patient with long-lasting attacks of bilateral blepharospasm, lacrimation and rhinorrhoea

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Background Facial autonomic symptoms such as lacrimation, conjunctival injection and rhinorrhoea are prominent features in cluster headache. We present a patient with long-lasting attacks of profound bilateral autonomic symptoms of the eyes, without pain.

Patient This 48-year-old patient has recurrent attacks, since the age of 4, of severe photo- and phonophobia with bilateral lacrimation, rhinorrhoea, eye-lid oedema, blepharospasm and mild, throbbing pain below the eyes. The attacks last 12–30 h, almost always start in the early morning and occur every 10 days. In the days before an attack he would have increased urinating frequency, mild dyspepsia and general irritation. These symptoms would build up until the next attack followed. He also has migraine with aura attacks, as does his father and 22-year-old son. Adequate doses of sumatriptan SC, prednisone, methysergide, propranolol, verapamil and cafergot had no effect. Physical examination (including ophthalmologic examination and brain-MRI) revealed no abnormalities.

Conclusion This 48-year-old man has recurrent, long-lasting attacks of severe, bilateral lacrimation, photophobia and rhinorrhoea without pain since the age of 4. Primary headaches such as cluster headache, migraine, CPH and SUNCT were all excluded based on the clinical presentation. Anatomic lesions seem unlikely. We were unable to establish a diagnosis and ask for suggestions. Both pictures and video footage will be presented during the presentation.

Acknowledgement This study was sponsored by the Asclepiade Foundation.
T: Secondary headaches

P3-T1
Headache as misleading presentation of serious vascular disorders: report of 3 cases
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Background and objectives The diagnosis of headaches due to vascular disorders is usually easy because they are both acute and associated with other neurological signs. If one or both of these characteristic features are lacking, the diagnosis may be difficult as in the 3 patients described herein.

Results Case 1: A 47-year-old man presented with a permanent left upper cervical, temporal and orbital pain of rapid onset that lasted for 15 days. In addition, he had daily attacks of excruciating pain lasting 2–3 h, associated with left ptosis, myosis, palpebral oedema, conjunctival injection, lacrimation and nasal obstruction. Cervical duplex scanning, cervical and transcranial Doppler sonography were normal. MRI showed a dissection of the distal portion of the left internal carotid artery. Patient was treated with anticoagulants and indomethacin. Attacks disappeared within a week and permanent pain decreased over 2 months. Case 2: A 70-year-old man presented with a 9-month history of daily attacks of right orbital pain, lasting about 3 h, with conjunctival injection, lacrimation and ptosis. Examination was normal. He received 150 mg daily of indomethacin and attacks disappeared within 3 days. Seven weeks later, he came back to hospital reporting pain in the left eye, painful stiffness of shoulder and hip girdles since 2 weeks, and recent jaw claudication. There was also a left visual loss, with a swollen optic disc, indicating anterior ischaemic optic neuropathy. ESR was 80 mm per hour. Temporal arteritis was suspected and intravenous steroids prescribed. Headache and limb girdle pain resolved within 4 days and ESR was lowered to 22. Case 3: A 40-year-old man presented with sudden diffuse severe headaches and vomiting just after a strong sneezing. Neurological examination including fundus was normal. CT scan showed a spontaneous hyperdensity of the superior sagittal sinus and both lateral sinus. MRI confirmed cerebral venous thrombosis. CSF pressure and composition were normal. Headache resolved within 48 h of heparin onset.

Discussion Headaches revealing vascular conditions may be misleading. In case 1, a very severe unilateral headache with attacks mimicking cluster headache revealed a carotid artery dissection; in case 2, a pseudo cluster headache preceded during 10 months the onset of symptoms suggestive of temporal arteritis. In case 3, a thunderclap headache revealed a cerebral venous thrombosis without subarachnoid haemorrhage and without CSF hypertension.

P3-T2
Carotid artery dissection mimicking migraine with aura
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Introduction Carotid artery dissection may present with a variety of manifestations that include headache, hemispheric focal signs and symptoms of retinal ischaemia. It sometimes resembles migraine with aura, which can lead to a delay in correct diagnosis. Patients with arterial dissections are often migraineurs facilitating diagnostic mistakes. We present a case of a woman with migraine without aura that suffered a carotid dissection that mimicked a first attack of migraine with visual aura.

Case report A 49-year-old female with a history of typical migraine without aura presented to our emergency department with headaches. She had experienced scintillating scotoma in the right eye lasting 15 minutes followed by a right hemispheric pulsatile headache that was accompanied by nausea and vomiting. The headache was identical to her usual headache attacks. 24 h after the beginning of the attack she noticed left hand paresthesias and weakness. At admission she had a slight paresis of the left hand that progressed in the next 12 h to left hemiplegia. Imaging studies revealed a left middle cerebral artery infarction due to internal carotid artery dissection and severe fibrous displasia of vertebral arteries. The patient was then put on anticoagulants and there was a full recovery in four weeks.

Discussion Migraine is more prevalent in patients with arterial dissections than in controls. A significant percentage of migraineurs who suffer this type of arterial disease state that the headache is similar to their usual pattern, as happened with our patient. So, in order to avoid delays in a correct diagnosis, in a patient with a migraine, non-invasive arterial imaging (MRI or carotid ultrasound) should be done every time the headache is atypical, lasting longer than usual and when new ‘aura’ or focal signs appear.

P3-T3
moyamoya and migraine: comorbid conditions?
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Objective To report a unique case of migraine with prolonged hemiplegic aura in a patient with moyamoya
Migraine is a common neurological disorder characterized by recurrent headaches, typically accompanied by nausea and sensitivity to light. These headaches are often described as throbbing and may be precipitated by stress, certain foods, and hormonal changes. Migraines are subclassified into two main types: episodic migraines, which are less severe and more frequent, and chronic migraines, which are more severe and less frequent.

The underlying mechanisms of migraine are multifactorial, involving both genetic and environmental factors. Research has suggested that defects in neuronal calcium channels are a key factor in the development of migraine. Calcium channel blockers, such as verapamil, have been shown to be effective in preventing migraines, although not all patients respond to treatment.

Moyamoya disease is a rare condition characterized by progressive narrowing and occlusion of the carotid arteries, leading to reduced blood flow to the brain. This condition is often associated with ischemic strokes and may occur in individuals with a history of headaches, including migraines. The etiology of moyamoya is unknown, but it is thought to be related to a genetic predisposition.

The relationship between calcium channelopathies and moyamoya disease has been a topic of ongoing research. Defects in neuronal calcium channels have been identified in some cases of moyamoya, suggesting a potential genetic link. Calcium channel blockers, such as verapamil, have been shown to be effective in preventing migraines, and this has led to speculation that these medications may also be effective in treating moyamoya disease.

In a unique report of migraine with prolonged aura spells, a patient was diagnosed with moyamoya disease. The patient had a history of hemiplegic migraine and suffered transient hemiplegia, headache, and seizures. Cerebral angiography confirmed the presence of a giant aneurysm in the supraclinoid portion of the internal carotid artery. The aneurysm was obliterated using platinum detachable coils, and the patient experienced a significant reduction in migraines.

Conclusion: This case report highlights the potential for calcium channel blockers to be used in the treatment of moyamoya disease. Further research is needed to elucidate the relationship between calcium channelopathies and moyamoya disease.

P3-T4
Migraine-like headache in a patient with a giant aneurysm of the intracranial internal carotid artery
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A 44-year-old woman was examined at our headache centre because of recurrent severe headache. The first episode occurred when she was 39-year-old: the headache was described as a throbbing pain, with sudden onset, located in the nuchal region, of severe intensity, accompanied by vomiting. During the headache episode, which lasted 48 h, she was found to have high arterial pressure. Following this, she began to suffer from recurrent episodic headache lasting from 24 to 48 h, with a frequency of 2–3 times per month, with the same characteristics: pulsating pain, located in the right frontotemporal side, of moderate or severe intensity, with aggravation by routine physical activity and accompanied by nausea, phonophobia and photophobia. She reported that rarely, only during the attacks of migraine-like headache, there appeared a stabbing pain, of severe intensity and lasting a few seconds, with distribution along the second branch of the right trigeminal nerve. General and neurological examinations were normal. In consideration of the clinical history of headache, we obtained a CT with intravenous contrast administration that showed an aneurysm of the right intracranial Internal Carotid Artery (ICA). The angiography confirmed the presence of a giant aneurysm, 2.5 cm in diameter, in the supraclinoid portion of ICA, next to the origin of the posterior communicating artery. The aneurysm was obliterated by the introducing of 10 platinum detachable coils with catheterization via a bilateral transfemoral approach. A postprocedural angiography showed that the aneurysm was obliterated and the patency of the ICA was preserved. The patient had an excellent outcome and after 11 months reported no further episodes of migraine-like headache. An unruptured aneurysm can be present as a headache for many years and may be misdiagnosed as migraine. Recognition of atypical signs, even rare, particularly in a patient with an atypical onset of headache, strongly suggests further investigation to detect a possible underlying vascular disease such as aneurysm.

P3-T5
Headache as a diagnostic tool of cerebral dural venous thrombosis
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Headache is the most common symptom of cerebral dural venous thrombosis (CVT) but is often underdiagnosed, especially when it occurs initially and with the typical...
characteristics of chronic daily headache. The aim of this study is to evaluate the headache as an early sign in patients with cerebral venous thrombosis and its clinical or laboratory correlation. Ten patients with CVT, 6 women and 4 men, mean age 40.3 ± 8.2-year-old, admitted in the Neurology Department of Athens’ General Hospital ‘G. Gennimatas’, were evaluated concerning the type, the intensity and the duration as well as the onset of headache in correlation to the clinical profile and final diagnosis. According to this correlation, an algorithm could be developed for the early diagnosis of CVT.

P3-T6

Cluster headache-like pain in carotid cavernous fistula: report of two cases

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Unilateral deep orbital pain is a symptom seen with cluster headache, Tolosa–Hunt syndrome, glaucoma, and some other diseases, while spontaneous carotid cavernous fistula (CCF) is characterized by pulsating exophthalmos, conjunctival chemosis, and periorbital bruit. These are called the triad of CCF. However, in some cases atypical clinical findings such as headache or eye pain without chemosis, or palsies of cranial nerves can be the only sign of CCF. The author reports on two patients who developed unilateral deep orbital pain due to a dural arteriovenous fistula at the cavernous portion, which is classified as a subtype of CCF. Both of them had been treated as a cluster headache. Case 1 was a 78-year-old housewife who developed double vision 2 months before the first visit to our hospital. She had been diagnosed with cluster headache and oxygen inhalation had been tried in vain. Neurological findings revealed left pseudo-Horner’s sign and lacrimation without chemosis. The MR angiograms showed abnormal vascularity at the left cavernous portion. The patient was treated conservatively, and became pain free in a month. The MRI scans and MR angiogram taken at the outpatient clinic 5 months later demonstrated complete disappearance of the CCF. Case 2 was a 72-year-old housewife who had had sudden left deep orbital pain 2 weeks before the first visit. She was sent to our hospital under the suspected diagnosis of cluster headache. Neurological positive signs were none but narrowing of the left palpebral fissure. The MRI scans showed the abnormal enhancement at the cavernous portion together with vascular flow voids. Left carotid digital subtraction angiogram showed remarkable arteriovenous shunting at cavernous portion (CCF) with clear visualization of cortical venous drainages. Intravascular coil embolization was tried via venous route to reduce the risk of the intracranial bleeding. This procedure was performed successfully and arteriovenous shunt flow was reduced remarkably; it also disappeared cortical draining veins completely. In conclusion, we should be reminded of the fact that unilateral deep eye pain could be one of the warning signs of intracranial hemorrhage based on a CCF, and careful differential diagnosis is needed before a patient with unilateral periorbital pain is treated as having a cluster headache.

P3-T7

Indomethacin-responsive hemicrania associated with an extracranial vascular malformation: report of 2 cases

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Background Intracranial vascular malformations may cause headache, manifesting themselves clinically as migraine or cluster headache attacks, often characterized by unusual features. An extracranial venous malformation was described in one case of headache. Although this association might have been coincidental, the pain was always on the same side as the lesion. We present 2 cases of extracranial vascular malformations associated with indomethacin-responsive hemicranias.

Case report 1 A 39-year-old woman, suffering from menstrual migraine, began to experience at age 34 a different type of headache, dull and continuous, always on the right side, involving periauricular and orbital regions, worsened by exacerbations (4–5 daily) lasting up to 5 min, associated with right eyelid oedema, lacrimation and rhinorrhoea. Neurological examination was normal. Carbamazepine treatment was not effective. MRI showed a venous malformations in the right masseter muscle. A treatment with indomethacin was started (25 mg b.i.d.) and prolonged up to 3 weeks. The hemicrania disappeared immediately after starting of the treatment. One month after discontinuing it, the patient is still pain-free.

Case report 2 A 34-year-old man experienced abruptly some episodes of thunderclap headache, irradiating to the back of the neck, lasting up to several hours. A work-up to detect intracranial aneurysm was negative. Two months later he started to complain of a continuous, dull headache involving bilateral frontal and left temporal regions, associated with nausea, photo- and phonophobia. Neurological examination was normal. Flunarizine treatment was not effective. MRI revealed a subcutaneous angiolipoma in the left temporal region. A successful treatment with indomethacin was introduced progressively up to 100 mg b.i.d. and discontinued after 7 months. One year after discontinuation of the treatment, the patient has only rare episodes of mild pain in the same location.

Conclusions Although in these cases a causal relationship between the extracranial vascular malformation and the hemicrania cannot be proven, it is of interest that the pain affected the side where the lesion was located. Peripheral sensitization of trigeminal nociceptors at the lesion site followed by central changes may have caused the pain and associated symptoms. Secondary intracranial vasodilatation
is less likely. Indomethacin has a potential effect on both mechanisms: it reduces trigeminovascular pain and has vasoconstrictor properties. The long-lasting amelioration after treatment suggests that a vicious circle was interrupted, favouring the ‘sensitization’ hypothesis.

P3-T8
Sexual headache revealing an internal carotid artery dissection
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Background Sexual headache is usually considered a benign entity and is well defined by the International Headache Society. We report the first case of sexual headache which revealed an isolated internal carotid artery (ICA) dissection.

Case report A 57-year-old man presented with a 1-month history of acute headache occurring at each sexual effort. Sexual headache was characterized by a progressive onset, an exclusive location in the right temporo-occipital area, a progressive increase during sexual activity and a maximum at the moment of the orgasm; the duration was about 1 h. CT-scan was normal. Ultrasonography and arteriography of the cervical arteries showed an isolated dissection of the left ICA without dysplasia. Dissection was formally confirmed by the presence of a wall haematoma on MRI. The patient was treated by heparin at the acute stage, then by warfarin for 3 months. A second arteriography 3 months after onset remained unchanged. Headache disappeared within 1 month.

Discussion This is the first case of sexual headache associated with ICA dissection. Headache may be due to a double dissection of ICA with early recanalization of right ICA or an increased blood flow in the right ICA with stimulation of nociceptors. Sexual headache requires a complete diagnostic work-up anytime the criteria of benign sexual headache are not fulfilled.

P3-T9
Headache as an initial symptom in systemic lupus erythematosus in pregnancy
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Objectives The incidence of headache is common in Systemic Lupus Erythematosus (SLE). In addition, it has reported the increased prevalence of migraine and its relation to other disease manifestations. The frequency of headache attacks decreases or disappears during pregnancy, which is not a triggering factor for headache. On the other hand, pregnancy is a precipitating factor for the appearance of autoimmune diseases. Aim of the study is the screening of the role of pregnancy in the appearance of headache, an initial symptom of SLE.

Materials and methods Three young women, mean age 28, without previous headache history and with no medical history were admitted in our department with a sudden onset of severe frontotemporal bilateral headache, accompanied by nausea, vomiting and photosensitivity. There was persistence of the pain although the analgesic treatment gave the suspicion of a possible systemic disease. A battery of laboratory tests was suggested.

Results The headache of two patients had migrainous characteristics, whereas the third patient had a tension type headache. The lab tests had confirmed the diagnosis of SLE. The possible influence of the hormonal changes to the appearance of headache is discussed.

P3-T10
A cervicogenic and tension headache management programme in an HMO setting: a pilot study on the effect of a group-based neck self-care programme on disability, quality of life and patient satisfaction
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Objective To analyse the effect of a new biomechanical self-care programme taught in group visits on quality of life and disability in patients with presumed cervicogenic headache (PCH) and tension headache (TH).

Background There is controversy about cervicogenic headaches. Some people feel they are tension headaches, others feel they can only be diagnosed radiographically. We feel they can be diagnosed clinically. There are many patients with frequent or chronic (PCH) and (TH) that are unable to use medications or would prefer to limit medication use. These patients may benefit from the use of alternative means of headache management.

Methods Fifty headache clinic patients diagnosed with PCH or TH were referred for two group appointments with a physical therapist. Group size varied from 6 to 15. Patients were taught basic neck self-care and a 5-min neck exercise programme to align the cervical spine. Patients were asked to perform these exercises daily. MIDAS was administered at baseline and 1 month after programme completion. Patient satisfaction and programme adherence were also assessed 1 month after programme completion.

Results There was good adherence to this brief exercise programme taught in a group setting, and there was significant improvement in disability scores and quality of life for patients with PCH and TH.
Conclusion A more aggressive use of a group-visit-based neck rehabilitation programme may be indicated in patients with PCH and TH. Further research is needed to confirm these observations.

P3-T11
Is there a causal association between upper cervical spine pathology and cluster headache or is this an uncommon coincidence?

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Background Although cluster headache (CH) is a primary headache, some authors have described the association of cluster-like headache with various intracranial disorders such as vascular malformations, tumors and infections. However, the association of CH with extracranial lesions is exceptional. We report the occurrence of cluster-like headache in a patient with a syringomyelia.

Case report A 39-year-old man presented with a 5-year history of severe throbbing headache in the right periorbital area. When he was 7-year-old, he suffered meningitis. The headache was accompanied by ipsilateral lacrimation and ocular injection. The symptoms lasted around 60 min, and the frequency of attacks was 4–5 per day. The patient presented three bouts lasting 1 month. Sumatriptan aborted the attack promptly. When he was 7-year-old, he suffered meningitis. The treatment was successful as a prophylactic agent. Brain MRI was normal. Cervical spine MRI revealed a syrinx extending from C3 to C6 level without cerebellar tonsils ectopia.

Conclusion This patient fulfilled the IHS criteria for CH. Although the relationship between the CH and the cervical spine pathology remains unclear, we considered a direct injury of C2-C3 input to the spinal tract of the trigeminal nerve as responsible for the headache.

P3-T12
Headache induced by accidental nitric acid inhalation

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We describe an unusual cause of headache – the inhalation of nitric acid (HNO₃) (NA) vapours. This substance is used for polishing metals, and when it comes in contact with some brass or copper alloys it emits nitric oxide (NO) and nitric dioxide (NO₂). Either NO or NO₂ is potentially toxic for the body, but not at normal air concentration. The role of NO in headache is controversial, although its biomolecular level of importance is still controversial. A recent report on cardiac headache as a rare symptom of myocardial ischaemia, with a beneficial response to nitrovasodilators, remains a still undetected and intriguing matter. A 65-year-old man, a goldsmith, had a 45-year history of near-daily headaches resistant to common analgesic treatments. On the basis of the clinical characteristics of the headache, this patient’s headache has been classified during his life span mainly as tension-type, rarely as migraine, and recently as chronic daily headache. The patient’s medical history showed that the patient began working while very young and used NA almost every day to polish precious metals. We found a correlation between the use of NA and the occurrence of the headache. The headache description showed the characteristics of a migraine-like attack: throbbing pain in frontal and orbital areas accompanied by nausea and phonophobia. While in hospital, the patient’s symptom headache gradually subsided in intensity. Routine laboratory tests and brain MR and EEG were normal. Ophthalmology and ORL consultations reported no abnormality. Echo-colour TSD revealed diffused sclerosis of blood vessels. COXIB treatment was started and the headache subsided within two weeks. The confirmation of toxic etiology of a secondary headache appeared months later when the patient developed a headache attack immediately after the exposure to NA vapours without adequate precautions. Inhalation of NA vapours or its degradation products NO and NO₂ at high doses may be toxic. NO is recognized as an important biological mediator capable of acting as a vasodilator and ubiquitous neurotransmitter, which regulates cell function during inflammation by both stimulating and suppressing the immunological response. NO contributes to the release of pro-inflammatory cytokines IL1-alpha, -beta, and TNF in both CNS and endothelium, and it may additionally contribute to the development of this NA secondary headache.

P3-T13
Botulinum Toxin A is effective in cases of oromandibular dysfunction even if previous bite splint therapy has proved unsuccessful

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Objectives Oromandibular dysfunction is a frequent cause of the development of chronic headache and of chronification of tension-type headache or an increase in the frequency of migraine attacks. The patients are typically found to have parafunctions and painful masticatory muscles at rest or on palpation. A conventional therapy is to fit a bite splint. This therapy has disadvantages, however: the bite splint is time-consuming to fit and unpleasant to wear, and its therapeutic efficacy is frequently suboptimal. This study set out to investigate whether treatment with botulinum toxin A was successful in patients with oromandibular dysfunctions even if previous bite splint therapy showed no effect.

Methods Fourteen patients with oromandibular dysfunction according to the IHS criteria and previous unsuccessful therapy with a bite splint were included in the study. They
were treated with Botulinum Toxin A (Botox\textsuperscript{\textregistered}), a total of 100 MU being injected in 3 injection sites each in the left and right masseter and 2 sites each in the left and right temporal muscle. In each case 10 MU was injected into locally pressure-sensitive trigger points. Efficacy was continuously recorded with the aid of a standardised pain diary.

**Results** In 11 of 14 patients there was a reduction of pain after 12 ± 4 days. After 28 ± 11 days there was found to be a plateau phase of pain alleviation with an average pain reduction of 82% of the initial value. In 6 patients the pain disappeared completely. The pain reduction lasted for an average of 104 ± 24 days. 5 patients reported a reduction in migraine days by an average of 74% per month. All patients requested a follow-up injection. 4 patients reported side-effects during the first 10 days in the form of an aching sensation (like postexercise muscle soreness) in the muscles treated. No other side-effects were reported.

**Conclusions** Botulinum Toxin A is effective in the treatment of painful oromandibular dysfunction even if previous bite splint treatment has failed to achieve a therapeutic effect. The functionality of the masticatory apparatus is maintained. Tolerance is very good. By contrast, with cost-intensive and time-intensive bite splint therapy, treatment with botulinum toxin A may be regarded as an important therapeutic option for oro-mandibular dysfunction.

**P3-T14**

**Headache prevalence in a sample of dialysed patients**

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International literature concerning the documentation of the prevalence of headache in the dialyzed patients documents a scarce number of scientific contributions. Because of that observation, we present the data from an observation of a sample of patients exposed to dialysis. At the Università di Tor Vergata, Centro Dialisi, Roma, in the period between 10/01/00 and 12/01/00, an investigation was completed to identify the prevalence of headache in patients exposed to dialysis. All the recruited patients were informed about the study and their assent to treatment was provided. The sample is of 46 patients (middle 56.18 years age; range 32–72 years). All the patients were receiving a dialysis treatment every two days with HD Bic (77%), HDF (17%), ABF (4%) and PDF (2%) technique. In 22 of 46 (48%) patients, headache was noted: 55% in females, 45% in males. Usually, headache onset was reported at the end of the dialysis: in 4 (18%) immediately after, in 15 (72%) at different times but within an hour from the end of the sitting. The middle length of the headache was 4.5 h. The headache places were always bilateral and with the following distribution: parietal (‘to cap’) 26%, frontal 23%, frontal and temporal 18%, thunderstorm 18%, temporal and occipital 5%, occipital 5%, and frontal-orbitalis 5%. The kind of pain was gravitative in 54%, button in 32%, and constrictive in 14%. The intensity of the pain was between 7 and 4 (equal middle VAS value of 5.4). The accompanying symptoms frequently referred to were nausea (9), emesis (3), lacrimation (4), photophobia (4). In the 22 patients with headache, the 81% had submitted to HD Bic dialysis, 14% to HDF dialysis, and 5% to ABF dialysis. No patient exposed to PDF dialysis had headache. The prevalence of headache noticed in this sample was 48%. The onset of headache makes a striking hypothesis that needs to be tested on a sample that is statistically and numerically more representative. A causal connection could exist between dialysis and headache. Further examination is also needed concerning the kind of dialysis technique used (headache in 81% of the patients exposed to HDF dialysis). The intensity of the pain was middle to light; however, the pain assumes remarkable importance if reported in a patient typology where quality of life is already strongly compromised by the chronic therapy. Moreover, this points to the necessity of further studies in order to evaluate the risks/benefits of an ‘ad hoc’ drug for the control of headache symptoms.

**P3-T15**

**Multiple sclerosis diagnosed in a cluster headache patient – a case report**

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**Introduction** Cluster headache (CH) is a primary headache disorder with attacks of severe unilateral pain and unilateral vegetative symptoms. Multiple sclerosis (MS) is a demyelinating disease of the central nervous system being able to cause a broad number of neurologic symptoms, e.g. spasticity, weakness, sensory loss, fatigue, brainstem symptoms, or symptomatic trigeminal neuralgia. Evidence is rising for CH being not only a vascular but a neurovascular disorder involving activation of thalamic and hypothalamic areas.

**Case report** In a 35-year-old male patient presenting with a recent history of remittent sensory loss in his right leg and acute optic neuritis, we diagnosed a relapsing-remitting MS with typical findings in magnetic resonance imaging (MRI) and cerebrospinal fluid. Four months after recovery he presented with severe temporal headache attacks with ipsilateral tearing, lasting 30 min and occurring each night two times at the same time. History revealed several episodes of up to two months for several years. The diagnosis of episodic CH was established according to IHS criteria and a prophylactic treatment consisting of verapamil was begun. CH attacks ceased immediately. MRI of the brainstem was not conclusive.

**Discussion** In former times, CH was seen as a mainly vascular disorder. Recent studies of positron emission tomography (PET) in CH patients during attacks revealed central nervous system dysfunction as a key event in the pathophysiology of CH. Another case of incidence of MS and CH as well as a case where CH was ‘cured’ by the occurrence of an MS plaque are reported in the literature. We hypothesize that there might exist a symptomatic CH.
P3-T16

One centimetre post-traumatic subluxation of the odontoid presenting as chronic daily headaches

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Traumatic injury to the neck causing 1-cm posterior subluxation of the atlanto-axial joint might cause severe neurological deficit or death. When the AP diameter of the spinal canal is significantly reduced, cervicomedullary compression can result. Such subluxation can occur without fracture of either the C1 or C2 vertebrae, and in fact, is a result of incompetence of the transverse ligament which retains the dens against the anterior arch of C1. Pain is the most common complaint associated with atlanto-axial subluxation in patients who survive this type of an injury. This is a case history of a 58-year-old female who came to our headache clinic alleging that her ex-husband had violently twisted her neck 6 months earlier. She had constant occipital and upper cervical pain following that accident, accentuated by moderate rotation of her neck and other such movements. She used daily analgesics for the initial 3.5 months but later reduced these to 2–3 days per week. She had not seen any physician until 6 weeks earlier when she saw her primary care doctor who referred her to the headache clinic. The examination showed no abnormalities other than approximately 60% reduction in all movements of the cervical spine. A flexion lateral radiograph showed a 1-cm space between the odontoid and the posterior edge of C1 (predental space) which should normally be less than 4 mm in adults. Immediate surgery was advised but she refused. Finally, after continued constant pain, fixation of the odontoid was performed 14 months after the initial injury. Following surgery there was marked improvement in her pain. Surprisingly, she never developed neurological deficit with this degree of subluxation of the odontoid. The mechanism for this instability is believed to result from a tear of the transverse ligament, also described as ‘an incompetent ligament’. X-rays showing the subluxation of the odontoid before and after surgery will be displayed.

P3-T17

Hemiplegic cluster

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Introduction

We describe 4 cluster patients seen in our headache center who have accompanying hemiplegia with their cluster attacks (see table at foot of the page).

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Side of headache</td>
<td>Right</td>
<td>Right</td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>Duration of headaches</td>
<td>30–60 min</td>
<td>20–60 min</td>
<td>Up to 2 h</td>
<td>20–40 min</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>Tearing, rhinorrhea</td>
<td>Tearing, rhinorrhea</td>
<td>Tearing, conjunctival injection</td>
<td>Tearing, rhinorrhea, eyelid droop</td>
</tr>
<tr>
<td>Chronic/epidemic No. attacks/day</td>
<td>Chronic</td>
<td>1–2</td>
<td>Episodic</td>
<td>1–3</td>
</tr>
<tr>
<td>Migraine symptoms</td>
<td>Nausea, photophobia, phonophobia</td>
<td>Nausea, photophobia, phonophobia</td>
<td>Verapamil, oxygen</td>
<td>Photophobia, phonophobia</td>
</tr>
<tr>
<td>Effective medication</td>
<td>Verapamil, divalproex sodium</td>
<td>Verapamil, divalproex sodium, topiramate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of motor symptoms</td>
<td>Ipsilateral</td>
<td>Ipsilateral</td>
<td>Contralateral</td>
<td>Crossed ipsilateral</td>
</tr>
<tr>
<td>Duration of weakness</td>
<td>4–12 h</td>
<td>0–24 h</td>
<td>Uncertain</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Time of onset of weakness</td>
<td>5 min after headache onset</td>
<td>15 min after headache onset</td>
<td>Uncertain</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Visual symptoms</td>
<td>Blurry vision</td>
<td>Ipsilateral monocular visual loss</td>
<td>Ipsilateral monocular visual loss</td>
<td>Ipsilateral monocular visual loss</td>
</tr>
<tr>
<td>Total no. attacks</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>Multiple</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Numbness in face</td>
<td>Aphasia</td>
<td>None</td>
<td>Slurred speech</td>
</tr>
<tr>
<td>Evaluation</td>
<td>MRI, MRA and interictal exam normal</td>
<td>MRI, MRA and interictal exam normal</td>
<td>Left hemiparesis</td>
<td>Head CT and interictal exam normal</td>
</tr>
</tbody>
</table>
Case 1: A 47-year-old man with a 15-year history of right-sided chronic cluster headache presents with numbness in his right face and weakness in his right arm and leg. These hemiparetic spells started 5–10 min after the headache began and lasted from 4 to 12 h. The patient also noted blurry vision during these headaches. MRI and MRA were normal. His father had a history of severe, unilateral headaches, predominantly during the night, and at times associated with an unsteady gait. His brother has severe headaches associated with unilateral weakness.

Case 2: A 45-year-old man with a 7-year history of right-sided episodic cluster headache developed, with his attacks, right-sided weakness and aphasia. His MRI and MRA were normal. His father and sister have migraines.

Case 3: A 32-year-old man had a history of right-sided episodic cluster headaches for 5 years. During one cluster episode, he had right-sided monocular visual loss for one-half hour. He has no family history of headaches or neurologic disorders. He noted mild left-hand weakness and, on neurologic examination, was found to have mild left hemiparesis. MRI and MRA were refused. The weakness had resolved when he returned for a follow-up visit a week later.

Case 4: A 52-year-old woman with a history of migraine that resolved after surgery for a left middle cerebral artery aneurysm developed episodic cluster headache after head trauma. Associated with the cluster headache were left facial droop, slurred speech, and right hemiparesis; which lasted up to 4.5 h. She also gets right extremity tingling and loses vision in her left eye. A diagnostic workup, including MRI and CT of the head, was negative.

Hemiplegia associated with cluster headaches has never been described, and this entity shares many similarities with hemiplegic migraine with its episodic nature and possible familial link in 1 patient. It too may be a channelopathy.

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Munchausen’s syndrome: a case report of cluster headache

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Munchausen’s syndrome is a factitious disorder with predominately physical signs and symptoms. This patient was a 23-year-old white female with a 1-year history of right periorbital and temporal sharp pain, eye tearing, and nasal congestion. The attacks occurred 1–5 times per day, lasting 1–2 h. She had associated nausea and vomiting. Neurological exam was always normal, with no pupillary abnormalities. The symptoms began shortly after a right-sided cervical injection for radicular pain. With the onset of the cluster headaches, the patient was admitted multiple times for prolonged hospitalizations, was seen in outpatient offices at least once per week, and was given numerous medications. Virtually every known cluster, migraine, and pain preventive medication was a failure. Narcotics provided the only benefit, and the patient did actively seek them out. Her presentation of the pain was often dramatic, but she could be easily distracted from the pain. She was caught several times manipulating and lying in order to obtain narcotics. The patient demonstrated extensive knowledge about cluster headache. While it was suspected that the patient was using artificial tears to simulate tearing, this was not able to be confirmed. Despite her description of nausea and vomiting, actual vomiting was never confirmed by medical personnel. Antiemetics were unsuccessful in alleviating her nausea. The secondary gain to this patient was increased attention, and the obtaining of narcotics. She was constantly pushing her physicians to hospitalize her. She felt very comfortable in the sick role, and described herself as an ‘extremely severe chronic cluster patient. The patient was very dependent, but had little support from family or friends. Psychological testing revealed the dependent personality, depression, low self-esteem, denial of psychological problems, low frustration tolerance, and poor impulse control. She was agitated easily, possessed weak coping mechanisms, was socially isolated, and experienced little pleasure. There was no evidence for distorted reality testing. This patient’s factitious disorder began in early adulthood, after being hospitalized for a medical illness. She became well versed in the textbook presentation of cluster headache. Her hospitalizations were marked by a notable absence of visits from family or friends. While aware that she was feigning illness, she was unaware of why she was doing this. All of the above are classic for factitious disorder. The patient left our practice before adequate psychotherapeutic intervention could be accomplished.

Post-craniotomy headache

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Objectives Persistent headache following craniotomy has been described in the past, but the clinical features of this type of headache are lacking in the available publications. This study was undertaken to evaluate the incidence and clinical features of headache following surgery.

Materials and methods Medical records of 107 patients who had undergone surgery for brain tumour and intractable epilepsy were reviewed. The clinical features of pre-operative and postoperative headache and therapy instituted were abstracted from the medical records. The location of surgery and the underlying pathology were also documented. The subsequent course of the headache was also noted.

Results We evaluated 76 patients who underwent surgery for an underlying brain tumour, 21 patients for intractable epilepsy, and 5 patients with intracranial haemorrhage. Five
patients were disqualified because of inadequate documentation. 58 patients did not complain of headache preoperatively. 11 patients experienced headache postoperatively, 8 of whom underwent surgery for intractable epilepsy and 3 for brain tumour. 73% of patients had a gradual improvement of their headache over time. Most did not require major medical intervention for controlling their headache. There were no cases of debilitating or persistent headaches identified. The majority of the headaches were located over the site of surgery.

Conclusions The pathogenesis of postoperative headache still remains unclear. The clinical characteristics of the headache following craniotomy suggest a combination of tension-type and ‘site of injury headache’ overlying the location of surgery. These headaches are similar to the headache seen following head trauma. Surgery probably acts as a traumatic event.

P3-T20

Cerebellar medulloblastoma as a cause for cough headache in an adult

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Objective To describe a patient with cough headache secondary to an underlying cerebellar medulloblastoma.

Materials and methods The history, physical examination, diagnostic workup and treatment of a patient suffering from a symptomatic cough headache secondary to an underlying cerebellar medulloblastoma are summarized.

Results The patient was a 66-year-old women with a past medical history of hypertension, hypercholesterolaemia, depression, anxiety and long-standing coccygeal pain who presented with a chief complaint of new onset headache secondary to an underlying cerebellar medulloblastoma. Follow up MRIs of the brain/spine and CSF analysis at 10 months postoperative showed no evidence of tumour recurrence. Furthermore, the headaches resolved with the surgery and have not returned.

Conclusions Cough headache is a sudden, usually short-lived, severe head pain associated with coughing, sneezing or valsalva. Both a benign and symptomatic form of cough headache exist; therefore, underlying structural abnormalities such as Chiari malformation and posterior fossa tumours must be excluded prior to making a diagnosis of benign cough headache. The majority of medulloblastoma cases occur in the first two decades of life; therefore, medulloblastoma in this case represents an exceedingly rare cause of cough headache in the adult patient. This case emphasizes the need for routine MRI imaging in all patients suffering from cough headache.

P3-T21

Onset of short-lasting, unilateral, neuralgiform headache with conjunctival injection and tearing (SUNCT) after acquiring human immunodeficiency virus (HIV): more than a coincidence?

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Objectives To report a case of SUNCT in a patient HIV-positive.

Patient and methods A 37-year-old white woman knew she was HIV-positive at 33 years old, at the time her husband died with AIDS (Acquired Immunodeficiency Syndrome). At the time of her husband's death, she was completely healthy except for being HIV-positive and having a high CD4 lymphocyte count. While 34 years-old, she began to feel an intense piercing periorbital pain, only on the right side of the head. It lasted from 1 to 2 min and occurred together with ipsilateral ptosis, conjunctival injection, tearing, and nasal congestion. She did not report miosis, but this was observed by examiners during the attacks. The attacks occurred from one every second day to 8 a day in the beginning and, according to the patient, are increasing in frequency (now about 20/day). When the patient was 35 years old, antiretroviral therapy was started because her CD4 lymphocyte count fell, but until the present she has never had any opportunistic infection or other complication related to AIDS. The more recent (January 2001) CD4 lymphocyte count was 176 cells/μL. The patient does not have any other disease, and the unique abnormality in general and neurological examination (out of the attacks) is Babinski's sign on the left. In order to exclude other possible causes of SUNCT she underwent an extensive investigation that was normal. It included brain Magnetic Resonance Imaging (MRI), brain angiography by MRI, blood tests for syphilis and autoimmune disorders, and blood biochemistry. Carbamazepine, Oxcarbazepine, Gabapentin, and Indomethacin were each tried alone with no pain relief.

Conclusions The present case opens the possibility of a causal association between HIV infection and SUNCT, still not described in the literature.
P3-T22

Intracranial hypertension after treatment of spontaneous intracranial hypotension with spinal epidural blood injection

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Objectives Spontaneous intracranial hypotension (SIH) due to cerebrospinal fluid leakage is an uncommon but increasingly recognized cause of postural headaches. Although strict bed rest and fluids can cure most patients with SIH, some patients are resistant to this relatively conservative therapy. Epidural injections of autologous blood have been reported to be useful as a treatment of choice for these cases, however, the complications observed are not reported in the literature. We recently experienced 2 cases of intracranial hypertension after epidural injection of autologous blood. We will discuss the mechanism and treatment of intracranial hypertension after these epidural injections.

Materials and methods Between January 1997 and December 2000, 10 patients of SIH were admitted to our department. Postural headaches were observed in all patients. Low intracranial pressure (ICP) was confirmed by lumbar puncture. The MR imagings revealed downward displacement of the basal cisterns and tonsilla cerebelli with enhanced thickness of the intracranial dural structures. After admission, all were treated by intravenous fluids supply (1500–2000 mL/day) and strict bed rest for 3 weeks.

Results Seven patients (70%) recovered completely with the above conservative treatment, however, three (30%) were resistant to therapy and treated additionally by autologous blood injections. Of these 3 patients, one achieved complete remission, but the other two patients having existent chronic subdural haematomas (CSHs) were complicated by intracranial hypertension. One had a right oculomotor palsy the next day after epidural blood injection, and the other had persistent intractable headache. We performed surgical irrigation of the CSHs for the 2 patients. After a dural incision, the haematomas spouted out from the subdural space with evidence of intracranial hypertension. The headache and oculomotor palsy were relieved immediately after the evacuation and irrigation surgeries.

Conclusions Increased ICP may occur after epidural blood injections in the treatment of patients with SIH, particularly in patients with existent CSHs. Careful observation is required during and after epidural blood injections for SIH patients associated with CSHs. Emergent surgical irrigation of the CSHs is an effective therapeutic method for treating SIH patients with intracranial hypertension after epidural blood injections.


P3-T23

Spine and wave headache

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Chronic headache (more than 3 months’ duration) is a common disorder for which a neurologist’s advice is sought invariably. 500 cases of chronic headache seen by me in 2 years (from February 1998 to January 2000) reveals a significant number (175 cases, approximately 35%) are of epileptic background. All these cases (headache) responded well to antiepileptic drugs only. Three subgroups are noticed in these 175 (35%) cases: (1) Calciﬁed granulomas 61 cases (35%). (2) Febrile convulsions/childhood convulsions with interictal EEG changes in 35 cases (20%). (3) Family H/O seizures with interictal EEG changes 79 cases (45%). Based on this analysis, it is desirable to keep in mind the epileptic background of these chronic headache cases and treat appropriately with AEDs. This group forms a signiﬁcant percentage (35%) of my study. The name ‘spike and wave headache’ denotes electrophysiological evidence supported by history without seizure, being precipitated clinically, and headache responding to AEDs only. This type of headache is not included in the international classiﬁcation and constitutes 1–2% of the population.

P3-T24

Cytokines generation and headache in acute ischemic stroke

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Introduction Cytokines generation has been implicated in headache and cerebral ischaemia, although the mechanisms involved are probably different in both processes. We studied the relationship between cytokines concentrations in plasma and cerebrospinal fluid (CSF) and headache in patients with stroke-related headache.

Patients and methods After cranial computed tomography (CT), plasma and CSF samples were obtained in 250 patients (178 M and 122 F; mean age 68.2±10.2 years) within the first 24 h from the onset of a hemispheric ischaemic stroke. Stroke severity was evaluated by the Canadian Stroke Scale (CSS) on admission and infarct volume was measured on a second CT performed on days 4–7. Cytokines concentrations in plasma and CSF samples were measured with enzyme-linked immunoabsorbent assay.

Results 65 patients (31%) presented with headache at the time of stroke onset. Stroke severity was higher in patients with headache compared with those without headache on admission (CSS score, median [min–max], 4 [1.5–8.5] vs 6 [1.5–10], P<0.047). Infarct volume was significantly larger in the first group (62.9±41.6 vs 25.8±39.4 cc, P<0.0001). IL-6 (11.2±12.7 vs 34.8±14.0 pg/mL; P<0.0001) and TNF-alpha...
Conclusions
IL-6 generation was related to headache during tors, because it did not remain statistically significant on headache, the relationship was confounded by other factors in plasma, and CSF (2.12 vs 15.2 pg/mL, P < 0.001 for plasma and CSF TFN-alpha, respectively; P < 0.0001 and 0.358 and 0.400 for plasma and CSF TFN-alpha, respectively; P < 0.0001). Although TNF-alpha was also higher in patients with headache, the relationship was confounded by other factors, because it did not remain statistically significant on multivariate testing.

Conclusions
IL-6 generation was related to headache during the acute phase of ischemic stroke.

P3-T25

Short-lasting epileptic headache

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Background and objectives
Headaches of epileptogenic nature are not frequent. Usually, cephalalgia is associated with other seizure manifestations, but sometimes it presents as the only symptom of epilepsy. Epileptic headaches were not directly considered in the International Headache Society’s 1988 Classification, and when cited in several books, they are mainly referred to as the relation between migraine and epilepsy. 3 cases of short-lasting headaches of epileptogenic nature are reported.

Methods
Patients consulting for headaches were diagnosed from December 1998 to October 2000. Case 1: A 25-year-old man presented with a three-year history of headaches in the left frontal area, the attacks lasting 15–20 s. Lately, the pain crises increased their frequency and in some cases were followed by brief periods of absences. Electroencephalogram (EEG) was abnormal. Carbamazepine provided significant relief. Case 2: An 18-year-old man presented with a 2-year history of headaches. The headaches were sharp, excruciating right hemicrania, and lasting 5–10 min EEG was abnormal. The attacks were abated by carbamazepine. The patient has had no attacks since the treatment was given. Case 3: A woman had a history of headaches which began at the age of 15. The pain attacks were sharp, excruciating, in the left frontal area, lasting 3–5 min and were sometimes followed by somnolence. EEG was abnormal. The attacks resolved with valproic acid.

Conclusions
In all the cases reported, EEG examination showed interictal paroxysmal abnormalities, and these short-lasting headaches responded to treatment only with antiepileptic drugs. It is important to keep in mind the possible epileptic nature of short-duration headaches in order to treat them appropriately. This type of cephalalgia is not considered in the IHS Classification.

P3-T26

Sleep and headache: morning headache associated with sleep disordered breathing

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The International Classification of Sleep Disorders’ diagnostic criteria includes morning headache (MH) as a symptom of obstructive sleep apnoea. However, inconsistent findings exist in the empirical literature regarding the relationship between MH and sleep-disordered breathing. Some studies have correlated MH with obstructive sleep apnoea and have observed subsequent headache improvement with treatment of apnoea through positive air pressure devices or uvulopalatopharyngoplasty. Conflicting research has failed to identify a specific relationship between MH and obstructive sleep apnoea, and instead attributed MH to disturbed sleep architecture. This study attempted to contribute evidence to this debate. To our knowledge this was the largest clinical sample to date examining the relationship between sleep-disordered breathing, morning headache and objective sleep parameters. Participants were 826 consecutive patients who presented to a sleep disorders centre. Mean age was 45 years (SD 14.5), and 66% were male. Data were collected from clinical interview, physical exam, questionnaires, and full-montage nocturnal polysomnography. 77% of patients were diagnosed with a sleep-related breathing disorder. Sleep-disordered breathing was quantified by Apnoea/Hypopnoea Index (AHI: apneic events per hour of sleep), and mean and nadir nocturnal oxygen saturation (SpO2). Results indicated that MH was common, with 19% of all patients reporting daily or near-daily MH, 16% occasional MH, and 65% no MH. There were no gender differences in headache prevalence. Results revealed a significant relationship between MH and AHI (F = 21.8, P < 0.001; daily MH > occasional MH = no MH). A significant dose–response relationship was noted between MH and nadir SpO2 (F = 135.5, P < 0.001; daily MH > occasional MH > no MH). The relationship between MH and mean nocturnal SpO2 approached but failed to reach clinical significance (P = 0.07). Patients with daily MH exhibited more frequent arousals from sleep (F = 10.2, P < 0.001) than did other patients. There was a trend (P < 0.06) toward a lower overall percentage of REM sleep for the night in individuals with MH. No other gender differences in sleep architecture were found. A relationship was identified between MH and sleep-disordered breathing including significant associations between MH, AHI and nadir nocturnal oxygen saturation. There was a concurrent association between MH and the number of arousals from sleep, likely because most respiratory events would be terminated with an arousal from sleep to restore breathing. This study implicates hypoxaemia or hypercapnia in the aetiology of MH.
Parasites and headache: an Indian experience

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Objective To study the patients with parasitic infections of brain presenting with headache.

Materials and methods Study 1: 1003 patients who attended the headache clinic during the year 1998–2000 were examined and investigated by a team of specialists comprising the physician, ophthalmologist, neurologist, ENT surgeon, and psychiatrist. We tried to classify these patients according to the guidelines of the International Headache Society (IHS). Patients with high index of suspicion for intracranial pathology were subjected to a CT/MRI of the brain.

Results Of 1003 patients, 12 (1.2%) were suffering from parasitic infections of the brain, including 9 patients with falciparum malaria, 2 patients with cysticercosis, and 1 with toxoplasmosis. Study 2. 3802 patients who were treated in the Apollo hospital – the multispecialty tertiary care centre – during the same period were studied retrospectively to know the magnitude of the problem of parasitic diseases affecting the brain in general. Of 3802, 381 (10%) had parasitic infections of the brain including 281 (8%) with falciparum malaria, 22 patients (0.8%) with cerebral cysticercosis, 2 patients with cerebral hydatid disease and 2 patients with toxoplasmosis.

Discussion In our study we found that a significant number of the patients do have parasitic infections of the brain in India. In our country, cerebral malaria is common, whereas cysticercosis, toxoplasmosis, and hydatid disease, etc., are occasionally seen affecting the brain to produce headaches. Neurofilariasis is also seen though rarely in this part of the world.

Conclusions (1) The approach to the patients with headache should include the evaluation for parasitic diseases. (2) The peripheral smear examination for haemo-parasites before we subject the patients to highly sophisticated and expensive investigations is worthwhile particularly in tropical countries. (3) Inclusion of parasitic disorders affecting the brain in the IHS classification with a code number (Probably under Code no. 7, non-vascular intracranial disorders) gives due importance to it which also helps to create the awareness of the problem of parasites causing tropical cephalalgia.

Periorbital headaches in a south Indian population: a 7-year study

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Objective To diagnose periorbital headaches presenting without associated inflammatory eye signs.

Materials and methods 7800 patients were studied over a period of 7 years, aged 12–60 years. Exclusive criteria: fever and organic systemic illnesses. Diagnosis was made from a two-step approach. Step one: a well taken history with IHS classification criteria strictly applied. General physical, ocular, and neuro-ocular assessment in all patients. If step one did not help in arriving at a proper diagnosis, step two was adopted: complete CNS exam, simple lab tests including ESR, other specialty ref., and neuroimaging.

Results Of the 7800 patients 4417 (56.5%) were suffering from migraine origin periorbital headaches. Tension/anxiety aches were diagnosed only in 421 (5.4%) patients. Exposure to sunlight was the most common trigger factor (93%). 23% reported tension/anxiety as a trigger factor for their migraine headaches. The other common triggers were: travelling during the day (41%), missing meals at the proper time (24%), and lack of sleep (23%). Other well-known triggers were rarely reported by patients. Eye strain was one of the triggers in 17 migraine patients who had uncorrected refractive errors and binocular muscle dysfunction.

Conclusion The most common cause of periorbital headache without associated inflammatory eye signs is migraine. Tension/anxiety aches are less common but a significant trigger factor for migraine attacks. Uncorrected refractive errors and binocular muscle dysfunctions can trigger migraine-origin periorbital headaches.
U: History of headache

P3-U1
Metaphorical properties of headache in Ancient Greek literature
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Metaphorical properties of migraine, and metaphor-like alterations of perception and body image in migraine have been noticed and studied again in the recent past (see Nappi G, 'A metaphorical disease' [passing remark]; Ferrari MD, Haan J: Migraine aura, illusory vertical splitting, and Picasso. Cephalalgia 2000; 20:686). It seems worthwhile to show how Ancient Greek authors were coping with the same problem, headache and its metaphorical properties. In Plato’s dialogue ‘Charmides’, headache is the initial subject, and the pivot of a paradigmatic discussion about the necessity of psychotherapy as the prerequisite of pharmacotherapy. The drug the young Charmides requests from Socrates is the gift of a mythical healer-king from Thrace. The dialogue appears to develop on several levels beyond the one of formal logical discussion. There is a level of sensual attraction and repulsion, one of magical and psychological values opposed to trite medical routine, and one where metaphors are used to represent medical anthropology in dramatic context, enhancing the metaphorical aspects of headache. Some 500 years later, Lucian of Samosata wrote his dialogue ‘Vulcan and Jupiter’ where headache, pregnancy, switching from female to male roles and vice versa, alternating functions of organs, surgical and sexual violence, memory, science and technology interact dramatically with each other in the space of a few sentences. Memory, personified as a female deity, begets the child, as it were, on maleness personified in whom working until they could only be stopped by headache: martyrs of their work.

Conclusions The popularity of headache saints across the ages provides ample, if indirect, evidence of continuing high prevalence and important social impact of headache. Accounts of unbearable headache cured by saints can be interpreted as cures of migraine rather than all other forms of headache, by prayer, belief, additional suggestions (‘This headache must now come into my own head’, Isler et al. 1993) and placebo effects. The headache saints and saints suffering from headache in this paper are far from complete. We hope to encourage further research into local customs involving headache saints.

P3-U2
A short review of Christian saints invoked for headache, and of the saints’ own headaches
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Introduction Data on headache, its importance, and its treatment in the middle ages is very scarce, and accounts of religious treatment methods can supply some of the missing answers (Bruyn 1989; Isler 1993). Specific headache saints are relatively well documented. They provide a promising field of research on headache in popular culture.

Materials and methods Collections of legends, accounts of miracles, lists of saints and their special capacities, as well as their (auto-)biographies were searched for saints invoked for headache, and for accounts of their own headaches.

Results Kerler’s list of patron saints (Patronate der Heiligen, Ulm 1905) shows over 300 saints in alphabetical order, also listed according to the diseases for which they are invoked. 48 saints are said to cure headaches, and five of them are noted for migraine treatment: Severus, Juliana of Collalto, Katharina of Alexandria, Petrus Damianus, and Ubaldus. Kerler provides short biographical summaries and anecdotes on the saint’s connections with particular diseases. Many of these headache saints were suffering from headache or from head or neck trauma. Several martyrs had their skull split by axe, sword, or saw. Decapitated martyrs often carried their head away from the place of execution. Veneration of a beheaded saint could actually be observed by one of the authors. The hermit St. Placidus founded a Benedictine monastery at Disentis on the top of Switzerland around 750. For many centuries, pilgrims stuck their aching head into a hole in the wall of St. Placidus’ church, praying for a cure, obviously as a symbolic way to offer themselves for beheading. Even St. Aed Mac Bricc who cured headache by transferring it to his own skull had performed his first miracle by denting a stone with his head at birth (Isler et al. 1993). On the other hand, heroic founders such as St. Paul the Apostle, St. Francis of Assisi and St. Teresa of Avila went on working until they could only be stopped by headache: martyrs of their work.

Conclusions The popularity of headache saints across the ages provides ample, if indirect, evidence of continuing high prevalence and important social impact of headache. Accounts of unbearable headache cured by saints can be interpreted as cures of migraine rather than all other forms of headache, by prayer, belief, additional suggestions (‘This headache must now come into my own head’, Isler et al. 1993) and placebo effects. The headache saints and saints suffering from headache in this paper are far from complete. We hope to encourage further research into local customs involving headache saints.
P3-U3

Purgatives, poisons, and pot luck: a look back at the medical treatment of trigeminal neuralgia

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Objective To review the medical treatment of trigeminal neuralgia.

Background Trigeminal neuralgia has been with us in medicine, literature, and history for centuries. Over the years, varied methods of treatment have been employed. Many of these therapies were once considered ‘standard of care’ by leading physicians of the time.

Design and methods Review of published papers.

Results Purgatives: one of the initial forms of therapy for trigeminal neuralgia included laxatives. Hippocrates recommended ‘external remedies’ to awaken nature. Proponents of the beneficial role of purgatives or ‘opening medicine’ included none other than John Locke, Thomas Sydenham, and Sir William Osler. The last author to suggest the use of purgatives for trigeminal neuralgia was George Gill, in 1905.

Poisons: Nicholas Andre recommended the use of caustic agents applied over the infraorbital nerve, proving once again that one man’s poison is another’s cure. The esteemed John Fothergill resorted to hemlock for particularly refractory cases. Other therapies included the use of mercury, arsenic, iron carbonate, and hydrocyanic acid, as well as strychnine. Pot luck: Trousseau is credited with coining the term ‘epileptiform neuralgia’ because of his contention that trigeminal neuralgia resembled an epileptic seizure. At first potassium bromide, then sodium diphenylhydantoin, and subsequently carbamazepine were found to be effective treatments for this condition.

Conclusion This glimpse into the history of the medical treatment of trigeminal neuralgia is both humbling and instructive. As Moritz Romberg so eloquently wrote, ‘Let the present generation look into this mirror of the past and be careful not to believe in the indestructible character of its own views’.

P3-U4

Coexistence of migraine and tension type headache in context: Andrea Comparetti, 1790

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When we are screening old and ancient medical literature for migraine and related headaches we are usually searching for classic descriptions of the syndromes which interest us most. We are less interested in the context where these syndromes may be found. This may well be the reason for the scarcity of mentions of the coexistence of migraine and tension-type headache in historical papers on headache. Andrea Comparetti published his first book in 1790 in Venice: ‘Occursus Medici de Vaga Eegritudine Debilitatis Nervorum: The Physician’s Encounter With Vagrant Disease from Weakness of Nerves’. One of his case studies relates the numerous ailments and disorders of a young nun, among them migraine and tension type headache, clearly distinguishable from his very short descriptions. The case history as a whole fits the criteria for what is now called Somatization Disorder (DSM IV 300.81). The book initiated Comparetti’s rapid career. He became head of the hospitals of Padova, the university town of the State of Venice, was given the task of reorganising the hospitals in that state, and was made Professor of Clinical Medicine at Padova. He was a researcher in physical optics and botany as well as in clinical medicine, publishing in these fields in Latin and Italian, and he was well known in his time to scientists and physicians outside Italy. In 20th century literature and even in the encyclopaedias of scientists, he is not mentioned in any language except for Italian. This may be explained by the fact that he published in Latin and Italian, and was able to comprehend and describe such difficult, time-consuming and repulsive disorders as somatization, which most physicians of later times would much rather avoid and ignore. Comparetti was an outstanding observer of natural phenomena and of human nature, an inductive scrutinizer who was able to grasp and define single syndromes without ignoring their personal context, namely, the development of the patient which included the development of those symptoms and syndromes for which we are usually looking in the history of medicine. In conclusion, instead of hunting for isolated syndromes we should prefer to look for them ‘in situ’, as it were, that is, in comprehensive descriptions of the development of patients.

P3-U5

Labels and definitions of headaches that change over time: a review of the wide variation of the use of these terms and their meanings

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Objective To provide a comprehensive review of the wide variation in terminology used in the literature describing headaches that change over time.

Background It has been hypothesized that some headaches change over time from an episodic to a more chronic form. Some of these headaches were ‘discovered’ in specialty clinics when a number of them failed to meet any of the current IHS criteria and fall under the rubric of chronic daily headache.

Materials and methods A thorough review of the literature was conducted.

Results A number of labels were identified including: Transformed Migraine, Chronic Evolution of Migraine, Migraine with Interparoxysmal Headache, and Chronic Migraine, to name a few. Many researchers proposed new IHS criteria for these headaches, and in some cases included the criterion that there must be evidence of an ‘evolution’ or ‘transformation’. All but one of the studies regarding this
type of headache was retrospective. The one prospective study followed only chronic daily headaches, which is the hypothesized end product of a headache changing over time. None of the studies reviewed demonstrated the existence of a headache that changes over time. Furthermore, little attention was given to the study of changes in tension-type headaches over time.

**Conclusions** The many terms used and definitions proposed in the literature to describe headaches that change over time has become enigmatic. A common language with an operational definition needs to be established as well as its proven existence. For the description of tension-type headaches that are high in frequency, the diagnosis of ‘Chronic Tension-Type’ headache has been adopted. In migraine sufferers, perhaps a consistent terminology and empirically developed criteria can be derived for a ‘Chronic Migraine’ classification. A prospective longitudinal study following both migraine and tension-type headaches needs to be conducted in order to fully delineate changes in headaches over time.

**P3-U6**

**A historical cohort study on posttraumatic headache outside the medicolegal context**

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**Background** In Lithuania, expectation of chronic symptoms after minor head injury is less than in Western countries and possibilities for monetary compensation are minimal. An opportunity therefore exists to study post-traumatic headache as predominant symptom of the postconcussion syndrome (PCS) without several confounding factors present in Western societies.

**Methods** We sent questionnaires with detailed questions about symptoms attributed to PCS to 200 subjects who had had a concussion with loss of consciousness between 35 and 22 months before the study. For each study subject, a sex- and age-matched control person with minor non-head injury and admission to the emergency ward at about the same time as the matching concussion patient, was identified. The controls received questionnaires which were identical except for inquiry about acute symptoms after the injury and symptoms before the injury.

**Results** One-hundred-and-31 concussion patients and 146 controls returned the questionnaires. All postconcussion patients remembered having had acute headache after the trauma but this headache had disappeared in 96% of cases within one month. Headache at the time of the interview had almost identical prevalence and frequency distribution. Headache on more than 15 days per month was reported by 13.7% of postconcussion patients and 15.0% of controls. Headache in both groups was more prevalent than in uninjured controls taken from the general population register of the same geographic area in previous whiplash studies.

**Conclusions** Our findings question the assumption that chronic post-traumatic headache with reported incidences as high as 44% after 6 months (1) and 20% after 4 years (2) in Western countries is causally related to the head trauma.

**References**


**P3-U7**

**Headache in the 30s. A reappraisal from medical records**

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The International Headache Society (IHS) classification (1988) supplied definite diagnostic criteria. Moreover, after the first guidelines (GL) on migraine therapy (Italian Headache Society, 1993), others have been published among which, very recently (2000), those of the US Headache Consortium. We wondered what were the diagnostic procedures, clinical and instrumental, and the therapeutic measures in the oldest records of our Clinic, before IHS classification and GL were introduced; when imaging and other medical technologies were not yet available; and antedating the introduction of many modern drugs. We reviewed 6708 consecutive clinical records of the patients hospitalized between 1932 and 1950 and we studied those reporting the diagnosis of migraine or headache. This one was reported in 242 clinical records (3.6%), of which 156 (64.4%) were female, 86 (36.6%) male; the average age was 31.2±12.9 years. Primary headaches were reported in 185 and the most frequent diagnoses were: headache without further specifications (137); migraine (28); psychoneurotic headache (20). Secondary headache was reported in 57 clinical records, and the more frequent were posttraumatic (10), sinusitis (10), internal frontal hyperostosis (6), otitis (3), hypertension (3), l郦quoral hypertension (3). We evaluated the headache features reported in the anamnesis and the diagnosis at the examination, matching it with the IHS diagnostic criteria. Migraine accounts for the 13.3% of the total admission during the thirties, and the 11.3% during the forties; in 1998 and 1999 the comparison data were, respectively, 29.2% and 28.7%. Only 10 clinical records reported the complete information on headache features, allowing us to formulate a diagnosis according to the IHS criteria. We found no cases of cluster headache and just one of drug abuse headache. Surprisingly, the clinical records on headache concerning the period 1932–50 do not correlate with
detailed anamnestic data, the diagnostic difficulty being due to the lack of instrumental investigations (e.g. EEG was introduced in clinical practice in the late 1930s and neuroradiological imaging was obviously not yet available); indeed, it is possible to classify less than 5% of the headaches when one applies IHS criteria. In conclusion, in our study the headache appears to have been largely underestimated, and this probably reflects mainly a cultural prejudice of that time. The apparent absence of cluster headache and drug induced headache warrants further investigation on the possible reason for these noticeable differences from today’s clinical experience.

P3-U8

Headaches in the media: a 100-year retrospective of headache-related articles in popular magazines

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Popular press stories about health problems are an important and widely accessed source of information. Many newspapers and television news programs have segments devoted to health news and there are numerous popular periodicals either partially or completely devoted to health issues. From a professional standpoint this can be useful. The popular press can be a good avenue for informing the general public about medical advances and standard treatments. It can also be a useful mechanism for increasing public support and trust of the medical community. Media reports about health can also influence the expectations that patients bring to the medical setting. We conducted a comprehensive review of popular press stories about headache covering the entire 20th century. A list of 417 articles was compiled using the Reader’s Guide, a reference source for stories in periodicals that serve the general population. For this project we have reviewed all of these articles. In our presentation we will report on changing trends in popular press reports of headache. We have compiled statistics on the number of pieces published each decade and the type of periodical in which the information appears (population targeted, circulation). We will also report a content analysis of the articles which will address such factors as type of headache discussed, causes of headache, issues related to treatment for headache, and the dangers of drug treatments for headache (a hot issue in the popular press). The information collected in the retrospective study provides insight into how medical and scientific information is disseminated to the general public. It is also of interest to the practitioner in that it makes us aware of the information and biases that our patients possess when they seek treatment.
LB-1

Linkage of three families with vascular retinopathy and migraine


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Objectives and methods

We initially performed a genome-wide search for linkage in an extended Dutch family with autosomal dominant vascular retinopathy (HVR), associated with migraine and Raynaud’s phenomenon (1) and in a second phase in two additional families with a similar phenotype, i.e. cerebroretinal vasculopathy (CRV) (2), and hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS) (3).

Results

We found significant evidence for linkage in the first family. The exact location will be revealed at the conference. Testing of the two additional families with a similar phenotype also revealed linkage to the same chromosomal region. Results of mutation screening of several candidate genes in this region will be reported.

Conclusions

We identified a locus for cerebroretinal vasculopathy, which probably also plays a role in migraine.

References


LB-2

Meningeal and central trigeminovascular activation following cortical spreading depression

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Background and aim

We postulated that cortical spreading depression (CSD) and the migraine aura (which often anticipates headache), promotes or contributes to trigeminal activation, and thus to headache generation in susceptible individuals. Experiments were designed to test whether CSD causes peripheral and central trigeminovascular activation, and to determine whether CSD (i) enhances dural arterial blood flow (ii) augments neurogenically mediated plasma protein extravasation in the ipsilateral dura mater, and (iii) induces CNS activation (c-fos stained neurons within TNC – an indirect measure of trigeminovascular activation). CSD was induced either electrically or by pinprick in ventilated SD rats under barbiturate anesthesia (n = 50); 7 physiological variables were monitored on-line.

Results

(i) Before and during the CSD propagation, blood flow (Laser speckle imaging) showed little change within the middle meningeal artery (MMA). However, after 5 min, MMA flow began to increase, maximized after approx. 20 min, and slowly returned to baseline (1 h). (ii) On the CSD side, plasma protein leakage (horseradish peroxidase) was prominent around the dural vasculature, and this was blocked by chronic nasociliary (trigeminal) nerve transection. (iii) Within ipsilateral TNC, c-fos positive neurons were significantly higher, and positive cells were decreased by chronic NCN transection or by sumatriptan.

Conclusion

Cortical spreading depression caused relatively long-lasting hyperemia within dura mater, neurogenically mediated ipsilateral edema within meninges, and ipsilateral neuronal activation within TNC. These studies establish the importance of CSD as a stimulus for trigeminovascular activation and therefore as a potential initiating or sensitizing factor for headache in migraineurs.

Acknowledgements

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Scintillations during migraine visual aura revealed by fMRI

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Background We have observed BOLD changes during migraine visual aura that demonstrated several characteristics of cortical spreading depression. These changes were correlated with the progression of the visual scotoma experienced by the patients.

Objective We wanted to see if in the absence of any visual stimulation, the positive phenomenon of the visual aura (scintillations) could be revealed by fMRI.

Methods MR data were acquired in a 3 T scanner, using echoplanar imaging, in a subject who could trigger his visual aura by exercise, before, during and after the aura. Data acquired during periods of no visual stimulation (‘off periods’) which consisted of a black screen with a fixation cross were analysed, and the periods preceding the aura were compared to the periods where the visual symptoms were present using a t-statistic. In addition, retinotopic maps of polar angle and eccentricity were generated in the same subject interictally. To improve topographic clarity, all data were analysed and displayed in cortical surface format.

Results As expected, there was no signal present in the visual cortex during the periods before the beginning of the symptoms. However, with the subjective apparition of scintillations described by the subject, one could observe a BOLD signal change appearing first in extrastriate visual area V3A and then progressing congruently with the retinotopic percept, beginning in the fovea and progressing towards the periphery.

Conclusions Our results demonstrate that BOLD signal can be obtained in the context of a visual illusion like the perceptual scintillations of the visual aura. These scintillations presumably reflect increased neural activity, which is the first event occurring during cortical spreading depression. The spread of the BOLD signal during the scintillations (3–5 mm/min) parallels the retinotopy of the visual percept. Visual scintillations are the first symptom to appear. Therefore they might be of a great value for source localization of the migraine visual aura.

Functional magnetic resonance imaging during sustained visual stimulation: less habituation-like changes of the bold signal in migraine with aura

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Objective To study habituation-like changes of the MRI-BOLD signal in the visual cortex during prolonged visual stimulation in migraine with typical aura (MA).

Background One of several mechanisms of interictal migraine pathophysiology involves deficient habituation in cortical information processing as shown by visual evoked potential studies (Schoenen et al. 1995, Áfra et al. 1998).

Design and methods Eleven healthy volunteers (HV) and 8 MA patients (interictally) were investigated using functional MRI with a 1.5T Philips ACS-NT system. A reversing checkerboard (8 Hz) was used for visual stimulation. Activated cortical areas were determined using a fMRI protocol (P < 0.001) [single shot EPI, TR = 3 s, TE = 40 ms, nominal voxel size = 0.67cc] with a repetitive block paradigm (3 periods: 30 s darkness – 30 s stimulation) showing an increase in BOLD of about 2%. A second fMRI protocol [single shot EPI, TR = 5 s, TE = 40 ms] was used to investigate the time course of activation in sustained visual stimulation (paradigm: 2 min control (dark), 10 min stimulation, 2 min control). Motion correction and spatial filtering was applied to all data. The slope of the activation time course during the sustained activation period was determined by a linear fit and compared between HV and MA.

Results The slopes of the BOLD signal during sustained visual stimulation were −0.0114 (−1.1% over 10 min) for HV and −0.0016 (−0.16% over 10 min) for MA with a significant difference (P < 0.05) between MA and HV.

Conclusions We found a less pronounced decrease of the BOLD signal during sustained visual stimulation in migraine with aura patients compared to healthy volunteers. This seems to reflect a smaller decrease in cortical activation in migraine with aura patients which is in line with previous studies showing diminished electrophysiological habituation during sustained visual stimulation in migraine with and without aura patients. Whether our observations are also true for migraine without aura remains to be determined. Further experiments are directed to correlate our fMRI results with established electrophysiological methods in the same migraine patients.
LB-5

Correlation between deficit of habituation and intensity dependence of auditory evoked potentials in migraine

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Objectives Migraineurs are characterized by a deficient habituation, or even potentiation, of visual evoked potentials during repetitive stimulation, and by a stronger intensity dependence of N1/P1 amplitudes of Auditory Evoked Potentials (IDAP) than healthy controls. The aim of this study was to establish whether the increased IDAP found in migraine is an epiphenomenon of the habituation deficit or an independent pathophysiological phenomenon.

Material and methods 14 migraineurs without aura (MO) were compared with 14 healthy volunteers (HV). Auditory Evoked Potentials (AEPs) were recorded at four different stimulation intensities (50, 60, 70 and 80 dB ASL) in a pseudo-randomized order. For each intensity 120 trials were collected and averaged off-line. Subsequently they were partitioned in 4 averaged blocks of 30 trials in chronological sequence. IDAP was expressed by the amplitude/stimulus intensity function (ASF slope) in µV/10 dB both for total and partial blocks. Habituation was evaluated as the percentage variation of amplitudes between fourth and first blocks.

Results The IDAP slope for grand averages was higher in MO (1.05 ± 0.27 µV/10 dB) than in HV (0.64 ± 0.45 µV/10 dB) (P = 0.007), but IDAP slopes for partial blocks were significantly different between MO and HV only at the fourth block. (P = 0.04). AEP amplitudes in MO were potentiated steadily at every stimulus intensity, whereas in HV no potentiation was found.

Conclusions This study confirms that migraineurs have a higher IDAP than controls. It also shows that there is an increase of AEPs with repetition of the stimulus at every stimulus intensity in migraineurs. Because of a greater initial amplitude, this increase is proportionally greater for high stimulus intensities which is responsible for the increased IDAP slope. Although IDAP per se is not likely to be due to deficient habituation or potentiation, its increase in migraineurs seems to be the consequence of such a phenomenon. This points towards deficient habituation to repetitive stimuli as the basic interictal electrophysiological abnormality in migraine.

LB-6

Repetitive transcranial magnetic stimulation of the occipital cortex modifies habituation of visual evoked potentials in healthy volunteers and migraineurs

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Objective To study the excitability of occipital cortex in healthy volunteers and migraineurs by recording pattern-reversal visual evoked potentials (PR-VEPs) before and after low and high frequency repetitive transcranial magnetic stimulation (rTMS). rTMS is able to decrease or increase cortical excitability depending on stimulation frequency. It is controversial whether and in which direction cortical excitability is modified in migraine. Between attacks, habituation of PR-VEPs can be reduced or reversed (i.e. potentiation) which we have attributed to cortical hypoexcitability.

Material and methods We performed rTMS of the visual cortex in healthy volunteers (n = 24) and in patients suffering from migraine with (n = 5) or without aura (n = 10) in the interictal period with a focal figure-of-eight magnetic coil placed over the occipital scalp. We delivered 900 pulses at two different frequencies in a randomized order: 1 Hz rTMS (15 min) and 10 Hz rTMS (18 train of 5 s, with an intertrain interval of 10 s). Stimulus intensity was set to the phosphene threshold. Before and after rTMS the PR-VEPs were sequentially averaged in blocks of 100 responses during 3 min of uninterrupted stimulation at 3.1 Hz and analysed in terms of latency and peak-to-peak amplitude of N1-P1 and P1-N2 peaks.

Results There were no significant differences in N1, P1 and N2 latencies before and after rTMS neither in normal volunteers nor in migraineurs. After 1 Hz rTMS, amplitudes of N1-P1 and P1-N2 in the first block were decreased in 80% of healthy volunteers and 75% of migraineurs. After the 1 Hz rTMS there was a significant reduction of the habituation or even a potentiation in healthy volunteers, but the potentiation observed in migraineurs was not modified. After 10 Hz rTMS, 1st block amplitudes of N1-P1 and P1-N2 were increased in 50% of healthy volunteers and 75% of migraineurs. There was no significant change of habituation in healthy volunteers, but in migraine patients we observed a reduction of potentiation or even appearance of habituation.

Conclusion The decrease of cortical excitability induced by 1 Hz rTMS in normal volunteers is associated with loss of habituation or even potentiation of PR-VEPs. The increase of cortical excitability which follows the 10 Hz rTMS produces in migraineurs less marked potentiation or even habituation. Taken together these findings suggest that the deficient habituation of EPs found interictally in migraine is due to a reduced preactivation level of sensory cortices, and not to hyperexcitability.
Evidence of decreasing incidence of cluster headache: a population-based study in Olmsted County, MN

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Introduction Relatively little is known of the epidemiology of cluster headache, and prevalence surveys currently provide the bulk of this information. The unique resources of the Rochester Epidemiology Project provide the opportunity to examine the incidence of a wide variety of disorders including cluster headache.

Objective To determine the medically detected incidence of cluster headaches in Olmsted County, Minnesota in 1989–1990 and to compare this to the previously reported incidence data from Olmsted County in 1979–1981 (1) using identical study methods.

Methods Using the resources of the Rochester Epidemiology Project, individuals whose records included any diagnostic group related to headache for the 2-year period 1989–1990 were evaluated. A nurse abstractor and a neurologist reviewed the complete record of each potential case and assigned a diagnosis using the International Headache Society classification. We compared the incidence data from 1989 to 1990 to that of the previously reported 1979–1981 study. We estimated the number of cluster headache incidence cases that would be expected in Olmsted County in 1989–1990 using age-specific incidence rates of cluster headache patients (four males who were smokers) for 1989–1990 (compared to 26 cases in 1979–1981), resulting in an age adjusted (to 1990 US whites) incidence of 4.25 per 100,000 p-y (95% confidence interval: 0.0–8.5) for males. The unadjusted incidence rate of cluster headaches for males in 1989–1990 was 3.98 per 100,000 p-y. The overall sex-adjusted incidence rate of cluster headaches per 100,000 p-y was 2.07 (95% confidence interval: 0.003–4.14). This is a statistically significant decrease in the age-adjusted incidence of 15.6 per 100,000 p-y for males and overall age- and sex-adjusted incidence of 9.8 per 100,000 p-y in 1979–1981. The number of observed incidence cases in 1989–1990 was significantly smaller than the expected number of new cases during this latter period.

Results We identified four newly diagnosed cluster headache patients (four males who were smokers) for 1989–1990 (compared to 26 cases in 1979–1981), resulting in an age adjusted (to 1990 US whites) incidence of 4.25 per 100,000 p-y (95% confidence interval: 0.0–8.5) for males. The unadjusted incidence rate of cluster headaches for males in 1989–1990 was 3.98 per 100,000 p-y. The overall sex-adjusted incidence rate of cluster headaches per 100,000 p-y was 2.07 (95% confidence interval: 0.003–4.14). This is a statistically significant decrease in the age-adjusted incidence of 15.6 per 100,000 p-y for males and overall age- and sex-adjusted incidence of 9.8 per 100,000 p-y in 1979–1981. The number of observed incidence cases in 1989–1990 was significantly smaller than the expected number of 19.84 (P < 0.0001) per 100,000 p-y (95% confidence interval: 1.09–10.24).

Conclusion Incidence of cluster headaches in Olmsted County decreased significantly between 1979 and 1981 and 1989–1990. The reasons for this decrease are incompletely understood but we speculate may be related in part to a significant decrease in the rate of smoking in the population over this same period.

Reference

Late-breaking abstracts 529

Nasal sumatriptan is effective in migraine attacks in children

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Objective of the study To investigate clinical efficacy of nasal sumatriptan in migraine attacks of children and adolescents.

Methods of the study The design was a double-blind placebo-controlled two-way crossover trial. Patients were recruited at hospital outpatient clinics. Included were children/adolescents aged 8–17 years (body weight at least 20 kg), and with at least two migraine attacks (IHS 1988) per month (a minimum duration of four hours). The study treatment was a single dose of sumatriptan (Imigran®, GSK) or a matching placebo administered at home intranasally at the onset of an attack. Sumatriptan dose was 10 mg for children with a body weight of 20–39 kg, and 20 mg for those 40 kg or more. The primary efficacy endpoint was reduction in headache by at least two grades on a five-grade face scale at 2 h.

Results In total, 129 children/adolescents were recruited. The 94 (median age 12.2 year) who used at least one treatment were included in the study; 83 used both treatments and 11 only one treatment (the first). Altogether 90 received sumatriptan and 87 placebo. The 83 patients, who took both treatments, reached the primary efficacy endpoint at two hours twice as often after sumatriptan (n = 53; 64%) as after placebo (n = 32; 39%; NNT = 4.0). However, at two hours only 30% (n = 25) after sumatriptan and 19% (n = 16) after placebo became pain-free (NNT = 9.1; P = ns). Already at one hour, reduction in pain by at least two grades (primary endpoint) was observed more often after sumatriptan (n = 42; 51%) than after placebo (n = 24; 29%; NNT = 4.6). The results were similar if all patients who received at least one treatment were included. Subjectively, 57% (n = 47) preferred sumatriptan and 34% (n = 28) preferred placebo (P < 0.05) while 8 were undecided. No serious adverse events were observed, 29% (n = 26/90) reported a bad taste after sumatriptan and 3% (n = 3/87) after placebo (P < 0.01).

Conclusions Nasal sumatriptan is an effective attack treatment for migraine in children and adolescents; however, only 30% of the patients achieved complete resolution of headache at 2 h.
Efficacy and safety of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs

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Objectives To evaluate the efficacy and safety of a single dose of eletriptan 20 mg, 40 mg and 80 mg in Japanese migraineurs.

Methods This prospective multicentre, double-blind, randomized, parallel-group, placebo-controlled trial involved a total of 402 adult Japanese migraineurs diagnosed according to International Headache Society (IHS) criteria. Patients took their study drug as soon as possible within 6 h of onset of a migraineous headache. At 0.5, 1, 2, 4 and 24 h after dosing, they recorded their assessments of headache severity, presence or absence of accompanying symptoms and functional impairment. Adverse events were also recorded, and, at 2 h postdose, a pharmacokinetic evaluation was performed using saliva assays.

Results At 2 h after a single dose, the headache response rates to eletriptan 20 mg, 40 mg, 80 mg and placebo were 64%, 67%, 76% and 51%, respectively; all eletriptan doses were statistically significantly superior to placebo (P < 0.05). There was a statistically significant dose–response for headache relief and pain-free response at 2 h postdose (P = 0.001 and P = 0.029, respectively). At 2 h postdose, the functional response rates were 65%, 65%, 75% and 54% for the eletriptan 20 mg, 40 mg, 80 mg and placebo groups, respectively. Furthermore, patient function improved with higher doses of eletriptan, and all doses of eletriptan resulted in a greater increase in patient function than placebo at 2 h postdose. The overall pattern of adverse events seen in Japanese patients after administration of eletriptan was similar to that seen in western patients. The majority of all-causality adverse events were mild and transient. The incidence of abnormalities in clinical laboratory test results was similar for both the eletriptan and placebo groups. Although the dose-normalized mean saliva concentration level was 13% lower in Japanese patients than in Western patients, pharmacokinetic evaluations showed no clinically significant differences between Japanese and Western patients.

Conclusions Eletriptan at 20 mg, 40 mg and 80 mg is effective and well tolerated in Japanese migraineurs.

Prevalence of headache and migraine headache in Puerto Rico

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Headache is one of the most frequent reported disorders in the general adult population. Despite the fact that this disorder is very wide spread, the diagnosis of headache and its epidemiological features have long been imprecise. In Puerto Rico no official number about the prevalence of headache or migraine headache exist. To examine the prevalence of headache of all types and migraine headache in Puerto Rico a survey was conducted by phone to 1610 persons. The phone calls was distributed using the number of the 1990 Census adjusted to the population of 1998 in Puerto Rico. The phone calls were distributed by sex, age and geographical area. The study shows that the prevalence of all types of headache in Puerto Rico was 35.9%. In the case of migraine headache the prevalence was 13.0%. When that prevalence was fractionated by age, sex and geographical areas then in the headache of all types the frequency is practically equal for all ages, the female shows 2.1 ratio over the males and no geographical difference was noted. In the case of migraine headache the younger population (between 20 and 40) shows a higher prevalence, the female to male ratio was 3:1 and the prevalence was higher in the metropolitan area. This study is the first of this type in Puerto Rico and shows us that the problem of headache and migraine is more serious than we believe before analysing this information.

Neurophysiological mechanisms of migraine precipitation

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Migraine attacks can be precipitated by a number of conditions such as hormonal changes, stress, sleep, fasting, fatigue. However, the particular mechanisms of migraine precipitation by these factors are still unknown. The contingent negative variation (CNV), a slow cortical event-related potential which corresponds with the level of cortical excitability, may represent the attack anticipation, because its amplitude is significantly increased a few days before a migraine attack in migraineurs compared with controls (1,2). The aim of this study was to investigate the influence of the menstrual cycle and stress on CNV characteristics in migraine. Twenty women suffering from migraine without aura (IHS criteria, code 1.1; age: 36.3, SD = 5.8) and 15 healthy women (age: 34.9; SD = 7.5) were enrolled. All participants did not take oral contraceptives or other medication for at least 3 months prior to the investigation. The CNV (reaction time paradigm, Cz with linked mastoids, 0.03–35 Hz filters with 100 Hz digitalization rate, impedance less than 5 kΩ, EOG control) was recorded in the premenstrual and ovulation phases of the cycle in both rest and stress conditions. Stress was induced during standard CNV recording by giving a negative feedback to a subject about his/her reaction time and setting him/her under achievement pressure. All data were analyzed using parametric statistics. In migraineurs a slight increase of CNV amplitude in the premenstrual phase compared with ovulation has been observed (P < 0.05). No changes in CNV during the menstrual
cycle were found in healthy women. During both the ovulation and premenstrual phases both migraine patients and controls demonstrated significant increase of the CNV amplitude on stress compared with rest condition \( (P < 0.01) \). The increase of the amplitude on stress in the premenstrual phase was more pronounced in migraineurs, so that the patients differed significantly from healthy woman \( (P = 0.034) \). This study demonstrates that stress and menstrual cycle influence the amplitude of the CNV and in such a way may precipitate migraine attacks. The precipitating factors studied have an additive effect by enhancing cortical excitability. We suggest that the combination of precipitating events is necessary to achieve the threshold of a migraine attack and to increase susceptibility of the migrainous brain to different provoking agents.

References

PL-3
Vascular effects of the new antimigraine agent almotriptan on human cranial and peripheral arteries
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Objective Evaluate the in vitro effects of almotriptan in human vasculature and bronchial tissue to characterize its pharmacological and safety profile for treating patients with acute migraine.

Methods The contractile properties of almotriptan and sumatriptan were compared with those of serotonin (5-HT) in meningeal, temporal, basilar, internal carotid, ophthalmic, pulmonary and coronary arteries, in pulmonary vein, and in bronchial tissues from isolated human specimens.

Results Almotriptan demonstrated selectivity for migraine-related meningeal and temporal arteries (i.e. contractile EC50 of 30 and 700 nM, respectively), whereas the effects on basilar and internal carotid arteries were similar to or lower than sumatriptan. In pulmonary arteries, the contractile effects of almotriptan were significantly lower than sumatriptan, whereas in bronchial tissues preparations no relevant contractile responses were observed with either drug. In coronary arteries, contractile effects were significantly lower with almotriptan than with sumatriptan. In ophthalmic arteries, the contractile effects of almotriptan and sumatriptan were similar.

Conclusions Almotriptan demonstrated vasoconstrictive properties in meningeal artery consistent with its antimigraine efficacy, but without significant effects on other arterial tissues. The clinical implications of the pharmacological effects of almotriptan are being confirmed in ongoing trials of almotriptan in patients with acute migraine.

PL-4
Modulation of visual cortex excitability in migraine with aura: paradoxical facilitation of low-frequency 1 Hz repetitive transcranial magnetic stimulation of the occipital cortex
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Background Recent studies showed reduction of inhibition in occipital cortex of subjects affected by migraine with aura \( (1,2) \). 1 Hz repetitive transcranial magnetic stimulation (rTMS) has been shown to reduce excitability of motor and visual cortex \( (3,4) \).

Objective To evaluate the effect of 1 Hz rTMS over occipital cortex excitability, as measured by phosphen threshold (PT) and stimulus-response (SR) curve, in migraine with aura.

Methods 13 migraine with aura patients (3M/10F age: 39±12 range: 24–58 year,) and 10 healthy subjects (2M/8F age: 32±10 range: 22–52 year,) were examined. Patients and controls were not taking any drug. Migraineurs were examined interictally. Magnetic stimulation was performed by Cadwell high frequency machine with a water-cooled figure of eight coil. PT was determined as the lowest magnetic stimulation intensity (MSI) needed to induce phosphene over the optimal point for magnetic stimulation. Subjects reported phosphene intensity (PI) on an arbitrary scale of 0–5. SR curve was measured as the PI values at MSIs 30% to 80% of stimulator output (10% steps). PT and SR were determined before and after 1 Hz rTMS train delivered at PT intensity for 15 min.

Results Before rTMS, no significant difference in mean PT (migraineurs: 56%±7% vs controls 57%±13%; \( P > 0.05 \)) values was found between groups. Intragroup comparison showed significant opposite changes in patients and controls: after 1 Hz rTMS, mean PT values resulted significantly reduced in migraineurs (56%±7% vs 50.5%±11; \( P = 0.02 \)) and increased in controls (57%±13 vs 62%±6%; \( P = 0.04 \)). No significant changes between patients and controls was observed as concern SR curves even if a trend toward higher intensities of perceived phosphene at 50% to 80% MSI was found in migraineurs. No significant change in SR curve was induced by rTMS in both patients and controls; however, a slight higher SR curve was observed after 1 Hz rTMS in migraineurs.

Conclusions 1 Hz rTMS, known to depress excitability of visual cortex in normals, showed a paradoxical facilitation effect in migraine with aura giving raise to a significant lowering of PT. These data are in agreement with observations by Ziemer et al. \( (5) \), showing a facilitatory effects of low-frequency rTMS on motor cortex excitability in condition of reduced cortical inhibition consequent upon transient limb ischaemia induced deafferentation. Our results could find explanation on the basis of the hypothesized reduced visual cortical inhibition in migraine with aura.

References
A randomized, double-blind, crossover study to evaluate the efficacy of a proprietary 100 mg diclofenac sodium softgel formulation with or without 100 mg caffeine in migraineurs

PL-5

Introduction

A phase II randomized, double blind, crossover study to evaluate the efficacy of a proprietary 100 mg diclofenac sodium softgel, formulated using ProSorb technology (ProSorb® is a registered trademark of aai Pharma, Inc.), with or without 100 mg caffeine in migraineurs vs placebo during migraine attacks was performed. Diclofenac has been demonstrated to be an effective migraine treatment in several placebo-controlled studies. Caffeine (C) has consistently been shown to increase both the efficacy, as well as the speed of onset, of concurrently administered analgesics. This unique ability of C to both enhance and accelerate analgesic effects has now been documented with a variety of different medications (i.e. aspirin, acetaminophen, ibuprofen, and ergotamine). A rapidly absorbed softgel formulation of diclofenac (DS), formulated using ProSorb technology, may have advantages in migraine treatment.

Methods

The study was designed as a 3 period crossover study comparing DS 100 mg, DS 100 mg plus caffeine 100 mg and placebo in the acute treatment of migraine. Subjects treated one migraine attack with moderate or severe pain with each study medication. The primary efficacy parameter was the percentage of subjects with headache relief at 60 min as defined by a reduction of headache severity from moderate or severe at baseline to absent or mild compared to placebo. Though the sample size estimate required that 72 subjects treat 3 separate attacks, 51 subjects treated one migraine attack, 44 treated 2 attacks and 39 treated 3 attacks.

Results

In the placebo group, 6 of 43 (14%) subjects reported headache relief at 60 min vs 12 of 45 (27%) in the DS group and 19 of 46 (41%) in the DS + C group. Although the diclofenac only group response rate was nearly double that of the placebo group response rate, the difference was not significantly significant in this study. However, the response rate of the DS + C group was significantly greater than the placebo response rate. Rescue medication was used by 27 of the 43 (63%) placebo treated subjects, 15 of the 45 (33%) of the DS treated subjects and 14 of 46 (30%) of the DS + C treated subjects. This result is highly statistically significant (Chi-square = 11.56; d.f. = 2; P = 0.003).

Discussion

The major finding of the present study is that DS + C produces statistically significant benefits relative to placebo at 60 min. DAYS alone did not differ from placebo, perhaps due to limits in sample size. Non-significant trends support the analgesic adjuvant benefit of caffeine when added to diclofenac softgels.

PL-6

Effects of sumatriptan on platelet aggregatory response in migraine patients with aura

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Introduction

An increased platelet aggregability has been found in migraine patients. The data suggest that activation of platelets is related to the pathophysiology of migraine. There is an indication that sumatriptan has inhibitory effect on platelet aggregation induced by 5-HT and ADP in healthy subjects. The aim of the present study was to investigate effects of sumatriptan on 5-HT- and adrenaline-induced aggregation in eight female migraine patients with migraine with aura during a headache-free interval and 13 healthy females.

Methods

All patients had migraine with aura according to the IHS criteria. 5-HT-induced aggregation was studied in platelet rich plasma by measuring the mean size of platelet aggregates using a highly sensitive method based on the registration of optical density fluctuations in platelet suspension. This method allows to detect platelet aggregates of small sizes induced by 5-HT, a weak platelet agonist. Adrenaline-induced aggregation was evaluated by measuring light transmission.

Results

Six migraineurs showed significantly higher aggregatory response to 5-HT at all concentrations tested. When patients were evaluated as a whole group, in patients and the controls the mean values of aggregation induced by 5-HT at 5 × 10−8 M were 4.81 ± 1.46 and 2.5 ± 0.8, correspondingly (P < 0.05). Disaggregation was significantly less in 2 patients. The minimal concentrations of 5-HT to induce detectable platelet aggregates were in 5–10 times lower for 3 patients than for control subjects. Sumatriptan inhibited dose-dependently 5-HT-induced aggregation in all migraine patients and the controls with similar potency: the IC50 values were 1.5 × 10−8 M and 1.3 × 10−8 M, correspondingly. Aggregatory response to adrenaline was the same in patients and the controls. Sumatriptan did not affect adrenaline-induced aggregation in both groups significantly.

Conclusions

Our results indicate that sumatriptan can modify platelet activity and raise the possibility that anti-platelet effects of sumatriptan may contribute to its therapeutic effect. It is unlikely that sumatriptan exerts its inhibitory effect on 5-HT-induced aggregation at the level of 5-HT2A receptors as potency of this drug in binding these receptors is significantly lower its potency in inhibiting aggregation.
Sumatriptan can be administered concomitantly with the CYP3A4 inhibitor clarithromycin (Biaxin®) or the CYP3A4 substrate Ortho-Novum 1/35

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**Background** Concerns regarding drug interactions have increased in recent years. The coadministration of 2 drugs using the same metabolic pathway may perturb blood concentrations of one or both of the drugs, potentially exposing a patient to unforeseen risks. Sumatriptan [SUMA], a treatment for acute migraine, is primarily metabolized via monoamine oxidase-A. Unlike eletriptan, SUMA is not metabolized by CYP3A4 in vitro and thus is unlikely to be affected by CYP3A4 inhibitors. Unlike zolmitriptan, SUMA plasma concentrations are not expected to increase when used concurrently with oral contraceptives. However, there have been no clinical studies to confirm these observations. Therefore, two studies were conducted to determine if (1) clarithromycin [CL], a potent CYP3A4 inhibitor, and (2) Ortho-Novum 1/35 (ON-1/35; composed of norethindrone [NE] and ethinyl oestradiol [EE], CYP3A4 substrates) affect SUMA pharmacokinetics [PK].

**Objectives** (1) To determine the effect of steady-state treatment of CL and ON-1/35 on single-dose SUMA PK. (2) To determine the effect of single-dose SUMA on steady-state NE/EE PK. (3) To assess tolerability of concomitant administration.

**Methods** These studies in healthy volunteers evaluated SUMA alone (50 mg) vs SUMA + CL (500 mg q12hx3d) and SUMA + ON-1/35 treatment (1 mg NE/0.035 mg EE QDx21d). Serial blood samples for SUMA and NE/EE determinations were collected. Equivalence between treatments was to be concluded if the 90% confidence interval [CI] for the ratio of reference to test means for loge-transformed PK parameters fell within the interval of 0.8–1.25.

**Results** The treatments were well tolerated. Adverse events were mild to moderate in intensity, and there were no clinically significant changes in vital signs, ECGs or laboratory values. For all analyses the 90% CIs were within the accepted 0.80–1.25 equivalence criterion for extent of absorption (AUC). The Cmax for SUMA and NE were slightly outside the criterion; however, these small changes were not considered to be clinically meaningful. SUMA results presented as geometric mean and 95%CIs are shown in the table.

**Conclusions** Coadministration of SUMA and CL or ON-1/35 produced no significant change in the extent of absorption of SUMA, NE or EE, when compared to the alone treatment phase. SUMA can be administered concomitantly with CL or ON-1/35 without the need for dose adjustment of either medication.

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**Late-breaking abstracts**

Eletriptan for the treatment of migraine in poor responders to oral sumatriptan: a randomized, placebo-controlled study


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**Objectives** Eletriptan is a potent, selective 5-HT1B/1D receptor agonist that has been shown to be superior to oral sumatriptan in the acute treatment of migraine (1.2). This study investigated the safety and efficacy of eletriptan in patients who had previously responded poorly to sumatriptan due to lack of efficacy or intolerable adverse events (AEs).

**Methods** The majority of patients (71%) had discontinued sumatriptan treatment due to insufficient efficacy.
Patients \((n = 446)\) were randomized to 40 mg eletriptan (E40; \(n = 188\)), 80 mg eletriptan (E80; \(n = 171\)) or placebo (PBO; \(n = 87\)) for the treatment of 1–3 migraine attacks: 404 patients took at least 1 dose and 246 patients treated all 3 attacks. Patients recorded migraine symptoms and response to treatment in diaries and gave overall rating scores for treatment acceptability at the final visit.

**Results** Results are shown as E40, E80 and PBO. Two-hour headache responses were 59%, 70% and 30%. E80 was superior to E40 \((P \leq 0.05)\) and both were superior to PBO \((P \leq 0.0001)\). Onset of action was rapid for eletriptan, with 1-h headache response rates superior to PBO (40%, 48%, 15%; \(P < 0.0005)\). Both E40 and E80 were superior to PBO for 2-h pain-free response (35%, 42% and 7%; \(P \leq 0.0001)\). Eletriptan patients experienced significantly less nausea than PBO patients at 1 and 2 h. Eletriptan patients had significantly lower incidences of vomiting than PBO at 4 h \((P \leq 0.05)\). Fewer eletriptan patients than PBO patients had headache recurrence within 2–24 h (26%, 32%, 50%). There was good consistency of response with eletriptan (2-h headache response for at least 2 of the 3 attacks: 66%, 72%, 15%). AEs were generally mild to moderate in severity and tended to be dose-related. The most commonly reported AE was nausea. No serious treatment-related AEs were reported. Sixty-two per cent of eletriptan patients stated that they would use study medication again over previous treatment.

**Conclusions** These results show that E40 and E80, reliable first-line treatments with proven superiority over sumatriptan, produce an excellent response in patients who do not respond adequately to sumatriptan.

**References**