CGRP-induced photophobia blocked by olcegepant and rizatriptan in a transgenic migraine model

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Objectives: To confirm the robust photophobic phenotype of nestin/hRAMP1 mice and determine the effect of olcegepant and rizatriptan in the light aversive behavior.

Background: While the initial triggering of migraine attacks remains unknown, it is widely accepted that trigeminovascular system activation and the neuropeptide calcitonin gene-related peptide (CGRP) play a key role in the pathophysiology of migraine. As previously reported, we have generated a transgenic mouse that is sensitized to CGRP by overexpression of the human receptor activity modifying protein 1 (hRAMP1) subunit of the CGRP receptor in the nervous system (nestin/hRAMP1 mouse).

Methods: Naive nestin/hRAMP1 mice with two different genetic backgrounds were tested in the light aversion test before and after intracerebroventricular (icv) administration of CGRP. The light aversion test is a natural conflict based assay. Mice were tested individually in a chamber with two compartments, half enclosed and dark and half open and lit, joined by a small opening in the center. Total time spent in the light was measured. We used two light intensities, 1000 and 50 lux, and chambers of different size, 60 × 60 × 45 cm and 27 × 27 × 20 cm. Olcegepant was coadministered icv with CGRP. Rizatriptan was administered subcutaneously with CGRP icv. To control for other possible causes of light aversion the potential effects of anxiety were studied by measuring thigmotaxis and unconditioned fear of predator odor from fox, trimethylthiazoline (TMT). General motor activity was assessed in open field and in the light aversion chambers.

Results: Untreated nestin/hRAMP1 transgenic mice spent 30% less time in the light than their littersmates (P < 0.0001). CGRP icv caused around 80% decrease in the time spent in the light (P < 0.001). CGRP-induced light aversion was prevented by olcegepant and rizatriptan. Studies analyzing motor activity, anxiety related behavior and morphology of the anterior segment of the eye of nestin/hRAMP1 and control mice revealed that none of these can fully explain the light aversive behavior displayed by nestin/hRAMP1 mice.

Conclusions: These results indicate that RAMP1 gene transfer can increase CGRP actions in the nervous system. Nestin/hRAMP1 transgenic mice are more light aversive than littersmates and this is greatly enhanced by icv administration of CGRP. Specificity of CGRP action was confirmed by co-injection of the CGRP receptor antagonist. This behavior can be objectively quantified and used as a surrogate of the photophobia commonly reported by migraine patients both interictally and more intense during a migraine attack. The replication of the CGRP-induced light aversive behavior in a different pedigree confirmed the contribution of nestin-cre driven hRAMP1 expression to the phenotype independent of the genetic context. The reproduction of the same results in a different testing chamber corroborates the robust phenotype. The effect of olcegepant and rizatriptan abolishing the CGRP-induced light aversion validate the usefulness of this model for future mechanistic studies.

Photophobia in migraine: a PET study of visual cortex hyperexcitability and its modulation by pain

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Objectives: We hypothesize that photophobia is related to an interaction between visual cortex hyperexcitability and trigeminal nociception.

Background: Photophobia is an abnormal sensitivity to light experienced by migraineurs during and also between attacks. Its pathophysiology remains unknown.

Methods: In order to verify this interaction, we used H2O15 PET to study the cortical responses of 7 migraineurs between attacks and 7 matched control subjects to luminous stimulations (at three luminance intensities: 0, 600 and 1800 Cd/m2) with and without concomitant trigeminal pain stimulation. In order to facilitate habituation, stimulations were started 30 seconds before PET acquisitions.

Results: When no concomitant pain stimulation was applied, luminous stimulations activated bilaterally the visual cortex in migraineurs (cuneus, lingual gyrus, posterior cingulate cortex), but not in controls. Concomitant pain stimulation allowed visual cortex activation in control subjects and potentiated its activation in migraineurs. These activations by luminous stimulations were luminance-intensity dependent in both groups. Concomitant stimulation by pain was associated with a different activation of posterior parietal cortex (BA7) in migraineurs and controls, depending on luminous stimulation intensity.

Conclusions: Our study confirms the lack of habituation and/or cortical hyperexcitability in migraineurs. Moreover, pain potentiated the activation by light in several visual cortex areas, including primary visual cortex, demonstrating multisensory integration in these areas. The difference in activation of BA7 between the two groups suggests that pain may elicit a different attentional response in migraineurs and controls.

A magnetic resonance angiography study for reversible cerebral vasoconstriction syndromes

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Objectives: To investigate the morphology, evolution, and clinical significance of vasoconstrictions seen on magnetic resonance angio-
Background: RCVS is characterized by recurrent thunderclap headaches and reversible cerebral vasoconstrictions. MRA is the study of choice for the diagnosis, evaluation and follow-up of vasoconstrictions; however, no systematic studies have been conducted to date.

Methods: Patients with RCVS were consecutively recruited from August 2000 to March 2009. Diagnosed with MRA examinations, the patients were followed up until complete or near complete normalization of their vasoconstrictions. The severity of vasoconstriction of the first and second segments of major cerebral arteries (M1, M2, A1, A2, P1, P2 and basilar artery) were scored on a five-point scale: 0 (0–< 10%), 1 (10–< 25%), 2 (25–< 50%), 3 (50–< 75%) and 4 (>75%). Subjects with at least one arterial segment with a vasoconstriction score of 3 or 4 were considered eligible cases. Mean vasoconstriction scores which were derived by averaging the vasoconstriction scores of bilateral arterial segments with the same designation or different arterial segments, were used to predict ischemic complications.

Results: Eighty-seven patients (M/F 8/79; average age, 48.7 ± 10.7 years) finished the study with a mean of 3.16 MRA exams per patient. The initial number of arterial segments involved was 5.3 ± 3.1 per patient. Segmental vasoconstrictions with a vasoconstriction score of 2 (57.9%) and length less than 5 mm (98.0%) were the most common finding. Post-stenotic dilatation was observed in 81.1% of stenotic arterial segments. Vasoconstriction was the most severe 18.1 ± 16.3 days after headache onset (See Figure 1), roughly similar to the timing of headache resolution (18.7 ± 10.4 days). Eight patients (9.2%) developed posterior reversible encephalopathy syndromes (PRES), located predominantly at the posterior watershed zones. Five (5.7%) patients (including 4 with PRES) had an ischemic stroke. A logistic regression forward model demonstrated that the M1–P2 mean vasoconstriction score was the best predictor for PRES (Odds ratio (OR): 8.8 (95% CI 2.3–34.3), \(P = 0.002\)), while M1 mean vasoconstriction score predicted stroke the best (OR: 3.6 (95% CI 1.3–10.4), \(P = 0.017\)).

Conclusions: RMA showed different patterns of vasoconstrictions between RCVS and subarachnoid hemorrhage. It is valid in the evaluation of vasoconstrictions and predicting outcomes in patients with RCVS. Vasoconstrictions in M1 are the most important determinant of ischemic stroke, while additional involvement of P2 raised the risks for PRES.

Figure 1

Conclusions: MRA showed different patterns of vasoconstrictions between RCVS and subarachnoid hemorrhage. It is valid in the evaluation of vasoconstrictions and predicting outcomes in patients with RCVS. Vasoconstrictions in M1 are the most important determinant of ischemic stroke, while additional involvement of P2 raised the risks for PRES.
Methods: For the clinical study, 20 legally-blind migraine patients were recruited through their headache specialists and interviewed either in person or by phone. Diagnosis of migraine and visual condition were determined by neuroophthalmologist/headache specialists using information gathered in the interview and available medical charts. For the pre-clinical studies, we used a variety of electrophysiological, anatomical and immunohistological approaches. Electrophysiological technique included extracellular and juxtacellular single-unit recording of thalamic dura-sensitive neurons. Anatomical and immunohistochemical techniques included anterograde tracing of retinal axons and juxtacellular labeling of previously characterized thalamic trigeminovascular neurons alone, or in combination with immunofluorescence for more detailed identification.

Results: (a) Exacerbation of migraine headache by light is experienced by blind subjects with damaged image-forming pathways who maintain light perception, but not by those devoid of visual and non-visual light perception. Migraine headache intensity under ambient light was rated 9.2 ± 0.2 on a 0–10 severity scale, compared to 6.2 ± 0.3 in a dim or dark environment; (b) ongoing activity of thalamic neurons that respond to electrical, mechanical and chemical stimuli of the dura increases 2 fold under ambient light (500 lux) and 4 fold under bright light (50,000 lux) shone directly on the contralateral eye compared to their activity rate in the dark; (c) 69% of dura/light-sensitive neurons were located in the lateral posterior nucleus (LP), or at the border of the posterior nucleus (Po) and LP; 23% were located in Po, and 8% in ventral postero medial thalamic nucleus (VPM). Dura-sensitive units unresponsive to ambient light were found more ventrally in Po, as well as in VPM and the ventral posterolateral thalamic nucleus; (d) juxtacellular filling of these neurons and anterograde labeling of retinal projections demonstrated multiple axosomatic and axodendritic connections in LP and the dorsocaudal region of Po; (e) using juxtacellular labeling, we mapped cortical projections of individual dura/light-sensitive thalamic neurons within the primary somatosensory, motor, retrosplenial, and parietal association cortices, as well as the primary and secondary visual cortices.

Conclusions: Photic information from the rat retina is integrated by dura-sensitive thalamic neurons that receive direct input from retinal ganglion cells and project extensively to cortical areas involved in nociceptive, visual, cognitive and motor functions. This novel retinothalamic-cortical pathway provides a means for photomodulation of dura-sensitive thalamic neurons and, thus, the severity of migraine headache.

OR06
Tonabersat, inhibitor of cortical spreading depression, has significant preventive effect in migraine with aura
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Objectives: Our objectives were to evaluate the efficacy and safety of tonabersat in the prophylactic treatment of migraine with aura.

Background: Migraine with aura (MA) is in all likelihood caused by a cortical spreading depression (CSD). Tonabersat inhibits CSD and we therefore investigated if tonabersat has preventive effect in MA.

Methods: In this randomized, double blind, placebo controlled, crossover trial we included 39 patients who had at least one aura attack per month during the last three months. Thirty-one patients were included in the statistical analysis of efficacy. Tonabersat 40 mg once daily was compared to identical placebo and patients kept a detailed diary allowing objective diagnosis of each single attack as MA, migraine without aura or other headache. All results are presented as medians.

Results: Attacks of aura with or without a headache were statistically significantly reduced from 3.2 per 12 weeks on placebo to 1.0 per 12 weeks on tonabersat (P = 0.01) (fig 1) while the other primary outcome parameter, migraine headache days with or without an aura was not significantly reduced, 3.0 to 3.0. Two of the secondary outcome parameters were statistically significantly reduced (tonabersat followed by placebo): attacks of migraine headache 2.2 to 2.0, P = 0.03; attacks of aura followed by headache 2.0 to 1.0, P = 0.03; while days with any headache (2.2 to 2.0), and days with rescue medication (2.9 to 0.0) were not statistically significantly reduced. Tonabersat was well tolerated but overall had more side effects than placebo.

Figure 1

Conclusions: Tonabersat showed preventive effect on attacks of migraine aura but no efficacy on non-aura attacks in keeping with its known inhibitory effect on CSD. The result supports that auras are caused by CSD and that this phenomenon is not involved in attacks without aura.

OR07
Oxygen inhibits neuronal activation in the trigeminocephalalgic complex after stimulation of the trigeminal autonomic reflex, but not via direct dural activation of trigeminal afferents
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Objectives: To understand the mechanism of action of oxygen treatment in cluster headache.

Background: Trigeminal autonomic cephalalgias (TACs), including cluster headache, are believed to involve activation of the trigeminal-autonomic reflex, but not via direct dural nociceptive, visual, cognitive and motor functions. This novel reflex activates trigeminal autonomic cephalalgias after stimulation of the superior salivatory nucleus (SuS) projections through the sphenopalatine ganglion, via the greater petrosal nerve of the VIIth (facial) cranial nerve. Cluster headache is specifically responsive to treatment with oxygen, and yet our understanding of its mode of action is unknown.

Methods: Rats were anesthetized with pentobarbitone (60 mg/kg) and cannulated for measurement of blood pressure and intravenous administration of supplementary anesthesia with propofol (15–20 mg/kg/hr i.v. infusion). We used models of trigeminovascular nociception using stimulation of the dural vasculature and a novel approach that activates the trigeminal-autonomic reflex, using SuS facial nerve stimulation, with intravalvular mast cell depletion and chemodenervation, to explore the effect of oxygen treatment on trigeminal nerve activation. We also looked at autonomic responses through blood flow observations of the lacrimal duct/sac.

Results: Meningeal vasodilation and neuronal firing in the trigeminocephalalgic complex (TCC), in response to dural electrical stimulation, was unaffected by treatment with 100% oxygen. Stimulation of the SuS via the facial nerve caused only marginal (3.3 ± 0.8%, P < 0.05) increase in dural blood vessel diameter, but did result in evoked firing in the TCC. Two populations of neurons were characterized, those responsive to 100% oxygen treatment, with a maximal inhibition of 33%, 20 minutes after the start of oxygen treatment (t15 = 4.4, P < 0.0001). A second population of neurons were not inhibited by oxygen (F2,6,5 = 1.13, P = 0.35, n = 10) and tended to have shorter latency. Oxygen also inhibited evoked blood flow changes in the lacrimal sac duct caused by SuS stimulation (F2,48 = 3.25, P < 0.05, n = 9).

Conclusions: The data provide the first systematic, experimental evidence for a mechanism of action of oxygen in cluster headache. The
data show oxygen has no direct effect on trigeminal afferents, acting specifically on the parasympathetic/facial nerve projections to the cranial vasculature to inhibit both evoked trigeminovascular activation and activation of the autonomic pathway during cluster headache. Moreover, the studies begin to characterize a novel laboratory model for the most painful primary headache syndrome known – cluster headache.

**MPF01**

Vascular supply and tissue demand are uncoupled both during and after cortical spreading depression

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Objectives: To characterize the integrated vascular and parenchymal response to cortical spreading depression, with a focus on hemoglobin saturation.

Background: Cortical spreading depression (CSD) is thought to be the origin of the migraine aura. Related depolarizations occur in stroke and brain injury. A striking component of CSD is the profound vascular changes (arterial constriction and dilation) that accompany its spread.

Methods: We investigated the downstream effects of CSD-associated vascular changes with a combination of optical intrinsic signal imaging, electrophysiology, K+ sensitive electrodes, and optical spectroscopy in mouse.

Results: We have previously reported an acute hemoglobin desaturation during CSD, with a magnitude comparable to ischemia. We extended our investigation into the post-CSD time period and identified a second desaturation, lasting approximately 70 minutes, and of nearly the same size as the acute desaturation. Like the acute desaturation, it was associated with a paradoxical arterial constriction in the setting of increased tissue demand. Though electrophysiological activity returned shortly after CSD, perfusion related changes in response to this activity were significantly delayed. Neurovascular coupling, defined as the coherence between EEG and OIS signal, was disrupted for tens of minutes in the wake of CSD. Recovery from CSD occurred only on reestablishment of a normal vascular response to electrophysiological activity. Experiments with K+ sensitive electrodes indicated that the vascular response could not be explained simply by changes in [K+].

Conclusions: Our findings highlight the importance of the vasculature in CSD, and emphasize the relative independence of vascular changes from the underlying cortical depolarization. Vascular/metabolic uncoupling associated with CSD may have important clinical consequences, and may represent a therapeutic target in migraine and other conditions in which CSD occurs, including subarachnoid hemorrhage, stroke, and traumatic brain injury.

**MPF02**

Interleukins IL-1β and IL-6 cause sensitization of trigeminal ganglion neurons leading to changes in the ganglion and trigeminal nucleus caudalis: implications for understanding their role in migraine pathology

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Objectives: The purpose of this study was to determine whether IL-1β and IL-6 would sensitize trigeminal ganglion neurons to capsaicin by evaluating changes in neurons and glial cells in both trigeminal ganglia and trigeminal nucleus caudalis (TNC).

Background: IL-1β or IL-6 are members of the interleukin family, which are a group of cytokines produced by many diverse cell types (neurons, glial cells, mast cells) that mediate sensitization of sensory neurons and regulate inflammatory and nociceptive responses. The levels of the pro-inflammatory cytokines IL-1β and IL-6, which can be released in response to cortical spreading depression and cortical hyperexcitability, have been reported to be elevated during migraine attacks. However, the role of IL-1β or IL-6 in migraine pathology is not well understood but is likely to involve sensitization of trigeminal nociceptors.

Methods: Male Sprague-Dawley rats were either left untreated (control), injected in the whisker pad with IL-1β or IL-6 alone, or with IL-1β or IL-6 two hours prior to injection of a subthreshold concentration of capsaicin in the eyebrow region. Both ganglia and the TNC were collected 1 hour after the final injection and sections stained for expression of connexin (Cx) and known pro-inflammatory signaling proteins.

Results: While a subthreshold concentration of capsaicin alone did not cause increased protein expression, injection of IL-1β or IL-6 prior to capsaicin resulted in significant increases in the levels of Cx 26 and 43, PKA, and NF-kb in trigeminal ganglion and levels of c-Fos, GFAP, and GLAST in the TNC. Cx 26 staining was increased in both trigeminal ganglion neurons and satellite glial cells while Cx 43 expression was increased primarily in satellite glia. Similarly, levels of NF-kb, a transcription factor that regulates expression of many pro-inflammatory/nociceptive genes, and the pro-inflammatory signal transduction protein PKA were greatly increased in response to co-treatment. Within the TNC, co-treatment with IL-6 and capsaicin resulted in elevated levels of c-Fos, a marker of neuronal activation, GFAP, a marker of glial activation, and GLAST, a glial protein that functions to remove excess glutamate from the extracellular space. Interestingly, treatment with IL-1β or IL-6 alone resulted in a large increase in GLAST expression in the TNC.

Conclusions: Results from our study provide evidence that IL-1β and IL-6 cause sensitization of trigeminal nociceptors, and therefore, may play a role in the pathogenesis of migraine by lowering the activation threshold to other inflammatory stimuli. Based on our findings, we propose that elevated levels of IL-1β and IL-6 function to facilitate increased expression of signaling proteins in neurons and glia within the ganglia and TNC that contribute to peripheral and central sensitization, respectively, and thus, play important roles in migraine pathology.

**MPF03**

Calcitonin gene-related peptide (CGRP) and its receptor antagonists BIBN4096BS (olcegepant) and CGRP (8–37) can modulate neuronal activity of the trigeminocervical complex of the rat when microinjected into the ventrolateral periaqueductal gray

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Objectives: To examine whether the neuropeptide calcitonin gene-related peptide (CGRP) and its receptor antagonists BIBN4096BS (olcegepant) and CGRP (8–37) can modulate neuronal activity of the trigeminocervical complex of the rat when microinjected into the ventrolateral periaqueductal gray

Conclusions: CGRP is implicated in the pathophysiology of migraine and CGRP receptor antagonists are effective acute antimigraine treatments. There is evidence from imaging, experimental studies, and clinical reports that periaqueductal gray (PAG) dysfunction may be involved in migraine pathophysiology. In particular, the ventrolateral PAG (vPAG) is responsive to activation of craniovascular afferents and its activation exerts a descending antinociceptive effect on neurons in the TCC.

Methods: Rats (n = 15) were anesthetized with x-chloralose (intravenously) during recordings and their cardio–respiratory functions main-
MMA and V1 receptive fields after bicuculline microinjection into the TCC neurons. CGRP and the CGRP receptor antagonists BBN4096BS and CGRP (8–37) were microinjected into the vlPAG and changes in the activity of the TCC neurons were monitored.

Results: Inhibition of the neural responses to stimulation of the MMA and V1 receptive fields after bicuculline microinjection into the vlPAG was considered as evidence of a functional connection between the vlPAG and the TCC neurons. CGRP increased neuronal responses to electrical stimulation of the MMA by 32.1 ± 4.6% (maximum mean response ± SEM; P < 0.05, n = 6). Conversely, BBN4096BS decreased the excitability of TCC neurons to this stimulation by 24.7 ± 6.2% (P < 0.01, n = 10) and CGRP (8–37) by 23.2 ± 11.5 (P < 0.05, n = 6) compared with saline controls that did not have a significant effect.

Conclusions: These data suggest that CGRP and its receptor antagonists, olcegepant and CGRP (8–37), modulate neurons in the vlPAG, suggesting that brain loci outside of the TCC may also play a role in the clinical effect of CGRP receptor antagonists in the treatment of migraine.

MPF04
Reduced cortical spreading depression induction threshold in the occipital brain region of familial hemiplegic migraine type 1 (FHM1) knock-in mice
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Objectives: To study the mechanisms and pathways involved in migraine pathophysiology in transgenic knock-in mice bearing the pathogenic FHM1 R192Q mutation, by investigating susceptibility to cortical spreading depression (CSD) in different regions of the cortex.

Background: We generated transgenic knock-in mice that contain a pathogenic FHM1 mutation in the pore-forming subunit of CaV2.1 (P/Q-type) voltage-gated calcium channels. FHM1 mice exhibit increased susceptibility to CSD induction. Electrophysiological studies suggest that this increased susceptibility is due, at least in part, to a cortical hyperexcitability. As most migraine auras are visual in origin, this suggests a selective vulnerability of the visual cortex to CSD induction. We investigated whether our FHM1 mice exhibit a similar bias for CSD in the visual cortex by mapping CSD susceptibility.

Methods: We measured induction threshold in the occipital and frontal cortices of mice bearing the FHM1 R192Q missense mutation. In addition, we investigated whether decreased threshold bears clinical relevance by examining the pathological consequences of CSD induction in wild-type and R192Q mice, using performance in the wire-grip test as a measure of neurological deficit.

Results: Our results revealed that the CSD threshold in R192Q mice is significantly lower in the occipital cortex than in the frontal cortex. Interestingly, age-matched wild-type mice showed no difference in threshold between frontal and occipital stimulation, with both thresholds being similar to the frontal cortex of R192Q mice.

Conclusions: Our results seem to indicate that the CaV2.1 channel mutation seems to differentially affect the vulnerability of the cortex to CSD, lowering the occipital threshold only in the R192Q brain. Our results support the hypothesis that migraine is a threshold disease, with genetics playing a primary role in determining not only susceptibility to experience a CSD, but also in determining the clinical outcome following CSD. In addition, our data are consistent with the clinical finding that aura usually originates in the visual cortex.

MPF05
A PET study of trigeminal nociception sensitization in migraineurs: importance of anterior cingulate cortex and midbrain nuclei
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Objectives: As for other sensory modes, we hypothesized that a lack of habituation and/or a cortical hyperexcitability exists in migraineurs nociception.

Background: Although it has been shown that migraine headache is related to pain central dysfunction, nociception has been poorly studied in migraineurs.

Methods: We used H215O PET to study the brain responses to 90-second tonic trigeminal heat pain in 7 migraineurs between attacks and matched controls. Stimulations were started 30 seconds before PET acquisitions. Subjects were asked to rate the pain verbally after each PET scan. In a preliminary clinical session, we determined the temperature thresholds to reach a pain level of 30% of maximum pain, and we observed the evolution in time of pain ratings at 25, 55, 115 and 175 seconds of pain stimulation.

Results: Clinically, there was a rise in pain ratings by migraineurs while pain ratings by controls remained stable (P < 0.001). In controls, but not in migraineurs, we observed an activation of a frontoparietal network (BA6/BA8 and BA7/BA19). Insultate activation was stronger in migraineurs. Other activations of the pain matrix were present in migraineurs but not in controls: anterior medium cingulate cortex (BA24), subgenual (BA25) and pregenual (BA32) anterior cingulate cortex (ACC), and cerebellum. In the midbrain, including the hypothalamus, we observed a significant difference between migraineurs and controls.

Conclusions: We have shown that tonic trigeminal heat pain induces a sensitization in migraineurs as opposed to constant pain in controls. In parallel we observed a stronger activation of the cortical pain matrix in migraineurs than in controls. However migraineurs failed to activate the same high-order fronto-parietal network as controls. This network is usually involved in top-down attentional processes, and its activation might have been elicited by the rating of pain, which was the only task performed by subjects. By contrast, in migraineurs, pain induced an activation of pregenual and subgenual ACC, which are involved in affective and attentional processes, suggesting a common neurobiology with depression. Such involvement of the ACC may be related to the stronger activation by pain of midbrain nuclei and hypothalamus in migraineurs than in controls, since these serotonergic and dopaminergic nuclei exercise a tight control on ACC activity.

MPF06
Alcohol induces headache in a rat model of migraine
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Objectives: We are currently studying the effects alcohol on the trigemino-neurovascular system which could provide new insights into the pathophysiology of headache induction using a trigger that is known to induce headaches in humans.

Background: A fundamental question in the pathophysiology of headache is “how is a headache induced?” The mechanism behind the induction of spontaneous headaches in migraineurs is unknown. Until recently, no animal models have been available to address this
question. The experiments described below combines a model of recurrent headache with alcohol, a common trigger of headache in humans, to produce an inducible headache in a rat.

Methods: Our laboratory has developed a behavioral model of recurrent headache in rats, which uses repeated inflammatory activation of the trigeminal nociceptive pathway to simulate repeated headaches. The rats are implanted with a chronic cannula above the dura for repeated infusions with an inflammatory soup while they are awake and freely moving. After 5–7 infusions, a stable change in trigeminal physiology is induced. There are four groups of rats in the preliminary studies described below. Two groups of rats received eight saline infusions followed by an acute ingestion of either saline or alcohol on a day when they did not receive an infusion though the cannula. Two additional groups of rats received eight inflammatory soup infusions followed by either an acute ingestion of saline or alcohol. Sensory thresholds were measured using a Von Frey Pressure test.

Results: In both groups that received saline infusions and the group that received inflammatory soup and saline gavage, there were no significant changes in sensory threshold following gavage compared to baseline state within each animal. The sensory threshold for the rats that received inflammatory soup and alcohol gavage decreased significantly at both early (up to two hours) and late (four to six) timepoints following gavage. Interestingly, their sensory thresholds showed decreased sensitivity within two hours following alcohol ingestion suggesting alcohol may have a relaxation or analgesic effect on the rats. However, at 4 to 6 hours, the rats rebound to a threshold below their baseline level indicating that the alcohol may have induced a painful state.

Conclusions: This observation provides insight into the effects of alcohol on trigeminal pain. This is the first demonstration of an inducible headache in a rat model that uses a trigger that also induces headaches in the humans. Future directions include examining the cellular mechanism behind this phenomenon.

MPF08
Calcitonin gene-related peptide differentially regulates expression of signaling molecules in trigeminal ganglion neurons and satellite glial cells

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Objectives: The goal of this study was to determine the in vivo effects of peripheral CGRP injection on key signaling proteins involved in regulation of inflammatory responses in trigeminal ganglion neurons and satellite glial cells.

Background: Levels of calcitonin gene-related peptide (CGRP) have been reported to be elevated in serum, cerebrospinal fluid, and saliva during migraine attacks. CGRP, which is a neuropeptide released peripherally and centrally in response to trigeminal nerve activation, is implicated in the underlying pathology of migraine. Trigeminal ganglion neurons are known to express CGRP receptors and CGRP has been shown to function in an autocrine manner to stimulate its own synthesis and release. However, the in vivo cellular effects of CGRP stimulation of trigeminal neurons on neurons and satellite glial cells within the trigeminal ganglion have not been investigated. Within the trigeminal ganglion, neuronal cell bodies are surrounded by satellite glial cells and together are thought to form a functional unit.

Methods: Immunohistochemistry was used to study the temporal and spatial expression of key signaling proteins in trigeminal ganglion neurons and satellite glial cells in response to injection of 10 μM CGRP into adult male Sprague-Dawley rats (n = 4). Statistical analysis was performed using Student's t-test with significance considered when P < 0.05.

Results: Injection of CGRP resulted in increased staining levels of the pro-inflammatory proteins p38, S100B, and iNOS in both neurons and satellite glial cells at 2 and 24 hours post injection. Interestingly, the staining levels of the anti-inflammatory cytokine IL-10, which were initially decreased by CGRP at 2 hours, were elevated at 24 hours. Similarly, the staining levels of the MAP kinase phosphatases MKP-1, MKP-2, and MKP-3, which function to suppress inflammatory gene expression, were elevated in response to CGRP injection in both neurons and satellite glial cells at 2 and 24 hours.

Conclusions: Our findings support a multifunctional role of CGRP in the underlying pathology of migraine by regulating expression of key signaling molecules, which are known to regulate inflammatory responses in trigeminal ganglion neurons and satellite glial cells. Furthermore, it is likely that CGRP release within the meninges during a migraine attack would initially stimulate trigeminal nerves and then promote changes within the ganglion that contribute to peripheral sensitization of trigeminal nociceptors.
MPS09
The PAC1 receptor is a new target for antimigraine treatment
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Objectives: To investigate which receptor would be important for headache or migraine attacks induced by VIP and PACAP38.

Background: VPAC1, VPAC2 and PAC1 receptors are expressed on cephalic perivascular nociceptors and their activation cause intracellular increase in cyclic adenosine monophosphate (cAMP). These receptors are activated by the secretin-glucagon peptide family such as vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide-38 (PACAP38).

Methods: Two groups of healthy subjects (12 in each group) and two groups of patients with migraine without aura (MO) (12 in each group) were randomly assigned to 200 pmol/kg VIP and 200 pmol/kg PACAP38 infusion. Each group underwent randomized, double-blind placebo-controlled crossover trials. Headache was scored on a verbal rating scale (VRS) during hospital (0–2 hours) and post-hospital (2–12 hours) phases. We recorded mean blood flow velocity in the middle cerebral artery (VMCA) and diameter of the superficial temporal artery (STA) by ultrasonography.

Results: PACAP38 caused delayed migraine-like attacks in 58% of MO patients (mean 6 hours, range 2–11) (P = 0.016). VIP infusion caused no migraine-like attacks in MO patients. In healthy subjects, VIP infusion caused delayed headache in 3/12, whereas PACAP38 infusion caused delayed headache in 12/12 healthy subjects. In MO patients, the VMCA was significantly decreased 20 min after start of VIP (-16.3%) and PACAP (-16.1%) infusion. The STA diameter increased significantly 20 min after start of VIP (45.9%) and PACAP (37.5%) infusion.

Conclusions: Both VIP and PACAP caused marked vasodilatation of cerebral arteries. However, PACAP, but not VIP, could induce delayed migraine-like attacks in MO patients. Recent human expression studies from our experimental lab (1) showed that mRNA for the PAC1 receptor is present in low abundance in vascular tissue compared to neuronal tissue, whereas mRNA for VIPAC1 and VPAC2 receptors is present in high amounts in vascular tissue. Furthermore, a PAC1 agonist does not cause vasodilatation of rat cephalic vessels (2). Both VIP and PACAP activate the VPAC1 and VPAC2 receptors responsible for the vasodilatation. Only PACAP activates the PAC1 receptor, which therefore might be responsible for the induction of migraine attacks by a neuronal non-vascular mechanism.

References:

MPS02
Botulinum neurotoxin type A for treatment of chronic migraine: pooled analyses of the PREEMPT clinical program 32-week open-label phase
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Objectives: To evaluate the long-term efficacy and safety of botulinum neurotoxin type A (BoNTA; BOTOX®) as headache (HA) prophylaxis in adults with chronic migraine (CM).

Background: CM is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated for CM, and currently none is specifically indicated.

Methods: Two phase 3, 24-week double-blind, parallel-group, placebo-controlled multicenter studies (PREEMPT 1 & 2), followed by a 32-week open-label (OL) phase, evaluated the efficacy and safety of BoNTA in CM. Patients were screened for 4 weeks using an electronic diary and randomized (1:1) to BoNTA (155 U – 195 U) or placebo injections every 12 weeks. After the 24-week double-blind phase, patients received 3 BoNTA treatments (weeks 24, 36, 48). Key endpoints for the double-blind and OL phase included mean change from baseline in number of HA days (primary PREEMPT 2; secondary PREEMPT 1 and HA episodes (primary, PREEMPT 1; secondary, PREEMPT 2). Statistical comparisons for the OL phase were made between treatment groups based on the double-blind phase treatment: BoNTA (B) or placebo (P), and thus are noted as B/B or P/B groups. Only pooled PREEMPT data for the OL phase are presented.

Results: 1384 adults were randomized to B (n = 688) or P (n = 696) in the double-blind phase. A statistically significant mean decrease from baseline (week 0) favoring B/B for number of HA days was found at all visits in the OL phase, including the week 56 exit visit.
(-11.7 B/B, -10.8 P/B; \(P = 0.019\)). Significant differences favoring B/B were found at week 28 (\(P = 0.036\)) and week 52 (\(P = 0.044\)) for frequency of HA episodes. At all visits in the OL phase, B/B had significantly decreased frequency of migraine days (week 56: -11.2 B/B, -10.3 P/B; \(P = 0.018\)), moderate/severe HA days (week 56: -10.7 B/B, -9.9 P/B; \(P = 0.027\)), and total cumulative hours of HA on HA days (week 56: -169.7 B/B, -145.7 P/B; \(P = 0.018\)) compared to P/B. Most patients (72.6%) completed the OL phase with few discontinuations due to adverse events (5.5% B/B, 3.7% P/B). No new safety or tolerability issues emerged.

Conclusions: The 32-week OL phase of PREEMPT supports BoNTA as a safe and effective long-term (\(> 24\) weeks) prophylactic treatment for CM. Mean improvements from baseline were observed for both treatment groups during the OL phase. Significant differences favoring BoNTA over placebo in the double-blind phase were observed at multiple visits for all efficacy endpoints evaluated in the OL phase, suggesting continued improvement with long-term BoNTA. Repeated treatment with up to 5 cycles BoNTA every 12 weeks was safe and well tolerated.

MPS03
Migraine with and without aura are associated with cardiovascular disease. The American migraine prevalence and prevention study
Bigal ME\(^1\), Santanello NC\(^1\), Buse DC, Kurth T\(^3\), Golden WM\(^1\), Robbins MS\(^2\) and Lipton RB\(^2\)
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Objectives: To contrast the rate of diagnosed cardiovascular disease (CVD) in individuals with migraine with aura (MA) and migraine without aura (MO) as compared with controls from the general population.

Background: Strong evidence suggests that MA is associated with stroke; additional evidence links MA with other forms of CVD.

Figure 1

Methods: As a part of the American Migraine Prevalence and Prevention study (AMPP), we identified migraineurs (\(n = 6102\)) and controls (\(n = 5243\)) representative of the US adult population. Migraine diagnosis was assigned using validated questionnaires. Self-reported medical diagnosis of heart attack and ischemic stroke were identified and evaluated as a function of headache diagnosis, in univariate and multivariate analyses.

Results: Figure 1 displays the rates of any of the 4 outcomes assessed in MA (top figure) and MO (bottom), by demographics [figure 1]. Prevalent myocardial infarction occurred in 1.9% of controls and 4.1% of migraineurs (odds ratio [OR] = 2.2, 95% CI = 1.7–2.7). ORs were highest for age groups 30–39 and 40–49 (3.5 and 4.2). ORs were higher in MA than MO across all age groups.

Stroke occurred in 1.2% of the controls, and 2.1% of the migraineurs (OR = 1.6, 95% CI = 1.2–2.2). Rates were 3.9% in MA (OR = 3.1, 95% CI = 2.2–4.4) and 1.12% of MO (OR = 0.9, 95% CI = 0.6–1.3). For MA rates for stroke were elevated for both genders and all ages older than 30, relative to controls. In our multivariate models we tested main associations after adjusting for gender, age, disability, triptan use, as well as for the CVD risk factors (diabetes, hypertension, smoking, and high cholesterol). Overall migraine remained significantly associated with myocardial infarction (OR = 2.2, 95% CI = 1.7–2.8), TIA (OR = 1.9, 95% CI = 1.5–2.5) and stroke (OR = 1.5, 95% CI = 1.2–2.1). MA was a significantly associated with the three outcomes. MO remained associated with myocardial infarction and TIA, but not stroke.

Conclusions: Both migraine with and without aura are associated with cardiovascular events. MA was associated with all outcomes. MO was associated with myocardial infarction and TIA.

Table: Main effect of migraine and of migraine subtypes in CVD outcomes after adjustments.

<table>
<thead>
<tr>
<th>CVD outcome</th>
<th>Migraine vs. Control</th>
<th>MA vs. Control</th>
<th>MO vs. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct</td>
<td>OR (95% CI) = 2.16</td>
<td>OR (95% CI) = 2.86</td>
<td>OR (95% CI) = 1.85</td>
</tr>
<tr>
<td></td>
<td>(1.70,2.76)</td>
<td>(2.14,3.82)</td>
<td>(1.41,2.42)</td>
</tr>
<tr>
<td>TIA</td>
<td>OR (95% CI) = 1.92</td>
<td>OR (95% CI) = 3.16</td>
<td>OR (95% CI) = 1.21</td>
</tr>
<tr>
<td></td>
<td>(1.50,2.47)</td>
<td>(2.54,4.44)</td>
<td>(0.99,1.62)</td>
</tr>
<tr>
<td>Stroke</td>
<td>OR (95% CI) = 1.54</td>
<td>OR (95% CI) = 2.78</td>
<td>OR (95% CI) = 0.97</td>
</tr>
<tr>
<td></td>
<td>(1.16,2.05)</td>
<td>(2.02,3.84)</td>
<td>(0.69,1.36)</td>
</tr>
</tbody>
</table>

MPS04
Cardiovascular profile in individuals with migraine from the population
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Objectives: To ascertain the prevalence of risk factors for cardiovascular disease in and the Framingham Risk scores migraineurs and controls.

Background: Among the many biologically plausible mechanisms by which migraine may be linked to cardiovascular disease (CVD), it has been suggested that persons with migraine with aura (MA) have a higher prevalence of CVD risk factors, including hypertension, diabetes, and hyperlipidemia. For migraine without aura (MO), the evidence is contradictory.

Methods: In individuals with migraine (ascertained using validated questionnaires) and controls, we obtained information on established risk factors for CVD (e.g. smoking, body mass index, hypertension, etc). We also assessed the cardiovascular risk profile using the validated modified Framingham risk score for CVD. This score, based
Migraine with and without aura are associated with risk factors in migraine with and without aura, relative to controls. We acknowledge the limitation that individuals with risk factors for CVD may visit a physician more frequently than those without, with a correspondent higher chance of being diagnosed for migraine.

**Conclusions:** Migraine with and without aura are associated with risk factors for CVD, as well as with increased Framingham scores, relative to control. We acknowledge the limitation that individuals with risk factors for CVD may visit a physician more frequently than those without, with a correspondent higher chance of being diagnosed for migraine.

**Results:** Our sample consists of 6102 migraineurs and 5243 controls. Overall, migraineurs were more likely than controls to have a history of medical diagnosis of diabetes (12.6% vs. 9.4%, OR = 1.4, 95% CI = 1.2–1.6), hypertension (33.1% vs. 27.5%, OR = 1.4, 95% CI = 1.3–1.6), and high cholesterol (32.7% vs. 25.6%, OR = 1.4, 95% CI = 1.3–1.5). They were also slightly more likely to currently smoke. MA was significantly associated with all risk factors in both genders. MO was significantly associated with diabetes, hypertension and high cholesterol in both genders, but not with smoking. Both individuals with MA and MO were significantly more likely to have more than one CV risk factor, relative to controls, for most demographic categories. Framingham risk scores were also significantly higher for overall migraine (mean = 10.7, SD = 5.4), MA (11.0; 5.4) and MO (10.6; 5.4) as compared to controls (8.5; 6.1) (P < 0.001 for all comparisons with controls). Scores were significantly higher in migraineurs of both genders (overall and for MO and MA), numerically higher for all age groups younger than 70 years and significantly higher for migraineurs in all age ranges from 30–59 years old.

**Objectives:** To validate the use of heavily T2-weighted magnetic resonance myelography (MRM) in patients with spontaneous intracranial hypotension (SIH).

**Background:** Computed tomographic myelography (CTM) is the study of choice to investigate the CSF leaks in patients with SIH. Our recent studies showed MRM is promising in the diagnosis and follow-up of patients with SIH.

**Methods:** Nineteen patients (6M/13F, mean age 37.9 ± 8.6 years) with SIH were enrolled, and underwent both MRM and CTM. The results of the CTM were used as the gold standard to verify those from the MRM, focusing on (1) CSF leaks along nerve roots, (2) epidural CSF collections, and (3) high-cervical (C1–C3) retrospinal CSF collections. Comparisons on each finding based on each patient and each level were done by kappa statistics and agreement rates. Targeted epidural blood patches (EBPs) were placed at the levels of identified CSF leaks.

**Results:** CSF leaks along nerve roots were localized in 14 patients (74%) on CTM, and two more patients (n = 16, 84%) were identified on MRM. The leaks most commonly occurred at the cervicothoracic junction (C7–T1 to T1–2) and mid-thoracic region (C4–5 to T6–7). The concordance between MRM and CTM was almost perfect for the cervicothoracic junction leaks (kappa = 0.89, P < 0.001, agreement = 95%), and substantial for the mid-thoracic leaks (kappa = 0.66, P = 0.002, agreement = 84%). The level-by-level concordance was substantial for both CSF leaks along nerve roots (kappa = 0.69, P < 0.001, agreement = 95%) and high-cervical retrospinal CSF collections (kappa = 0.73, P < 0.001, agreement = 92%), and moderate for epidural CSF collections (kappa = 0.47, P < 0.001, agreement = 72%). Fourteen patients received targeted EBPs at the level(s) of identified leaks, and ten of them (71%) had sustained symptomatic relief after a single attempt.

**Conclusions:** This is the first study to validate the use of heavily T2-weighted MRM for patients with SIH. Our results suggest that this non-invasive technique may be a good alternative to CTM prior to targeted EBPs.

**MPS06**

**Antimigraine drug sumatriptan decreases blood flow in cortical and scalp surface arteries during migraine attacks – a near infrared spectroscopy and skin laser flowmeter study**

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**Objectives:** To evaluate the cortical blood flow changes before and after administration of sumatriptan injection during migraine attack.

**Background:** It is known sumatriptan injection introduce vasoconstriction in the brain. However, there is no adequate explanation for pathophysiology, especially, how to act to cortical blood flow and pain relief.

**Methods:** We investigated patients with migraine according to International Classification of Headache Disorder II (ICHD-II). Four
patients with migraine without aura and four normal subjects were submitted for this study. Twenty-four channel near-infrared spectroscopy (NIRS) were recorded during migraine headache attacks. We attached 3 × 4 probes for each hemisphere covered over the bilateral temporal and parietal lobes. The data was sampled with 10 Hz (100 msec intervals). The changes of oxygenated hemoglobin (oxy-Hb) were analyzed. In addition, continuous and noninvasive measurement of blood flow in the outermost layer of the skin by the skin laser flowmeter (SLF). SLF was placed on right side of the forehead. The data was sampled at 30 s intervals. Four patients and 4 control subjects were treated with 3 mg of sumatriptan or saline injection during NIRS and SLF recording and the changes of oxy-Hb were observed continuously for 15 minutes.

**Results:** Significant correlation was only seen between oxy-Hb and SLF in migraine patients. And correlated with the reduction of oxy-Hb and SLF, all migraine patients showed remarkable and quick relief of the symptom assessed by visual analog scale (VAS) after sumatriptan injection. Figure 2 shows a representative data from observations of NIRS and SLF anatomically proved effect of sumatriptan injection. Figure 2 shows a representative data from migraine patient. The vertical axis represents oxy-Hb and SLF, and the horizontal axis corresponds to time. Arrow (↓) indicates the moment of injection.

**Conclusions:** We conclude that NIRS is the only method that can observe sumatriptan effect from the viewpoint of cerebral blood flow change, directly and continually in vivo. In addition, simultaneous observations of NIRS and SLF anatomically proved effect of sumatriptan. These data suggest that sumatriptan induced blood vessel contraction at the cortical and scalp surface during migraine attack.

**MPS07**

Cortical spreading depression and associated neuronal Fos expression in rats are affected differentially by chronic treatment with lamotrigine, valproate or riboflavin

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**Objectives:** To study in rats the effects of two anti-migraine preventives, lamotrigine (LTG) and riboflavin given as flavin mononucleotide (FMN), on KCl-induced CSD and subsequent Fos immunoreactivity in cortical neurons. To compare these drugs with sodium valproate (VPA) that was previously studied in the same model.

**Background:** Cortical spreading depression (CSD) is thought to be the underlying mechanism of the migraine aura. CSD increases the expression of Fos, a marker of neuronal activation, in the ipsilateral hemisphere. CSD inhibition in rats was suggested to be the common denominator of preventive anti-migraine drugs like valproate (Ayata et al., 2006), but this hypothesis cannot be accepted without reservation (Schoenen 2006).

**Methods:** Five groups of male Sprague-Dawley rats (n = 10) were treated daily during 4 weeks with i.p. LTG (15 mg/kg in DMSO), FMN (50 mg/kg in saline) or VPA (200 mg/kg). DMSO and saline served as controls. CSD was induced during 2-hour KCl application on the occipital cortex in anesthetized rats and DC potentials were recorded at two sites: posterior (occipito–parietal, bregma P-4, R+2) and anterior (frontal, bregma A+1, R+2). Fos immunoreactive nuclei were counted in the cortical layers of the anterior site.

**Results:** LTG inhibited markedly CSD at both recording sites. This was paralleled by a significant reduction of Fos expression in all layers of the frontal cortex compared to DMSO. VPA had no significant effect on CSD at the posterior site, but decreased CSD at the frontal site where it also reduced Fos. By contrast, FMN increased CSD at the posterior site, while having no effect in the frontal cortex where Fos nonetheless tended to increase. NaCl and DMSO had no significant effect on CSD or Fos expression.

**Conclusions:** We show for the first time that lamotrigine has the most pronounced inhibitory effect on CSD, which may explain its selective therapeutic effect on the migraine aura. Valproate seems to act chiefly on CSD propagation, but not on its occurrence. The mild CSD-promoting trend of riboflavin might be explained by attenuation of the metabolic stress favoring neurono-glial recovery. Fos expression parallels CSD frequency and involves differentially all cortical layers.

**MPS08**

The presence of psychiatric comorbidity does not portend poorer treatment outcome

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**Objectives:** To examine the impact of psychiatric comorbidity on migraine treatment outcome.

**Background:** Migraine is highly comorbid with both mood and anxiety disorders. These comorbidities are widely thought to portend poor treatment outcome. Empirically, few studies have demonstrated this effect, and in at least one study, endorsement of depressive symptoms has been associated with greater decreases in disability over treatment.

**Methods:** After one month of optimal acute therapy, 232 severe migraine sufferers (79% female) were randomized into one of four groups: Placebo, Propranolol, Behavioral Migraine Management (BMM) + Placebo, and BMM + Propranolol. Participants were followed for 4 months of behavioral treatment and/or dose adjustment, and for an additional one year follow-up period. At baseline, a psychiatric evaluation was conducted using the PRIME-MD. Disability was measured at office visits using the Headache Disability Inventory (HDI; Jacobson et al., 1994). Mixed models analyses were conducted to determine whether either an anxiety or mood diagnosis was associated with disability over the course of the trial.

**Results:** Three results were found, none of which was consistent with the common assumption that individuals with psychiatric comorbidity make smaller treatment gains than individuals without psychiatric comorbidity. In general, mood disorder diagnoses were
associated with greater decreases in headache-related disability over the course of treatment, $F(1, 257.090) = 4.661, P < 0.05$. Additionally, a significant three-way interaction between mood disorder diagnosis, treatment group, and time $F(3252.237) = 3.664, P < 0.05$, indicated that individuals with a mood disorder diagnosis demonstrated less of a decrease in the placebo group than individuals without a mood disorder diagnosis. Finally, anxiety disorder diagnoses were not associated with treatment change in either direction, $F(1259.327) = 0.001, P = 0.982$.

Conclusions: The presence of a comorbid mood disorder predicts greater decreases in disability over the course of behavioral and pharmacological migraine treatment, although these individuals experience greater benefit from the addition of behavioral treatment or preventative medication to an acute care regimen. Individuals with psychiatric comorbidity do not appear to be handicapped in their ability to benefit from migraine treatment, regardless of treatment type (e.g., behavioral or pharmacological).

MPS09
Chronic daily headache in returning United States army personnel with mild head trauma or blast exposure
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Objectives: To determine the characteristics of, and factors associated with, CDH in US soldiers with a history of mild head trauma or blast exposure.

Background: Headaches and mild head trauma are common in deployed US Army personnel. Chronic daily headache (CDH) is an especially disabling form of headache. Little is known about chronic daily headache in combat veterans.

Method: Soldiers who screened positive for a concussion, head injury, or blast exposure at the Traumatic Brain Injury Program at Ft. Lewis, WA between June and October 2008 completed a 13-item, self-administered headache questionnaire. All soldiers had returned from Iraq or Afghanistan in the previous 3 months. Analysis of the soldiers with chronic daily headache (CDH), defined as headaches occurring 15 or more days per month for the previous 3 months, was performed and compared to soldiers without CDH. Data were obtained from the headache questionnaire as well as medical record review.

Results: 196 of 978 (20%) soldiers had chronic daily headache (CDH). The mean headache frequency was 23 days/month for the CDH group and 5.3 days/month for the non-CDH group. Headaches were migraine type in 66% of soldiers with CDH and 48% of soldiers without CDH. Headaches started a median of 11 months prior to deployment in 64% of soldiers with CDH and 48% of soldiers without CDH. Headaches began within 1 week of a concussion or blast exposure in 64% of soldiers with CDH compared to 36% of soldiers without CDH. 57% of soldiers with CDH and 60% of soldiers without CDH experienced a concussion while deployed. 63% of concussions in soldiers with CDH resulted in loss of consciousness compared to 33% in soldiers without CDH. The median number of concussions per soldier was 1 for both groups. 62% of soldiers with CDH had been exposed to a blast compared to 76% of soldiers without CDH. Both groups had a median of 3 blast exposures per soldier. 49% of soldiers with CDH used abortive headache medications at least 15 days per month compared to only 1% of soldiers without CDH. The mean PTSD checklist score was 44.8 for soldiers with CDH and 37.2 for soldiers without CDH. 33% of soldiers with CDH screened positive for PTSD compared to 15% of soldiers without CDH. The mean military acute concussion evaluation (MACE) score was 25.9 for soldiers with CDH and 27.0 for soldiers without CDH.

Conclusions: In five returning soldiers with a history of concussion or blast exposure has CDH, Factors associated with CDH include migraine-type headache, concussion with loss of consciousness, headache onset within 1 week of trauma exposure, frequent use of analgesic medications, and symptoms of PTSD.

PO01
Triptan use patterns among migraine sufferers: results of the American migraine prevalence and prevention study (AMPP)
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*1*Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; *2*Global Outcomes Research, Merck Pharmaceuticals, Whitehouse Station, NJ, USA; *3*Research, Vedanta Research, Chapel Hill, NC, USA

Objectives: To describe patterns of triptan use in episodic migraine (EM) over a 1 year period, in the US population.

Background: Despite its importance, several barriers have prevented migraine sufferers from achieving satisfactory control of their disease. In the US, the proportion of individuals using prescription medication for the acute treatment of migraine increased by 32.2% over the past 15 years, from 37% to 49%. Nonetheless, the pattern of use of prescription medication (e.g., single medication use or combination therapy) both within and between classes of medication is not well characterized. Among the several existing barriers for good outcomes, acute medication use is inconsistent.Although triptans improved the lives of millions of migraineurs, paradoxically, the number of patients using triptans as acute treatment for migraine has remained essentially stable over the last five years with only an estimated 4 million migraine sufferers utilizing triptan medications. This implies that with each new patient diagnosed and prescribed a triptan, there is a triptan user that discontinues use of triptans.

Methods: In 2005, mailed questionnaires were sent to 24,000 severe headache sufferers identified in a 2004 US population survey. Respondents who met ICHD-2 criteria for migraine and had 14 or fewer headache days per month were included in these analyses. Respondents were asked to identify all of the medications they “currently” used to treat their “most severe type of headache”. Medications were categorized into eight classes, including triptans. Data from triptan use was included in these analyses.

Results: Data were available on 11,388 respondents with EM. 18.3% of migraine sufferers used triptans to treat their headaches. Of triptan users, 21.7% used only triptans, 38.7% also used one additional class of medications, 23.7% used two additional classes, and 15.9% used three or more additional classes of medication. Among those who used triptans combined with other classes of medications, 43.3% used NSAIDs, 34.0% used acetaminophen, 34.8% used aspirin or other combination analgesics, 7.7% used barbiturate combinations, 13.1% used opioids, 4.6% used isometheptene combinations, and 2.6% used ergotamine. (Percent total to more than 100% because many individuals used multiple classes of medications.)

Figure 1

Conclusions: A minority of migraine sufferers are current users of triptans, and the overwhelming majority of triptan users also use other classes of acute treatment. These findings suggest that triptan monotherapy does not fully meet the acute treatment needs of migraine sufferers.
PO02
The pharmacokinetics and tolerability of telcagepant, a novel calcitonin gene related peptide (CGRP) receptor antagonist, in healthy subjects and migraineurs
Han TH1, Blanchard RL1, Palcza J1, De Lepeleire I1, Laethem T1, Martucci A1, Willson K1, Xu Y1, Boyle J1, Butterfield K1, Mahon C1, Ermlich S1, Matthews C1, Xiao A1, de Hoon JN2, Gutierrez M3, Van Bortel L3, Bieberdorf FA2, Van Hecken A2, Depre M2, Sinclair S1, Panbianco D1 and Murphy G1
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Objectives: The pharmacokinetics and tolerability of telcagepant were examined in healthy human subjects and in patients during and between acute migraine attacks.

Background: Telcagepant is a novel, orally active and selective calcitonin gene related peptide (CGRP) receptor antagonist being developed for the acute treatment of migraine with and without aura.

Methods: A total of 162 adult subjects were enrolled in five separate, randomized clinical studies: (1) double-blind, placebo-controlled single rising oral dose study with healthy subjects, (2) open-label, single-dose oral dose proportionality study with healthy subjects, (3) open-label, single-dose intravenous dose proportionality study with healthy subjects, (4) double-blind, placebo controlled multiple oral dose escalation study with healthy subjects, (5) double-blind, placebo controlled single oral dose study with patients. Blood samples were collected through 48 hours to assess the pharmacokinetics.

Results: Telcagepant was rapidly absorbed with a Tmax of approximately 0.5 to 1.5 hours after oral administration. The terminal half-life was approximately 8 to 11 hours after a single intravenous dose, which is similar to the apparent terminal half-life observed after a single oral dose. Oral administration of telcagepant resulted in modestly greater than dose proportional increases in exposure, while intravenous administration of telcagepant resulted in approximately dose proportional increases in exposure. After multiple-dose administration, steady state was achieved in approximately 3 days. The exposures of telcagepant were similar in patients during and between migraine attacks. Telcagepant was generally safe and well tolerated.

Conclusions: The pharmacokinetics of telcagepant are well suited for the acute treatment of migraine and are similar in patients during and between migraine attacks. Telcagepant was generally well tolerated following both oral and intravenous administration.

PO03
Assessment of the long term safety and tolerability of telcagepant for the intermittent treatment of acute migraine: a double-blind, active-controlled study
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Objectives: To compare the long term safety and tolerability of telcagepant 300 mg OSE capsule or 280 mg tablet (TEL) and rizatriptan 10 mg (RIZ) in intermittent migraine with and without aura (M ± A). Triptan-related adverse events (AEs) were the primary end points.

Background: Telcagepant is a novel oral calcitonin gene-related peptide (CGRP) receptor antagonist being developed for acute migraine with and without aura (M ± A), and its efficacy in treating a single M ± A attack was demonstrated in 2 pivotal trials.

Methods: Adults meeting IHS criteria for M ± A were recruited worldwide and randomized (2:1) to double-blind treatment with TEL or RIZ. Patients administered study medication to treat an acute mild, moderate, or severe migraine. Patients were allowed to administer a second dose within 2–24 hours for non-response or migraine recurrence. Patients could treat up to 8 M ± A/month with study medication for up to 18 months. Safety assessments included spontaneous reports of AEs and collection of vital signs, ECGs, and laboratory assessments.

Results: Of 1068 patients randomized, 640 (90%) patients treated at least one attack with TEL and 313 (88%) treated at least one attack with RIZ; 19,820 attacks in total were treated with TEL and 10,981 with RIZ. The mean number of attacks treated per patient during the study were 31 TEL and 35 for RIZ. Fewer triptan-related AEs (asthenia, chest pain, chest tightness, paraesthesia, hyperesthesia, dysesthesia, dizziness, nausea, fatigue, nasopharyngitis, vomiting, upper abdominal pain) were reported with TEL compared to RIZ. The most common AEs appeared to have generally similar incidence proportions between the treatment groups. The most commonly reported AEs (incidence > 3%) with TEL were dry mouth (9.7%), somnolence (9.0%), dizziness (8.9%), and fatigue (4.7%). No severe adverse events were reported. Patients on TEL experienced > 3 x elevation in hepatic transaminases, but without elevated bilirubin. All elevations were transient, one was 2 months following the last dose, and one was associated with elevated CPK from a muscle injury.

Conclusions: TEL is generally well tolerated when administered for the intermittent treatment of M ± A for up to 18 months. Tolerability with respect to the incidences of triptan-related AEs and drug-related AEs generally favor TEL over RIZ.

PO04
Efficacy and tolerability of MAP0004, a novel orally inhaled therapy, in treating acute migraine
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Objectives: To evaluate the efficacy and safety of MAP0004, a novel orally inhaled formulation of dihydroergotamine, in the treatment of an acute migraine attack compared to placebo.

Background: Individual migraine patient treatment needs are often unmet by currently available therapies, including the seven triptans, due, in part or in whole, to inconsistency of response, high recurrence rates, slow onset of action, and potential for medication overuse headaches (MOH). Intranasal dihydroergotamine (IV DHE) provides rapid relief, low recurrence rates, and no reported MOH. However, IV DHE is difficult to administer and titrate, and often has poor tolerability. MAP0004 is a novel inhaled formulation of DHE with similar Tmax and AUC (and lower Cmax) as that of IV infusion, but is self-administered through non-invasive oral inhalation. A Phase 2 study of MAP0004 showed onset of pain relief for acute migraine pain in as fast as 10 minutes, with good 2-hour pain response rates and 2–24-hour sustained pain-free rates, and was well-tolerated, with no serious or severe adverse events. The present, larger, Phase 3 study was undertaken to further evaluate the safety and efficacy of MAP0004 in treating acute migraine attacks.
Methods: This is a randomized, double-blind, placebo-controlled, two-arm, multicenter study. The four co-primary efficacy endpoints were pain relief, nausea free, photophobia free, and phonophobia free at 2 hours post-dosing. The secondary endpoints included pain-free rates at 2 hours, sustained pain relief and pain-free at 2–24 and 2–48 hours, pain relief at 10 minutes, and time to onset of pain relief. Safety evaluations included clinical assessments, laboratory evaluations, extensive pulmonary function evaluations, and cardiac evaluations.

Results: 908 subjects were randomized in the efficacy portion of the trial. Those who treated at least one qualifying headache and recorded a response, the mITT population, will be included in the primary analysis. Final data analysis is not complete. However at the time of IHC 2009, top line data for the primary endpoints, pain relief at 2 hours, nausea, photophobia and phonophobia free rates at 2 hours, for both the active drug and placebo and the p values for the same will be presented. Time to onset of pain relief (calculated by plotting the relief time for each group and noting the first time point at which the two curves statistically separated for the first time and maintained that separation up to 2 hours), 2–24 and 2–48 sustained pain relief and pain-free rates will also be presented. Comprehensive safety data for acute use of MAP0004, including clinical adverse events, vital signs, laboratory chemistry, and pulmonary and cardiac testing will also be presented.

Conclusions: The safety and efficacy of MAP0004, potential advantages and possible risks/adverse events will be discussed.

PO05
A randomized, prospective, cross-over, double blind, placebo-controlled multicentre study to assess the efficacy and tolerability of almotriptan 12.5 mg in menstrually-related migraine
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Objectives: To assess the clinical efficacy and tolerability of almotriptan 12.5 mg (A) in patients suffering from menstrually-related migraine (MRM), in a multicenter, randomised, double-blind, cross-over, placebo (P) controlled study on the treatment of two consecutive MRM attacks in two distinct menstrual cycles followed by an open follow-up phase (treatment with A of two further MRM attacks in two distinct menstrual cycles).

Background: MRM is a common form of migraine affecting about 60% of female migraineurs. Not many prospective studies on MRM treatment with triptans have been published up to now and no data with almotriptan are available.

Methods: MRM sufferers, diagnosed fulfilling ICHD-II criteria, were recommended to take the drug as soon as possible. Main variable was the 2 hours pain free (PF) patients’ percentage. Secondary variables were: number and percentage of patients achieving sustained pain free (SPF), number and percentage of patients achieving SPF and reporting no adverse event (SNAE), rescue medication use (% of patients), evolution of migraine associated symptoms (nausea, vomiting, phonophobia, or photophobia), number and type of adverse events.

Results: 147 patients were randomized to A–P (n = 74) or P–A (n = 73). 122 patients (ITT) completed the double-blind phase (A–P n = 63; P–A n = 59). All patients were MRM sufferers with regular menstrual cycles, with a minimum of one year history of migraine and a minimum of 6 month history of regularly occurring MRM. Descriptive statistics highlighted that: 1) about 50% of MM attacks occurred between the 1st and 2nd day of menstrual period, 2) moderate headache occurred in 50% to 60% of migraine attacks and 3) an association with other symptoms (nausea, vomiting, etc) was present in about 90% of patients. The study reached the main objective to demonstrate the superiority of A vs. P in terms of PF patients at 2 hours being the percentages in ITT Population (n = 122) of 48.4% and 26.2% for A and P respectively (RR 1.81; 95% CI: 1.28–2.57; P = 0.0008) and in PP Population (n = 110) of 49.1% and 23.6% for A and P respectively (RR 2.02; 95% CI: 1.37–2.99; P = 0.0004). All other items examined as secondary endpoints also demonstrated the superiority of A vs P: SPF 36.1% vs. 17.2% (P = 0.0022); SNAE 33.6% vs. 16.4% (P = 0.0061); rescue medication use 39.3% vs. 59.8% (P = 0.0004). As for migraine associated symptoms, a significant difference (A vs. P at 2 hours) was found for nausea (19% vs. 36.7%, P = 0.0007), photophobia (33.1% vs. 49.2% P = 0.0083) and phonophobia (30.6% vs. 41.7% P = 0.0566). During the open phase similar or even better percentages for all the evaluated parameters were recorded. Adverse events occurred in about 6% of patients both during A and P treatment.

Conclusions: Almotriptan demonstrated its efficacy and tolerability in the symptomatic treatment of MRM.

PO06
A combination of metoclopramide and/or caffeine does not improve the efficacy of frovatriptan in the acute treatment of migraine
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Objectives: Evaluate whether adding metoclopramide and/or caffeine improves the efficacy of frovatriptan.

Background: Many migraine attacks are accompanied by gastric status which is known to potentially impede drug absorption, resulting in inconsistent relief of pain. Clinicians commonly combine adjunctive agents such as metoclopramide or caffeine with oral anti-migraine agents in an attempt to improve drug absorption. Unfortunately, research evidence to support this practice is not well established. This study was designed to determine if the co-administration of metoclopramide and/or caffeine with frovatriptan in the acute treatment of migraine enhances the efficacy of frovatriptan alone.

Methods: This randomized, double-blind, crossover, active comparator trial compared orally administered Frovatriptan 2.5 mg+ Placebo (FPBO) alone or in combination with Caffeine 35 mg (FC), Metoclopramide 10 mg (FM), or both (FMC) to study the efficacy of each combination. Subjects served as their own controls, receiving all four combinations of study product across four separate migraine attacks. Subjects kept a detailed diary of their attacks (pain, associated symptoms, disability). A total of 49 persons recruited from a large primary headache center and a research database (97% female, ages 19–62, years with headache > 20.10 years, mean headaches/month = 4.8) with ICHD-II criteria primary migraine with or without aura treated 4 attacks. After patients were screened and provided their consent, they were instructed as to when to take the medication and how to complete their attack diary. The primary measure of interest was 2, 4, and 24 hour headache pain relief. Other measures of interest were time to meaningful relief and 2, 4, and 24 hour pain-free, migraine-free, and disability comparisons among the four arms. Data were analyzed using Chi-square, ANOVA, McNemar’s test and Kaplan–Meier survival analysis as appropriate using SPSS.

Results: Baseline results show no difference in baseline migraine pain or associated symptoms at the time of dosing for any treatment arm(s). Table 1 shows that the 2, 4, & 24 hour pain relief did not differ across treatments arms. Similarly, there were no differences among any of the groups in regards to time to 2, 4, & 24 pain-free, migraine-free, or disability ratings. The groups also did not differ in regards to adverse events.
Conclusions: The results of the current findings indicate that adding metoclopramide and/or caffeine to frovatriptan does not enhance the efficacy or pain-free status of the medication. This finding suggests that although these compounds have been used in clinical practice for the purpose of enhancing clinical efficacy, clinicians should purposefully evaluate the contributions of such therapies as they may only contribute to the potential for side effects and polypharmacy related complications.

PO07
Impact of cutaneous allodynia on the responsiveness of rizatriptan in acute migraine headaches
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Objectives: To compare the responsiveness of acute migraine headache attacks to Rizatriptan in patients with and without cutaneous allodynia.

Background: Allodynia, a manifestation of central sensitization, is not routinely evaluated during clinical interviews even though its therapeutic implications are known. It has been suggested that presence of cutaneous allodynia may decrease the responsiveness to triptans.

Methods: 101 consecutive episodic migraine patients (ICHD II) were evaluated using a semi structured questionnaire for allodynia and were divided into two groups; those with allodynia and those without. The responsiveness to 10 mg of Rizatriptan was assessed in terms of VAS percentage reduction for next two attacks through telephone interviews. In the first attack, the patients took the drug at the start of allodynic symptoms or at two hours after the start of the headache, whichever earlier. In the second attack, the patients took the drug immediately after the onset of headache. The level of significance was considered at < 0.005.

Results: The age range of the study population was between 12 to 50 years (mean ± SD is 28.42 ± 8.83) years. There were 82 (81.2%) females and 19 (18.9%) males [M: F = 4.3:1]. 47 (46.5%) patients reported allodynia. More females had cutaneous allodynia (P ≤ 0.001). There were no significant differences between those with and those without allodynia in terms of age, disease duration, headache frequency and severity (by MIDAS). Aura was present in 16 (15.8%) patients (all visual auras). More patients with allodynia had auras but difference just failed to reach the statistical significance (P = 0.052). At 2 hours after rizatriptan intake, reduction in VAS percentage (compared to baseline) was lesser (31.37 ± 19.96) in patients who took the drug after development of allodynia or at 2 hours than those without allodynia (40.04 ± 20.24) [(P = 0.016)]. When the patients took the drug immediately during the second headache episode, reduction in VAS percentage at 2 hours was 63.77 ± 26.97 in non-allodynic patients compared to 72.07 ± 27.90 with those with allodynia (P = 0.092). When the first attack and second attack were compared in the allodynic group, reduction in VAS percentage was significantly greater during the second attack when rizatriptan was taken immediately after headache onset.63.77 ± 26.97 vs. 36.01 ± 20.47) [P = 0.001].

Conclusions: Patients who took rizatriptan after development of allodynia derived less benefit than those without allodynia. Patients who took rizatriptan immediately after the onset of headache derived equal benefit irrespective of alloodynic status. In alloodynic patients when rizatriptan was taken immediately following a headache episode, significantly more relief was derived compared to an episode when the drug was taken after the development of allodynia. Rizatriptan should therefore be taken immediately after the onset of migraine headache before the development of allodynia.

PO08
Abstract withdrawn

PO09
Can nose-to-brain transport of anti-migraine drugs along the trigeminal nerve improve therapeutic effects while minimizing the risk of systemic adverse events?
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Objectives: The objective is to analyse the apparent disconnect between recent PK-data and clinical results achieved with Sumatriptan nasal powder delivered with a novel device in view of recent knowledge on the pathophysiology of migraine and on mechanisms of nose to the brain transport.

Background: The trigeminovascular system plays a key role in the pathophysiology of migraine. Calcitonin-gene-related-peptide (CGRP) released at trigeminal nerve endings is a potent vasodilator. Triptans inhibit CGRP-release to counteract vasodilatation, whereas CGRP-antagonists block the CGRP-receptors. Key sites of action are the trigeminal ganglion and the trigeminal nerve endings of cerebral vessels located inside the blood-brain-barrier (BBB). Limited ability of triptans and CGRP-antagonists to pass the BBB may, in part, explain the high doses needed in therapy. High serum concentration of triptans may cause chest symptoms and asthenia related to vasoconstriction. Daily dosing of the oral CGRP-antagonist Telcagepant may increase liver enzymes and limit the therapeutic potential.

Methods: The novel bi-directional nasal delivery concept allows significantly enhanced delivery of sumatriptan powder to the mucosa innervated by the olfactory and trigeminal nerves. A 3-way randomised cross-over phase I study compared, the pharmacokinetics of nasal sumatriptan (7.5 mg and 15 mg) [s1] to 6 mg subcutaneous sumatriptan (SC) and along with assessment effects on EEG in 12 migraineurs during the migraine-free phase using the GTN-induced migraine model. The therapeutic effect was assessed in an in a single attack, three-way Phase II placebo-controlled study. Patients (n = 109) with a moderate to severe migraine attack, received 7.5 mg nasal Sumatriptan to the side of the migraine, 15 mg split between the two nostrils or placebo (1:1:1).

Results: Sumatriptan powder was rapidly absorbed with a Tmax similar to SC (20 min vs. 12 min) and much shorter than published data on 100 mg tablets (120 min) and 20 mg nasal spray (90 min). Results from the GTN challenge show that despite a Cmax 9-fold lower (10.8 ± 7.1 vs. 96.4 ± 25.4 ng/ml) the clinical efficacy and qEEG effects for nasal powder were similar to 6 mg SC. The clinical outcome for 7.5 and 15 mg were very similar and results for 7.5 mg are reported. Pain-free rate at 2 hours was 54.1% (25% placebo; P < 0.03). Headache relief was greater already at 60 minutes (73.0% vs. 37.5%; P = 0.004) and increased at 2 hours (83.8% vs. 43.8% P < 0.001). Sustained pain-free rate at 48 hours was 47.4% vs. 21.9% for placebo (< 0.05).

Conclusions: Pain relief comes faster and lasts longer for 7.5 mg nasal sumatriptan than 20 mg liquid nasal spray and 100 mg tablets with fewer adverse events (historical comparison). We speculate that the improved delivery achieved with the novel nasal device offers a unique combination of fast initial rate of systemic absorption and direct drug transport to the trigeminal ganglion and other CNS structures. This can explain how a small dose of sumatriptan power delivered to the side of the migraine can provide clinical outcome similar to SC with minimal systemic exposure.
PO10
Sumatriptan powder delivered by a novel nasal device provides excellent sustained pain-free plus no adverse events scores in acute migraine
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Objectives: A new composite endpoint has been developed to allow comparison of different migraine headache treatments. The endpoint combines Sustained Pain-Free (SPF) defined as freedom from pain within 2 hours, with no use of rescue medication or headache recurrence within a period of minimum 24 hours and the absence of Adverse Events (AEs) over the same period. The new composite endpoint SPF plus no AEs (SNAE) is defined by SNAE = SPF (1-AE) (Dodick 2007). The objective was to calculate the SNAE for the sumatriptan succinate powder delivered with the OptiNose nasal device and compare the results with marketed triptan formulations and new migraine therapies

Background: Delivery of 7.5 mg and 16 mg sumatriptan powder (delivered dose) using the novel OptiNose nasal device has shown excellent pain relief at 2 hours and SPF rates with a low dose of 7.5 mg sumatriptan delivered to the side of the migraine. The results compare favourably with all marketed triptan formulations. Rapid initial absorption (Tmax = 20 min) as well as possible direct nose-to-brain transport may explain the excellent clinical results despite minimal systemic exposure. The trigeminovascular system plays a key role in the pathophysiology of migraine. Compared to a conventional hand actuated spray used to deliver the marketed triptans, the novel device increases several fold the delivery to the mucosa innervated by the trigeminal nerve. This offers a potential new route for direct transport along the trigeminal nerve to the trigeminal ganglion and other brain structures involved in the pathogenesis of migraine

Methods: We used previously reported results from a single attack in-clinic three-armed placebo controlled phase II study with 7.5 mg and 15 mg sumatriptan powder in 109 migraine patients (1:1:1) delivered with the novel OptiNose nasal delivery device to calculate SNAE rates and compared them to published data.

Results: The absolute SPF rates at 48 hours were 47.4% and 48.6% and absolute AE rates were 17.9% and 23.1% for the 7.5 and 15 mg delivered doses, respectively. The most common side effect was a bitter taste accounting for the majority of AE’s (10.3%, 12.8% respectively). The SNAE rates for 7.5 mg and 15 mg OptiNose nasal sumatriptan powder were 38.9% and 37.4%, compared with a median of 13% (range 6–22%) for marketed oral triptans, 18.3% for the new sumatriptan/naproxen combination (85/500 mg) and 25.6% (Phase II) and 12.7% (Phase III) for a new oral CGRP-antagonist (300mg telcagepant).

Conclusions: Due to the high SPF rates and low AE rates for the OptiNose nasal sumatriptan powder, the SNAE becomes higher than all marketed triptan formulations, a new sumatriptan/naproxen combination and a new oral CGRP-antagonist (telcagepant). The SNAE results must be interpreted with caution, but if confirmed in future studies, the fast onset of action coupled with superior SNAE results suggest that nasal delivery of sumatriptan powder with the OptiNose device offers the attributes considered most relevant to patient satisfaction and safety.

PO11
Abstract withdrawn

PO12
Acute treatment of migraine in patients with cardiovascular disease or risk factors
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Objectives: To evaluate patterns of acute treatment of migraine among patients with concomitant cardiovascular disease (CVD) or cardiovascular (CV) risk factors.

Background: Precaution regarding cardiovascular risk associated with certain classes of acute migraine medications (e.g. triptans, NSAIDs, and ergotamine) may impact treatment decisions.

Methods: Data were generated from the General Electric (GE) Centricity research database, an electronic medical record used by over 20,000 physicians. Based on ICD-9 codes, we identified newly diagnosed migraineurs and medications prescribed for migraine within 2 days of diagnosis. We assessed the presence of diagnosed CVD, CVD risk equivalents (diabetes, cerebrovascular disease, peripheral vascular disease), and CV risk factors (advanced age, hypertension, dyslipidemia, obesity, current smoker, family history of CVD), and used relevant variables to calculate Framingham risk scores (FRS). We then evaluated the influence of CVD and CV risk factors on the likelihood of receiving a prescription medication for treatment of acute migraine.

Results: Of 74,424 newly diagnosed migraineurs, 2.8% had documented CVD, 11.9% had uncontrolled hypertension (defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 in the prior year), and an additional 8.0% had ≥ 4 CV risk factors or a CVD risk equivalent. Medications were prescribed for 46.2% of newly diagnosed migraine patients with ≤ 1 CV risk factor, 43.6% of patients with 2–3 CV risk factors (OR 0.90, 95% CI 0.87–0.93), 40.2% of those with ≥ 4 CV risk factors (OR 0.78, 95% CI 0.78–0.86), 41.7% of those with uncontrolled hypertension (OR 0.84, 95% CI 0.80–0.88), 36.0% of those with CVD risk equivalents (OR 0.66, 95% CI 0.61–0.70), and 29.4% of those with CVD (OR 0.49, 95% CI 0.44–0.53). Thus, migraine patients with CVD had approximately twice the odds of low-risk patients to go untreated; more than 7 out of 10 patients with CVD were not prescribed medication within 2 days of diagnosis compared with a little more than half of those with ≤ 1 CVD risk factor. Similar results were seen when migraineurs were stratified by FRS, and after multi-variate adjustment.

Conclusions: Migraineurs with CVD and CV risk factors are significantly less likely to be treated with prescription drugs at diagnosis than migraineurs with ≤ 1 CVD risk factor. In addition, almost half of low-risk migraine patients do not receive prescription treatment at diagnosis. Increased number of risk factors decreases the likelihood of being treated with any prescription therapy for the acute treatment of migraine.

PO13
Patterns of acute migraine medication use in individuals with cardiovascular disease or risk factors
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Objectives: To examine acute medication use patterns among migraine patients with cardiovascular disease (CVD) or cardiovascular (CV) risk factors.

Background: Medications used in the acute treatment of migraine (e.g. triptans, NSAIDs, and ergotamine) may impact treatment decisions.

Methods: Data were generated from the General Electric (GE) Centricity research database, an electronic medical record used by over 20,000 physicians. Based on ICD-9 codes, we identified newly diagnosed migraineurs and medications prescribed for migraine within 2 days of diagnosis. We assessed the presence of diagnosed CVD, CVD risk equivalents (diabetes, cerebrovascular disease, peripheral vascular disease), and CV risk factors (advanced age, hypertension, dyslipidemia, obesity, current smoker, family history of CVD), and used relevant variables to calculate Framingham risk scores (FRS). We then evaluated the influence of CVD and CV risk factors on the likelihood of receiving a prescription medication for treatment of acute migraine.

Results: Of 74,424 newly diagnosed migraineurs, 2.8% had documented CVD, 11.9% had uncontrolled hypertension (defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 in the prior year), and an additional 8.0% had ≥ 4 CV risk factors or a CVD risk equivalent. Medications were prescribed for 46.2% of newly diagnosed migraine patients with ≤ 1 CV risk factor, 43.6% of patients with 2–3 CV risk factors (OR 0.90, 95% CI 0.87–0.93), 40.2% of those with ≥ 4 CV risk factors (OR 0.78, 95% CI 0.78–0.86), 41.7% of those with uncontrolled hypertension (OR 0.84, 95% CI 0.80–0.88), 36.0% of those with CVD risk equivalents (OR 0.66, 95% CI 0.61–0.70), and 29.4% of those with CVD (OR 0.49, 95% CI 0.44–0.53). Thus, migraine patients with CVD had approximately twice the odds of low-risk patients to go untreated; more than 7 out of 10 patients with CVD were not prescribed medication within 2 days of diagnosis compared with a little more than half of those with ≤ 1 CVD risk factor. Similar results were seen when migraineurs were stratified by FRS, and after multi-variate adjustment.

Conclusions: Migraineurs with CVD and CV risk factors are significantly less likely to be treated with prescription drugs at diagnosis than migraineurs with ≤ 1 CVD risk factor. In addition, almost half of low-risk migraine patients do not receive prescription treatment at diagnosis. Increased number of risk factors decreases the likelihood of being treated with any prescription therapy for the acute treatment of migraine.
Background: Concerns about cardiovascular risk associated with certain classes of acute migraine medications (e.g. triptans, NSAIDs, and ergotamine) may impact treatment decisions.

Methods: Data were generated from the General Electric (GE) Centricity research database, an electronic medical record used by over 20,000 physicians. We identified patients newly prescribed triptans or other medications for acute treatment of migraine. We assessed the presence of diagnosed CVD, CVD risk equivalents (diabetes, cerebrovascular disease, peripheral vascular disease), and CV risk factors (advanced age, hypertension, dyslipidemia, obesity, current smoker, family history of CVD), and used relevant variables to calculate Framingham risk scores (FRS). We then evaluated the influence of CVD and CV risk factors on the likelihood of receiving certain classes of prescription medication (triptans, ergots, NSAIDs, opioids and opioid combinations, barbiturate combinations, and other) for acute treatment of migraine.

Results: Of the 52,581 patients who received ≥ 1 prescription medication for migraine during the identification period, 34,326 (65.0%) received at least one triptan and 18,255 (35%) did not. After triptans, the most commonly prescribed classes of medication were opioids (14.9%) and NSAIDs (13.0%). Among migraine patients who received prescription treatment, 14.7% had documented CVD or uncontrolled hypertension (defined as systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 in the prior year), and an additional 8.9% had ≥ 4 CV risk factors or a CV risk equivalent. Triptans were prescribed for 71.5% of migraine patients with ≤ 1 CVD risk factor, 65.9% of patients with 2–3 CVD risk factors (OR 0.77, 95% CI 0.74–0.80), 56.0% of those with ≥ 4 CVD risk factors or CVD risk equivalent (OR 0.48, 95% CI 0.45–0.51), and 53.8% of those with CVD or uncontrolled hypertension (OR 0.47, 95% CI 0.44–0.49). Thus, migraine patients with CVD or at high CV risk had less than half the odds of receiving a triptan compared to low-risk migraineurs. Conversely, whereas 11.2% of migraineurs with ≤ 1 CVD risk factor received an opioid, 31.1% of those with CVD did (OR 3.59, 95% CI 3.19–4.04). Similar results were seen when migraineurs were stratified by FRS and after multivariate adjustment.

Conclusions: A substantial proportion of patients with contraindications to triptans receive them. Nonetheless, migraine sufferers with CVD, uncontrolled hypertension, or multiple CV risk factors are less likely to receive guideline-recommended therapy.

PO14 Intractable headache response in a pediatric acute care unit
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Objectives: The objective of this study is to evaluate the efficacy of pharmacological treatments used in a pediatric inpatient acute care unit for primary intractable headache in children.

Background: Headache is the third leading cause of referral to a pediatric emergency room/emergency department. The average referral for primary headache in a tertiary pediatric emergency room is emergency room pediatric emergency room 3.2% of all visits. Evaluation, and treatment of these patients do not follow strict guidelines due to lack of appropriate double blind prospective studies. The Headache Center at a large Midwestern pediatric hospital has recently developed a Headache Acute Care Unit to more effectively respond to the intractable headache patient’s needs with a defined standardized evaluation and treatment protocol. Patients previously evaluated at the Center are managed directly in the Acute Care Unit, without the need to go through the ED.

Methods: A retrospective review of 297 patients seen in the last 18 months was evaluated. Patients with an acute headache exacerbation not responding to their recommended outpatient therapy are treated in the unit. Typical treatment is an intravenous combination therapy including prochlorperazine and ketorolac. If the patient has had side effects to prochlorperazine, it was replaced with metoclopramide. A retrospective analysis of the response and effectiveness of therapies were reviewed. Both headache freedom (primary outcome) and a 50% reduction in headache severity were analyzed. Acute headache response was also compared between different groups.

Results: 195 patients received prochlorperazine with the remainder treated with metoclopramide. Patients receiving metoclopramide were more likely to have severe headaches on admission: 7.57 ± 1.78 compared to 7.16 ± 1.91 (P = 0.03). 59% were headache free in the metoclopramide group compared to 68% in the prochlorperazine group; both groups were comparable in the total improvement of the headaches. 35% of Chronic Migraine (> 15 headache per month) became headache free, while 78% of the episodic migraine were headache free upon discharge. Patients with chronic daily continuous headache had the poorest response with only 7.4% becoming headache free compared to 52% of the chronic daily intermittent. Patients admitted for an acute exacerbation during their menstrual period had a response rate of 63% compared to 59% females without menstrual headaches with the total headache improvement significantly better in the non menstrual group.

Conclusions: A pediatric acute headache care unit offers more targeted therapies to intractable headache. Characterizations of the headache prior to admission can help predict response to acute therapy. Further studies are needed to evaluate sustained benefit from treatment 48–72 hours after discharge.

PO15 Triptan persistence among newly initiated users in a pharmacy claims database
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Objectives: To describe persistence and prescription refill patterns in migraine patients newly treated with triptans.

Background: Persistence to prescribed therapies is an integral part of migraine care. Given that migraineurs can experience infrequent or regular attacks, estimating persistent triptan use for a population of new users over time has not been well explored.

Methods: From a managed care organization pharmacy claims database in the US, we identified migraineurs receiving new triptan treatment between 2001 and 2005. New triptan users were defined as not having received a triptan prescription or a non-specific migraine medication prescription within 15 days of a migraine diagnosis in the year prior. To be included for analysis, all migraineurs were continuously enrolled for a minimum of three years and had a minimum of two years follow-up time. Prescription refill information was gathered for up to two years for each patient, and persistence was defined as sustained refills of the index triptan prescription regardless of duration between refills.

Results: Within a two-year period, 40,892 migraineurs received a new triptan prescription. The mean age for the index triptan sample was 38 years of age, 79% were female, and 55% had point-of-service insurance coverage. Most patients (n = 22,031; 53.8%) received no refill of their initial index triptan over the two-year follow up period. Of these, 25.5% (n = 5626) discontinued prescription migraine therapy, 7.4% (n = 1635) switched to a different triptan, and the majority (n = 14770; 67%) switched to a non-triptan migraine medication at the time of their second migraine prescription. The probability of remaining persistent for one or more index triptan refills was 46.2%. The
probability of remaining persistent for two or more index triptan refills decreased to 33%. By the time of the 6th refill of the index triptan, only 10% (n = 4241) of the initial sample was persistent to their index prescription. The mean time to index triptan discontinuation for this sample of newly initiated triptan users was within 463.16 days (SD = 262.82) in a two-year period.

Figure 1

Conclusions: More than 50% of migraine patients discontinued their initial triptan after only one prescription. While a small proportion of them discontinued prescription migraine therapy for the duration of the observation period, the majority switched prescriptions. Among patients who switched from the index triptan at second prescription, 90% switched to a non-triptan prescription medication for migraine.

PO16
Acute medication use patterns in episodic migraine: results of the American migraine prevalence and prevention study (AMPP)
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Objectives: To describe patterns of acute medication use for episodic migraine in the US.

Background: Evaluating patterns of acute migraine treatment in the population is an important first step towards optimizing interventions for migraine care. Although prior studies have shown that over 95% of the migraine sufferers use acute treatment, only a minority use migraine-specific agents and overall satisfaction with therapy is low. In a related abstract, we examined patterns of triptan use in the US population. Herein we present data for other classes of acute medications.

Methods: In 2005, questionnaires were mailed to 24,000 severe headache sufferers identified in a 2004 US population survey. This study includes the 11,388 respondents who met ICHD-2 criteria for migraine and had 14 or fewer headache days per month. Respondents were asked to identify all medications they currently used to treat their “most severe type of headache.” Medications were categorized into eight classes: simple analgesic over-the-counter (OTC) products (e.g., acetaminophen), combination OTCs (e.g., Excedrin®), NSAIDs (both OTC and prescription), triptans, barbiturate products, opioid products, isometheptene products (e.g., Midrin®), and ergotamines.

Results: Almost all migraine sufferers used acute treatment for their headaches (91.7%). 38.7% used monotherapy, 33.5% used treatments from two classes, and 19.5% used treatments from three or more classes. Rates of monotherapies were: simple OTC analgesics: 10.5%, combination OTCs: 7.3%, NSAIDs: 14.0%, triptans: 3.9%, barbiturates: 0.8%, opioids: 1.3%, isometheptene: 0.7%, and ergotamine: 0.1%. Opioids were used by 13.0% of the sample, but only 11.2% of them used opioids as monotherapy, and 54.0% reported using medications from two or more additional classes. Similarly, barbiturate medications were used by 6.9% of migraineurs, but only 13.5% of them used monotherapy whereas, almost half (47.6%) used medications from two or more additional classes. A similar pattern of polypharmacy was seen across all medication classes, demonstrating a high rate of unmet treatment need in acute therapies for migraine.

PO17
Oral triptans in hemiplegic, basilar and other migraine associated with neurological symptoms – long term experience
Mathew NT
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Objectives: To assess the safety, tolerability and efficacy of oral triptans in the treatment of acute attacks of migraines associated with neurological symptoms.

Background: Based on unsubstantiated assumptions that neurological symptoms of migraines such as hemiplegia are due to brain ischaemia and that triptans make ischemia worse, hemiplegic and basilar migraines are contraindications for triptan therapy, even though they were never studied in controlled trials.

Methods: Seventy-five patients with various neurological symptoms during migraine attacks (hemiplegic 34, basilar 13, prolonged visual aura 7, dysphasia 7, migranous vertigo 8, confusional and amnesic migraine 6) were allowed to treat acute episodes with aural triptans, at the onset of headache. A total of 432 episodes were treated over a period of 15 years. Patients with history or risk factors for vascular disease were excluded. Detailed diary of attack symptoms were kept for treated/untreated attacks.

Results: None of the patients reported any worsening or prolongation of their neurological symptoms, except one who reported that the aura was more prolonged than usual in one of the attacks. Headache and associated symptoms responded equally well to triptans as their attacks without neurological symptoms. Quality of life and disability significantly improved in these patients, compared to their previous medications such as opioids and butalbital combination analgesics.

Conclusions: Oral triptan therapy is safe and effective in complicated migraine.

PO18
Prophylactic agents do not influence the acute efficacy of transcranial magnetic stimulation in migraine with aura
Almaraz AC, Dilli E and Dodick DW
Neurology, Mayo Clinic Arizona, Scottsdale, AZ, USA

Objectives: To determine the effect of prophylactic medications on the efficacy of Transcranial Magnetic Stimulation (TMS) in the acute treatment of migraine with aura.

Background: Low frequency TMS has recently been shown to be effective for the acute treatment of migraine with aura. TMS may result in an action potential discharge and refractory period that disrupts cortical spreading depression (CSD). Migraine prophylactic medications may reduce the frequency of migraine attacks by elevat-
ing CSD threshold. The interaction between migraine prophylactic agents and TMS is unknown.

Methods: Subgroup analysis was performed on the study, “Transcranial Magnetic Stimulation is effective for the acute treatment of migraine with aura”. Analysis of the primary efficacy endpoint (pain-free at 2 hours - PFR) between TMS and Sham groups was performed based on non-randomized prophylactic use.

Results: One hundred sixty-four subjects eligible treated at least one migraine with aura attack with TMS (n = 82) or Sham stimulation (n = 82). Baseline pain intensity at the time of treatment for the first attack was no pain (31%), mild (40%), moderate (23%) or severe pain (6%). Prophylactic medications were used by 37% (31/82) and attack was no pain (31%), mild (40%), moderate (23%) or severe (3%) in both groups. TMS+ patients had significantly higher PFR than Sham+ patients (P = 0.002). There was no difference in PFR between TMS-treated patients on prophylactic agents (Sham+) (P = 0.0011). There was a significant difference in PFR between TMS- and Sham+ patients (P = 0.4061).

Table 1: TMS vs. Sham Pain Relief at 2 Hours based on Prophylactic Use

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pain at 2 hours</th>
<th>Sham (n = 82)</th>
<th>TMS (n = 82)</th>
<th>Absolute risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uses Prophylactic</td>
<td>Yes</td>
<td>30 (96.8%)</td>
<td>22 (64.7%)</td>
<td>32.07%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1 (3.2%)</td>
<td>12 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>Does Not Use</td>
<td>Yes</td>
<td>34 (66.7%)</td>
<td>28 (58.3%)</td>
<td>8.33%</td>
</tr>
<tr>
<td>Prophylactic</td>
<td>No</td>
<td>17 (33.3%)</td>
<td>20 (41.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Interaction of Prophylactic Use between Sham vs. TMS

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Pearson Chi Squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham+ vs. TMS+</td>
<td>0.0012</td>
</tr>
<tr>
<td>Sham- vs. TMS-</td>
<td>0.3917</td>
</tr>
<tr>
<td>Sham+ vs. Sham-</td>
<td>0.0014</td>
</tr>
<tr>
<td>TMS+ vs. TMS-</td>
<td>0.5600</td>
</tr>
</tbody>
</table>

Conclusions: Prophylactic medications do not appear to influence the treatment response to TMS. The better response in sham-treated patients not on prophylactics may indicate a more responsive or different patient phenotype than those currently using prophylactics. These findings will need to be verified in a larger patient sample randomized by presence/absence of prophylactic medications.

PO19

Elevated saliva calcitonin gene-related peptide (CGRP) levels during acute migraine predict therapeutic response to rizatriptan

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Objectives: 1) To measure calcitonin gene-related peptide (CGRP) levels in the saliva of individuals with migraine during the premonitory period, mild headache, moderate to severe headache, and post resolution phases as compared to baseline (interictal) CGRP levels. 2) To correlate response to rizatriptan administered during moderate headache with levels of CGRP levels measured in saliva.

Background: CGRP is implicated in the underlying pathophysiology of migraine. To date no study has measured changes of saliva CGRP through the clinical evolution of a migraine attack and correlated saliva CGRP levels to clinical response to therapy.

Methods: Data were summarized using tables and descriptive statistics. Statistical analysis was performed with the non-parametric Signed-rank test using Minitab15 statistical software. Results of statistical analyses were considered significant at P < 0.05. Responding subjects were defined as those who were symptom free at the time of the last collected saliva sample and did not have to rescue. Non-responding subjects were defined as those who rescued with an additional dose of rizatriptan or another medication or who were not symptom free at the end of the collection period.

Results: Statistically significant elevations of CGRP were noted in the premonitory, mild headache, and moderate to severe headache phase of the migraine compared to baseline (interictal) levels. A better therapeutic response to rizatriptan was observed in subjects with elevated saliva CGRP levels. Successful treatment with rizatriptan correlated with saliva CGRP levels returning to near baseline levels. In the rizatriptan non-responder group, no significant change in saliva CGRP levels was found at any phase of the migraine attack.

Conclusions: Elevation of saliva CGRP is predictive of responsiveness to rizatriptan. In the rizatriptan responsive population, CGRP levels are elevated beginning with the premonitory period and throughout mild and moderate/severe headache. Successful response to rizatriptan correlated with return of saliva CGRP levels to near baseline (interictal) values.

PO20

Acute migraine therapy with frovatriptan vs. sumatriptan: comparison based on sustained pain-free response with no adverse events

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Objectives: To compare frovatriptan and sumatriptan using composite outcomes of efficacy and tolerability derived from a randomized, double-blind, placebo-controlled, active-comparator trial.

Background: Triptans are recommended first-line medication for moderate to severe migraine. Satisfaction with triptan therapy depends on many factors, including speed and degree of relief, relapse, and tolerability. Measures that incorporate multiple variables give a better estimation of the medication.

Methods: Patients aged ≥18 years with a ≥1-year history of migraine (International Headache Society criteria) and 1–8 moderate or severe attacks/month (previous 2 mo) treated 1 attack with frovatriptan (2.5 mg), sumatriptan (100 mg), or placebo. Patients rated migraine severity immediately before and 2, 4, 6, 12, and 24 hours postdose; adverse events (AEs) were recorded. This post hoc analysis evaluated sustained pain-free (SPF) response (pain-free at 4 h with no rescue medication or recurrence within 24 h), SPF with no AEs (SNAE; calculated by tabulating the actual number of patients with SPF and no AEs), sustained pain response (SPR; reduction from moderate/severe to no/mild pain at 2 h and at 4 h and no rescue medication or recurrence within 24 h), and SPR with no AEs (SPR-NAE). Endpoints were analyzed using a 2-sample test for equality of proportions without continuity correction.

Results: Demographics were similar across groups; 85.6% (1032/1206) were women, 96.8% were white (1167/1206), and mean (SD) age was 40.7 (10.5) years. Efficacy was assessed using the intent-to-treat population (n = 1196). 99% per group dosed at moderate to severe headache. The proportion experiencing ≥1 AE was 36.0% for frovatriptan (171/475), 43.6% (209/479) for sumatriptan (P = 0.02 vs. frovatriptan), and 27.7% (67/242) for placebo. The SNAE rate (4–24 h) was 10.4% (49/472) for frovatriptan, 9.1% (43/474) for sumatriptan (P = 0.50 vs. frovatriptan), and 2.9% (7/241) for placebo. The SPRNAE rate (2–24 h) was 12.3% (58/472) for frovatriptan, 12.9% (61/474) for sumatriptan (P = 0.79 vs. frovatriptan), and 6.6% (16/241) for placebo. The SPRNAE rate (4–24 h) was 17.8% (84/472) for sumatriptan, 16.9% (80/474) for sumatriptan (P = 0.75 vs. frovatriptan), and 8.3% (20/241) for placebo.
Conclusions: Composite outcomes incorporating speed and degree of relief, relapse, and tolerability are most informative when choosing a triptan that will provide greatest patient satisfaction. In this head-to-head trial, SNAE and SPRNAE rates for frovatriptan and sumatriptan were equivalent. Thus, patients might benefit from a trial of frovatriptan if they have longer duration or recurrent migraine, or difficulty tolerating sumatriptan.

PO21
Migraine treatment in the emergency department – what’s really happening?

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Objectives: To provide an in-depth analysis of migraine treatment in the Emergency Department.

Background: Acute headache is a common chief complaint in the emergency department (ED), representing five million visits annually, and accounting for 3–4% of all ED visits. Up to 60% of these patients may suffer from migraine. There are many challenges to treating migraine in the ED, and migraine treatment in the ED is often suboptimal. We designed a retrospective study to determine local practice patterns in preparation for initiating an educational program and algorithm for migraine treatment in the ED. The study reviewed records and charge data for ED visits at two university-affiliated hospitals in Rochester, New York, of patients with a discharge diagnosis of migraine during the 2005 calendar year.

Methods: After a preliminary analysis to determine the reliability of diagnosis codes, charts of 156 randomly-selected, completed ED visits for migraine (ICD-9 346.X) were reviewed and the following data were abstracted: demographics, mode of transportation, history of migraine, headache characteristics, laboratory and imaging tests performed, documentation to justify obtaining imaging studies, treatment administered, patient condition at discharge, discharge instructions, medications prescribed, number of visits during the calendar year, notation of drug abuse, payer and hospital charges. Data were analyzed using SPSS for Windows.

Results: Most patients were women (81%), Caucasian (64%) or African-American (30%). 80% had a documented history of migraine and 25% arrived by ambulance. Among 156 patients with completed visits, neuroimaging studies were performed in 35 patients (22%), and only four of them had no documented justification for ordering imaging studies. Seventy-eight patients (50%) had a “last resort” when the patient’s home medication fails. However, half of the patients were not candidates for receiving migraine specific treatment. Although almost all of the neuroimaging studies were justified, radiology charges were a major contributing factor to the overall financial burden of emergency migraine care. As a retrospective study of “real world” practice, the limitations of this study include reliance on the ED providers’ diagnostic code, lack of a standardized interview to confirm ICHD-2 diagnosis, possible regional care pattern bias, and inconsistency of data recorded in the medical record.

PO22
Impact of age, gender, race, baseline pain intensity, and aura on migraine pain relief with the fixed combination of acetaminophen, aspirin, and caffeine

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Objectives: Evaluate pain relief with the fixed combination of acetaminophen 250 mg, aspirin 250 mg, and caffeine 65 mg (AAC) in 3 migraine studies relative to patients’ age, gender, race, baseline pain intensity, and presence of aura at baseline.

Background: Three identically designed, randomized, placebo (PBO)-controlled, multi-center migraine studies were conducted with AAC. (Arch Neurol 1998; 55: 210) The primary endpoints for these studies were pain intensity difference (PID) and headache responders (HR) (pain reduced to mild or none) at 2 hours after treatment.

Methods: The 3 studies enrolled moderate to severe migraine sufferers for treatment with AAC or PBO given as a single 2 tablet dose. Pain was assessed for up to 6 hours on a 4-point scale (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain). Mean change in PID (scale 0 to 3) and HR (scale 0 to 100) were evaluated for patient categories differentiated by age (< 30, 30–39, 40–49, ≥ 50 years), gender, race (white or other), baseline pain intensity (moderate or severe), and baseline aura (aura or no aura) using descriptive statistics.

Results: The combined number of patients from the 3 studies included: AAC n = 602, PBO = 618. PID range for the 4 age categories at 2 hours was: AAC (0.9–1.1), PBO=(0.3–0.6) (P < 0.001); gender male: AAC = 1.0, PBO = 0.5 (< 0.001); female: AAC = 1.0, PBO = 0.4 (< 0.001); race white: AAC = 1.0, PBO = 0.4 (P < 0.001); other: AAC = 1.0, PBO = 0.6 (P < 0.003); baseline pain intensity moderate: AAC = 0.9, PBO = 0.2 (P < 0.001); severe: AAC = 1.3, PBO = 0.8 (< 0.001); and baseline aura: AAC = 0.9, PBO = 0.4 (P < 0.002); no aura: AAC = 1.0, PBO = 0.4 (P < 0.001). Headache responders range for the 4 age categories at 2 hours was: AAC (54.8–62.9), PBO= (28.0–36.9) (P < 0.001); gender male: AAC = 62.1, PBO = 35.5 (P < 0.001); female: AAC = 58.3, PBO = 32.2 (P < 0.001); race white: AAC = 59.6, PBO = 32.3 (P < 0.001); other: AAC = 57.4, PBO = 36.8 (P < 0.012); baseline pain intensity moderate: AAC = 68.3, PBO = 38.3 (P < 0.001); severe: AAC = 41.6, PBO = 22.0 (P < 0.001); and baseline aura: AAC = 62.1, PBO = 32.9 (P < 0.001); no aura: AAC = 48.4, PBO = 32.5 (P = 0.039). Similar results were observed up to the last study time point at 6 hours.

Conclusions: Overall relief of migraine pain, as measured by PID and HR, was significantly greater with AAC than PBO regardless of age, gender, race, baseline severity (moderate or severe), or the presence or absence of aura. For age, gender, race, and presence/absence of aura, the PID scores and HR percent with AAC were similar between the subgroups in each category. For baseline pain intensity, PID scores were larger among patients with severe baseline pain intensity, while HR percentage was greater among patients with moderate baseline pain intensity.

Table 1.

<table>
<thead>
<tr>
<th>Combined Outcomes, n (%)</th>
<th>Frovatriptan (n = 472)</th>
<th>Sumatriptan (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNAE</td>
<td>49 (10.4)</td>
<td>43 (9.1)</td>
</tr>
<tr>
<td>SPRNAE, 2–24 h</td>
<td>58 (12.3)</td>
<td>61 (12.9)</td>
</tr>
<tr>
<td>SPRNAE, 4–24 h</td>
<td>84 (17.8)</td>
<td>80 (16.9)</td>
</tr>
</tbody>
</table>
PO23
Acute anti-migraine efficacy and tolerability of Zelrix™, a novel iontophoretic transdermal patch of sumatriptan
Goldstein J1, Pugach N2, Smith T3, Nett R4, Angelov AS5 and Pierce MW6
1San Francisco Clinical Research Center, San Francisco, CA, USA; 2Brighton Research Group, LLC, Virginia Beach, VA, USA; 3Mercy Health Research-Neurology Ryan Headache Center, St. Louis, MO, USA; 4Texas Headache Associates, San Antonio, TX, USA; 5Medical, NuPathe Inc., Conshohocken, PA, USA

Objectives: To evaluate the efficacy and tolerability of Zelrix™, an iontophoretic transdermal delivery of sumatriptan, for the acute treatment of migraine.

Background: Migraine, an episodic headache disorder, is associated with neurologic, gastrointestinal, and autonomic symptoms. Gastrointestinal (GI) symptoms, nausea and vomiting, are commonly associated with migraine and can range from severe to incapacitating. Triptans, the most effective and gold standard abortive treatment of migraine headache, may produce unsatisfactory results for many patients. In about 30% of patients, migraine-associated nausea and vomiting prohibit oral administration of triptans. In addition, many patients suffer gastroparesis, adversely impacting drug absorption and pharmacokinetics. This results in delayed, inconsistent, or incomplete relief. Zelrix™ is a single use, disposable transdermal patch, which delivers sumatriptan using iontophoresis. This non-invasive technology uses low-level electrical energy to facilitate transdermal drug transport. With the use of Zelrix™, the rate and amount of drug delivered is controlled electronically, thereby achieving a consistent dosage with each use.

Methods: This was a randomized, double-blind, placebo controlled, Phase III clinical trial in 530 patients treated at 37 investigative sites in the US. Patients (age 18–65 years) with IHS defined migraine headache were allocated to treat a single moderate to severe migraine attack with Zelrix™ or a placebo patch. The assessments included degree of pain freedom, relief from photophobia, phonophobia, nausea, sustained headache pain relief, and use of rescue medication. Tolerability was evaluated by adverse event reports and skin examinations at patch removal and the final study visit.

Results: Results will be available in the summer of 2009 and will be presented at The IHC meeting in September 2009.

Conclusions: Conclusions will be available in the summer of 2009 and will be presented at The IHC meeting in September 2009.

PO24
The EVA study. Interest of a visual analogue scale in managing the acute treatment of migraine attack
Lucas C1, Romatet S2, Mekies C3, Alfai B4 and Lanteri-Minet M5
1Neurology, Hôpital Roger Salengro, Lille, France; 2Neurology, Hôpital de Poissy St Germain, St Germain en Laye, France; 3Neurology, Clinique des Cèdres, Toulouse, France; 4Medical Department, Almirall SAS, Paris, France; 5Pain Department, Hôpital Pasteur, Nice, France

Objectives: The objectives of this study were to assess the reproducibility of a visual analogue scale (VAS) measuring treatment satisfaction and to assess its stability across three consecutive migraine attacks in patients not changing treatment.

Background: Guidelines for the acute treatment of migraine headaches issued by the French Health Authorities include a four-item questionnaire. Three score groups on the VAS were identified: a score of 7–10 corresponding to an adequate treatment response, a score of 0–4 corresponding to an inadequate response, and an intermediate score of 4–7 which was not predictive.

Methods: This was an open-label, prospective observational study of three groups of migraineurs treated by neurologists. Patients with a VAS score of 7–10 stayed on their current treatment, patients with a score of 0–4 were switched to almotriptan and those with a score of 4–7 could either stay on current treatment or be switched to almotriptan at the neurologist’s discretion. Patients switching to almotriptan made up the EVA ALMO group and those continuing previous treatment made up the EVA VASCO group. All patients rated treatment satisfaction four times using the VAS: (1) during the inclusion consultation, (2) at home within 24 hours of the inclusion consultation, (3) at home following three consecutive attacks and (4) during a closing consultation 24 hours later. At the closing consultation, they also answered the four-item questionnaire. Stability and reproducibility were evaluated by inter-class correlation coefficients and the paired Wilcoxon test.

Results: 368 patients were included, 182 in the EVA VASCO group and 186 in the EVA ALMO group. The VAS score was reproducible and stable in the EVA VASCO group. In the EVA-ALMO group, it was not reproducible between ratings (1) and (2), with treatment being rated as more satisfactory during the consultation than at home. The score was reproducible in the EVA ALMO Group between ratings (3) and (4). For the patients with initial VAS scores of 4–7, the scale was helpful to patients for evaluating evolution of treatment satisfaction at the closing consultation.

Conclusions: The VAS treatment satisfaction score is reproducible and stable over consecutive attacks in patients not changing treatment. This VAS may be a useful tool for managing acute headache treatment in migraineurs not entirely satisfied with treatment.

PO25
Non-inhaled administration of 100% carbon dioxide represses capsaicin mediated activation of neurons and glia in the trigeminal nucleus caudalis
Strider JW, Garrett FG and Durham PL
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Objectives: The goal of this study was to determine whether administration of 100% CO2 to the nasal mucosa inhibits activation of inflammatory nociceptive pathways in the trigeminal nucleus caudalis (TNC).

Background: Activation of trigeminal nerves is implicated in the pathology of migraine. Recent clinical evidence from multiple randomized placebo controlled trials supports the use of non-inhaled intranasal delivery of 100% CO2 for treatment of migraine. The mechanism of action is not well understood but is likely to involve repression of the stimulated release of CGRP following trigeminal nerve activation, inhibition of neuronal-glial cell signaling within the ganglion, and possibly blocking activation of second order neurons in the trigeminal nucleus caudalis. We have previously found that CO2 suppresses stimulated CGRP secretion and neuron-glia signaling in trigeminal ganglia.

Methods: Sprague Dawley rats were injected with capsaicin to induce inflammation and cause activation of the trigeminal nerve. To determine the effect of CO2 administration, animals were left untreated (control) or treated with 100% CO2 at a flow rate of 10 ml/sec for 40 sec immediately before stimulation with capsaicin, or 10 minutes after injection with capsaicin. The trigeminal nucleus caudalis was removed one hour following capsaicin injection. The level of expression of c-Fos, GFAP, and GLAST was determined by immunohistochemistry.

Results: Capsaicin was found to stimulate increased expression of c-Fos, a marker of neuronal activation, and GFAP, a marker of glial.
activation, in the trigeminal nucleus caudalis one hour post injection. Significantly, the stimulatory effect of capsaicin on TNC neurons and glial cells was greatly reduced in animals treated with CO₂ prior to capsaicin injection or post capsaicin stimulation. A somewhat surprising finding from this study was the observed increase in the expression of the glial high affinity glutamate transporter (GLAST) in response to CO₂ administration. Importantly, the upregulation of GLAST has been shown to have neuroprotective effects mediated by the internalization of excess glutamate from the extracellular space through these transporters expressed by glia and astrocytes.

Conclusions: Results from this study provide the first evidence of a unique regulatory mechanism by which CO₂ inhibits neuron and glia activation in the trigeminal nucleus caudalis in response to inflammatory stimuli. Furthermore, data from our study provide evidence that CO₂ may not only function to abort migraine attacks but may be beneficial as a migraine preventative therapy.

PO26
Dihydroergotamine and its use in migraine with posterior fossa symptoms
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Center for Headache and Pain, Cleveland Clinic, Cleveland, OH, USA

Objectives: To assess the safety and efficacy of DHE in patients with symptoms of BTM that do not meet criteria for BTM.

Background: Dihydroergotamine (DHE) has been used for decades to treat migraine, but is currently contraindicated in patients with hemiplegic migraine and basilar-type migraine (BTM). BTM has strict criteria in the International Classification of Headache Disorders-2nd edition (ICHD-II) in which there must be migraine with aura of two non-motor neurologic symptoms called posterior fossa symptoms (PFS), or symptoms arising from the brainstem. These include vertigo, dysarthria, tinnitus, hypacusia, diplopia, ataxia, decreased level of consciousness, bilateral visual field symptoms, and simultaneous bilateral paresthesias. 2 Migraine can have any of these PFS as an aura or as part of the attack and not meet criteria for BTM. Concern for infarction in BTM with use of vasoconstrictors such as DHE and triptans stems from the older theory of a vasculature etiology for migraine (vasoconstriction during aura, vasoconstriction during pain). Newer evidence suggests a neurogenic basis for migraine, and thus contraindications for vasoconstrictors may not apply in BTM.3,4

Methods: A retrospective analysis was performed on patients with migraine with a single PFS admitted to the outpatient infusion room at the Center for Headache and Pain who received intravenous DHE. Incidence and types of adverse events (AEs) as well as pain levels were reviewed and analyzed for safety and efficacy. Pain was assessed via the Visual Analog Scale (VAS). DHE side effect outcomes were expressed as the proportion of those having negative effects, and 95% confidence intervals were created around these. Change in pain measurements was evaluated by the Wilcoxon matched-pairs signed-ranks test with error (α) set to 0.05.

Results: Fifty patients were reviewed for the study, aged 19–59 years (mean 38.4 years). Sixty-two percent of patients had migraine without aura; 38% had migraine with aura (MWA). The most common PFS was vertigo, experienced by 66% of all patients. Of 19 patients with MWA, only 8 had a PFS during their aura, most commonly bilateral visual field symptoms (3/8). The mean severity of pain decreased from 6.2/10 VAS prior to DHE infusion to 3.1/10 when completed (P < 0.0001). Sixty-two percent of patients achieved complete relief (0/10 VAS) with DHE co-administered with other medications. While 9/50 (18%) experienced AEs during DHE infusion, only 3 patients stopped infusion completely during administration of DHE. The most common AE was nausea (6%). No neurologic or cardiac events occurred during administration of DHE.

Conclusions: DHE provoked no serious AEs in patients with migraine with one PFS. AEs were minimal, and DHE was effective in most of the patients. This study was retrospective by intention, because DHE is contraindicated in BTM. Because of more recent theories on the neurogenic etiology of migraine, larger, adequately powered, prospective controlled studies are indicated to assess the safety of DHE in BTM.

References:
1. Silberstein SD. Cephalalgia 2004
2. Graham JR, Wolf H. Arch Neurol Psychiatr. 1938

PO27
Frovatriptan effectiveness and tolerability in more than 10,000 patients previously using other triptans or nonsteroidal anti-inflammatory drugs
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Objectives: To compare the effectiveness and tolerability of frovatriptan vs previous therapy with other triptans or analgesics/nonsteroidal anti-inflammatory drugs (NSAIDs).

Background: Current migraine therapies include analgesics or NSAIDs for mild to moderate migraine and triptans for moderate to severe migraine or when nonspecific medications fail.

Methods: 16,737 German migraineurs prescribed frovatriptan 2.5 mg to treat 1 migraine participated in this multicenter postmarketing surveillance study in primary care. Patients recorded headache characteristics, frovatriptan dose, response time, recurrence, satisfaction, and tolerability. This subanalysis included prior users of analgesics/NSAIDs and triptans.

Results: 8353 patients previously used NSAIDs and 1848 previously used triptans. At baseline, NSAID users reported more frequent and severe headaches than previous NSAIDs users at baseline, suggesting that they were more difficult-to-treat patients. However, frovatriptan showed good effectiveness and tolerability in both NSAIDs and triptans group with the triptans group. However, both groups rated frovatriptan as better than previous therapy for effectiveness and tolerability, and 84%–94% continued using frovatriptan.

<table>
<thead>
<tr>
<th>Table 1: Frovatriptan vs. Previous Therapies</th>
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<tbody>
<tr>
<td>NSAIDs</td>
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<tr>
<td>Better headache effectiveness, n (%)*</td>
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<tr>
<td>Better tolerability, n (%)*</td>
</tr>
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</table>

Conclusions: Previous triptan users reported more frequent and severe headaches than previous NSAIDs users at baseline, suggesting that they were more difficult-to-treat patients. However, frovatriptan showed good effectiveness and tolerability in both NSAIDs and triptans users, and ≥ 84% of patients continued using frovatriptan. Frovatriptan might be a good option in migraineurs who respond poorly to another triptan or NSAIDs therapy.
PO28
A novel nasal powder device improves delivery to the nasal mucosa innervated by the trigeminal nerve. A new avenue to therapeutic success in migraine?
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Objectives: The objective was to compare the deposition patterns of a conventional spray pump with that of the novel nasal powder device used in recent Phase I & II studies.

Background: Key sites of action for triptans and CGRP-antagonists are the trigeminal ganglion and trigeminal nerve endings of cerebral vessels located inside the blood-brain-barrier (BBB). Limited BBB penetration of triptans and CGRP-antagonists may, in part, explain the high doses needed in therapy. High serum concentration of triptans and CGRP-antagonists increase the risk of adverse events and limit the therapeutic potential. Animal studies show direct preferential nose-to-brain (N2B) transport of triptans along the olfactory and trigeminal nerves. Delivery to the upper posterior regions of the nose may increase direct N2B transport and limit systemic exposure. Recent Phase I & II studies with the novel device have shown fast initial absorption similar to SC injection and faster than tablets and liquid nasal sprays and excellent clinical outcome only matched by SC, with much lower systemic exposure (historical comparison).

Methods: The bi-directional delivery device exploits the posterior connection between the nasal passages persisting when the velum automatically closes during oral exhalation. The regional deposition and clearance patterns of the device used in the Phase I & II studies were compared to a traditional hand-actuated liquid spray pump in 7 healthy subjects by gamma camera imaging after administration of either ⁹⁹ᵐTc-labeled lactose powder or liquid ⁹⁹ᵐTc-DTPA-aerosol. The gamma camera images were aligned with sagittal MRI’s to identify nasal regions. Proper correction for tissue attenuation of gamma rays was performed.

Results: Compared to a traditional spray pump the novel nasal powder device achieved a sevenfold larger initial deposition in the upper posterior third of the nose (Powder: 18.3% ± 11.5 vs. Spray: 2.4% ± 1.8; P < 0.02) and threefold deposition in the upper posterior 2/3 of the nose innervated mainly by the olfactory and trigeminal nerves (Powder: 53.5% ± 18.5 vs. Spray: 15.7% ± 13851 P < 0.02). Cumulative exposure (area under the deposition vs. time curve) for 32 minutes following delivery shows a similar pattern. The ratio for cumulative exposure in the upper posterior third is 3.7 (Powder/Spray), (P < 0.04) and 2.2 for the upper posterior 2/3rd (P < 0.04). Inter-subject reproducibility of initial and cumulative deposition was higher for the powder device.

Conclusions: Compared to a conventional spray pump, the novel breath actuated bi-directional powder device used in the Phase I & II sumatriptan studies provides significantly larger deposition in the upper posterior segments of the nasal mucosa beyond the nasal valve innervated by the olfactory and trigeminal nerves. Taken together, the fast initial absorption, fast onset of pain relief and sustained pain freedom with minimal systemic exposure achieved by sumatriptan powder, suggest that the enhanced deposition achieved with the novel device translates into true clinical advantages. The results open new therapeutic opportunities in management of pain and CNS disorders.

PO29
Transcranial magnetic stimulation for the treatment of migraine aura?
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Objectives: To study the effects of transcranial magnetic stimulation (TMS) on cortical spreading depression (CSD), the experimental correlate of aura.

Background: TMS relies on the conversion of electrical pulses to magnetic fields which generate small intracranial currents and it has been suggested as a possible therapeutic opportunity. In a recent study TMS was shown to be a potential novel treatment for migraine with aura.

Methods: Rats were anaesthetised with sodium pentobarbitone (60 mg/kg) and cannulated for measurement of blood pressure, administration of experimental drugs and anaesthesia. Three cranial burr holes were drilled and laser Doppler probes and glass micro-electrodes were used to record the blood flow and extra cellular field potential (DC shift) changes characteristic of CSD. A needle was lowered into the cortex to induce CSD and a single pulse of TMS was applied over the corresponding hemisphere. TMS was delivered using a bespoke in vivo TMS system (Neuralieve, CA) with variable mountable coils mounted on a micromanipulator.

Results: Needle prick (NP) induced characteristic changes in cerebral blood flow and DC shift, with an initial hyperaemic then oligemic response. Coil 1 (rise time 100 μs) failed to inhibit the majority of CSD’s with only 1 of 8 blocked up to a maximum of 600 V (~1.38 T). Coil 2 (rise time 170 μs) was able to inhibit 5 of 9 CSD’s when administered post NP, and only 2 of 8 when administered pre-NP, with a range of 400–600 V (~1.11–1.63 T).

Conclusions: The results demonstrate a biological rationale for the use of TMS to treat migraine aura. CSD, the animal correlate of aura was susceptible to TMS, with the wave of neuronal excitation blocked in over 50% of tests with a bespoke coil. The study further identifies that time to peak intensity of stimulation may be an important component in the response to TMS and highlights the need for further characterization to optimize treatment strategies.

PO30
Standardized study of almotriptan in the early treatment of migraine (START): an international primary care observational study
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Objectives: Evaluation of effectiveness and tolerability after early intake of almotriptan for acute migraine in primary care patients. A secondary objective was to assess the impact of increasing patient awareness of the benefits of early intake on treatment outcomes.

Background: The recent “Act when Mild” randomized, double-blind, placebo-controlled trial clearly demonstrated the clinical benefits of early intake (in the first hour while pain was still mild) with almotriptan in the treatment of acute migraine patients attending neurology clinics (Goadsby P. et al, Cephalalgia. 2008; 28(4):383–91). However, most migraineurs are treated in primary care and the START study was designed to evaluate the early intake of almotriptan in everyday practice.
Methods: This international, prospective, observational study designed to assess the effectiveness of almotriptan 12.5 mg for acute migraine headache was approved by the applicable Ethics Committees and conducted according to ICH standards. Patients previously diagnosed with migraine were assessed by their GPs at baseline and asked to record up to 3 migraine attacks in personal diaries and to return after up to 2 months. The primary endpoint was the % of patients Pain Free 2 h after initiating treatment (2hPF). Secondary endpoints included the Sustained Pain Free (SPF) rate, functional disability and tolerability. Half of each country’s centers randomly received leaflets to promote the benefits of early intake.

Results: 501 patients (77.8% female; mean age 42 years) were enrolled in 64 primary care centers; 228 in Spain, 145 in France and 128 in Italy. 434 evaluable patients entered the ITT analysis, reporting a total of 1174 migraine attacks. 11.75% of the attacks were treated with early intake. In the early intake attacks (138) the treatment results were: 65.22% 2hPF rate, 59.42% SPF rate and 51 min mean time loss. In the non-early intake attacks (1036) the treatment results were: 37.64% 2hPF rate, 32.82% SPF rate and 1 h 46 min mean time loss. The difference in the 2 h PF rates between the groups was statistically significant ($P < 0.001$), and this was also the case when only the first attack was assessed (61.90% vs. 35.37%; $P < 0.001$). The % of patients who received advice about early intake and took their medication early at least in one attack was 19.89% which was similar to the 22.66% seen in the non-informed group ($P = 0.484$). Patients who had not taken triptans and/or NSAIDs previously had a 48% 2 h PF rate, vs. 40.57% ($P = 0.296$) for those who had. The safety population included 456 patients. 61 patients (13.38%) reported 88 adverse events (AEs). Only two were considered treatment related. The majority were mild, the most common being low back pain ($n = 6$), influenza (5), pharyngitis (4) and cystitis (4). No serious AEs were reported.

Conclusions: This study confirms the good effectiveness and tolerability of almotriptan in acute migraine patients treated by GPs in everyday practice, and clearly shows the benefits of early intake.

PO31
Open label study to evaluate the early and late treatment of migraine with DHE NS (Migranal®)
Latsko M and Silberstein SD
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Objectives: To examine the use of DHE NS (Migranal®) in the early and late treatment of migraine in subjects with cutaneous allodynia.

Background: Early migraine treatment with triptans, before the onset of central sensitization, is more effective than late treatment. In contrast, pre-clinical studies and a pilot study with injectable DHE do not show a difference in treatment outcome for patients treating early or late.

Methods: Epidemic migraine subjects with a history of cutaneous allodynia were instructed to treat two qualifying migraines at home: one attack at 1 hour after the onset of throbbing pain, and one attack at 4 hours after onset of throbbing pain. Head pain, the presence of allodynia, migraine associated symptoms, and the use of rescue medication were assessed at defined time intervals from baseline through 24 hours after taking study medication.

Results: 64 subjects were screened: 39/64 (60.9%) treated two headaches and 9/64 (14.1%) treated one headache. Of subjects who treated two headaches, 22/39 treated per protocol, defined as ≤ 1.25 hr. after onset of throbbing (early) and ≥ 3.5 hr after onset of throbbing (late). Pain level in per protocol subjects prior to early treatment was mild in 3/22 (13.6%), moderate in 14/22 (63.6%) and severe in 5/22 (22.7%). Pain level prior to late treatment was mild in 2/22 (9.1%), moderate in 13/22 (59.1%), and severe in 7/22 (31.8%). Subjects who treated one early and one late headache, irrespective of compliance with time of treatment ($n = 34$), were pain free at 2 hours post study drug in 8/34 (23.5%) with early treatment and 11/34 (32.4%) late treatment (McNemar Test; Exact; $P = 0.508$). Of these subjects, those who treated 2 headaches per protocol ($n = 22$) were analyzed; 4/22 (18.2%) and 8/22 (36.4%) were pain free at 2 hours post study drug when treating early and late, respectively (McNemar Test; $P = 0.289$). Pain reduction at 2 hours post study drug administration in subjects who treated per protocol ($n = 22$) was analyzed using a 4 point pain scale. When pain reduction was defined as a 1 or more point decrease at 2 hr post study drug compared to baseline, 8/22 (36.4%) and 9/22 (40.9%) had pain reduction with early and late treatment, respectively (McNemar Test; $P = 1.000$). When pain reduction was defined as a 1 or more point decrease, 14/22 (63.6%) and 15/22 (68.2%) had pain reduction with early and late treatment, respectively (McNemar Test; $P = 1.000$). There were no significant differences between early and late treatment with study medication with respect to the outcomes of pain relief and pain reduction at the two hour assessment.

Conclusions: This pilot study suggests that DHE, unlike triptans, may be as effective with late treatment as with early treatment in subjects with allodynia. However, it is possible that this study did not demonstrate a difference because of the small number of subjects and, therefore limited power. These findings warrant larger placebo-controlled studies.

PO32
Prior acute treatment of migraine is not a predictive factor of sumatriptan/naproxen sodium (SumaRT/ Nap) response or superiority over the components
Leiner S, Richard N, McDonald S, Thompson A and Wentz A
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Objectives: To evaluate the efficacy & tolerability of sumatriptan 85 mg with RT technology and naproxen sodium 500 mg in subjects with a history of prior medication usage for the acute treatment of migraine.

Background: Pharmacotherapy that concurrently targets serotonin dysmodulation and inflammation during migraine improves outcomes over monotherapy. Two pivotal trials demonstrated that SumaRT/Nap is more effective than the components. Previous triptan or NSAID utilization for the acute treatment of migraine has been postulated as a predictor of subject response to the SumaRT/Nap combination.

Methods: Two replicate, randomized, double-blind, placebo-controlled, single attack (moderate/severe) multicenter-studies of migraineurs were conducted. Subjects were randomized to: SumaRT/Nap, sumatriptan 85 mg RT (SumaRT), naproxen sodium 500 mg (NAP), or placebo (bo). Diary data were collected through 24 h postdose. Endpoints of 2 h pain-free (PF) and 2–24 h sustained pain-free (SPF) were compared between SumaRT/Nap and other treatments for different subgroups of prior medication usage (sumatriptan, other triptans, NSAIDs; subjects were not limited to one subgroup). Adverse event profiles were evaluated.

Results: 2857 subjects (98%) enrolled had previously taken acute migraine medications, including sumatriptan (37%), other triptans (32%) and NSAIDs (39%). Subjects were demographically similar to participants in other migraine studies [Caucasian 89%; females 87%; mean age 40 years; 18 years of migraine].

Efficacy: PO32 Program Abstracts 23

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PO33
Prediction of therapeutically effective dose of COL-144 based on relationship between plasma concentrations and headache response
Liefaad L1, Drenth H-J1, Pilgrim AJ2, Dussaute B2, Rupniak N3, DiSanto AR3 and White J2
1LAP&P Consultants BV, Leiden, The Netherlands; 2CoLucid Pharmaceuticals Inc, Durham, NC, USA; 3ARD Pharmaceutical Consulting Inc, Gobles, MI, USA

Objectives: To predict an oral dose range of COL-144 that is at least as effective as sumatriptan in the acute treatment of migraine.

Background: COL-144, a Neurally Acting Anti-Migraine Agent (NAAMA), is a selective agonist at 5-HT1F receptors that, unlike triptans, is not a vasoconstrictor. In a Phase II trial with an adaptive dose allocation design, the efficacy of COL-144 given as an i.v. infusion (2.5–45 mg over 20 min) was measured. The relationship between plasma concentration and headache response was analyzed using population pharmacokinetic-pharmacodynamic (PK-PD) modeling. A subsequent Phase I trial studied the PK of an oral liquid formulation of COL-144 (25–400 mg) (see Pilgrim et al, this meeting). Using the relationship between plasma levels and headache response, together with the oral PK of COL-144, an effective oral dose range was predicted.

Method: A population PK model was developed to describe the concentration-time profile of COL-144 in plasma after oral administration. Using this PK model, combined with the concentration-effect relationship, an effective dose range for oral administration of COL-144 was predicted. Ideally, the minimal effective oral dose of COL-144 should give a faster onset of headache response and/or higher response rates than intranasal sumatriptan: Pain Relief (score 3/2 to 1/0; placebo corrected) should be at least 12% after 30 min, 34% after 60 min and 43% after 120 min. (Salonen, R. 2001;21:18–20). Data analysis was performed using NONMEM® version 6.2.

Results: The developed PK-PD model adequately described the headache scores after all doses (Figure 1). The model was used to predict the pain relief at 30 minutes after oral dosing of COL-144 (Figure 2). The uncertainty of the parameter estimates was used to indicate the uncertainty of this prediction. The target level derived from published sumatriptan data is indicated in Figure 2. The predicted oral dose range needed to reach the therapeutic target exposures determined after i.v. administration is 170 mg and above.

Conclusions: The relation between exposure and response (headache scores) was well described by the categorical population PK-PD model. By using this model a likely effective oral dose range was identified. This modelling has been used to guide dose selection for an oral dose ranging study using an oral tablet formulation.

PO34
COL-144, an orally bioavailable selective 5-HT1F receptor agonist for acute migraine therapy
Pilgrim AJ1, Dussaute B2, Rupniak NMJ1, White J1, Mazur D2 and DiSanto AR3
1CoLucid Pharmaceuticals Inc, Durham, NC, USA; 2Clinical Pharmacology, Parexel International, Berlin, Germany; 3ARD Pharmaceutical Consulting Inc, Gobles, MI, USA

Objectives: To evaluate the oral bioavailability, safety and tolerability of a solution of COL-144 and to compare this with a tablet formulation.

Background: COL-144, a Neurally Acting Anti-Migraine Agent (NAAMA), is a selective agonist at 5-HT1F receptors. Unlike triptans, COL-144 has a piperidine chemical structure, lacks activity at 5-HT1D receptors and is not a vasoconstrictor. In a previous double-blind, placebo-controlled group sequential adaptive trial, COL-144, given as an intravenous infusion, was effective in relieving migraine headache. Doses of 2.5 to 45 mg were studied and the
PO35
Evaluation of consistency of adverse events after treatment of multiple attacks with a fixed-dose single tablet of sumatriptan and naproxen sodium (SumaRT/Nap)
Lipton RB1, McDonald SA2, Richard NE2 and Derosier FJ2
1Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; 2NS MDC, GlaxoSmithKline, RTP, NC, USA

Objectives: To examine the consistency of adverse events in subjects that treated 4 of 4 attacks with SumaRT/Nap.

Background: In clinical practice, medications are used acutely to treat multiple migraine attacks by patients who choose to continue using them. Multiple attack studies provide an opportunity to assess consistency of side effects across multiple attacks. The most commonly reported side effects in the triptan class, including SumaRT/Nap, are nausea, dizziness, dry mouth, paresthesia, somnolence, and dyspepsia. The most concerning side effects are the triptan sensations which mimic cardiovascular events, i.e. neck/throat/jaw pain/tightness/pressure and chest pain/discomfort.

Methods: Two identical randomized, multi-center, double-blind, placebo-controlled, multiple-attack, early intervention, cross-over trials of adult migraineurs were conducted. Subjects were randomized to 1 of 3 treatment arms. In 4 of the arms placebo was inserted to treat exactly one attack. In the fifth arm, all 4 attacks were treated with Suma/NapRT; analysis is limited to subjects in this arm to simulate clinical practice and to avoid sequence and carry-over effects. Results from the 2 studies were pooled. Adverse events (AEs) were summarized by frequency of 1/4, 2/4, 3/4, and 4/4 and included nausea, dizziness, dry mouth, somnolence, chest pain/discomfort and neck/throat/jaw pain/tightness/pressure.

Results: A total of 223 subjects treated at least one attack and 188 (73%) treated all 4 attacks providing data on 752 migraines. At least one AE of any type occurred in 21% (40/188) of subjects and in 9.8% (74/752) of attacks. The AEs of interest (at least one) occurred in 9.6% (18/188) of subjects and in 4.1% (31/752) of attacks. The incidence and frequency of AEs are summarized in the table. In this sample, the most commonly reported AE was dry mouth (n = 6); two-thirds of subjects had dry mouth in just 1 of 4 attacks. Chest pain/discomfort (n = 3) was rare and occurred just once in one subject, 3 times in one subject, and 4/4 times by the third subject. Only one subject reported neck/throat/jaw pain/tightness/pressure in one attack. Nausea, dizziness, dry mouth, somnolence, chest pain/discomfort and neck/throat/jaw pain/tightness/pressure were rare and generally non-recurrent.

Table: Consistency of Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>4 of 4</th>
<th>3 of 4</th>
<th>2 of 4</th>
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<tbody>
<tr>
<td>Dry mouth (n = 6)</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nausea (n = 5)</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness (n = 3)</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest pain/discomfort (n = 3)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia (n = 2)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>Paresthesia (n = 2)</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Somnolence (n = 2)</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck/throat/jaw pain/tightness/pressure (n = 1)</td>
<td>1</td>
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</table>

Conclusions: Among subjects randomized to SumaRT/Nap for 4 migraine attacks, most treat all 4 attacks. In this population of consistent treaters, adverse events were uncommon on a per subject basis and rare on a treated attack basis. Adverse events on a single attack were rarely predictive of adverse events on subsequent attacks. These results are only generalizable to those who choose to treat 4 of 4 attacks.

PO36
Migraine evolution and variability: innovative correlations
Mueller L
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Objectives: The objective of the study was to examine the intra- and inter-individual variability of acute migraine evolution and correlate variables to quality of life and global satisfaction predictions.

Background: Migraine is a prevalent and disabling condition, quantifiable by various disability and quality of life (QOL) instruments. Standard therapeutic outcomes in abortive trials include pain relief and freedom at 2 and 4 hours, and recurrence rates within 24 hours after dosing. Recurrence rates beyond 24 hours are rarely captured. Few studies have explored other individual or composite variables predictive of improved QOL or treatment satisfaction.
Methods: One hundred episodic migraineurs with or without aura were enrolled from the University Headache Center to complete detailed diaries of 10 migraines each. Questionnaires included set time points of times 0, 30 mins, 1, 2, 4, 24, 48, and 72 hours in relation to first abortive dosing for pain intensity (0–3) and disability (0–4). Any changes in data between set time points, and any additional medication dosings were recorded in real time. A 24 hour QOL and 72 hour global satisfaction with treatment assessment was obtained for each headache.

Results: Preliminary results from the first 10 completers (100 migraines) are presented. Marked variability was found within and between patients for 2 and 4 hour pain freedom, 24 hour and greater than 24 hour pain recurrence, 24 hour QOL and 72 hour global satisfaction. In addition to these standard abortive outcomes, an innovative calculation of area under the curve (AUC) for pain and for disability over time is depicted. Standard measures and integrals are correlated to QOL and treatment satisfaction.

Conclusions: Preliminary results of the first 100 migraines confirm the marked variability of headache characteristics during a migraine within and between patients. Innovative methods of examining the evolution of each migraine attack, including recurrence beyond 24 hours and integrals of pain and disability, clarify the magnitude of influence on QOL and treatment satisfaction. Improved understanding of these associations may define new, clinically meaningful therapeutic outcomes.

PO37
Characteristics of pediatric patients presenting for acute intravenous treatment of refractory migraine
Vaughan PS, Kabbouche MA, Checray SK, LeCates SL, Powers SW, Hershey AD

Objectives: To describe the characteristics of children and adolescents with an intractable headache requiring acute outpatient pediatric headache treatment.

Background: Migraines affect over 10% of children and exceed 20% in adolescents. Migraine headache is often under recognized and young patients can be severely affected. Patients with migraines refractory to home acute treatment are often referred to an emergency department and is the third leading cause of referral to the CCHMC emergency room. In September of 2007, an acute outpatient headache treatment unit was established to provide rapid and effective initiation of standardized intravenous headache treatment in an outpatient setting.

Methods: Retrospective analyses of 305 patient encounters (ages 6–24) that have received acute treatment utilizing a standardized intravenous headache treatment protocol were analyzed. An extensive pre and post treatment headache questionnaire that provided information about the history of the present headache as well as information pertinent to confirm diagnosis of a migraine condition per the International Criteria for Headache Disorders, 2nd edition was completed as part of a semi-structured interview. This included associated headache symptoms and characteristics, school days missed, pre- and post-pain scores, healthy lifestyle habits, date of last menses and disability scores.

Results: The female: male was 4.45:1; the mean age of patient receiving acute treatment was 15.3 ± 2.67 years old; the mean headache duration was 12.5 ± 17.35 hours; and the mean severity was 6 ± 2.29 on a 0–10 pain scale. The patients had averaged missing 2.35 ± 5.63 school days missed prior to treatment. Episodic migraine (< 15 headaches per month) occurred in 65.5% of the patient encounters at the time of treatment. 13.1% of the patient encounters report an “always” or continuous headache. 19.5% of 118 adolescent females reported a menstrually-related migraine without aura and 10.1% reported that the headache was “maybe” related to menses.

Conclusions: Patients with intractable headaches requiring intravenous treatment are more likely to be teenage girls with a headache that has persisted for 5 days and is moderate to severe in intensity. This occurs more frequently in patients with episodic headaches. The relationship to menstrual patterns in this group needs to be further investigated. Recognition of these patterns of patients requiring this more intense level of treatment should lead to development of plans to provide earlier, more effective acute treatment to prevent further disability and transformation into chronic daily headaches.

PO38
Evaluation of the relationship body mass index (BMI) to response and tolerability after treatment with sumatriptan 85 mg formulated with RT technology/naproxen sodium 500 mg (SumaRT/Nap) for the early intervention treatment of migraine
Winner PK, Brandes JL, Thompson AH, Derosier P, Richard N and McDonald SA

Background: Migraine headache is often under recognized with SumaRT/Nap trials including TRX105850, TRX105852, TRX106571, and TRX106573. Response was defined as 2 hour pain-free or 2–24 hours sustained pain-free. Tolerability was defined as percent of subjects with at least one adverse event (AE) and percent of subjects with at least one drug-related AE. BMI was categorized as follows: underweight (UW), < 18.5; normal weight (NW), 18.5–24.9; overweight (OW), 25.0–29.9; obese (O), 30.0–34.9; morbidly obese (MO), ≥ 35.0. Statistical significance was set at P ≤ 0.05.

Results: BMI categories: 2 hour pain-free (n = 572): UW = 8 (67%), NW = 113 (47%), OW = 71 (43%), O = 36 (40%), MO = 25 (39%). There is a statistically significant association (P < 0.05) between BMI groups and 2 hour pain-free rates, with the UW and NW groups experiencing higher response rates than the OW, O, and MO groups. Sustained pain-free (n = 572): UW = 6 (50%), NW = 82 (34%), OW = 46 (28%), O = 25 (27%), MO = 19 (30%). There was not a statistically significant association (P > 0.05) between BMI groups and sustained pain-free rates. There was no association between BMI groups and incidence of AEs or drug-related AEs.

Conclusions: SumaRT/Nap was found to be efficacious and well-tolerated across all BMI groups.
PO39
Sphenopalatine ganglion (SPG) stimulation during acute migraine and cluster headaches
Ansarinia M1, Rezaei A2, Tepper SJ2,3, Mohajer P3, Steiner CP2, Stanton-Hicks M4 and Narouze S4
1Headache, Headache Specialists, Las Vegas, NV, USA; 2Neurological Restoration, Cleveland Clinic, Cleveland, OH, USA; 3Center for Headache & Pain, Cleveland Clinic, Cleveland, OH, USA; 4Pain Management, Cleveland Clinic, Cleveland, OH, USA; 5Anesthesia, Southern Nevada Pain Specialist, Las Vegas, NV, USA

Objectives: We report the results of a novel acute treatment for cluster and migraine headaches involving electrical stimulation of the sphenopalatine ganglia (SPG).

Background: The SPG is known to have autonomic connections (sympathetic, parasympathetic) and is implicated in the pathophysiology of cluster and migraine headaches. SPG blocks and lesioning have also demonstrated safety and efficacy for these conditions.

Methods: The study was IRB approved and included refractory migraine and cluster patients who underwent SPG stimulation during an acute headache. Headaches were present spontaneously or were triggered prior to stimulation. Under fluoroscopic guidance, a stimulating electrode was placed at the ipsilateral SPG. Stimulation was initiated at severe to maximal headache intensity.

Results: Cluster - Five patients underwent an initial stimulation trial and three returned for a second trial for a total of eight evaluations. Out of 19 distinct headaches of clinically maximal intensity or VAS scores of 8 and above, 11 resolved completely, 3 were partially improved (> 50% VAS reduction) and 5 had minimal to no relief. Migraine – Ten patients underwent an initial stimulation trial and one returned for a second trial of stimulation for a total of eleven evaluations. One evaluation did not result in stimulation due to technical limitations for needle placement. In the 10 stimulation evaluations, 2 patients had complete headache resolution, 2 patients had headache relief (> 50% VAS reduction) and 6 had minimal or no relief. In both patients with complete headache resolution, headaches were triggered several times during the evaluation. Headaches resolved twice in one and three times in the other patient. In both groups, associated nasal congestion and periorbital edema were improved with stimulation. Clinical outcome corresponded to the location of electrode placement anatomically and physiologically. There were no complications except for one case of transient episcleritis. Headache response occurred within 5 minutes of stimulation.

Conclusions: This study suggests a role for SPG stimulation for treating cluster and migraine headaches. Clinical outcomes were linked to accurate anatomical/physiological placement of the stimulation electrode. SPG stimulation appears to be modulating the circuitry involving cluster and migraine headaches.

PO40
Effectiveness and tolerability of frovatriptan in patients with short- vs. long-duration migraine treated in primary care
Harper S, Campbell J and Hu X
Medical Affairs, Endo Pharmaceuticals Inc., Chadds Ford, PA, USA

Objectives: To evaluate the effectiveness and tolerability of frovatriptan based on migraine duration (short: < 24 hours; long: ≥ 24 hours) vs. patient-reported baseline migraine duration.

Background: Migraineurs differ broadly in their migraine characteristics and response to therapies. With unsatisfactory response, medication switching is recommended.

Methods: 16,737 German primary-care migraineurs prescribed frovatriptan 2.5 mg treated 1 attack in this multicenter postmarketing study. Patients recorded headache characteristics, frovatriptan dose, response time, recurrence, satisfaction, and tolerability.

Results: At baseline, 55.8% (9075/16253) reported long-duration migraine and 44.2% (7178/16253) reported short-duration migraine; 79.2%–83.5% were women. At baseline, more patients with long- vs. short-duration migraine reported migraine with aura (46.8% [4199/8977] vs. 31.3% [2215/7088]; P < 0.001), frequent attacks (≥ 3/mo; 55.5% [4893/8811] vs. 30.6% [2132/6973]; P < 0.001), severe attacks (61.7% [5584/9047] vs. 33.9% [2427/7156]; P < 0.001), and previous triptan use (13.3% [1207/9075] vs. 8.1% [584/7178]; P < 0.001). Both groups administered frovatriptan 30 minutes (median) after attack onset (median of 1 tablet/attack/group). However, most patients with long-duration migraine dosed when pain was severe (58.9% [5323/9041]) and were more likely to require > 1 tablet (35.9% [3121/8705]) vs. patients with short-duration migraine (18.5% [1308/7065]; P < 0.001), most of whom dosed when pain was moderate (53.5% [3828/7156]; P < 0.001). Mean (SD) time to effect was 47.9 (32.9) and 42.0 (26.8) minutes for the long- and short-duration groups, respectively (P < 0.001).

With frovatriptan, 76.5%–96.3% in each group reported headache duration <24 hours; for the long-duration group, the rate was significantly better than the baseline duration (P < 0.001). 24-hour recurrence rate (P < 0.001) and percentage with headache duration <24 hours (P < 0.001) were significantly different between groups. Most patients in both groups rated frovatriptan more effective (87.4% [7901/9042]; 88.9% [6336/7127]) and tolerable (70.2% [6303/8982]; 72.4% [5118/7073]) vs. previous therapy. 93.1%–95.0% of patients continued frovatriptan.

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Long-duration migraine</th>
<th>Short-duration migraine</th>
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</thead>
<tbody>
<tr>
<td>No 24-h recurrence, n (%)</td>
<td>6362/8955 (71.0)</td>
<td>6223/7121 (87.4)</td>
</tr>
<tr>
<td>Duration &lt;24 h, n (%)</td>
<td>6863/8966 (76.5)</td>
<td>6782/7040 (96.3)</td>
</tr>
</tbody>
</table>

Conclusions: ≥ 77% of patients in both groups achieved a headache duration of < 24 hours after switching to frovatriptan. This is clinically important, as most patients reporting migraines lasting ≥ 24 hours at baseline had an improved response with frovatriptan. In both groups, the majority rated frovatriptan more effective and tolerable than previous therapy. In patients with poor results using other therapies, including those with long-duration migraine, a trial of frovatriptan may be beneficial.

PO41
Effectiveness and tolerability of frovatriptan in migraine patients switching from analgesics/nonsteroidal anti-inflammatory drugs, ergotamines, and other acute therapies
Harper S and Campbell J
Medical Affairs, Endo Pharmaceuticals Inc., Chadds Ford, PA, USA

Objectives: To evaluate the effectiveness and tolerability of frovatriptan vs previous migraine therapies in a primary care population of migraineurs.

Background: Many migraineurs use nonspecific medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) prior to or instead of first-line triptans for the acute treatment of migraine. Patients using analgesics/NSAIDs or ergotamines report lower levels of satisfaction than patients using triptans and might benefit from first-line triptan use.

Methods: This multicenter postmarketing surveillance study included 8134 German migraineurs prescribed frovatriptan 2.5 mg to treat a single attack. Patients recorded headache characteristics, frovatriptan dosing, time to response, recurrence, treatment satisfaction, and adverse reactions (ARs).

Results: 81.0% (6587/8134) of patients were women; mean (SD) age was 43.0 (12.1) years. 37.7% (3069/8134) and 60.5% (4924/8134) of patients using triptans and might benefit from first-line triptan use. Many migraineurs use nonspecific medications (eg, nonsteroidal anti-inflammatory drugs [NSAIDs]) prior to or instead of first-line triptans for the acute treatment of migraine. Patients using analgesics/NSAIDs or ergotamines report lower levels of satisfaction than patients using triptans and might benefit from first-line triptan use.
8134) had 3–4 attacks/mo and 50.4% (4099/8134) ≤ 2 attacks/mo. 97.5% (7928/8134) had used previous therapies (analgesics/NSAIDs: 53.4%; ergotamines: 19.8%; other: 17.9% [including triptans other than frovatriptan]). The most common reasons for switching to frovatriptan were insufficient effectiveness (65.4%) or tolerability (20.3%). Most patients dosed with frovatriptan when headaches were moderate/severe (94.2%); the mean (SD) time to dosing after attack onset was 60.7 (92.7) minutes (median, 30.0 minutes), and time to effect was 45.7 (30.5) minutes (median, 40.0 minutes). 71.6% (5822/8134) of patients treated the attack with 1 tablet (mean, 1.3 [0.5]). Attack duration was shorter with frovatriptan (< 24 hours, 83.4%) vs. previous therapy (< 24 hours, 42.2%) and most patients and physicians associated frovatriptan with better headache effectiveness and tolerability. ARs (n = 34) were infrequent (0.32% [26/8134]), and 92.2% (7502/8134) of patients would continue frovatriptan therapy.

**Table 1. Ratings of Frovatriptan vs Prior Therapies**

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 8134)</th>
<th>Physicians (n = 8134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better headache effectiveness, n (%)</td>
<td>7196 (88.5)</td>
<td>7226 (88.8)</td>
</tr>
<tr>
<td>Better tolerability, n (%)</td>
<td>5656 (69.5)</td>
<td>5968 (73.4)</td>
</tr>
</tbody>
</table>

**Conclusions:** In this primary care sample, migraineurs achieved effective and tolerable headache relief when switching to frovatriptan from analgesics/NSAIDs, ergotamines, and other medications. With frovatriptan, most patients (83.4%) reported an attack duration of < 24 hours and rapid onset of effectiveness (< 1 hour). Frovatriptan was rated more effective (89%) and tolerable (70%–73%) than previous therapies. Patients not responding to or tolerating other acute medications might benefit by switching to frovatriptan.

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**PO42**

**Self-reported survey on clinical meaningfulness of subcutaneous sumatriptan by self-injection in Japanese patients with migraine**

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**Objectives:** To assess the clinical meaningfulness of subcutaneous sumatriptan by self-injection in Japanese patients suffering from migraine.

**Background:** The use of subcutaneous sumatriptan by self-injection is considered for cases where severe attacks of migraine significantly disabled the daily and social life of the patient or cases in which frequent vomiting or other symptoms associated with migraine make regular controlling the condition with oral drug therapy alone difficult. However, the exact role that this Imigran kit would be expected to play in the management of Japanese patients with migraine has not yet been defined, and the necessity of collecting further evidence has been pointed out.

**Methods:** The study enrolled all of the 96 patients suffering from migraine (diagnosed on the basis of the ICHD-II) who visited a clinic and for whom the self-injection was prescribed prior to October 2008. In the study, a mail-based questionnaire survey was conducted. Prior to the study, written informed consent was obtained from each patient.

**Results:** 41 patients were included in the analysis. Of these 41 patients, 65.9% were female, with a mean age of 38.8 ± 11.5 years. Migraine with aura (MA) was diagnosed in 70.7% of the patients, and allodynia was diagnosed in 73.2%. The mean time to relieve a migraine attack was 65.8 ± 26.8 minutes. The attack was relieved within 60 minutes of the self-injection in 75.6% of all cases. The mean time to use the kit following occurrence of an attack was 121.7 ± 38.8 minutes. The time to relieve an attack differed significantly between the MA group (82.5 minutes) and the migraine without aura (MO) group (24.8 minutes) (P = 0.004). Severity of the disability experienced in daily life activities tended to be higher in the patients of the MA group compared to those of the migraine without aura group, although the difference was not statistically significant (P = 0.732). The Kaplan-Meier method revealed that the median time to relieve an attack differed significantly between the MA and MO (30 minutes and 15 minutes) (Long-rank test, P < 0.0184). The Cox proportional hazards model analysis suggested that the presence of aura, severity of the disability experienced in daily life activities and gender are factors possibly determining the time to relieve an attack of migraine.

**Conclusions:** On the basis of the results of this study, the following cases of patients with migraine can be inferred to required prescription for the self-injection are: (1) cases in which the attack cannot be controlled well with oral-dose medication; (2) cases in which complaints of an aura (fortification spectrum/scintillation scotoma) and/or allodynia are made, and (3) cases in which daily life activity is disabled to a considerable extent.

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**PO43**

**Examination of pharmacological therapy and migraine management in Ontario emergency departments**

Nijjar SS, Pink LR and Gordon AS

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**Objectives:** The aim of this study is to examine the diagnosis and management of migraine patients within Ontario emergency departments.

**Background:** Despite advances in treatment, patients with migraine have been underdiagnosed and undertreated specifically in emergency departments. In addition, great variability exists with respect to diagnosis, management and treatment of migraine patients in emergency departments. In particular, serotonin receptor agonists appear to be used rarely.

**Methods:** A prospective survey will be constructed inquiring as to how emergency physicians diagnose and manage patients with migraine. Questions will be focused on the use of serotonin receptor agonists, the rationale behind the use or disuse of, and acute headache protocols. The survey will also inquire into the use of ICHD-2 criteria in diagnosing migraine by emergency physicians, medication prescribed on discharge, and referrals made to outpatient specialists. These surveys will be distributed to and anonymously completed by emergency physicians in a number of departments in the province of Ontario.

**Results:** We hypothesize that serotonin receptor agonist are being underutilized in emergency departments. This may be related to inadequate diagnosing of migraine using appropriate ICH-2 criteria. Furthermore, it is anticipated that many department headache protocols do not include such treatment. It is suspected that prophylactic care and discharge management of migraine patients is suboptimal in emergency departments.

**Conclusions:** Management of migraines can be improved within emergency departments and patients can be better channeled toward appropriate outpatient care.

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**PO44**

**New therapy to prevent migraine attacks just before onset**

Teramoto J

Neurology, Teramoto Neurology Clinic, Nagoya, Aichi, Japan

**Objectives:** Migraine without aura is considered to be often accompanied with frequent tension-type headaches when attacked according to an ICHD-II comment. Muscular tenderness often appears before a migraine attack. We tried to abort the muscular symptom, consequently to stop the migraine attack.
Background: Thirty-four patients with migraine without aura accompanied with nuchal tenderness before attack. Males were 7 and females 27. The age ranged from 23 to 58, with the mean of 40.5 ± 8.7 years old. The affected period of migraine was from 5 to 44 years.

Methods: The patients were given 2 mg of trihexyphenidyl per os at the appearance of muscular tenderness in each.

Results: In eleven cases (32.4%) migraine attacks were more than 50% prevented in frequency, and in 13 cases (38.2%) less than 50% and 10 cases proved not effective or unknown.

Conclusions: We consider such muscular tenderness could not be independent but was closely connected with the migraine, and the muscular symptom might be similar to cervical dystonias except for the lack of stereotypy. Thus, we used trihexyphenidyl. We succeeded in stopping a migraine just before an attack like a “Patriot missile”. We accept that this therapy would be useful to prevent triptan overuse headache.

PO45 Botulinum neurotoxin type A for treatment of chronic migraine: PREEMPT 1 trial double-blind phase

Aurora SK1, Schim JD2, Cutrer FM3, Ward TN4, Blumenfeld A2, Lay C5, Patel S6, Lei X6 and Turkel CC6

1Swedish Neuroscience Institute, Seattle, WA, USA; 2The Neurology Center, Encinitas, CA, USA; 3Neurology, Mayo Clinic, Rochester, MN, USA; 4Neurology, Dartmouth Hitchcock Medical Center, Lebanon, NH, USA; 5Medicine, Womens College Hospital, Toronto, ON, Canada; 6Allergan, Inc., Irvine, CA, USA

Objectives: PREEMPT 1 evaluated efficacy and safety of botulinum neurotoxin type A (BoNTA; BOTOX®) as headache (HA) prophylaxis for adults with chronic migraine (CM).

Background: CM is a disabling, undertreated, complex neurologic HA disorder. Few preventive treatments have been investigated; none is specifically indicated for CM.

Methods: This phase 3, 24-week, double-blind, placebo-controlled multicenter study, followed by 32-week open-label phase, evaluated the efficacy and safety of BoNTA in CM (ICHD II migraine and ≥15 HA days/month). Subjects at 56 North American sites were screened for 4 weeks using an electronic diary. Qualified subjects were randomized (1:1) to BoNTA (155 U–195 U) or placebo (PBO) injections every 12 weeks. Study visits were every 4 weeks. The primary efficacy endpoint was a mean change from baseline for number of HA episodes at week 24. Secondary efficacy variables were mean change from baseline for the number of HA days, migraine/probable migraine (M/PM) days, M/PM episodes, and acute HA pain medication intake.

Results: Screened 1713 subjects; 679 randomized to BoNTA (n = 341) or PBO (n = 338). Most were female (85.4%), Caucasian (90.4%), with mean age of 41.7 years. At baseline there was a statistically significant imbalance in mean number of HA episodes (BoNTA 12.3 ± 13.4 vs PBO 11.8 ± 13.4, p = 0.033). For mean change in HA episodes, despite a large within-group decrease from baseline, no between-group significant difference was observed (-5.2 BoNTA-5.3 PBO, p = 0.344). The mean number of HA days at baseline were similar (20.0 BoNTA/19.8 PBO, p = 0.571). Statistically significant mean changes from baseline favoring BoNTA were seen for number of HA days (-7.8 BoNTA/-6.4 PBO, p = 0.006) and M/PM days (-7.6 BoNTA/-6.1 PBO, p = 0.002). Despite within-group decreases from baseline for M/PM episodes (-4.8 BoNTA/-4.9 PBO, p = 0.206) and acute HA pain medication intake (-10.3 BoNTA/-10.4 PBO, p = 0.795), there were no significant between-group differences. The BoNTA group had significantly less disability as measured by the Headache Impact Test (HIT-6) (-4.7 BoNTA/-2.4 PBO, p < 0.001) and significantly better quality of life (QoL) as measured by the Migraine Specific QoL questionnaire (restrictive p < 0.001; preventative P = 0.005; emotional P = 0.001). Adverse events (AEs) were 59.7% for BoNTA vs 46.7% PBO. Serious AE incidence was low (3.9%). Few subjects (4.1% BoNTA/0.9% PBO) discontinued due to AEs.

Conclusions: Despite large within-group decrease in HA episodes (the primary variable), no post-treatment between-group difference was seen. A significant baseline imbalance in HA episodes may have confounded the results. BoNTA significantly reduced some secondary endpoints, including HA days, and other endpoints, resulting in improved functioning and overall QoL. Repeat treatment with BoNTA was safe and well tolerated.

PO46 Botulinum neurotoxin type A for treatment of chronic migraine: PREEMPT 2 trial double-blind phase

Dodick DW1, Smith TR2, Becker WJ3, Gendolla A4, Relja M5, Martin V6, Reyes C7, Lei X7 and Turkel CC7

1Neurology, Mayo Clinic Arizona, Phoenix, AZ, USA; 2Ryan Headache Center, St. Louis, MO, USA; 3Clinical Neurosciences, University of Calgary, Calgary, AB, Canada; 4Kliniken Ruhrhalsinsel, Essen, Germany; 5Neurology, Medical School University of Zagreb, Croatia; 6Internal Medicine, University of Cincinnati, Cincinnati, OH, USA; 7Allergan, Inc., Irvine, CA, USA

Objectives: To evaluate botulinum neurotoxin type A (BoNTA; BOTOX®) efficacy and safety as headache prophylaxis in adults with chronic migraine (CM).

Background: CM is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated for CM, and none is currently approved for use.

Methods: This phase 3, 24-week, double-blind, parallel-group, placebo-controlled multicenter study, followed by a 32-week open-label phase, evaluated the efficacy and safety of BoNTA in CM (ICHD II migraine and ≥15 headache days/month). Subjects at 66 sites (50 North American; 16 European) were screened for 4 weeks using an electronic diary. Those qualified were randomized (1:1) to BoNTA (155 U-195U) or placebo injections every 12 weeks. Study visits occurred every 4 weeks. The primary efficacy endpoint was a mean change from baseline for the number of headache days at week 24. Secondary efficacy variables were mean change from baseline for number of headache episodes, migraine/probable migraine (M/PM) days, cumulative hours of headache on headache days, moderate/severe headache days, and proportion with severe HIT-6 impact category score.

Results: 1621 subjects were screened; 705 were randomized to BoNTA (n = 347) or placebo (n = 358). Most were female (85.4%), Caucasian (89.8%), with a mean age of 41 years. BoNTA was significantly favored over placebo for the primary endpoint, frequency of headache days (-9.0 BoNTA/-6.7 placebo, P < 0.001) and all 5 secondary endpoints. For frequency of headache episodes, there was a decrease from baseline with a statistically significant between-group difference favoring BoNTA (-5.3 BoNTA/-4.6 placebo, P = 0.003). The BoNTA group also experienced significantly fewer M/PM days (-8.7 BoNTA/-6.3 placebo, P = 0.001), cumulative hours of headache on headache days (-132.4 BoNTA/-90.0 placebo, P < 0.001), and moderate/severe headache days (-8.3 BoNTA/-5.8 placebo, P = 0.001). Significantly fewer BoNTA subjects remained categorized as severely affected (HIT6) at week 24 (P = 0.003) compared to placebo. Adverse events (AEs) were reported for 65.1% of BoNTA and 56.4% of placebo subjects. Few subjects (3.5% BoNTA and 1.4% placebo) discontinued due to AEs.

Conclusions: In PREEMPT 2, BoNTA was effective as prophylaxis of headache in adults with CM. BoNTA treatment resulted in statistically and clinically meaningful improvements for all efficacy parameters evaluated, including primary endpoint (headache days). BoNTA significantly reduced headache-related disability and improved functioning and overall quality of life. Repeat BoNTA treatment was safe and well tolerated.
PO47
PRISM study: occipital nerve stimulation for treatment-refractory migraine
Lipton RB1, Goadsby PJ2, Cady RK3, Aurora SK4, Grosberg BM1, Freitag FG5, Silberstein SD6, White DM1 and Jaax KN7
1Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; 2UCSF Headache Center, University of California, San Francisco, San Francisco, CA, USA;3Headache Care Center, Clinvest, Springfield, MO, USA; 4Pain and Headache Center, Swedish Medical Center, Seattle, WA, USA; 5Outpatient Service, Diamond Headache Clinic, Chicago, IL, USA; 6Department of Neurology, Thomas Jefferson University, Philadelphia, PA, USA; 7Neuromodulation, Boston Scientific, Valencia, CA, USA

Objectives: To investigate the safety and efficacy of occipital nerve stimulation (ONS) for the preventive treatment of refractory migraine.

Background: ONS may offer a safe and effective alternative to the currently limited therapeutic options available to migraine sufferers that fail pharmacological management.

Methods: This multi-center, double-blind, randomized controlled trial enrolled participants who (1) met the 2004 International Classification of Headache Disorders (ICHD-2) diagnostic criteria for migraine with aura, migraine without aura, and/or chronic migraine; (2) presented as drug-refractory (failed therapy with at least two acute and two preventive medications); and (3) had ≥6 days per month of long-duration (>4 hours) migraine with moderate/severe pain (migraine day). Those overusing acute medications at baseline, per ICHD-2 criteria, were included as a pre-specified analysis subgroup. Prior to implantation, both arms received 5–10 days of percutaneous trial stimulation, using their randomized settings, to evaluate the response to a trial of percutaneous treatment. At 12 weeks, sham subjects were converted to active settings. Diary follow-up continued for 52 weeks.

Results: Of 179 patients screened for enrollment, 140 eligible subjects were randomized, 132 were implanted and 125 completed 12-week follow-up. For the primary endpoint, reduction in migraine days/month evaluated 12 weeks after implantation. At 12 weeks, sham subjects were converted to active settings. Diary follow-up continued for 52 weeks.

Conclusions: Active ONS did not produce statistically significant benefits in relation to sham stimulation on the primary endpoint. Heterogeneity in treatment response suggests that there may be a treatment responsive subgroup. Future studies should endeavor to identify and randomize patients likely to respond to stimulation, based in part on the absence of medication overuse and a favorable response to a trial of percutaneous treatment.

Table 1.

<table>
<thead>
<tr>
<th>Status at most recent FU group by years of FU</th>
<th>LFX score (see Text)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥4</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Total</td>
<td>≥4</td>
</tr>
</tbody>
</table>

Objectives: Evaluate the effectiveness of long term use of methadone (MTD) in treatment of MOH due to short acting narcotics.

Background: Treatment of MOH requires removal of the agent that has been overused and produced the MOH. When the MOH producing agent (MOHA) is a narcotic, this may be particularly difficult as some patients have great difficulty discontinuing narcotics. This report deals with use of MTD, a long acting, non-euphoriant opiate, in management of these subjects.

Methods: Methadone has been employed in the OUMC Headache Clinic since 1999 to treat patients with refractory, narcotic-induced MOH. Before MTD is prescribed, subjects must have: 1. clear evidence that the narcotic is the MOHA and 2. failed at least 6 preventative antimigraine (PAM) agents. Patients may then be offered MTD following education about risks and benefits and agreeing not to obtain opiates elsewhere. Treatment was determined on an individual basis including dose of MTD and use of any other medications. Outcome was evaluated by grading headache-related limitation of level of function (LFX) at job or home as follows: 0 - fully functional; 1-miss work < 3 days/mo., no decrease in LFX; 2-miss work 3-6 days/mo., LFX <50%; 3-miss work > 6 days/mo., LFX <50% 10-15 days/mo.; 4 - cannot work, inactive due to headache >50% of time. Patients were seen in follow-up (FU) at least every 6 months. The study was approved by the Human subjects Board of University of Oklahoma.

Results: Thirty subjects who met criteria above were identified of which 23 had been treated for ≥4 years. Table 1 provides the LFX scores by group and subgroup at initiation of MTD, and at the most recent evaluation. For the LFX score, 17% improved 3 levels, 33% improved 2 levels, 33% improved 1 level while 17% were unchanged or worse (Table 2). MTD dose at most recent visit was ≤20 mg in 4 subjects, 21-100 mg in 16, 101-200 mg in 4, 201-300 mg in 2 and >300 mg in 4. Concomitant PAM was employed in most patients. Anxiolytics, primarily clonazepam, were used in 40%. There were 4 treatment failures who discontinued MTD. One other subject successfully discontinued MTD after returning to intermittent headache.

Conclusions: In a selected population of 30 subjects with highly refractory MOH due to narcotics, MTD therapy resulted in significant improvement in functional status in 60% and modest improvement in another 27%. MTD can significantly improve function in intractable MOH due to narcotics.

Table 1. LFX scores at onset of MTD therapy and most recent follow-up

<table>
<thead>
<tr>
<th>LFX score (see Text)</th>
<th>Status at initiation Group by years of FU</th>
<th>Status at most recent FU group by years of FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>≥4</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>Baseline days/month</td>
<td>≥4</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td>Total</td>
<td>Total</td>
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<tr>
<td>Change at 12-weeks</td>
<td>≥4</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td>Total</td>
<td>Total</td>
</tr>
<tr>
<td>P-value</td>
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Table 1.
**PO49**  
**Botulinum neurotoxin type A for treatment of chronic migraine: analysis of the PREEMPT chronic migraine subgroup with baseline acute headache medication overuse**  
Silberstein SD1, Blumenfeld AM2, Cady Rk3, Turner IM4, Sirimanne M6, DeGryse RE6 and Turkel CC6  
1Neurology, Thomas Jefferson University, Philadelphia, PA, USA; 2The Neurology Center, Encinitas, CA, USA; 3Headache Care Center, Springfield, MO, USA; 4Island Neurological Associates, PC, Plainview, NY, USA; 5Allergan, Inc., Irvine, CA, USA  

**Objectives:** Evaluate the efficacy and safety of botulinum neurotoxin type A (BoNTA; BOTOX®) as headache (HA) prophylaxis for the PREEMPT chronic migraine (CM) subgroup who were overusing acute HA medications at baseline.  

**Background:** CM is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated for CM, and currently, none is specifically indicated. Up to 73% of CM patients overuse acute medications.  

**Methods:** Two phase 3, double-blind, parallel-group, placebo-controlled, multicenter studies (PREEMPT 1 & 2) evaluated the efficacy and safety of BoNTA in adult CM. Patients were screened for 4 weeks using an electronic diary and randomized (1:1) to BoNTA (155 U–195 U) or placebo (PBO) per baseline acute medication overuse strata (MedO yes/MedO no). Participants in the MedO yes subgroup had taken acute HA medications ≥2/week with intake ≥15 days for simple analgesics and/or intake ≥10 days for other medications during the 4-week baseline period. Study injections were given every 4–12 weeks for other medications during the 4-week baseline period. Study injections were given every 4 weeks up to 100 mg/day. They were evaluated at baseline and to the fourth month of treatment.  

**Results:** 1384 adults were randomized to BoNTA (n = 688) or PBO (n = 696). Most patients met criteria for baseline MedO (65.5%, [906/1384]). Pooled PREEMPT analyses of this subgroup (BoNTA n = 446/PBO n = 460) demonstrated a statistically significant decrease favoring BoNTA treatment for both key endpoints; mean change from baseline in HA days (BoNTA-8.2/PBO-6.2; P = 0.001) and HA episodes (BoNTA-5.4/PBO-5.1; P = 0.028) at week 24. BoNTA also significantly reduced moderate/severe HA days (BoNTA-7.7/PBO-5.7; P < 0.001), migraine/probable migraine days (BoNTA-8.1/PBO-6.0; P < 0.001), cumulative HA hours on HA days (BoNTA-114.46/PBO-70.8; P < 0.001), and the proportion of individuals categorized as “severe” on the Headache Impact Test (HIT-6) (BoNTA 71.0%/PBO 81.9%; P < 0.001). No between group differences were seen for acute medication intake, which suggests that the clinical improvements were due to BoNTA and not to reduced acute medication use. Most patients in this subgroup had adverse events (AEs) (62.2% BoNTA/50.2% PBO). Few patients discontinued due to AEs.  

**Conclusions:** PREEMPT subpopulation analyses demonstrated that BoNTA is an effective and safe prophylactic treatment for CM patients with baseline MedO. BoNTA resulted in highly significant improvements compared to placebo for multiple HA symptom measures. BoNTA significantly reduced HA-related disability and improved functioning and overall quality of life for this difficult-to-treat subgroup of patients. Repeat treatment with BoNTA was safe and well tolerated.

**PO50**  
**Effectiveness of topiramate treatment in patients with medication overuse headache: a case-series study**  
Neurology, Hospital Universitario Miguel Servet, Zaragoza, Spain; Internal Medicine, Hospital Royo Villanova, Zaragoza, Spain; Internal Medicine, Hospital San Jorge, Huesca, Spain; Internal Medicine, Hospital C: Barbastro, Barbastro, Huesca, Spain; Neurology, Hospital Clínico Universitario, Zaragoza, Spain; Neurology, Hospital Clínico Universitario, Zaragoza, Spain; Internal Medicine, Hospital C: Calatayud, Calatayud, Zaragoza, Spain  

**Objectives:** We report our experience of topiramate in patients with MOH and CM not previously treated with a prophylactic agent.  

**Background:** Medication overuse headache (MOH) is a secondary headache (appendix of ICHD-2) and chronic migraine CM is the most common subtypes of MOH in specialty care. Topiramate is a drug of first choice for the prophylaxis of CM.  

**Methods:** Of a database of 700 outpatients with migraine we selected those with MOH. They had several moderate-severe migraine attacks per month and frequent headache (≥15 days per month) and overused medication. They had never received prophylactic treatment. From the first day all the patients received the same plan of treatment: suppression of the medication of abuse and establishment of the preventive treatment. Topiramate was started in 4 weeks up to 100 mg/day. They were evaluated at baseline and to the fourth month of treatment. Effectiveness was assessed by: - Change in mean number of days with headache and severe migraine attacks in the previous month and at the fourth month of treatment with topiramate. - Responder rate (≥50% reduction in mean of days with headaches and severe migraine attacks) at the fourth month of treatment. - Reversion from MOC to non-MOC. - Reversion from CM to non-CM.  

**Results:** Of 106 ITT outpatients with migraine we selected those with MOH. They had several moderate-severe migraine attacks per month and frequent headache (≥15 days per month) and overused medication. They had never received prophylactic treatment. From the first day all the patients received the same plan of treatment: suppression of the medication of abuse and establishment of the preventive treatment. Topiramate was started in 4 weeks up to 100 mg/day. They were evaluated at baseline and to the fourth month of treatment. Effectiveness was assessed by: - Change in mean number of days with headache and severe migraine attacks in the previous month and at the fourth month of treatment with topiramate. - Responder rate (≥50% reduction in mean of days with headaches and severe migraine attacks) at the fourth month of treatment. - Reversion from MOC to non-MOC. - Reversion from CM to non-CM.  

**Results:** Of 28 patients (26.4%) who suspended the treatment with topiramate 75% continued with MOH. The relative risk (RR) of continued MOC was greater in the group that suspended the topiramate than the group that continued with treatment (RR = 5.5, 95%IC = 2.3 to 11.9, P<0.001). Fifty-nine (62.1%) of 95 patients stopped fulfilling criteria of CM. In the group that responded there was significant decrease (P = 0.0001) in mean number of days with headaches in the fourth month: 17.9 to 4.8 days and in mean number of severe attacks at the fourth month: 7.0 to 1.7 (P = 0.0001). The mean percentual reduction in number of days with headaches and severe migraines at the fourth month was: 68.5% and 71.2% respectively.  

**Side effects:** 66.6% patients, none of them was serious.  

**Conclusions:** Topiramate showed to be effective when it was in use from the beginning together with the suppression of the medication of abuse in the treatment of the MOC. The patients who suspended topiramate had a major relative risk of continuing with MOC.
PO51
Reduction of medication-overuse headaches (CTTH, CM, NDPH) after simple advice. the akershus study on chronic headache
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1Head and Neck Research Group, Research Centre, Akershus University Hospital, Lorenskog, Norway; 2Faculty Division, Ullevaal University Hospital, University of Oslo, Oslo, Norway; 3Faculty Division, Akershus University Hospital, University of Oslo, Lorenskog, Norway; 4Helse Ost Health Services Research Centre, Reasearch Centre, Akershus University Hospital, Lorenskog, Norway; 5Department of Neurology, Ullevaal University Hospital, Oslo, Norway

Objectives: We investigated the course of medication-overuse headache in the general population a short medical advice.

Background: There is need for more research on cost-effective management of medication-overuse headache.

Methods: Our cross-sectional epidemiological survey included an age and gender stratified sample of 30,000 persons aged 30–44 years from the general Norwegian population. Persons with chronic headache (≥15 days per month on average for at least 3 months or ≥180 days per year) and medication-overuse, received short information about medication-overuse and possible interaction with the headache in a clinical setting. They were followed-up 1½-years later. The diagnostic criteria of the International Classification of Headache Disorders were applied. Data splitting methodology was used in the analysis.

Results: The participation rate was 85%. 109 persons were followed-up. 92% had chronic tension-type headache (CTTH), while co-occurrence of CTTH and migraine was found in 53% of these. 6% had chronic migraine (CM) and 3% had new daily persistent headache (NDPH). The mean duration of CTTH, co-occurrence of CTTH and migraine, CM and NDPH were 13, 18, 18 and 8 years, respectively, while the mean duration of medication overuse was 8, 10, 6 and 5 years, respectively. The mean medication days were significantly reduced from 22 days to 6 days per month, and 76% were no longer medication overusers 42% did no longer have chronic headache and the headache index (frequency × intensity × duration) was significantly reduced by 36%.

Conclusions: Advice improves primary chronic headaches with medication overuse in the general population.

PO52
Inpatient vs. day hospital withdrawal treatment for chronic migraine with medication overuse
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Objectives: Purpose of this study was to determine 1) the clinical course of 2 samples of chronic migraine patients with medication overuse 24 months following two different treatment interventions (in-patient or day-hospital withdrawal); 2) whether functional impairment, assessed by the MIDAS questionnaire, improved upon treatment.

Background: Patients with chronic migraine (CM) and medication overuse are particularly difficult to treat, with no one approach being universally accepted. The abrupt withdrawal is considered the first step for helping these patients to stop medication overuse. Different strategies have been discussed, and it has emerged that the day-hospital setting can be effective to perform withdrawal in these patients.

Methods: Two groups of sufferers from CM and medication overuse were enrolled: for group A, 146 patients, an in-patient withdrawal was performed, for Group B, 173 patients, a withdrawal in a day hospital schedule. 78 patients of group A were seen for the last follow-up, 24 months after withdrawal and 51 patients of group B. Three measures were used to assess outcome: 1) number of headache days/month; 2) number of analgesic pills consumed/month; 3) Total Score from the Migraine Disability assessment Questionnaire (MIDAS). All patients were provided a semi-standardized in-patient or day-hospital withdrawal treatment. After 6 days, patients started prophylaxis for migraine according to their general characteristics.

Results: Patients of both groups improved significantly at 24 months follow up: days of headache per month (group A: 25.9 vs. 11.2; group B: 23.6 vs. 9.9), medications/month (group A: 48.7 vs. 12.6; group B: 31 vs. 9.6), and the measure of functional impact from the MIDAS questionnaire improved (MIDAS total score: group A: 78.5 vs. 29.1; group B: 69.8 vs. 16.5).

Conclusions: These findings confirm previous results in patients followed with long follow-up after in-patient withdrawal; also after day-hospital withdrawal the improvement is maintained until 2 years post treatment. The day-hospital modality, not so expensive respect to a regular hospitalization, is effective when the patients are followed and instructed carefully about the treatment and the use of the pharmacological compounds. The confidence and the compliance, although we did not measure any of these variables, were relevant: patients came every morning to the clinic, where they were carefully managed and reinforced by daily explanations about the expectancies from the therapy. Although our results are encouraging, with a homogeneous group of patients and pretty long-term follow up, they cannot be definitive. The major limitation is the absence of a control comparison condition. We felt it was important, as first step, to test this new option of withdrawal, for finding alternative approaches a part from the well-known in-patient withdrawal. On the basis of these significant findings, we believe it may prove fruitful to compare different treatment approaches for this particular category of patients in order to find more effective methods for the patients and money-saving procedures at the same time.

PO53
Botulinum neurotoxin type A treatment improves health-related quality of life and reduces the impact of chronic migraine: results from the double-blind phase of the PREEMPT clinical program
Lipton RB1, Varon S2, Grosberg B3, McAllister PJ4, Freitag F5, DeGryse RE2 and Turkel CC2
1Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; 2Allergan, Inc., Irvine, CA, USA; 3Neurology, Montefiore Headache Center, Bronx, NY, USA; 4Associated Neurologists of Southern Connecticut, Fairfield, CT, USA; 5Diamond Headache Clinic, Chicago, IL, USA

Objectives: To determine the impact of botulinum neurotoxin type A (BoNTA; BOTOX®) on health-related quality of life (HRQoL) in adults with chronic migraine.

Background: Chronic migraine (CM) is a disabling condition associated with low HRQoL, diminished workplace productivity, and high healthcare resource utilization.

Methods: During the 24 week double-blind, placebo-controlled period of 2 phase 3 studies, 1384 adults with CM were randomized to BoNTA (n = 688) or placebo (n = 696) injections at baseline and at week 12. The Headache Impact TestTM (HIT-6), a 6-question survey used to measure the impact of headaches on patients’ lives, was obtained at baseline and every 4 weeks. HIT-6 scores range from 36 to 78 with higher scores reflecting greater adverse impact. The Migraine Specific Quality of Life Questionnaire v.2.1 (MSQ) captures information about the long-term adverse impact of migraine on HRQoL in 3 domains: Role Restrictive (RR), Role Preventative (RP), and Emotional Functioning (EF). MSQ scores range from 0 (low function) to 100 (high function). The MSQ was obtained at baseline and every 12 weeks. For change scores computed relative to
baseline, a positive value reflects improvement in HRQoL. Pooled PREEMPT 1 & 2 data from the 24 week double-blind phase are presented.

Results: Baseline mean total HIT-6 scores were comparable in the treatment groups (65.5 BoNTA [SD = 4.05], 65.4 placebo [SD = 4.32], P = 0.638). A statistically significant between-group difference favoring BoNTA over placebo was observed for change in HIT-6 score from baseline at week 24 (-4.8 BoNTA [SD = 7.04], -2.4 placebo [SD = 6.09], P < 0.001) and at all other time points during the double-blind phase. Baseline mean MSQ scores for all 3 domains were comparable between the 2 treatment groups (P = 0.974, P = 0.825, and P = 0.806). Statistically significant between-group differences were found for all 3 domains of the MSQ assessed at week 12 and at week 24.

Conclusions: Treatment of CM with BoNTA is associated with less adverse headache impact, and improved HRQoL. The magnitude of the improvement in HRQoL is highly statistically significant and reflects clinically meaningful improvements in functioning and vitality, and a decrease in psychological distress, associated with treatment with BoNTA compared with placebo.

Table 1. MSQ Mean change (Δ) from baseline scores

<table>
<thead>
<tr>
<th>Domain</th>
<th>BoNTA Mean ± SD</th>
<th>Placebo Mean ± SD</th>
<th>P-value</th>
<th>Δ Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive</td>
<td>38.5 ± 16.2</td>
<td>38.7 ± 16.1</td>
<td>0.974</td>
<td>16.2 ± 9.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Preventative</td>
<td>56.1 ± 13.0</td>
<td>56.1 ± 13.0</td>
<td>0.825</td>
<td>13.0 ± 8.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional</td>
<td>42.1 ± 18.3</td>
<td>42.4 ± 18.3</td>
<td>0.806</td>
<td>17.9 ± 9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>All 3</td>
<td>13.0 ± 8.0</td>
<td>18.3 ± 11.0</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Δ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Role</td>
<td></td>
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<tr>
<td>All 3</td>
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<td>18.3 ± 11.0</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Δ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td></td>
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</tr>
</tbody>
</table>

PO54

Migraine prevalence in patients aged up to 50 with acute cerebrovascular insult (CVI) treated in St. Sava Hospital during 2008

Milošević Kovacevčić NJ1 and Nikolić VM2

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Objectives: The objective of this study was to determine percentage incidence of migraine in patients with acute CVI compared to the population of patients with acute CVI without pre-morbid migraine, all of whom were aged up to 50 and 50 and were treated in St. Sava Hospital during the year 2008. Migraine prevalence up to the above said age is the largest in extent, whereas the incidence of other cerebrovascular disease risk factors is the smallest. This is why other factors minimally affected the result set forth as the objective of this study.

Background: It is well known that patients with complicated migraine or migraine with aura may suffer migraine infarction with small incidence that fail to rise above 1% of all brain strokes. Vast majority of patients with acute cerebrovascular disease in the whole territory of Belgrade are treated In St. Sava Hospital. Given the incidence of migraine in general population, the goal in this study was to determine migraine prevalence in patients aged up to 50 with acute CVI, as well as to prove migraine infarction within this population.

Methods: Statistical processing of the data obtained from the computerized database of St. Sava Hospital was applied.

Results: In the period from 1 January 2008 to 31 December 2008, 6476 patients with cerebrovascular disease were admitted in St. Sava Hospital. Ischemic insult occurred in 4610 of these patients, out of whom 752 patients were aged up to 50 and 50. 405 of them were male and 347 were female patients.

Hetero-anamnestic and auto-anamnestic data revealed that, within this age group of patients, 30 male patients and 45 female patients used to have migraine headaches. Out of these 75 patients, 3 patients suffered from migraine with aura (2 of them were female and 1 was male), while another woman aged 38 suffered from migraine with aura and had neurologic deficit in terms of hemiparesis on the right within the aura. The neurologic deficit was retained even after the migraine attack. Neuro-imaging methods confirmed the left temporal-parietal position of an ischemic lesion. This case represents the only confirmed instance of migraine infarction.

Conclusions: This study showed that migraine prevalence in patients with acute CVI is not larger than migraine prevalence in general population. In addition, a single instance of migraine infarction was confirmed in a female patient in her 30s who suffered from migraine with aura.

PO55

Short-term effectiveness of simple advice as withdrawal strategy in simple and complicated medication overdose headache

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Objectives: The aim of this study was to to compare the effectiveness of intensive advice to withdraw the overused medication as withdrawal strategy in patients with simple and complicated MOH having migraine as primary headache.

Background: The effectiveness, in complicated MOH, of doctor’s advice alone (i.e., without adjunctive pharmacotherapy) has not yet been established.

Methods: One hundred consecutive patients (82 females, mean age 39 ± 12 years) fulfilling the appendix ICHD-II criteria, for MOH participated in the study. Exclusion criteria were co-existent severe medical or psychiatric illnesses, treatment with migraine prophylactic drugs within the past three months and overdose of opioids, and barbiturates containing agents. MOH was defined as complicated in patients satisfying at least one of these criteria: a) a current diagnosis or history of co-existent, significant and complicating medical illnesses b) a current diagnosis of mood disorder, anxiety disorder, eating disorder or substance addiction disorder, c) relapse after previous detoxification treatment, d) psycho-social and environmental problems. Withdrawal therapy was considered successful if, after 2 months, the patient had had reverted to an intake of NSAIDs lower than 15 days/ month or to an intake of other symptomatic medication lower than 10 days/month.

Results: Fifty-one patients had simple MOH and 49 patients had complicated MOH. Eleven patients dropped out from the study (simple MOH 5.6%, complicated MOH 16.3%, P > 0.05). By considering all the patients enrolled in the study we have been able to detect 79% of the patients, 92.1% of patients with simple MOH and 65.3% of patients with complicated MOH (P < 0.01).

Conclusions: Simple advice is a highly effective in simple MOH and effective in the majority of complicated MOH patients, and should be regarded as the first step in a step-care approach to managing MOH.

PO56

Medication and metabolic syndrome in chronic migraine

Anjum MW, Marmura MJ and Young WB

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Objectives: To explore the relationship between metabolic syndrome and migraine.

To determine the effect of preventive medications on Body Mass Index (BMI) and screen patients for metabolic syndrome.
Background: Metabolic Syndrome is a combination of risk factors which are related to atherosclerotic cardiovascular disease. Recent studies suggest metabolic syndrome is more common in patients with migraine and that obesity is a risk factor for chronic migraine. Many medications that treat headache can cause changes in weight and body mass index (BMI). Studies also indicate medication overuse can alter endocrine function and perpetuate chronic migraine. This indicates acute and preventative medications may affect the risk of metabolic syndrome in patients with migraine.

Methods: We recruited patients with chronic migraine or with history of chronic migraine who were prescribed topiramate, nortriptyline, duloxetine, venlafaxine or any combination of these drugs for headache prevention. Patients were recruited from our practice. We excluded patients taking other anti-epileptics, other antidepressants, daily neuroleptics or beta blockers. We determined demographic information, acute and preventative medications, acute medication usage and frequency by questionnaire and chart review. We determined weight and blood pressure and measured C-reactive protein, fasting lipids and glucose. We calculated BMI from the time before beginning the current medication regimen.

Results: We interviewed 38 patients with chronic migraine and received lab results from 22 patients, 6 (27%) men and 17 (73%) women. Age range for all patients was 17–59 (mean age 40.5). Of these patients, 9 (41%) had significant decrease in BMI on a stable medication regimen and 4 (18%) significant increase. Women over 50 were significantly more likely to experience significant weight loss (5 of 6) than the remainder of patients. *P* = 0.498. Three (14%) patients had metabolic syndrome. Four (18%) patients met criteria for acute medication overuse, one of which met criteria for metabolic syndrome. Dyslipidemias (low HDL and hypertriglyceridemia) were the most common risk factors.

Conclusions: In clinical practice, chronic migraine patients on preventative medications may experience significant weight changes as measured by BMI. The study confirms this but suggests that many patients experience weight loss rather than weight gain. Women over 50 with chronic migraine lost weight more often. A minority of patients in this study met criteria for metabolic syndrome. It is unclear to what extent chronic and acute medications affect this risk, particularly with respect to dyslipidemias and weight.

Table 1. Changes in BMI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Number of Patients (n = 22)</th>
<th>Average BMI (prior to regimen)</th>
<th>Average BMI (current regimen)</th>
<th>BMI change gain of &gt;0.5</th>
<th>BMI change loss of &gt;0.5</th>
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</thead>
<tbody>
<tr>
<td>Topiramate only</td>
<td>10</td>
<td>25.9</td>
<td>25.6</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Nortriptyline only</td>
<td>4</td>
<td>25.4</td>
<td>24.9</td>
<td>0</td>
<td>1</td>
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<tr>
<td>Duloxetine only</td>
<td>2</td>
<td>30.4</td>
<td>30.4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Venlafaxine only</td>
<td>2</td>
<td>22.4</td>
<td>22.1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Topiramate + Venlafaxine</td>
<td>4</td>
<td>23</td>
<td>22.4</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. Risk Factors in Metabolic Syndrome

<table>
<thead>
<tr>
<th>Condition</th>
<th># patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension or on medication</td>
<td>2</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30)</td>
<td>3</td>
</tr>
<tr>
<td>Elevated fasting glucose or diabetes</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>7</td>
</tr>
<tr>
<td>Low HDL</td>
<td>4</td>
</tr>
<tr>
<td>Acute medication overuse</td>
<td>5</td>
</tr>
</tbody>
</table>

PO57 Botulinum neurotoxin type A for treatment of chronic migraine: the double-blind phase of the PREEMPT clinical program

Dodick DW1, Aurora SK2, Turkel CC3, DeGryse RE3, Silberstein SD4, Lipton RB5, Diener H-C6 and Brin MF3,7
1Neurology, Mayo Clinic Arizona, Phoenix, AZ, USA; 2Swedish Neuroscience Institute, Seattle, WA, USA; 3Allergan Inc, Irvine, CA, USA; 4Neurology, Thomas Jefferson University, Philadelphia, PA, USA; 5Neurology, Albert Einstein College of Medicine, Bronx, NY, USA; 6Neurology, University of Essen, Essen, Germany; 7Neurology, University of California, Irvine, Irvine, CA, USA

Objectives: PREEMPT (Phase III REsearch Evaluating Migraine Prophyaxis Therapy with Botulinum Toxin Type A) was designed to confirm the efficacy and safety of botulinum neurotoxin type A (BoNTA; BOTOX®) as headache (HA) prophylaxis in adults with chronic migraine (CM).

Background: CM is a prevalent, disabling, and undertreated neurologic disorder. Few preventive treatments have been investigated; none is specifically indicated for CM.

Methods: Two phase 3, 24-week double-blind, parallel-group, placebo-controlled multicenter studies (PREEMPT 1 & 2), followed by a 32-week open-label phase, evaluated the efficacy and safety of BoNTA in CM (ICHD II migraine and ≥ 15 HA days/month). Eligible patients were screened for 4 weeks using an electronic diary. Qualified subjects were randomized (1:1) to BoNTA (B) (155 U–195 U) or placebo (P) injections every 12 weeks for 2 cycles. Study visits occurred every 4 weeks. Key endpoints were change from 28-day baseline compared to the 28 days ending at week 24 for frequency of HA days (primary PREEMPT 2; secondary PREEMPT 1) and HA episodes (primary PREEMPT 1; secondary PREEMPT 2). Since PREEMPT 1 & 2 had different primary endpoints, pooling was judged as acceptable to generate a complete summary of the clinical program. Results of the pooled analysis are presented here; the results of PREEMPT 1 & 2 are presented in separate abstracts.

Results: A total of 1384 adults were randomized to B (n = 688) or P (n = 696). Although results for HA days showed significant benefit of B over P in both PREEMPT 1 & 2, results for HA episodes were statistically significant only in PREEMPT 2. Pooled analyses demonstrated a large mean decrease from baseline in frequency of HA days with statistically significant between-group differences favoring B over P at week 24 (-8.4 B, -6.6 P; *P* < 0.001) and all other time points. The mean change from baseline for the frequency of HA episodes was also significantly different favoring B at all time points, including week 24 (-5.2 B, -4.9 P; *P* = 0.009). At all time points for 5 of the 6 remaining efficacy variables, there was a significant difference favoring B. Adverse events (AEs) occurred in 62.4% B, 51.7% P. However, most patients reported AEs that were mild to moderate in severity and few discontinuations (2.8% B, 0.7% P) resulted from AEs.

Conclusions: PREEMPT confirms that BoNTA is an effective prophylactic treatment for CM. BoNTA resulted in highly significant improvements compared with placebo for multiple HA symptom measures, including frequency of HA days and HA episodes. BoNTA treatment also significantly reduced HA-related disability and improved functioning, vitality, psychological distress, and overall quality of life. Repeat treatment with BoNTA was safe and well tolerated.
PO58  
Safety and tolerability of the MAO inhibitor isocarboxazid (Marplan) in the prophylactic treatment of migraine  
Harris HW  
Clinical and Medical Affairs, Validus Pharmaceuticals, Parsippany, NJ, USA  

Objectives: The purpose of this open-label pilot study was to evaluate the safety and tolerability of the MAO inhibitor isocarboxazid (Marplan) in the prophylactic treatment of migraine.

Background: Drugs currently used for prophylaxis include tricyclic antidepressants and selective serotonin reuptake inhibitors. We undertook the present study to evaluate the potential utility of the MAO inhibitor isocarboxazid (Marplan) for prophylactic treatment of migraine.

Methods: Male and female subjects 18–60 years of age were recruited. For inclusion, a subject must have had a diagnosis of migraine headache according to the International Headache Society criteria. The subject must have had approximately 3–12 migraine headaches per month for the 3 months prior to entering the screening period. Major exclusion criteria included a history of cluster headache, migraine with prolonged aura, and atypical forms of migraine. Isocarboxazid (Marplan) treatment was initiated at a dose of 20 mg per day and gradually increased as tolerated to a maximum dose of 60 mg per day. Concomitant use of triptans, NSAIDs, antidepressants and other commonly used anti-migraine agents was prohibited. The Headache Assessment Scale and other assessments were recorded at Baseline, and Weeks 1, 4, 8, 12, 16, and 20. Primary safety and efficacy analyses were based on the intention-to-treat population. Safety data included laboratory data, adverse events, vital signs, and ECGs. The primary efficacy measure was within-subject change from baseline in migraine frequency.

Results: Fourteen subjects had at least one post-baseline assessment, and seven subjects completed the full 20 weeks of treatment. The tolerability of isocarboxazid (Marplan) in this study was similar to that reported in depression trials. Insomnia, irritability, and sexual dysfunction were the most common adverse events reported. Five subjects (31%) withdrew due to adverse events. The mean dose for completers at the end of the study was 20 mg per day and gradually increased as tolerated to a maximum dose of 60 mg per day. Concomitant use of triptans, NSAIDs, antidepressants and other commonly used anti-migraine agents was prohibited. The Headache Assessment Scale and other assessments were recorded at Baseline, and Weeks 1, 4, 8, 12, 16, and 20. Primary safety and efficacy analyses were based on the intention-to-treat population. Safety data included laboratory data, adverse events, vital signs, and ECGs. The primary efficacy measure was within-subject change from baseline in migraine frequency.

Conclusions: The present study reports robust efficacy in a small open-label trial of isocarboxazid (Marplan) in the prophylactic treatment of migraine. This mechanistically novel and intriguing approach to migraine prophylaxis warrants further investigation.
PO60
Migraine prevention with low doses of propranolol and amitriptyline: correlation with nitric oxide production
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Objectives: To access clinical efficacy of propranolol versus amitriptyline for the prophylactic treatment of migraine, correlating with the measures of plasma NO.

Background: Migraine treatment is currently focused on pain relief and on long-term reduction in frequency, severity, and duration of the attacks. In addition, nitric oxide (NO) plays a key role in the pathogenesis of migraine. In this respect, migraineurs have an increased sensitivity to the exogenous NO donor glyceryl trinitrate (GTN) when compared with non-migraineurs.

Methods: Women migraineurs (n = 162) were recruited. All patients had completed a headache diary during a four-week run-in period. Blood samples were collected during the headache-free period and a further sample during the first four hours of the attack before starting any prophylactic treatment and at the end of each month, throughout three months of prophylactic treatment. First group, migraineurs used propranolol: 25 patients (60 mg/day); 29 (80 mg/day) and 25 (120 mg/day). Second group used amitriptyline: 28 patients (12.5 mg/day); 28 (25 mg/day) and 27 (50 mg/day). The primary endpoint was the number of patients with a reduction of at least 50% (responders) in the mean number of days of headache (NDH) and headache severity index (HSI) when the baseline period was compared with each treatment period. The second efficacy parameter was the evaluation of decrease in plasma nitrate (or NO production). Statistical comparisons for migraine parameters between baseline (month 0) and month three were performed with Kruskal-Wallis analysis and chi-square test to compare headache relief according to the schema of prophylactic treatment. Differences in NO concentrations (mean ± SEM) were estimated using Anova and Dunnett’s post test. In all tests P < 0.05 was considered statistically significant.

Results: 78 out of 240 (32.5%) patients did not complete the study. The main reasons for discontinuation were adverse events (22.5%), lost to follow-up (9.5%), withdrawal of consent (0.8%), and uncooperative (1.2%). A significant reduction in HSI and NDH parameters was observed at one month (P < 0.001) with amitriptyline users (12.5, 25, or 50 mg/day) and with propranolol users (60, 80, or 120 mg/day), from the second month of treatment (P < 0.001). Considering the > 50% reduction in NDH after the 12-week maintenance phase, no differences were observed between any of the treatments used or the respective doses. The nitrate plasma levels during the headache-free period had a significant decreased after the treatment with: propranolol, 60 mg/day (20.3 ± 1.0 μM), 80 mg/day (22.3 ± 1.2 μM) and 120 mg/day (21.5 ± 1.5 μM); amitriptyline, 12.5 mg/day (22.3 ± 1.2 μM), 25 mg/day (23 ± 1.3 μM) and 50 mg/day (21.3 ± 1 μM).

Conclusions: The use of low doses of propranolol and amitriptyline as preventive treatment for migraine are efficacious, have a high tolerability and protective effect in perivascular neurogenic inflammation by the decrease of NO levels.

PO61
The study for effects of topiramate on pediatric migraineurs who especially have the symptom of aura
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Objectives: To study therapeutic effects of topiramate on pediatric migraine, especially accompanying with aura.

Background: The fact that the effect of topiramate on pediatric migraineur was better in the patients of classical migraine, that is to say, aura-accompanied migraine than migraine without aura has been experienced.

Methods: We reviewed the medical records of 27 patients who were diagnosed as migraine and treated with topiramate for more than one month and compared the group of migraine with aura with group of migraine without aura. We defined that complete cure is the state of symptom free for over two months after topiramate medication for at least one month.

Results: Of the 27 patients, 11 had migraine with aura, 16 were migraine without aura. Of the 16 patients who had migraine without aura, 3 were completely cured and 8 were incompletely cured - decreased over 75% in frequency of headache attack, and 5 were not cured. Of another 11 patients who had migraine with aura, 9 were completely cured, and 2 improved more than 75% in frequency of headache attack (P = 0.01).

Conclusions: Topiramate was effective in migraine headache, especially distinctly effective in patients of migraine with aura.

PO62
Chronic daily headache and medication overuse headache: Japanese case series in the headache clinic of Tottori University Hospital
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Objectives: To survey chronic daily headaches (CDH) and medication overuse headache (MOH) in Japanese headache sufferers.

Background: CDH and MOH are often refractory. Little is known in Japanese cases.

Methods: We reviewed all out-patients of the headache clinic of Tottori university hospital from January 2006 to March 2009, retrospectively.

Results: We identified 680 headache sufferers and 192 CDH cases (28.2%, > 4 hours/day, > 15 days/mo and > 3mo). According to ICHD-II and the revision/appendix criteria, 80 cases were MOH (75 migraine and 5 tension type), 24 were chronic migraine (CM), 67 were chronic tension-type headache (CTTH), eight were new daily persistent headache (NDPH), two were hemicrania continua (HC) and the remaining eleven were diagnosed as other types/subtypes. Mean age of MOH patients was 44.9 years old (± 15.6 [SD], range 14–80, M:F = 11:69). Mean duration of daily headache at the first visit was 5.7 years (± 6.4, 3 mo. – 30 years). Seventy-six patients overused analgesics/NSAIDs and nine overused triptans (five overused both). Twelve cases were carried out only diagnosis. We followed up 68 cases out of 80 MOH patients. Mean observation periods were 18.6 mo (2 -165 mo). At the 2 mo after the diagnosis, 48 patients discontinued the overused medication successfully and 20 used the medications more than 10 days. Fifty five patients improved their headache (< 15 days/mo.), and 13 did not improve. At the 6 month after diagnosis, we followed 41 cases. Twenty six subjects were in good condition, eight patients got the recurrence of MOH, and eight did not improve. At the one year after the diagnosis (32 cases), 16 were good, and 10 got the recurrence. Prophylactic medications were prescribed to 63 subjects as followings; lomerizine 40
PO63
Migraine patient with synesthesia: a small amount of prophylactic medicine was effective
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Objectives: We experienced a patient with migraine with aura, who has synesthesia. By treating this patient, we found the sensitivity to sounds, and she said she had difficulty to understand sentences. So, the purpose of the study is to analyze the sensitivity to several kinds of prophylactic medicine in the patient with synesthesia.

Background: Synesthesia is famous for colored letters and colored sounds, but the real condition is not scientifically clarified yet.

Methods: We found a patient with migraine with aura, who has synesthesia. She is 26 years old, and she noticed that she has synesthesia for more than ten years. She noticed she saw every letter of alphabet and Japanese character and every number in a specific color. She also saw specific color when she listens to drills. During scintillating scotoma, she saw special color changes in the visual field. Sumatriptan 50 mg was effective for headache attack in the patient. Since frequency of headache attack was 5–10/month, we treat the patient with two kinds of prophylactic medicine.

Results: Since frequency of headache attack was 5–10/month, we treat the patient with lomerizine hydrochloride, a calcium channel blocker which is effective to prevent migraine. Although we gave usual dose of lomerizine hydrochloride 10 mg/day for the first week, she became depressed and synesthesia was disappeared in few days. She could not see “colored letters” and could not feel “colored sounds”, and she said she had difficulty to understand sentences. So, we decreased the dose of lomerizine hydrochloride to 1/5 of usual dose. This small amount of lomerizine hydrochloride was effective to prevent migraine, but in a month she became headache free and synesthesia was disappeared again. To prevent migraine attack we used propranolol hydrochloride as a second choice. As she was very sensitive to lomerizine hydrochloride, we used small amount of propranolol hydrochloride 2 mg/day. This small amount of propranolol hydrochloride was also effective to prevent migraine, but she became slightly depressed and “colored letters” became weak color. Finally propranolol hydrochloride 1.5 mg/day was effective in this patient.

Conclusions: Since propranolol hydrochloride suppress the spreading depression in the cortex, we would like to suggest the cortex of person with synesthesia is very sensitive to propranolol hydrochloride and calcium channel blocker. Although we experienced only one migraine patient with synesthesia, this case suggests the relationship between spreading depression and synesthesia.
agreement over a prolonged period of time, and pizotifen is a drug with potent 5-HT2 receptor blocking activity that doesn’t cause chemistry dependence. Pizotifen is the most widely used 5-HT2 receptor antagonist in migraine prophylaxis, because of its superior efficacy compared with cyproheptadine, and incidence and severity adverse effects with pizotifen is lower compared with methysergide. Actions mediated by 5-HT2 receptors which could be relevance to migraine comprise cranial vasconstriction, increased cranial capillary permeability and platelet aggregation, and some central nervous system effects and neuroendocrine functions. However, pizotifen has a slightly better safety profile and poor unavailable in US.

**Methods:** 27 women with more than 15 migraine attacks/month received pizotifen 0.5 mg/day for 3 months. Another group, 35 women with over 15 migraine attacks/month received amitriptyline 12.5 mg/day. All patients completed a daily headache diary over a 30-day baseline period during a 90-day treatment period. The primary endpoint was a reduction in migraine frequency during the last 30 days of the trial compared to the baseline period. In medical research, the placebo effect is an important methodological tool. Although medical ethics committees are becoming increasingly resistant to the use of placebo in migraine trials, placebo nevertheless remains the pivotal comparator in trials of migraine medications.

**Results:** The number of days with headache significantly decreased during the last 30-day treatment period compared to the baseline phase during the 90-day treatment period with pizotifen 0.5mg/day (25.3 ± 1.2 vs. 8.6 ± 2.1, P < 0.01) and amitriptyline (22.2 ± 2 vs. 3 ± 1, P < 0.001) (ANOVA). The adverse events were tolerable in both groups during all treatment; increase of weight was observed in patients that used pizotifen (30%, n = 8) and to amitriptyline group (15%, n = 5).

**Conclusions:** These data suggest that, in the dosage used, pizotifen is at least as effective as amitriptyline and both drugs in low doses minimize the adverse events that promote lost in follow-up. Pizotifen may be considered effective for migraine prevention in adults, such as anti migraine agents of first line.

**PO66**

**From NMDA theory of chronic migraine to polyamines dietary implementation – preliminary data**

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**Objectives:** A) To evidence the role of NMDA antagonists on hyperalgesia and allodynia, B) To attempt to modulate NMDA-mediated sensitization via endogenously produced substances. That ought to result in relieving chronic migraine and in reducing hyperalgesia and allodynia.

**Background:** Since 1994 we proposed NMDA pathways modulation by using NMDA antagonist with the aim of dechononicization of chronic migraine with abuse.

**Methods:** A) Ketamine and dextromethorphan, specific reversible antagonists at NMDA receptor sites, can decrease vascular hyperalgesia and allodynia. Briefly, vascular/visceral hyperalgesia was evaluated during a non-invasive sharp stretching of the vein wall. Pain is directly proportional to migraine severity. Allodynia, estimated by using Von Frey hairs, has the same pattern of evolution of vascular hyperalgesia. Ketamine (100 mcg/Kg/os) and dextromethorphan (2 mg/Kg/os) decreased hyperalgesia and allodynia (P > 0.0001 versus baseline, VAS 0–10) and versus ascorbic acid (7 mg/Kg/os). Patients (n = 210, 159 female; mean age 35.3 ± 4.1 SD) were divided in 3 matched groups randomly receiving ketamine, dextromethorphan or ascorbic acid. Thirty minutes after administration, patients were tested by operators not informed of the given treatment. B) We attempt to modulate functioning of NMDA receptors by acting on polyamines as spermine, spermidine, putrescine that are in the intestinal lumen come from dietary intake. Mentioned polyamines are interconvertible after they taken into cells in backward conversion. The substances act via negative modulation of NMDA receptors. Putrescine derives from ornithine (7 mg/Kg/os/day) and SAMe (6.5 mg/Kg/os/day); pyridoxine (6.5 mg/Kg/os/day) is needed for decarboxylation, catalytic for polyamines. Compounds were given in a group of chronic migraine (15 attacks/month or over) suffers (n = 1951), 1050 females, age range 38–45 years). The therapeutic programme was compared to the assumption of ascorbic acid (7 mg/Kg/os/day) (n = 1538), 978 females, age range 37–45 years). Chronic migraine sufferers randomly received therapy programme by a physician not aware of the background of the two protocols. A 30-days treatment period followed a 2 weeks run-in during which only acute anti migraine drugs were allowed: sumatriptan (100 mg) or indomethacin (100 mg), at most 10 tablets.

**Results:** In 641 patients (378 females, mean age 33.4 ± 3.7 SD) receiving precursors of polyamines there was a decrease of hyperalgesia and allodynia (P < 0.1). Amelioration of chronic migraine versus pre-diet values started at day 7–10. First decrease of pain severity (VAS 0–10) was P < 0.01 at day 9. At day 30 there was a decrease of monthly number of attacks (P > 0.001) paralleled by a decrease of acute anti-migraine treatments (baseline mean 27.4 ± 3.5 SD vs. 7.5 ± 2.1 SD; P > 0.0001), vital parameters and routine examinations indicate no abnormality at day 15 and 30. No effect on migraine course, on hyperalgesia and allodynia was ever observed in ascorbic acid group.

**Conclusions:** Results suggest the possibility to negatively modulate NMDA pathways by using polyamines: A way which is accepted by a growing number of subjects desiring a physiologic-like therapies.

**PO67**

**Anticephalgic photoprotective premедакated mask: a report of a successful study of a treatment for migraine and/or tension headaches**

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**Objectives:** This study was performed to determine the efficacy of an anticephalgic photoprotective mask in conjunction with a topical medication containing bromyina and rhus toxicodendron in the treatment of migraine and/or tension headache.

**Background:** Many clinicians are seeking headache treatment modalities with improved safety profiles. A premедакated mask would serve not only as a delivery system for benign topical medication, but simultaneously provide photorelief and exert external pressure which may alleviate vascular headaches by collapsing painfully distended extracranial arteries and reducing peripheral sensitization.

**Methods:** Thirty-three patients were given masks and tubes of topical medication containing the bromyina and rhus toxicodendron. They were instructed to apply the medication to their frontalis and/or temporalis regions in the event they should suffer a headache and apply a photoprotective mask. Furthermore, they were instructed to take their usual oral or parenteral medications if required for the relief of the headache. They subsequently filled out forms rating the degree of relief which they attributed to the topical medication and the mask using a 0–10 scale. At the interview following the completion of their participation in the study, the patients were also simply asked if this form of treatment helped or not.

**Results:** Thirty out of 33 patients stated the medication and the mask were effective over and above the normal degree of relief they were receiving from their oral and/or parenteral medications. This study demonstrated a significant efficacy rate (91%) in the treatment of migraine and/or tension headache with the anticephalgic mask in conjunction with a topical cream containing bromyina and rhus toxicodendron.

**Conclusions:** This study demonstrated a significant efficacy rate in the treatment of migraine and/or tension headache with the anticephalgic mask in conjunction with a topical cream containing bromyina and rhus toxicodendron.
PO68
Nocebo is the enemy, not placebo. A meta-analysis for the nocebo effect in headaches
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Objectives: To explore the prevalence and significance of nocebo effect in clinical trials for primary headache disorders.

Background: The nocebo phenomenon is the antipode of placebo and includes several nonspecific side effects that cannot be direct related to the specific pharmacological action of a pharmaceutical treatment. It is also include expected side effects that are basically mediated by the patients’ fear that the drug most likely will harm instead of help them. In clinical practice often migraineurs fail to tolerate a long sequence of medical treatments rising doubts for the origin of the experienced side effects.

Methods: We performed a PubMed systemic review of all post millennium published randomized and placebo controlled studies for migraine (M), tension-type headache (TTH) and cluster headache (CH) treatment (acute and prophylactic). The prevalence of nocebo was estimated as the ratio of patients treated with placebo and reported at least one side effect vs. all placebo treated patients. The significance of nocebo was estimated as the ratio of patients treated with placebo and discontinued the treatment because of intolerance vs. all placebo treated patients.

Results: In symptomatic treatment for M the prevalence and significance was estimated as 19.1% ($\pm$ 0.01 95% CI) and 0.31% ($\pm$ 0.0015 95% CI), respectively, whereas in preventive medical treatments was 20.5% ($\pm$ 0.01 95% CI) and 4.6% ($\pm$ 0.01 95% CI). In trials for prevention of TTH the nocebo prevalence and significance were 28.4% ($\pm$ 6.66 CI) and 4.23% ($\pm$ 2.5 CI). In symptomatic treatment of CH the prevalence of nocebo was 17.14% ($\pm$ 7.73). Not enough good data to calculate nocebo effect was available for TTH acute treatment and CH prevention.

Conclusions: Nocebo is very prevalent in trials for primary headaches, in the preventive treatments in particular. These findings are noteworthy for clinical practice where the phenomenon may be larger since patients with medical hesitations avoid participating in clinical trials. Thus, nocebo behavior may be considered as a significant cause for treatment failure.

PO69
From nocebo effect to the hypothesis of nocebo comparison and psychometric tests as entry criteria in headache trials
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Objectives: To establish nocebo effect in different groups of patients versus general unselected population. To evidence possible placebo and nocebo related neuroimaging changes. To evidence possible role of mood regulation of both placebo and nocebo effects: their relevance in trials.

Background: Placebo is a phenomenon largely studied. Nocicebo effect indicates the worsening of pain after treatment.

Methods: A) The experience was carried out on: A) severe migraine sufferers (7–10 attacks/month) exempt from any other pathology and from any mood-behaviour disturbance (DMS IV, MPI, Wang, Zung test) $n = 171$ (98 females, mean age 32.3 ± 4.2 SD), B) subjects suffering from depression $n = 101$ (67 females, mean age 33.9 ± 3.9 SD) evaluated according DMS IV and above test C) healthy controls ($n = 89$, 46 females, mean age 32.1 ± 4.1 SD) selected on the basis of routine examines and headache exemption. Thus, no psychometric evaluation was ever performed, here. The 3 groups were matched for age, sex, cultural-social level. A total of 361 subjects were subdivided into two conditions aimed to study the modulation of visceral and somatic painful stimuli. Following a 3 days wash-out period, we measured visceral pain threshold, by using a non-invasive stretching of vein walls and somatic pain threshold, by using a pressure algometer. Each subject underwent 3 sessions: placebo or nocebo randomly administered following a prior experience. Each one of the sessions was followed by a 1 hour interval period to avoid temporal summation. We used green or red coloured instruments in agreement to verbal suggestion: no pain, high pain, respectively. Prior experience consisted in stimuli given with blue coloured instrument to the participants included in group A, B and C. ANOVA was used to compare nocebo red-associated and placebo green-associated responses. B) fMRI, PET, TCI 64 channels were used in a subgroup of group C ($n = 78$, 45 females; mean age 33.2 ± 3.4 SD) during both nocebo and placebo testing. Statistic Analysis: F-test Bonferroni for multiple comparison and Students’ t test were used.

Results: No relevance of the prior experience, no difference between placebo-green associated and nocebo-red associated response in migraine, difference was evident (Bonferroni $P > 0.01$) in controls and in depression (Bonferroni $P > 0.01$). The result open discussion on placebo and nocebo in severe migraine with no psychometric sign of mood disturbance. Neuroimaging indicates activation of medial pain system (affective-cognitive pain pathway). Placebo effect was related to the activation of nucleus accumbens, playing a role in depression and in compulsive disorders, and basal ganglia, associated to depressive disorders.

Conclusions: So, it may be inferred that placebo and nocebo effectiveness may relate to the psychological set-up of some subjects. Thus, it seems correct to introduce a control versus nocebo in headache trials since it may predict the lack of effectiveness being a direct index of variables playing against active compounds. Entry criteria including psychometric testing may also be correct.

PO70
Could saccadometry be beneficial in the diagnosis and understanding of migraine?
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Objectives: We used a novel oculometric methodology as a quantitative and clinically applicable method to study reaction-time distributions in migraineurs to aid diagnosis and understanding of the pathophysiology of migraine.

Background: Migraine is the commonest neurological disorder, yet diagnosis and classification are difficult and unreliable, with the underlying mechanisms poorly understood. Research has been limited by insufficient data as well as a paucity of objective and quantitative methods for measuring higher neurological function. A recent review of neurophysiological investigations for headache disorders concluded that the best test currently available (analysis of Visually Evoked Potentials) is subjective as well as clinically impractical, and often lacks sufficiently reliable sensitivity and specificity data. Other techniques, such as QEEG and TMS, have also produced inconsistent results, whilst functional neuroimaging is restricted by cost and practicality. Over the last decade there has been increasing interest in the study of reaction times, in particular for saccades (saccadometry), which reflect high-level, essentially cortical, mechanisms of decision. Saccadometry has proved clinically helpful in objective analysis of other neurological conditions such as Parkinson’s and Huntington’s Disease, we explored whether it might be useful in investigating migraine.

Methods: We performed a cross-sectional study using a simple visual step-task. Using a non-invasive, miniaturised, portable saccadometer, we obtained reaction-time distributions for 32 migraineurs and compared them with age- and sex-matched controls. Previous studies have typically reported only mean or median reaction times, but
we obtained further distributional parameters that have been useful in other neurological conditions: standard deviation, and the incidence of early saccades forming a sub-population of very fast responses.

**Results:** We found that the reaction-time distributions of migraineurs were significantly different from those of non-migraineurs ($P < 0.001$). In part this was due to significantly less variability (1.01 vs. 1.13; $P < 0.05$); in addition, fewer migraineurs (31%) showed early saccades, compared with non-migraineurs (56%; $P < 0.05$). A likelihood ratio analysis gave a sensitivity and specificity of 72% and 44% respectively.

**Conclusions:** Our study presents a novel method for assessing high-level neurological function in migraineurs, which is more clinically applicable, objective, quantitative and rapid than current methods. The potential uses of this technique are threefold. Firstly, the quantitative differences demonstrated here could further understanding of migraine pathophysiology. Related to this, the consistency of saccadic reaction-time distributions within individuals provides an attractive opportunity for longitudinal interictal monitoring and possible prediction of attacks. Finally, in conjunction with clinical evaluation, saccadometry has much potential for improving the current diagnostic armoury.

Authors AC, DPC and AVR contributed equally.

**PO71**

**A vertical VAS scale in a diagnostic headache diary gives valid headache intensity measurements**

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**Objectives:** The object of the present study was to validate a vertical VAS scale for headache intensity using the traditional horizontal VAS as gold standard.

**Background:** A key variable to monitor in prospective headache studies is pain intensity. In the International Classification of headache disorders (ICHD-II) a verbal rating scale is used. Visual analogue scales have been suggested to be better and more versatile instruments for pain monitoring (VAS).

**Methods:** Outpatients with headache and subjects with chronic headache from a population-based study were presented with the headache diary containing a modified vertical VAS scale for headache intensity. A standard horizontal VAS scale was also presented. Both scales were presented twice. Diagnosis was made according to the ICHD-II by neurologists trained in headache diagnostics.

**Results:** VAS scores consistent with the specific headache diagnoses were found using both horizontal and modified vertical scales. Scores on the horizontal versus the vertical scales did not differ significantly in the major headache groups. For test-retest evaluation, effect sizes and Cohen’s delta values were 0.003 to 0.028 for the major primary headache groups with about 1% change from test to retest. Correlation coefficients were 0.896 or greater. Bland-Altman analysis showed good agreement between modified vertical and traditional horizontal VAS scores. Correlation coefficients were 0.855 or greater.

**Conclusions:** Our modified vertical VAS scale incorporated into a headache diary is valid for registration of headache pain intensity. We suggest more widespread use of this approach in the evaluation of headache treatments.

**PO72**

**A standard atheoretic parameter for optimizing clinical trials and forensic medicine**

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**Objectives:** To propose the first atheoretic standard parameter to optimize planning of clinical trials. Pivotal step is represented by the attempt to validate a modified, standard parameter for the classification of tension type headache (International Headache Criteria ICHD-II A 2.1, A 2.2, A2.3).

**Background:** The method uses jolting of the head instead of “routine physical activity such as walking or climbing stairs” that is reported in description and at point C.4. Routine physical activity is extremely different according with the subjects and with the work the subject performs. In other words the parameter can change with the patient under observation. If routine differs according with the subject, a parameter is seemingly needed to be introduced. We propose “head jolting” that is rotation of the head 2–3 times per second. This standard manoeuvre induces headache worsening or headache-like sensation in migraine sufferers only, being migraine pain directly proportional to the severity of the suffered disease (i.e. A2.1, A2.2, A2.3). We propose to introduce this manoeuvre as the first, mandatory criteria for diagnosis.

**Methods:** 2007 consecutive headache patients (1659 females; mean age 32.5 ± 5.1 SD) were evaluated at the first visit. History of headache, duration and frequency /month, medication satisfaction and recurrence were considered. Jolting of the head has to be done after a 48 hours wash-out period from of any acute, abortive treatment suited to abort headache pain. That to avoid possible alteration of the results. Indeed, a type of pharmacological treatments can change pain pattern.

**Results:** Diagnostic results of the testing: Of the 2007 patients (1439 females, 569 males; mean age 33.4 ± 4.4 SD), 922 (613 females, 309 males; mean age 32.8 ± 4.3 SD) were initially diagnosed as suffering migraine International Headache Criteria IHC DII A 1.1 or 1.5.1. The remaining as tension type headache sufferers. Following the introduction of the criteria of head jolting the number of migraine sufferers became 1997 (1438 females, 559 males; mean age 33.5 ± 2.9 SD). Remaining patients ($n = 10, 1$ female) remained classified as tension type headache sufferers. The evidence was that the diagnostic result of head jolting on behalf of the previous criteria showed a sensitivity = 0.97, specificity = 0.60.

**Conclusions:** Results suggest the new standardized parameter we introduce can aid diagnosis. That seemingly indicates that standardized, objective/semi-objective criteria and manoeuvres ought to avoid diagnostic traps due to: a) difficulties in focusing experience of pain not as infrequent in patients, b) diagnostic traps as referred pain or defensive muscle contraction pain, c) alteration of the pain pattern due concurrent medication use or over-use. To introduce standard criteria ought to be noteworthy when planning trials in that the result of the study itself might change the final results. Indeed, a drug could be licensed as working yes or not for a type of headache or a completely different one. Moreover, forensic medicine seems to need of a list of standard parameter and manoeuvres.

**PO73**

**Surgical intervention altering the natural history of chronic migraine. Is chronification of migraine headache a harbinger of peripheral afferent nerve involvement?**

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**Objectives:** To compare the rates of conversion of patients that fit the criteria for chronic migraine (ICHD 2ed 1.5.1, G4.3.1) who were
Cluster headache: may a switch in catabolic pathways of serotonin trigger the attacks?

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Objectives: We intended to study the levels of serotonin (whole blood [WB], platelet [PQ] and plasma [PL]), its two metabolites melatonin and 5-HIAA, in episodic and chronic CH patients, during an active period, between, during and after the attack. Levels of the enzymes monoamine oxidase (MAO), N-acetyl-transferase (NAT) and hydroxyindole-O-methyltransferase (HIOMT) were studied at baseline.

Background: Cluster headache (CH) is characterized by unilateral attacks of pain. The mechanisms triggering the attacks are unknown. It has been suggested that serotonin (5-HT) and melatonin metabolisms are abnormal in CH.

Methods: 210 CH patients and 210 age and sex matched controls were prospectively included in the study (142 males and 43 females).

Serotonin and 5-HIAA levels were determined by high-performance liquid chromatography (HPLC). Melatonin levels were determined by radioimmunology and its chemical identity was controlled by HPLC and mass-spectrometry. Enzymatic activities were measured by radioenzymology.

Results: Samples were available for 174 patients at baseline, 45 during the attack and 22 post-attack. Between attacks, the serotonin levels in whole blood did not differ between patients and controls (322 vs. 325 nmol/l, P > 0.999) but plasma levels were higher (59.7 vs. 5.5 nmol/l, P < 0.001) and platelet levels were lower (1.24 vs. 2.24 nmol/l, P = 0.013). Baseline levels of melatonin in CH patients were in the low normal range, but still significantly lower than controls (0.11 vs. 0.18 nmol/l, P = 0.043). 5HIAA baseline levels did not differ between patients and controls (52.0 vs. 47.7 nmol/l, P = 0.675). During the attack, serotonin levels (WB, PQ and PL) did not vary significantly, but melatonin levels rose (0.10 baseline vs. 0.14 attack nmol/l, P = 0.029) and 5-HIAA levels decreased (35.7 nmol/l during baseline vs. 37.9 nmol/l during the attack, P = 0.012) in a mirror-like fashion. This phenomenon is seen in episodic and in chronic patients and is confirmed with intra-patient variation analysis. Concerning the enzymatic activities, only HIOMT is diminished in CH patients.

Conclusions: Our results suggest that the CH attack may be triggered by a rise in melatonin plasma concentration in patients with a low baseline level. This rise may be the result of a transient shift of serotonin catabolism in 5-HIAA toward the melatonin pathway in the pineal gland, since the majority of plasma melatonin is produced by this structure. CH patients do have higher 5-HT plasma levels and low platelet levels despite normal whole blood levels. This imbalance suggests a dysfunction of the release and/or intake of 5-HT by the platelets. Low melatonin levels may be explained by diminished HIOMT activity. How the serotonergic and melatonergic particularities interact in CH patients is to be determined, but transporters like VMAT or SERT, involved in release of serotonin, linked to both systems, may be of interest for further studies.

PO76

The treatment of trigeminal neuralgia with percutaneous balloon compression of the gasserian ganglion

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Objectives: To evaluate the efficacy of percutaneous balloon compression of the gasserian ganglion (PBC) in patients with trigeminal neuralgia (TN) refractory to medical and prior surgical treatment.

Background: Trigeminal neuralgia (TN) is a painful, debilitating condition and the most common of the facial neuralgias. The International Association for the Study of Pain defines TN as “sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve”. The annual incidence of TN is 4 to 5 in 100,000. For the most part, medical treatment remains the mainstay in TN. A review of the literature revealed several randomized controlled trials that studied different medications. From all of them, Carbamazepine (CBZ) appeared to be the most effective with a 58% to 100% positive response rate. Other medications including oxcarbazepine, pimozone, gabapentin, baclofen, lamotrigine, and tizanidine are felt to be somewhat effective as well. However, there is a group of patients whose symptoms are refractory to medical treatment and surgery remains their only viable alternative for pain relief. The following experience reflects our efforts trying to find the most minimally invasive, cost effective and safest technique while maintaining a high yield of positive results and low long-term recurrence. The technique becomes even more attractive because of the possibility of being...
performed in poor countries, in small rural hospitals and in ambula-
tory centers with relative ease.

Methods: A retrospective study of 206 patients was conducted from 1991 to 2005. All patients suffered from TN and had failed prior treatment. All patients underwent PBC of the gasserian ganglion by the same surgeon. A strict inclusion and exclusion criteria was utilized. The surgical technique performed was described by Mullan in 1983 and general anesthesia was used. Average balloon compression was 1.3 minutes. Persistent postoperative deficits were considered to be any postoperative symptoms that remained present for more than 2 months. There was no mortality.

Results: Patients were followed up clinically for at least 3 years. From the 206 patients of the series, there were a total of 230 interventions. 213 (93%) had immediate relief of the pain. After a 3 year follow up, from the 230 interventions 35 (15%) had developed recurrent symptoms. From this group, 21 opted to have PBC repeated and they all obtained complete relief afterwards.

Conclusions: From the author’s experience, PBC of the gasserian ganglion is an excellent choice in the treatment of TN refractory to medical and previously failed surgical treatment. This is especially important when considering elderly patients which may represent a higher risk for other procedures like microvascular decompresion. Because this technique is also minimally invasive and has a lower cost, its availability and utilization in poor countries and small rural clinics gives it greater significance.

PO77
Oxygen and cluster headache: results from the United States cluster headache survey
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Objectives: To present results from the largest survey ever done of cluster headache (CH) patients living in the US concerning the use of Oxygen (O2) as an acute treatment.

Background: CH patients were randomly solicited via approximately 9,000 emails and internet advertisements. Only patients who were diagnosed by a neurologist were able to participate.

Methods: Total survey consisted of 187 multiple choice questions of which 84 questions dealt with oxygen use, efficacy and economics. Survey was placed on an Internet website from October 12, 2008 to December 12, 2008.

Results: 1134 individuals completed the survey (816 male, 318 female). 868 patients had episodic CH while 266 had chronic CH. 93% were aware of O2 being an acute therapy, 34% had never tried O2. 70% stated O2 was effective (ECH > CCH 72% vs. 61%). 50% had tried O2 alone to abort CH, but only 25% were currently using O2 as a sole abortive > 80% of the time. 44% had to first suggest O2 therapy to their physicians to get it prescribed. There was an equal distribution (28% each) of physician type (general practitioners, general neurologist, headache specialist) who initially prescribed O2. Reasons why a physician would not prescribe O2 included: did not know that O2 was used for CH 32%, did not believe it worked 44% and stated medical literature not convincing 16%. Patient or physician had to submit medical literature 44% of the time to get reimbursement for O2. Only 64% of insurers covered O2 for CH. 50% of those using O2 never received training on proper use of O2 cylinder equipment or mask. 45% had to find a source to buy O2 on their own. On oxygen prescriptions only 45% specified a flow rate, 50% stated CH as diagnosis and 28% indicated a specific mask type. 12% of CH patients had used welders O2 (non-prescription, less expensive) stating economic reasons including having no insurance. Oxygen delivery systems: 11% using nasal cannula, 29% standard mask, while 47% high concentration non-rebreather mask. Initial flow rates prescribed: 23% 7 lpm, 51% 8–12 lpm, 18% 13–15 lpm, 8% 16–25 lpm. During therapy 41% start and 34% end using 7–10 lpm, 17% start and 14% end using 11–12 lpm, 28% start and 34% end using 13–15 lpm, 7% start and 10% end at 16–20 lpm and 6% start and 8% end at 21–25 lpm. O2 aborted a CH completely in less than 15 minutes for 36%, 16–30 minutes 30%, while taking ≥ 45 minutes in 22%. Of those using O2 plus another abortive agent, 38% administer the other abortive before, 6% after starting O2, while 56% only administer if O2 did not work.

Conclusions: In the US despite the obstacles of getting O2 prescribed, covered by insurance, finding an O2 source and having no instruction on how to use it, O2 still remains a viable treatment option for CH patients. A significant portion of CH patients find O2 to be an effective acute therapy although many need to increase the flow rate of O2 during an acute attack and very few use O2 as sole therapy to treat most of their attacks. From this survey physicians and CH patients need more education on the use and prescribing of O2 for CH while headache specialists need to better recognize what CH patients are actually doing with O2 therapy at their homes.

PO78
Bilateral occipital nerve stimulation for chronic cluster headache
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Objectives: Cluster headache is a severely debilitating headache disorder with orbital, supraorbital and temporal localized pain attacks, accompanied by ipsilateral autonomic manifestation. Usually, it appears in bouts (cluster periods) of 6 to 12 weeks followed by periods of remission. Neuromodulatory treatments including deep brain stimulation and occipital nerve stimulation offer a new and promising possibility for treatment of these patients.

Background: However, a fraction of cluster patients develop a chronic course. These patients suffer from medication refractory cluster attacks or intolerable side effects of the prophylactic treatment. Neuromodulatory treatments including deep brain stimulation and occipital nerve stimulation offer a new and promising possibility for treatment of these patients.

Methods: Five chronic cluster patients underwent bilateral occipital nerve stimulation. Effectiveness of treatment measured by frequency of cluster attacks and use of attack abortive treatment, side effects, and improvement of quality of life (using SF 36) were recorded.

Results: On average the patients had three to five cluster attacks a day before treatment. After implantation of the device within four weeks the attack frequency was reduced by 50%. The intake of abortive treatment of attacks (zolmitriptan nasal or subcutaneous sumatriptan) was reduced by more than a half. Three patients even had pain free days, which they did not have over the past years. Moreover, patients showed reinforced effect on oxygen treatment which was not sufficient in the pre-treatment phase. Consecutively, prophylactic treatment could be reduced over time. Pain intensity measured by numeric rating scale (0–10) declined from median 8 to 3.5 under stimulation. All patients reported significant improvement of quality of life. One adverse event appeared with a defect contact of an electrode, what mad a surgical revision necessary.

Conclusions: In conclusion bilateral occipital nerve stimulation offers a hopeful additional treatment option for chronic cluster headache refractory to medical treatment. In comparison to deep brain stimulation it is a safer and noninvasive method, but more research is needed to establish it in the clinical routine.
PO79  
Cardiac safety in cluster headache patients using supra-maximum dose of verapamil  
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Objectives: The aim of this audit study was to evaluate the cardiac safety of supra-maximum doses (≥720 mg) of verapamil used in cluster headache (CH) treatment.

Background: The dose of verapamil used for CH is approximately double the dose used in cardiovascular disease, most likely because verapamil is a substrate for the efflux transporter P-glycoprotein in the blood-brain barrier. According to evidence, starting dose is 360 mg and the dose can be increased with 80 mg every second week until 720 mg depending on effect and adverse events. Some patients may need dose higher than 720 mg. Few data are available concerning the cardiac safety of such supra-maximum doses.

Methods: The notes were assessed for patients with episodic CH or chronic CH attending two headache specialty centers (Marseille and Nice) participating in the French Observatory of Migraine and Headaches from December 2004 to December 2008. Patients had a diagnosis of CH according to the ICHD-II and were systematically monitored by EKG if verapamil was used. Audit study considered three patients groups: CH patients, CH patients using verapamil and CH patients using verapamil with a supra-maximum dose (defined as ≥720 mg). In the third group the following data were collected for each patient: sex, age, diagnosis (episodic CH, primary or secondary chronic CH), duration of verapamil use, supra-maximum dose of verapamil achieved, duration of use of such a supra-maximum dose of verapamil, concomitant medications, clinical adverse events related to verapamil (constipation, asthenia, hypotension, edema, dyspnea, impotence). EKG performed before verapamil introduction was compared with EKG done at the supra-maximum dose of verapamil achieved.

Results: Among 200 CH identified, 29 (14.8%) - 28m/1w; 42.8 ± 10.7 years - used verapamil with a dose ≥720 mg (720 mg: 16; 840 mg: 2; 960 mg: 7; 1200 mg: 1; 1440 mg: 3). EKG changes concerned 11 (38%) patients: bradycardia (heart rate < 60 bpm) in 7 patients, first degree heart block (PR interval > 0.2 s) in 2 patients, second degree heart block in 1 patient and third degree heart block in 1 patient. EKG changes have been considered as serious adverse events related to verapamil discontinuation in 2 patients and a dose reduction in 1 patient. SAE concerned patients using verapamil without concomitant medications expect sumatriptan or zolmitriptan as attack treatment. SAE were delayed-onset in three patients (72, 71 and 24 months after the supra-maximum dose was achieved). SAE occurred without clinical adverse event expect in patient who presented a third-degree heart block with syncope during a consultation.

Conclusions: This audit study confirmed data previously collected by Queen Square group [Neurology 2007; 69: 668-675]. Supra-maximum doses of verapamil use exposes CH patient to high cardiac risk and further management CH guidelines should included systematic EKG monitoring during titration but also at each evaluation if maintenance of supra-maximum dose is need.

PO80  
Results from the United States cluster headache survey  
Rozen TD1 and Fishman RS2  
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Objectives: To present results from the largest survey to date of cluster headache (CH) patients living in the US.

Background: With the support of CH based organizations and the AHS, CH patients were randomly solicited via approximately 9000 emails and internet advertisements to participate in a survey. Only patients who were diagnosed with CH by a neurologist were able to participate.

Methods: Survey consisted of 187 multiple choice and fill in questions and was placed on an Internet website from October 12, 2008 to December 12, 2008. Survey addressed clinical, epidemiologic and economic issues related to CH.

Results: 1134 individuals completed the survey (816 male, 318 female). 868 patients had episodic CH (male: female 2.9:1) while 266 had chronic CH (male:female 1.8:1). Highlights: 71% had their first ever CH at 30 years of age or younger, 35% 20 years of age or younger, while 20% of CCH started after age 40 years vs. 10% ECH. Predominant eye color was blue 33%, brown 33% and hazel 21%. Brown eye color was most common in ECH; blue most common in CCH. Diagnosis was typically initially made by a general practitioner or a general (non headache specialist) neurologist. Average time to correct diagnosis was usually either less than 1 year (25%) or 10 years plus (22%). 73% had a smoking history and 72% had at least one parent who smoked while the patient lived with that parent. 45% continued to smoke at the same rate as before CH onset. 16% had never smoked prior to CH onset. 50% stated alcohol triggered a headache while 85% would stop drinking during a CH cycle. Weather changes triggered CH in 36%. 17% had an immediate family member with CH and 52% had a family member with migraine. 55% had thoughts about suicide while 2.2% tried to commit suicide. Depression was the most common comorbid condition occurring in 24% while lung cancer was rare occurring in only 3 patients. Clinically, auras occurred in 21%, almost all lasting less than 25 minutes; lacrimation most common associated symptom 91%, photophobia/phonoaphobia 45% and nausea 36%. Bilateral pain was rare, but more common in CCH 8.3% vs. ECH 1.5%. 50% of the patients would physically hit themselves during a headache. Almost equal distribution of headache onset times during 24-hour day; peak 2:00am. Most common months to start cycle March, April, September, and October. Treatment: Only injectable sumatriptan and oxygen were deemed effective acute treatments, but 52% had never tried injectable sumatriptan and 34% had never tried oxygen. Only 8% had a GON block. Most recognized preventives were deemed ineffective in > 70%+ of patients. Verapamil was never tried in 37%, while lithium, valproic acid, gabapentin, methysergide, methylergonoine, and topiramate had not been tried in > 70%+. 17% lost their job secondary to CH while 9% had to quit work or go on disability. Almost 50% of survey responders were not currently seeing a neurologist.

Conclusions: In the US many CH patients are not currently seeing a neurologist, are not being exposed to recognized acute and preventive therapies and are not finding treatment to be effective when prescribed. This is leading to job loss and disability. This survey will help define the clinical description of CH.

PO81  
Treatment of acute cluster headache with a sublingual hydro-alcoholic solution of Sumatriptan: an open pilot study with dose ranging  
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Objectives: To investigate the efficacy and tolerability of a sublingual hydro-alcoholic solution (35%) of Sumatriptan (2 mg, 4 mg and 6 mg) in the acute treatment of cluster headache (CH) in an open-label pilot study.

Background: Subcutaneous Sumatriptan is efficient in acute CH, but some patients have problems with injections and the device is expensive.
Methods: 23 patients (21 males) met the ICHD-II criteria for episodic (n = 7) or chronic CH and were enrolled in our study. All 23 patients were usual good responders to subcutaneous Sumatriptan 6 mg. They received sublingual Sumatriptan (12 received 2 mg, 5 received 4 mg and 6 received 6 mg). The primary efficacy measure was “headache response” (defined as headache improvement from “very severe”, “severe” or “moderate” pain to “mild” or “no” pain) at 10 (T10) and 20 (T20) minutes after treatment.

Results: Overall, at T10, 25% responded and at T20, 50% responded. With the 2 mg dose, headache response was achieved at T10 by 33% and at T20 by 60%. With the 4 mg dose, headache response was achieved at T10 by 40% and at T20 by 60%. With the 6 mg dose, headache response was achieved at T10 by 16% and at T20 by 33%. The tolerance was good without any reported adverse event for each dose.

Conclusions: We conclude that a sublingual hydro-alcoholic solution of Sumatriptan (2 mg and 4 mg) might be an alternative therapy for the treatment of cluster headache attacks. The 6 mg dose seemed less efficient than the others because the dissolution of the 3 dosages is the same in 0.75 ml of hydro-alcoholic solution. The absorption was probably only residual for the 6 mg dose. To optimise all the results, we must increase the alcoholic degree by 10 or 15° and also change the place of administration of the solution, not sublingual where there is a lot of production of spittle which lessens the concentration but between cheek and gum.

PO83
Clinical features of cluster headache: many Japanese patients keep still during attacks
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Objectives: To investigate the features of cluster headache (CH) in Japan, especially behavior during attacks.

Background: The inability to keep still during attacks is one of the typical features of CH. However, previous Japanese study reported that 46% CH patients were lying quietly and 9% were walking around.

Methods: 75 consecutive new CH patients were enrolled in this study. The diagnosis of CH was verified according to International Headache Society (IHS)-II criteria. Sex, type of cluster headache, duration of attacks, time of onset of attacks, autonomic features, nausea, vomiting, photophobia, phonophobia, pain intensity estimated by visual analogue scale (VAS), and behavior during attacks were investigated. Pain intensity was estimated by visual analogue scale (VAS) and between 80/100 and 100/100 on VAS was defined as severe pain.

Results: Among the 75 patients, 80% were males; 97% had episodic CH, 3% had chronic CH. Duration of attacks was less than 1 hour in 16%, between 1-2 hours in 60%, and between 2-3 hours in 60%. Associated symptoms were cranial autonomic features in 97%, nausea in 41%, vomiting in 16%, photophobia in 27%, and phonophobia in 27%. 87% had severe pain; however 79% endured the pain with keeping still during attacks.

Conclusions: In a previous study, 85.7% patients had severe pain and 88.1% patients performed a complex sequence of multiple actions during attacks. However, many Japanese patients of CH endured the pain with keeping still during attacks. Given the results of the same pain intensity, differences in behaviors during attacks may reflect differences in racial, social and cultural factors.

PO82
Migrainous features in cluster headache
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Objectives: To assess in patients with cluster headache (CH) the prevalence of headache characteristics and associated symptoms usually related to migraine.

Background: CH is a headache disorder clearly defined by ICHD-II criteria. Nevertheless diagnosis is delayed in many patients. One reason for this delay might be the presence of migrainous features during CH attacks.

Methods: We are currently performing the first survey on CH in Austria including 76 patients (18% women, mean age 43 ± 10 years) with CH according to ICHD-II up to now. All patients completed a structured questionnaire. In this presentation, we will focus on migrainous features comprising pulsating pain, aggravation by or avoidance of physical activity, nausea, vomiting, photophobia, phonophobia and aura symptoms in CH attacks.

Results: Seventy-eight percent of the patients had episodic CH and 22% had chronic CH. Three percent gave a personal history and also change the prevalence of headache characteristics and associated symptoms usually related to migraine.

Conclusion: Migrainous symptoms are common in CH and not related to a personal or family history of migraine. Even though frequency and duration of attacks clearly differentiate CH from migraine, the presence of migrainous symptoms in CH might cause misdiagnoses in patients with infrequent or long-lasting attacks.

PO84
Occipital nerve stimulation: is peripheral approach effective in cluster headache?
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Objectives: To observe effectiveness of Occipital Nerve Stimulation (ONS) in patients with Cluster Headache as an alternative treatment to hypothalamic deep brain stimulation (DBS).

Background: Cluster Headache is one of the primary headaches that features with bouts of extremely intensive pain. Surgical options after poor conservative treatment outcome consisted of ablative surgery or deep brain stimulation with various results.

Methods: We present 6 patients with bad pain control despite pharmacological treatment with an ONS device. Two bilateral subcutaneous leads are implanted to stimulate the occipital nerves. After 1–2 weeks trial period they were implanted with the implantable pulse generator. We describe treatment and clinical improvement. Preliminary results are presented at 6–15 months follow up. Target follow up will be 2 years.

Results: 6 patients: 3 male, average age: 51 years (32-66). Mean reduction in acute medication and symptoms for all patients are: Medication: -53%, Crisis: -61%, Intensity: -60%, Duration: -71%. Conclusions: We propose ONS as alternative treatment to DBS in selected patients with Cluster Headache. ONS approach has low surgical and technical morbidity and based on our experience, the ther-
apy learning curve can be achieved in short time. The use of a rigorous prospective protocol to include and follow-up patients appropriately is essential to evaluate effectiveness of this treatment and long term therapy success.

Table: Patients' outcomes (mean values and range)

<table>
<thead>
<tr>
<th>Follow-up time</th>
<th>Preventive medication during crisis</th>
<th>No of crisis</th>
<th>Intensity (VAS)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt1 15 months</td>
<td>no change</td>
<td>91% (84-100%)</td>
<td>99% (92-100%)</td>
<td>98% (96-100%)</td>
</tr>
<tr>
<td>Pt2 12 months</td>
<td>no change</td>
<td>58 (46-64%)</td>
<td>45 (67-78%)</td>
<td>47 (27-63%)</td>
</tr>
<tr>
<td>Pt3 12 months</td>
<td>no change</td>
<td>92% (52-100%)</td>
<td>91% (48-100%)</td>
<td>100% (100%)</td>
</tr>
<tr>
<td>Pt4 9 months</td>
<td>no change</td>
<td>48% (20-100%)</td>
<td>76 (46-98%)</td>
<td>13% (0-38%)</td>
</tr>
<tr>
<td>Pt5 6 months</td>
<td>no change</td>
<td>-69% (10-88%)</td>
<td>-42% (60-70%)</td>
<td>-87% (75-98%)</td>
</tr>
<tr>
<td>Pt6 6 months</td>
<td>no change</td>
<td>+44% (0-75%)</td>
<td>-35% (30-40%)</td>
<td>-32% (26-43%)</td>
</tr>
</tbody>
</table>

PO85
Unilateral headaches beyond migraine and cluster headache
Seidel S, Lieba-Samal D, Vigl M and Woeb C
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Objectives: To describe imaging findings, response to indomethacin and final ICHD-II diagnoses in patients presenting with unilateral headaches not resembling migraine or cluster headache and to compare characteristics of primary.

Background: Unilateral headache is a hallmark of migraine and cluster headache. Apart from those, it may be due to paroxysmal hemicrania, SUNCT, primary stabbing headache or secondary headache disorders clearly defined in ICHD-II. However, little is known about the diagnostic value of the ICHD-II criteria in differentiating unilateral headaches different from migraine and cluster headache.

Methods: Initially retrospective and subsequently prospective investigation of consecutive patients presenting to the general outpatient clinic, Department of Neurology, Medical University of Vienna with unilateral headaches not fulfilling ICHD-II criteria of migraine and cluster headache. All patients were diagnosed and managed by S.S.

To increase diagnostic validity, a data file including all details required for establishing headache diagnoses according to ICHD-II was forwarded to two other headache specialists (D.L.-S., M.V.) for re-classification. Both were blinded regarding the initial diagnosis. D.L.-S. was unaware and M.V. was aware of the imaging findings. In case of disagreement, C.W. was responsible for the final diagnosis.

Results: Between June 2008 and April 2009, 41 patients fulfilled the inclusion criteria of this case series. One subject was lost to follow-up. Cranial magnetic resonance imaging (MRI) was performed in 40 patients and showed a structural pathology in 12 (30%). The lesion was intracranial in 7 patients, extracranial in 5 and was considered to be causally related to the headache in 10. Thirty six patients underwent an indo-test and took oral indomethacin 75 mg b.i.d. for 3 days. Twenty of them (56%) reported subjective improvement of headache by > 80%. According to ICHD-II headache was classified as (probable) paroxysmal hemicrania in 6 patients and primary stabbing headache in 7. In one additional patient, probable hemicrania continua was considered, a diagnosis not available in ICHD-II. Headache was definitely secondary in 3 patients (attributed to a disorder of the teeth in 2 and acute sinusitis in 1). It was probably secondary in 7 and could not be classified in 17 patients. Patients with primary headaches showed higher headache frequency (45 ± 46 vs. 0.3 ± 2 per day, P < 0.001), shorter headache duration (P < 0.001) and fewer MRI pathologies (P = 0.002) than those with secondary or unclassifiable headaches. In contrast, the response to indomethacin did not differ in the two groups.

Conclusions: In patients presenting with unilateral headache different from migraine and cluster headache, paroxysmal hemicrania and primary stabbing headache are diagnosed most frequently, but the majority cannot be classified according to ICHD-II. A disorder definitely or probably related to headache can be found in 25%. The indo-test does not reliably differentiate between primary and secondary or unclassifiable headaches.

PO86
Cluster headache: the significance of the “migrainous” phenomena
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Objectives: The aim of this study was to determine the presence and significance of the MF in patients with cluster headache.

Background: There are only a few studies that examined the presence of autonomic features during migraine attacks and there are no studies about presence of features that are commonly associated with migraine (MF) in patients with cluster headache.

Methods: The examination was performed in cohort of 155 patients with cluster headache diagnosed and treated in our Headache Center during the last eight years. The presence of the MF (photo-, phono-, osmophobia, nausea/vomiting and aura) was examined by the questionnaire designed for this study. The demographic features of the patients, the pain characteristics, autonomic phenomena associated with attack and efficacy of prophylactic therapy were compared between cluster headache patients with and without MF.

Results: There were 38 (24.5%) cluster headache patients with at least one of MF. Nausea/vomiting were present in 18.1%, photophobia in 12.3%, phonophobia in 5.2%, osmophobia in 0.6% and aura in 2.6% of patients.

Conclusions: “Migrainous” features in patients with cluster headache are common and have been widely underestimated in the past. One out of four cluster headache patients regularly experiences one or more MF during their attacks. In cluster headache patients with accompanying MF headache attacks are longer, more often worsened by head movements, and associated with facial sweating.
PO87
A systematic review of the triptan class of drugs for the treatment of cluster headache
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Objectives: To assess the efficacy and tolerability of a single dose of any triptan for acute treatment of a single attack of cluster headache.

Background: The triptan class of drugs is used for the treatment of primary headaches. The severity, rapid onset and short time to peak intensity of cluster headaches, necessitates treatment that is swift and effective. The clinical impression is that triptans are useful, but there is no systematic review.

Methods: Cochrane CENTRAL, MEDLINE and EMBASE were searched for relevant randomised, double-blind, placebo controlled trials of single dose triptans treating single attacks of cluster headache, of at least moderate intensity, in adults. Dichotomous data for pain relief, use of rescue medication and adverse events were extracted and used to calculate relative risk (RR) and numbers needed to treat (NNT) with 95% confidence intervals. Primary measures of treatment success were headache relief (HR: pain intensity decrease from moderate/severe/very severe to mild or none) and pain free (PF) at 30 min.

Results: Six relevant trials were identified evaluating sumatriptan or zolmitriptan by oral, intranasal or subcutaneous routes. Data for individual drugs, doses and routes of administration were limited. For zolmitriptan all doses and routes were better than placebo for HR at 30 min, except for 5 and 10 mg oral doses (NNT for 10 mg intranasal 2.8 (2.1 to 4.3)), and for PF at 30 min, except for 5 mg oral (NNT for 10 mg intranasal 3.3 (2.4 to 5.4)), with a trend for dose response. For sumatriptan outcomes were reported at 15 min, and all doses and routes were better than placebo (NNT for 6 mg subcutaneous for HR at 15 min 2.4 (1.9 to 3.2), and for PF at 15 min 3.3 (2.4 to 5.0)), with no dose response. Fewer patients used rescue medication with triptan, but more experienced adverse events, very few of which were serious or led to withdrawal.

Conclusions: This analysis demonstrates that the triptans are effective and well tolerated for the acute treatment of cluster headache, providing patients with rapid relief from debilitating pain.

PO88
Attack cessation and remission induction with 2-bromo-LSD for cluster headache
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Objectives: An open-label trial of the ergot-based non-hallucinogen 2-bromo-LSD (BOL) for the treatment of episodic and chronic cluster headache.

Background: Anecdotal patient reports as well as a clinical case series led by one of the authors (JHH) describe attack cessation, early termination of attack series, and remission induction/extension in cluster headache patients who self-administer the hallucinogens LSD and/or psilocybin. Evaluation of a non-hallucinogenic analog could clarify whether these reported effects are associated with hallucinogenicity or are due to other chemotherapeutic mechanisms.

Methods: 4 subjects with active cluster headache refractory to standard treatments were administered in an outpatient research setting in Hannover, Germany approximately 30 µg/kg of BOL on 3 separate occasions separated by 5 days. Subjects maintained a headache diary prior to and post treatments for at least two months. The Clinical Global Impressions Scale (CGI) was obtained at baseline and follow-up interviews.

Results: Subject 2 reported a 30% reduction in pain intensity for 2 months after final BOL treatment and a 73% reduction in attack frequency for 4 months; the other three subjects report complete or nearly complete remission of all headache symptoms for at least 2 months after final BOL treatment.

Table 1.

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Sex (m/f)</td>
<td>m</td>
<td>m</td>
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<tr>
<td>Age (years)</td>
<td>28</td>
<td>46</td>
<td>47</td>
<td>43</td>
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<td>Body weight (kg)</td>
<td>68</td>
<td>83</td>
<td>106</td>
<td>105</td>
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<td>Years of illness</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>Side of headaches</td>
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<td>left</td>
<td>left (1999–2005)</td>
<td>right (since 2005)</td>
</tr>
<tr>
<td>Cluster headache form</td>
<td>episodic</td>
<td>chronic</td>
<td>chronic since 2001</td>
<td>none</td>
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</tbody>
</table>

<table>
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<tr>
<th>Treatments (acute)</th>
<th>oxygen</th>
<th>sumatriptan</th>
<th>forverapamil</th>
<th>forverapamil</th>
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<tbody>
<tr>
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<td>sumatriptan</td>
<td>forverapamil</td>
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<tr>
<td>Verapamil</td>
<td>240 mg/d</td>
<td>240 mg/d</td>
<td>240 mg/d</td>
<td>methylergolate (1978); prednisone (only for 5 days); verapamil (320 mg/d for 3 months); lithium for 3 months</td>
</tr>
<tr>
<td>BOL (30 µg/kg)</td>
<td>2.0 mg</td>
<td>2.5 mg</td>
<td>3.1 mg</td>
<td>3.1 mg</td>
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<tr>
<td>Blood side effects</td>
<td>heady feeling</td>
<td>&quot;rubby feeling&quot;</td>
<td>&quot;tripy feeling&quot;</td>
<td>&quot;tripy feeling&quot;</td>
</tr>
<tr>
<td>Vital signs during BOL</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td># of attacks in the week prior to BOL</td>
<td>7</td>
<td>8</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Attacks per week after last BOL dose</td>
<td>0</td>
<td>2.3 (1st 4 months); 0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Duration of reported improvement (since BOL)</td>
<td>6 months and ongoing</td>
<td>4 months and ongoing</td>
<td>2 months and ongoing</td>
<td></td>
</tr>
</tbody>
</table>

No significant adverse effects were observed/reported, including no evidence of hallucinogenic intoxication.

Conclusions: If the hallucinogenics psilocybin and LSD have important treatment effects for cluster headache, BOL – a non-hallucinogenic analog of LSD – may be safer for further research as indicated by these findings. Though open-label, BOL may be the first non-hallucinogenic agent identified to significantly modify the course of living with this severely debilitating disease.

PO89
Acute cephalalgia following endoscopic foreheadplasty surgery
Lassegard JC
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Objectives: The purpose of this research is to describe, using a mixed methods approach, the phenomenon of acute cephalalgia (AC) following Endoscopic Forheadplasty Surgery (EFS). The specific aims are to: 1) Describe the lived postoperative acute cephalalgia experience among participants undergoing EFS; 2) Ascertain from the participants’ perspective, what effective or ineffective means to diminish postoperative pain will be reported; 3) To describe the pain characteristics of the experience using a standardized pain scale; 4) Identify the association between pain and trigeminal nerve activity. The research questions that will guide in investigation are: How do patients describe the lived experience of postoperative pain after
EFS? What are effective and ineffective pain management strategies following EFS? What pain descriptors are used to describe the characteristics of the pain? What is the correlation between patients expressed pains, written medication diary and trigeminal nerve activity.

**Background:** Postoperative headache pain, frontal paresthesia, nerve damage, altered sensation in supratrochlear area, and prolonged numbness following EFS have been reported by surgeons. EFS is a minimally invasive surgical procedure to address undesirable facial aging or brow lines and correct genetic or traumatic facial deformities. Following EFS, patients, nurses and surgeons report postoperatively AC lasting from 48 hours to seven days unrelied with current pain medication protocols. Few reports if any demonstrate actual cause or successful postoperative pain management for EFS surgical patients. Hypothetically, inadvertent nerve trauma during surgical dissection triggers a neurological cascade resulting in uncontrolled cephalalgia. Two common trigger zones responsible for migraine headaches involve branches of the trigeminal nerve which are included in the dissection during EFS. Post-traumatic craniotomy patients and migraine sufferers describe cephalalgias with no universally effective pain management protocols. Prolonged acute pain can advance to chronic pain resulting in: suffering, dehydration, decreased nutrition, immobilization, strokes, pulmonary and cardiovascular complications, and unanticipated hospitalizations. Uncontrolled postoperative pain is a recognized medical priority. Currently there are no preliminary research studies explaining the cause of postoperative AC or effective treatment guidelines for EFS patients.

**Methods:** Two different research methodologies will be utilized in this study to describe participant AC following EFS. The first will include a descriptive qualitative phenomenological design focusing on the participant’s experience. The second part of the study will include quantitative methodology using: the self - testing Short Form McGill Pain Questionnaire (SF-MPQ), a pain medication diary, a portable electronic device to measure pain levels, and an non-invasive sensory nerve conduction device to measure nerve activity.

**Results:** Results pending theoretical model will be presented

**Conclusions:** The results of this study will determine the existence of acute cephalalgia pain in postoperative Endoscopic Foreheadplasty surgical patients.

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PO90

Zonisamide in prophylaxis therapy of the episodic and chronic cluster headache. An open study

Pizza VV, Busillo VV and Agresta AA

NeuroOrthoTraumatology, Neurophysiopathology Unit, Vallo della Lucania, Italy/Salerno, Italy

**Objectives:** The aim of our study is to evaluate the efficacy and tolerability of zonisamide in prophylaxis therapy of ECH and CCH.

**Background:** The prophylactic therapy of the episodic (ECH) and chronic cluster headache (CCH) is based on verapamil and carbamazepine. Besides several patients are not responders at these drugs. In these cases the use of antiepileptic drug has been proposed. Zonisamide, a new antiepileptic drug, has been reported efficacy in the migraineuses patients. The drug has mechanisms of action that suggest it may reduce the neuronal hyperexcitability. These mechanisms include facilitation of dopaminergic and serotoninergic neurotransmission, reduction of glutamate-mediated synaptic excitation and increased gamma-aminobutyric acid (GABA) release. Zonisamide has a favourable pharmacokinetic profile which includes high oral bioavailability and a long half-life (63 hours), permitting a once or twice daily dosing regimen. Recent clinical experience indicates a place for zonisamide in the management of headache disorders.

**Methods:** 13 patients (pz), (4 F, 7 M) mean age 42.8 years (SD 5.8), range 36–56 years, suffering from ECH (8pz) and CCH (5 pz) (ICHD ’04 criteria) were studied. In all patients with ECH prophylaxis therapy with verapamil, carbamazepine and valproic acid was failed in the past and patients with CCH continued therapy with carbamazepine (2 pz) and verapamil (1 pz). During the three months evaluation period zonisamide was administered (starting dose 25 mg/die, target dose 100 mg/die). All patients filled a headache-diary card during the evaluation.

**Results:** In patients with ECH the basal frequency of attack/days and 1, 2, 3 months respectively was 4.2 (SD 1.9); 2.4 (SD 0.9), 1.6 (SD 0.9), 0.8 (SD 1.1) [P < 0.0001]. In patients with chronic CH the basal frequency of attack/days and 1, 3, 6 months respectively was 2.8 (SD 1.3); 0.4 (SD 0.3), 0.2 (SD 0.2), 0.1 (SD 0.1) [P < 0.005] (T-test analysis). In all patients zonisamide was well tolerated (5 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).

**Conclusions:** These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none patients withdrew the study. Our study suggests that zonisamide could be an alternative or complementary prophylaxis therapy for ECH and CCH. Controlled studies are warranted to determine the efficacy of zonisamide in prophylaxis therapy for ECH and CCH.

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PO91

Involvement of latent herpes zoster virus in the development of forehead allodynia and aggravation of cluster headache (interim report)

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1Department of Health Services and Hospital Administration, Tokyo Women’s Medical University, Tokyo, Japan; 2Department of Neurosurgery, Tokyo Women’s Medical University, Tokyo, Japan; 3Department of Neurology, Kitasato University School of Medicine, Sagamihara, Japan; 4Department of Neurology, Dokkyo Medical University, Tochigi, Japan

**Objectives:** The aim of the present study is to preliminarily confirm an association between cluster headache and herpes simplex in 1985 (Joseph R et al. BMJ 1985; 209: 1625–6.). We, however, lately experienced several cases developed forehead allodynia and aggravated cluster headache after onset of herpes zoster. Accordingly, we deemed latent herpes zoster virus (varicella-zoster virus, VZV) infection in the trigeminal and occipital innervations areas may be involved in the development of forehead allodynia and aggravation of cluster headache.

**Methods:** We conducted a retrospective review of 27 patients (female vs. male = 1:2, mean age 38.0 ± 8.6 years) diagnosed with migraine (based on the ICHD-II) who had measured values of antibody titer to VZV. Ethic aspect was considered based on the ethic guideline of clinical research published in Japan.

**Results:** VZV antibody titer in 70% of 27 patients was increased (female vs. male = 1:2, mean age 38.0 ± 8.6 years) diagnosed with migraine (based on the ICHD-II) who had measured values of antibody titer to VZV. Ethic aspect was considered based on the ethic guideline of clinical research published in Japan.

**Results:** VZV antibody titer in 70% of 27 patients was increased with reactivation. In 4 patients, VZV antibody titer in episodic duration was trended to be high, Thus, VZV antibody titer was expected to detect initiation of episodes of cluster headache. It was deemed that central sensitization in the trigeminal and occipital innervations areas is developed due to reactivation of VZV.

**Conclusions:** We’re further investigating DNA test in tears to detect antigen of VZV in pre- and post-episodic points.

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PO92

Analysis of the increasing ratio of females with cluster headaches

Teramoto J, Kato S, Murao N and Tanigaki Y

Neurology, Teramoto Neurology Clinic, Nagoya, Aichi, Japan

**Objectives:** Female cluster headaches are reportedly increasing. We examined this problem in our clinic.

**Background:** Among Teramoto Neurology Clinic outpatients, five hundred and eighty-three cases of cluster headache born after 1931 were examined. Males were 477 and females 106.
PO93
Amloride-sensitive epithelial sodium channels: a novel therapy for migraine with aura?
Holland PR1,2, Akerman S1 and Goadsby PJ1
1Headache Research Group, Dept of Neurology, University of California, San Francisco, San Francisco, CA, USA; 2Centre for Cognitive and Neural Systems, University of Edinburgh, Edinburgh, UK

Objectives: To study the effects of Amloride on different in vivo models of migraine and to further test its clinical effectiveness in a cohort of severe migraine with aura patients.

Background: The epithelial sodium channels (ENaCs) have been postulated to play a role in nociception and are widely expressed throughout the trigeminovascular system. Amloride, a blocker of ENaCs has demonstrated anticonvulsant potential in vivo, thus blockade of the amloride-sensitive ENaCs could be a novel mechanism for the development of new anti-migraine treatments.

Methods: Rats were anesthetised with sodium pentobarbitone (60 mg/kg) and cannulated for measurement of blood pressure, administration of experimental drugs and anesthesia. Amloride was then administered at 5 or 10 mg/kg and its effects were tested on different models of trigeminovascular activation including, neurogenic dural vasodilation, cortical spreading depression (CSD) and trigeminal nucleus caudalis electrophysiology. We further examined the use of psalmotoxin, which blocks a specific subtype of the ENaCs (acid sensing ion channel 1a) on the CSD model and amloride 10 mg/day in patients suffering migraine with persistent aura.

Results: Amloride was shown to block cortical spreading depression (CSD), the experimental correlate of aura, and inhibited trigeminal activation. Subsequently, it demonstrated good clinical efficacy, reducing aura and headache symptoms in three of five patients with otherwise intractable aura. Psalmotoxin, which specifically blocks the acid sensing ion channel (ASIC). ASIC 1a, also inhibited the majority of CSDs induced indicating that amloride may be acting via ASIC1a channels.

Conclusions: The results identify both a trigeminovascular and cortical experimental effect for amloride that translated directly into a promising preventive treatment strategy for the aura of migraine and the underlying pain. The study further identified that the actions of amloride are likely via the acid sensing ion channel subgroup of epithelial sodium channels.

PO94
IV tramadol for successful treatment of chronic daily headache (CDH)
Knoderer WR, Kruzer JC, Cagle J and Scott-Kruz VB
Anodyne Headache and PainCare, Dallas, TX, USA

Objectives: Tramadol is used orally for chronic pain in the USA, but no IV form is available. We utilized an IV sterile preparation, made from active medication, to treat refractory CDH headaches in the clinic.

Background: Tramadol has a dual mechanism of action: that of mild mu receptor opioid agonism and blockade norepinephrine and serotonin re-uptake into nerve endings. It is on the market for chronic pain, and past open-label studies by the authors showed it to be effective to reduce refractory migraines in the outpatient clinic. We used this medication for chronic daily headaches (CDH) in this open-label study.

Methods: Tramadol, 50 mg/ml, was given IV in the clinic to patients with intractable CDH. 92 patients were treated with IV tramadol, after placement of an antecubital IV line and with pulse oximetry monitoring. A 50 mg test dose was given and 50–100 mg was given every 7–10 minutes with monitoring of headache severity by the patient on a 0–10 scale to maximal reduction of their headache.

Results: All patients treated for CDH had response to IV tramadol. Average dose of tramadol was 497 mg (range 250–1000 mg), given over 88 minutes in the clinic. Average reduction in severity (0–10 scale) was 76% after treatment VAS 7.1/10 before treatment and 1.7/10 after IV treatment. No side effects other than transient drowsiness, lightheadedness or nausea were noted. 67 patients were subsequently placed on oral tramadol. Headaches returned within 24 hours in 22 patients not treated with oral tramadol. 36% of patients treated had a total reduction of CDH to 0/10 with an average time of abolition of 3.4 days. Side effects included 12% with transient nausea or dizziness/drowsiness. 24% of patients had been tried on oral tramadol prior to IV treatment with this medication IV. 52 patients were placed on oral tramadol based on our successful treatment in the clinic.

Conclusions: IV tramadol is very effective in treating intractable CDH in the outpatient clinic. It has virtually no toxicity IV and can be the starting point for oral treatment. Typical dosage IV compares to daily oral dosing. Tramadol IV offers a new possibility in treating intractable CDH and even migraines effectively and safely in the clinic and should be studied in a double-blind manner. The mechanism(s) for its effects are discussed above, but blockade of NE and 5HT re-uptake and weak mu opioid receptor blockade are main mechanisms of action. This is the first report of IV tramadol efficacy in treating CDH.

PO95
Effectiveness of olanzapine, amisulpiride and paliperidone in chronic daily headache
Kourounalos N2, Foutouli M1, Kalamakiianaki K1 and Nikolakaki E1
1Neurology, General Hospital of Chania, Chania, Greece; 2Psychiatry, General Hospital of Athens “G. Gennimatas”, Athens, Greece

Objectives: The aim of this study is to provide evidence for the effectiveness of three atypical antipsychotics in the treatment of Chronic Daily Headache (CDH).

Background: Neuroleptics have long been used in treating acute headache, mainly because of the drugs’ actions in monoaminergic neurotransmission. However, their use in headache never became popular, mainly due to their side effects. With the recent advent of atypical antipsychotics and their improved adverse effect profile, treatment options for headache have expanded.

Methods: Study was prospective. Sample consisted of 40 patients with CDH (according to criteria of ICHD-II). Ten of them were trea-
ted with olanzapine, twenty with amisulpiride and ten with paliperidone. Criteria of sample selection were: a) experiencing CDH, b) being negative for a psychiatric DSM-IV diagnosis and c) having previously failed treatment with at least 3 different agents approved for treating CDH. Daily dose (in mg) of olanzapine varied from 2.5 to 10, of amisulpiride from 25 to 100 and of paliperidone, 3 mg. Treatment effectiveness was approached by obtaining and comparing (t-test) mean values, measured one month before and three months after treatment initiation in all 50 cases. Values concerned: a) headache frequency (HF) in days per month, b) headache duration (HD) in hours per day, and c) headache intensity (HI) using a 1–10 scale.

Results: Olanzapine resulted in a statistically significant decrease in mean: HF from 27.5 before treatment to 4.9 after treatment ($P < 0.01$, t-test), HD from 20.2 before treatment to 2.3 after treatment ($P < 0.01$, t-test) and HI from 6.0 before treatment to 1.5 after treatment ($P < 0.01$, t-test). Side effect noted was body weight increase in seven out of ten patients ranging from 2 to 8 kg. Amisulpiride resulted in a statistically significant decrease in mean: HF from 24.6 before treatment to 4.4 after treatment ($P < 0.01$, t-test), HD from 21.0 before treatment to 7.5 after treatment ($P < 0.01$, t-test) and HI from 6.1 before treatment to 2.0 after treatment ($P < 0.01$, t-test). Side effects noted were insomnia, anxiety and weight gain in overall three out of twenty cases. Paliperidone resulted in a statistically significant decrease in mean: HF from 26.0 before treatment to 4.0 after treatment ($P < 0.01$, t-test), HD from 20.0 before treatment to 7.0 after treatment ($P < 0.01$, t-test) and HI from 5.5 before treatment to 1.0 after treatment ($P < 0.01$, t-test). Severe extrapyramidal side effects were noted in two out of ten cases.

Conclusions: Atypical antipsychotics seem effective for treating CDH by significantly decreasing HF, HD and HI. Placebo-controlled trials are required to confirm findings, as well as studies with greater therapeutic choices available for this often treatment-refractory condition.

PO96 Prophylaxis of new daily persistent headache (NDPH): response to clonazepam in four patients
Tarshish SC, Robbins MS, Napchan U, Buse D and Grosberg BM

Objectives: To report four NDPH patients with significant improvement on clonazepam.

Background: NDPH is a primary chronic daily headache disorder often associated with an inconsistent and suboptimal treatment response, regardless of the therapeutic modality employed. Medications typically employed in the treatment of other primary headache disorders often produce unsatisfactory results in patients with NDPH. Clonazepam has recently been reported as effective for prevention of migraine in patients failing three classes of standard preventive therapies.

Methods: Case reports are presented on four patients presenting to a tertiary headache center who met ICHD-II criteria for NDPH. All patients were treated with clonazepam 0.5 mg once or twice daily for at least one month.

Results: Of the four patients, 50% were female, 75% were in their 40’s at the onset of the headache, and 75% had a history of other headache types that were phenotypically different from their daily headache, including episodic migraine without aura ($n = 1$), episodic tension-type headache ($n = 1$), and nummular headache ($n = 1$) before developing NDPH. NDPH onset occurred between 6 months and 2 years prior to presentation to the headache clinic. One patient reported a premorbid anxiety disorder. All patients had normal general and neurological exams, and unremarkable neuroimaging and routine laboratory testing. Prior to the trial of clonazepam, patients failed an average of five preventive medications (range 3–7), reported average daily headache pain scores ranging from 4 to 7 (on a scale of 0 to 10), and experienced 20 or more days per month of moderate to severe headache pain. Treatment with clonazepam 0.5 mg once to twice daily resulted in a reduction of 90% or greater in the frequency of moderate to severe headache days in 75% of patients, and a 50% reduction in the other patient. Two patients continued to have daily pain, but experienced a reduction in their average pain by two points on a scale of 0 to 10 (from 7/10 to 5/10 and 4/10 to 2/10). Withdrawal of the agent in one patient rapidly led to headache recurrence.

Conclusions: We report on four NDPH patients who demonstrated significant reductions in headache frequency and severity using clonazepam. This is the first report of the effectiveness of clonazepam in the treatment of NDPH. If the favorable response observed in our patients can be confirmed in other cases, it would broaden the therapeutic choices available for this often treatment-refractory condition.

PO97 Intravenous haloperidol therapy for new daily persistent headache
Loftus BD
Neurology, Bellaire Neurology, Bellaire, TX, USA

Objectives: Determine efficacy of IV Haloperidol use in treating New Daily Persistent Headache.

Background: Therapy for new daily persistent headache has been elusive. New Daily Persistent Headache is associated with elevated levels of intrathecal tumor necrosis factor alpha. Intravenous haloperidol has been shown to decrease proinflammatory cytokines including tumor necrosis factor alpha. Intravenous haloperidol is also effective for acute migraine and migraine status.

Methods: After checking an EKG to rule out prolonged QT syndrome, four patients who met the criteria for New Daily Persistent Headache were given IV Haloperidol 5 mg in 500 cc normal saline infused over 30 minutes. Three patients under the age of 50 were premedicated with 50 mg of IV diphenhydramine. All patients were told to have diphenhydramine 25 mg tablets available at home to take if they got a dystonic reaction. Demographic data is in table 1. Patient 4 is unique in that he has had 70 years of NDPH with a break of 13 years during periactin therapy and 3 years with Sam-e therapy.

Results: Two of the four patients (2, 4) had complete resolution of their headaches after a single infusion of IV Haloperidol. These patients have been followed for 120 and 30 days respectively. One patient (3) began to have headache free mornings and mild headache each evening but did not require any acute analgesics. This is in contrast to daily headaches requiring acute analgesics along with one completely disabling headache per week. She elected to redose with IV Haloperidol at 30 days. This was on the day the abstract was prepared. One patient’s (1) headache disappeared with the IV Haloperidol infusion but returned 2 days later. One patient (2) had severe fatigue for 2 days. Another patient (3) had mild akathisia for 24 hours.

Table. Patient Demographics

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age</th>
<th>Sex</th>
<th>Years of Headache</th>
<th>Number preventatives attempted</th>
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<td>4</td>
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<td>M</td>
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</table>

Conclusions: IV Haloperidol appears to be a relatively useful treatment for new daily persistent headache and should be studied.
further. Haloperidol has been shown useful for both acute migraine and chronic migraine. The mechanism of action has been presumed to be its anti-dopaminergic effect. This may also be the mechanism of action in New Daily Persistent Headache. IV Haloperidol has shown to decrease levels of tumor necrosis factor alpha in peripheral blood. Elevated intrathecal levels of tumor necrosis factor alpha in both patients with refractory chronic migraine and new daily persistent headache. Studying medications that reduce tumor necrosis factor alpha or have an anti-dopaminergic effect but not both may help to elucidate the relative importance of these potential mechanisms.

PO98
Botulinum toxin treatment in herpetic neuralgia and allodynia: possible pharmacotherapeutic mechanisms of botulinum toxin
Seo M-W and Lim M-H
Department of Neurology, Jeonbuk National University Hospital, Jeonju, Jeonbuk, Republic of Korea

Objectives: We report this previously mentioned case and discuss the possible pharmacotherapeutic mechanisms of BTX-A therapy on herpetic neuralgia and allodynia.

Background: There are several types of neuropathic pain including allodynia, hyperalgesia, as well as general pain. Due to its diversity and complicated mechanisms, a variety of treatments including antidepressants, ant epileptics, local anesthetics, opioids, NMDA antagonists, and other have been utilized to alleviate neuropathic pain. However, these treatment regimes are more or less ineffective. Recently, it has been demonstrated that botulinum toxin type A (BTX-A) exhibits analgesic effects in patients with neuropathic pain. We report a case of herpetic neuralgia and allodynia which were significantly improved with BTX-A therapy.

Methods: Case Report A 74-year-old man, with a history of hypertension, diabetes mellitus, and small vessel disease of the brain, had complained of severe burning pains in the right side of his chest wall around the dermatome of T4-6. This had been occurring for 3 weeks prior to presentation. A physical examination revealed a herpetic eruption and allodynia over the pain sites. The diagnosis of herpetic neuralgia was made and conventional pharmacologic treatments (i.e. tricyclic antidepressants, gabapentin, carbamazepine, pregabalin) were prescribed, albeit with minimal improvement. He persistently complained about neuralgic pain and related insomnia. We decided to inject botulinum toxin into the injured areas. One hundred Units of BTX-A (Dysport) were injected subcutaneously, divided among 10 sites using a 23-gauge needle. In addition to the neuralgic pain, the allodynia also improved dramatically.

Results: It has been demonstrated that hyperactivity of A-beta afferents following nerve injury could result in touch-evoked pain as well as spontaneous pain via a presynaptic activation of C afferent terminals. Significant anti-allodynic effects of various NMDA glutamnergic receptor antagonists have also been reported in neuropathic cases involving both animal and human subjects. These studies suggest that glutamate release might be partly involved in the pathomechanisms of allodynia. Subcutaneous application of BTX-A relieved the central burning pain and allodynia in two patients with spinal cord pathology. Various mechanisms regarding the effect of BTX-A on neuralgic pain have been suggested. These include: 1) inhibition of peripheral and central sensitization; 2) chemodenervation of the motor endplate; 3) anti-inflammatory effects; and 4) direct effects on muscle nociceptors. The precise mechanism of allodynia remains unclear. Inhibition of glutamate release by BTX-A at various levels including the primary afferent terminals might be responsible for the pharmacotherapeutic mechanisms of BTX-A in Herpetic allodynia.

Conclusions: This case demonstrated that BTX-A was very effective on the treatment of the herpetic neuralgia and allodynia.

PO99
What is the best practice for handling telephone medical complaints in an ambulatory neurology practice with a subspecialty in headache?
Moriarty MA
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Objectives: To determine the best practice for handling telephone medical complaints in an ambulatory neurology practice with a subspecialty in headache.

Background: Twenty-five percent of care delivery in internal medicine practices is conducted by telephone. Faulty triage accounts for 84% of errors identified in malpractice claims when telephone practices are cited. This represents significant risk to patients and a medical liability to ambulatory headache practices without telephone triage guidelines.

Methods: In reviewing the literature, the search terms headache and migraine were combined with telephone triage, telephone consultation, phone consultation, and telephone care in MEDLINE, EMBASE, Pubmed, CINAHL, and the Cochrane Library collection. No citations were found. The search was broadened to controlled randomized trials (Level 1, A, B), controlled trials and quantitative abaktses (Level 2, A, B) on telephone triage in primary care. Nine studies were reviewed.

Results: Adequately trained triage personnel with written treatment algorithms produces positive patient satisfaction ratings and safety assessments comparable to on-site care, saving provider time and economic costs. No translation of telephone triage standards for headache practices currently exist.

Conclusions: The evidence suggests that use of guidelines for telephone triage promotes safe, cost effective, quality care. Education of telephone operators in the unique needs of this population must be considered for successful implementation of evidence-based guidelines for telephone triage in headache patients. Patient satisfaction with this delivery method is essential for adoption to standard practice.
tion score” (RAS) which could range from 0 to 10. The primary outcome was defined as the percentage of GPs changing from a low (0–3) or medium (4–6) RAS at baseline to a high (7–10) RAS one month after the training.

Results: 951 GPs were randomized and 556 trained. A RAS was available before and one month after the training among 481 physicians (283 live interactive workshop, 198 e-learning). The percentage of GPs having progressed from a low/medium to a high grade was 13.6% in the e-learning group and 38.5% in the live presentation of GPs having progressed from a low/medium to a high grade was available before and one month after the training among 481 physicians.

Conclusions: These results are not in agreement with the literature data. Several explaining factors can contribute to these results: the participant mean age of 50 (French generation insufficiently familiarized with computing), insufficient mean time dedicated to the e-learning (11 min) and the attractiveness of the live training due to interactivity. However, the e-learning method is appealed to expand. To be effective, the e-learning training should use specific and interactive materials different from those used in live interventions.

PO101
Long-acting opioids for refractory chronic migraine: patient selection and guidelines for use
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Objectives: To provide a practical guideline for opioid use in refractory CM pts.

Background: Many patients with chronic migraine (CM) are refractory to our usual therapies. There have been a number of studies demonstrating limited rates of success with long-acting opioids (LAO’s).

Methods: This guideline was developed from the author’s studies on LAO’s, as well as a review of the literature.

Results: Patient Selection: Choose patients who: 1. fulfill criterion for refractory CM, 2. are reliable and well-known to the physician, 3. have demonstrated a good response to short-acting opioids (SAO’s), without abusing SAO’s, 4. are older (younger pts. develop tolerance more readily), 5. do not have a moderate to severe personality disorder, 6. do not have severe anxiety and/or depression.

Multidisciplinary Approach: A biopsychosocial approach involves practitioners such as: psychotherapist/physical therapist/biofeedback, etc. They play a vital role in active coping, which is a key to avoiding disability. Improving functioning is vital.

3 Phases of Treatment: In the initiation phase, screening and risk assessment are done, and the opioid agreement is signed. Assessed are: pain level, moods, and functioning. If possible, obtain: consultation with family members, the primary care physician, and a psychologist. The 2nd, intermediate phase includes ongoing assessment (with each visit) of pain level, functioning, moods, and abuse or AE’s. A brief PE assesses for slurring, abnormal gait, and pupillary abnormalities. The 3rd phase is switching or withdrawing of the opioid, due to abuse or declining efficacy.

Dosing and Titrations: Higher doses rarely work out well long-term. The usual range in our practice is: methadone, 3 to 40 mg daily, morphine (long-acting), 20 to 90 mg daily, oxycodone CR, 20 to 60 mg per day, and the fentanyl patch, 25 to 50 mcg. The Opioid Agreement: Evidence is lacking as to the efficacy of agreements. Each practice should adapt their own, which sets limits, educates, discusses termination criteria, etc. Do not label it a contract.

Urine Testing: The 2 purposes are: 1. to identify other substances, and 2. to detect levels of the opioid. Do random testing; chromatographic is better than aminogram.

Breakthrup Pain: Prescribing short-acting opioids increases abuse rates. Try and avoid layering opioids on top of opioids.

Tolerance: Younger pts. are more likely to become tolerant. To change opioids, start at 40 to 70% of the equivalent dose.

Heed Red Flags!!: Minor aberrant behaviors early in treatment are often overlooked. Pay attention to these red flags, particularly in pts. new to the practice.

Abuse and Chemical Coping: Pervasiveness and severity of abusive behaviors must be considered. All addicts are chemical copers, but not all chemical copers are addicts. Opioids should not be used for moods/stress/anxiety.

Conclusions: In a small number of patients, long-acting opioids may significantly improve pain and quality of life. With careful patient selection and close monitoring, certain patients may do well long-term.

PO102
Corporate-understanding of the significance of headache: a questionnaire survey to the managers in companies in Japan
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Objectives: To identify corporate-understanding of the significance of headache through questionnaire survey to the managers in companies in Japan.

Background: There are approximately 30 million patients suffering from chronic headache in Japan. Utilizing the media, Japanese Headache Society and pharmaceutical companies encourage the patients with headache to consult a medical doctor. However, such consultation, and also diagnosis and treatment of primary headache have not been increasing so far. Most of the managers in companies probably tend to prohibit the employees from consulting the medical doctor because they regard headache as a common condition in healthy subjects and do not understand the significance of headache as one of the important diseases. When the employees with headache wish to take a rest from their work and consult a doctor, the understanding of their managers about headache is especially important.

Methods: We sent the questionnaire concerning headache to the managers in 16 companies such as pharmaceutical companies and their related companies throughout Japan, and asked how they understand about headache. According to the fact whether the companies deal in triptans or not, they were divided into two groups; the one dealing in triptans (= T group) and the other not dealing in triptans (= NT group). Then we compared the difference between the two groups.

Results: We received the answers from 1396 managers (mean age was 46.3 ± 5.7 years); 879 managers in T group and 517 managers in NT group. Both 96.1% in T group and 99.0% in NT group revealed the understanding migraine. They also understood that the migraine interfered with their daily life. On the other hand, the rate of the manager’s understanding cluster headache was especially low (16.2%) in NT group compared with 73.3% in T group. Concerning the manager’s recognition of the drugs for migraine, the ratio of their recognizing the existence of not only abortive medication such as triptans but also preventive drugs in NT group was lower (triptans 47.6%, preventive drugs 21.7%) compared with (triptans 69.6%, preventive drugs 57.9%) in T group. The most of the managers in both groups (70.8% in T group, 85.3% in NT group) advised the employees to consult a medical doctor when they wished to take a rest from their companies because of their headache.

Conclusions: Although there were some differences among companies, the managers in companies in Japan had fairly good understanding for headache regardless of dealing in triptans. Much more community-based campaign should be performed for employees to talk with their managers about headache and consult a doctor.
PO103

A study of headache in general practice to identify diagnosed and undiagnosed migraine, and headache incorrectly labeled as migraine

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Objectives: To study headache presenting in the General Practice setting and to assign participants to categories of headache type using the International Headache Society’s (IHS) diagnostic criteria.

Background: Migraine headache is a very common occurrence in the general population, with 12–15% of the Irish population said to suffer from migraine. Yet it remains an underdiagnosed condition with many sufferers never receiving a diagnosis and many others being incorrectly labeled as migraineurs.

Methods: Using the International Headache Society’s diagnostic criteria for migraine, a questionnaire was designed and circulated to patients presenting to two General Practice surgeries. The results were analyzed according to the IHS criteria. Participants were assigned to categories of headache accordingly. The assignment of patients to categories of headache using the diagnostic criteria was analyzed and the results were compared with the literature.

Results: The percentage of headache sufferers in the study population was 88.9%. The general headache category represented 60.2% of this. Migraine headache represented a further 11.1%, consisting of 6.1% with migraine not previously diagnosed, and 5.0% previously diagnosed and fulfilling the IHS criteria. Previously diagnosed migraine not substantiated by the criteria represented 6.5% of the study population. A further 11.1% of the population had headache with migraine qualities but not meeting the criteria.

Conclusions: The diagnostic criteria used by the IHS are the gold standard in migraine diagnosis but they are extremely specific and in the General Practice setting they exclude a significant portion of patients with migraine qualities to their headaches from diagnosis. Further research into more practical and less exclusive criteria to be used in the primary care setting is required.

PO104

Towards the validation of an extended headache questionnaire: prognostic value of specific clinical history questions

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Objectives: To validate an extended headache questionnaire by assessing the positive or negative prognostic value of its individual questions.

Background: Headache questionnaires are used to make a systematic inventory of clinical patient characteristics. It is partly unknown to what extent such questionnaires and their individual questions provide valid information or how they can guide history taking.

Methods: Headache patients (>18 years old) who contacted a headache specialist (neurologist or anesthesiologist) were asked to complete an extended headache questionnaire consisting of 66 questions. Participants with migraine (IHS criteria), tension type headache (IHS criteria) or cervicogenic headache (CEH; Sjaastad criteria) were included. The diagnosis of the headache specialist was used as the gold standard. The prognostic value of all individual questions was analyzed by means of logistic regression with ‘headache diagnosis’ as the dependent variable and Odds Ratios (OR) were calculated.

Results: The questionnaire was completed by 63 patients (cervicogenic headache, n = 23; migraine, n = 29; tension type headache, n = 11; mean age 42.83 ± 15.64 years). For migraine, eight clinical history questions had a positive prognostic value, the most significant being ‘throbbing headache’ (OR: 13.3) and ‘side shifting unilateral headache’ (OR: 8.7). Seven negative prognostic indicators were identified, the most significant being ‘concomitant neck pain’ (OR: 0.3) and ‘reduced cervical range of motion’ (OR: 0.5). For tension type headache, only two negative prognostic clinical history questions i.e. ‘a familial history of headache’ (OR: 0.2) and ‘photophobia’ (OR: 0.3) were found. Regarding the diagnosis of CEH, five variables could be identified with a positive prognostic value, the most significant being ‘occipital start of the headache’ (OR: 6.4) and ‘provocation of the headache by specific neck movements’ (OR: 6.0). Six variables showed a negative prognostic value, especially ‘vomiting’ (OR: 0.1) and ‘frontal/ocular start of the headache’ (OR: 0.2).

Conclusions: Using the negative and positive prognostic indicators identified in the present study, the value attributed to specific patient characteristics can be estimated more precisely leading towards an optimized assessment of headache patients.

PO105

Validation of disease progression in a population of migraineurs

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Objectives: To validate the Staging Questionnaire.

Background: Conceptually migraine can be understood as a potentially progressive disease that evolves from an episodic pain syndrome into chronic disease. The major differentiating diagnostic feature defining episodic and chronic migraine is headache frequency. However, medical management of migraine patients with frequent and chronic migraine is often complicated by co-morbid diseases such as depression, anxiety, irritable bowel syndrome and fibromyalgia. In addition complex psychosocial factors often add additional disease burden. To date, there has been little effort to understand and stage patient complexity based on a global assessment of migraine and co-morbid disease. A Staging Questionnaire has been suggested to assist clinicians with the stratification of the migraineur’s disease (Lipton, Cady, Farmer, Bigal. Managing Migraine: A Healthcare Professional’s Guide to Collaborative Migraine Care. Hamilton, Canada: Baxter, 2008, 95).

Methods: Subjects: A total of 87 patients (19 males, 68 females) with a diagnosis of migraine answered questionnaires mailed to them prior to their appointment at a Midwest headache center. The subjects’ mean age was 40.57 (SD, 13.81) with a range from 16 to 75 years.

Instruments: Besides the 5-question Staging Questionnaire, the subjects answered McGill Pain Questionnaire (Short Form), Headache Impact Test (HIT), Zung Depression Scale, and the number of headache free days per month.

Procedure: Upon arriving for their appointment, subjects gave the answered questionnaires to the receptionist. These were scored and compiled.

Results: The Staging Questionnaire demonstrated internal consistency (Chronbach’s α = 0.70), even with its multidimensional nature and self-report format. The Staging Questionnaire was significantly correlated (P < 0.001) with the McGill affective pain scale (r = 0.58), the McGill sensory scale (r = 0.55), the McGill total score (r = 0.59), the Zung (r = 0.56), the HIT (r = 0.58), and headache free days per month (r = -0.62). The four stage model was also compared with a more traditional two stage model (episodic versus...
chronic migraine) in terms of effect size, using $\eta^2$ in the general linear model. The four stage model showed much larger effect sizes across all measures (0.395 compared to 0.316), on the McGill affective scale (0.319 compared to 0.216), the McGill sensory scale (0.257 compared to 0.195), McGill total scale (0.325 compared to 0.235), the Zung (0.273 compared to 0.213), the HIT (0.295 compared to 0.205) and headache free days per month (0.296 compared to 0.125).

Conclusions: The Staging Questionnaire is a valid measure that plots the progression of disease from Stage 1 through 4. It addresses the multidimensional qualities of the migraineur and this evolution of migraine. Its significant correlations with the other valid measures indicate that in five questions, the questionnaire encompasses the rating of pain, disability, and depression, suggesting that the disease progression of migraine is much more than an increased frequency of headaches. This staging tool may enable clinicians to tailor therapeutic and educational interventions to the needs of the patient.

PO106 Migraine prevalence in patients aged up to 50 with acute cerebrovascular insult (CVI) treated in St. Sava Hospital during 2008
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Objectives: The objective of this study was to determine percentage incidence of migraine in patients with acute CVI compared to the population of patients with acute CVI without pre-morbid migraine, all of whom were aged up to 50 and 50 and were treated in St. Sava Hospital during the year 2008. Migraine prevalence up to the above said age is the largest in extent, whereas the incidence of other cerebrovascular disease risk factors is the smallest. This is why other factors minimally affected the result set forth as the objective of this study.

Background: It is well known that patients with complicated migraine or migraine with aura may suffer migraine infarction with small incidence that fails to rise above 1% of all brain strokes. Vast majority of patients with acute cerebrovascular disease in the whole territory of Belgrade are treated in St Sava Hospital. Given the incidence of migraine in general population, the goal in this study was to determine migraine prevalence in patients aged up to 50 with acute CVI, as well as to prove migraine infarction within this population.

Methods: Statistical processing of the data obtained from the computerized database of St. Sava Hospital was applied.

Results: In the period from 1 January 2008 to 31 December 2008, 6476 patients with cerebrovascular disease were admitted in St. Sava Hospital. Ischemic insult occurred in 4610 of these patients, out of whom 752 patients were aged up to 50 and 50. Four hundred and five of them were male and 347 were female patients. Hetero-anamnestic and auto-anamnestic data revealed that, within this age group of patients, 30 male patients and 45 female patients used to have migraine headaches. Out of these 75 patients, 3 patients suffered from migraine with aura (2 of them were female and 1 was male), while another woman aged 38 suffered from migraine with aura and had neurological deficit in terms of hemiparesis on the right within the aura. The neurological deficit was retained even after the migraine attack. Neuro-imaging methods confirmed the left temporoparietal position of an ischemic lesion. This case represents the only confirmed instance of migraine infarction.

Conclusions: This study showed that migraine prevalence in patients with acute CVI is not larger than migraine prevalence in general population. In addition, a single instance of migraine infarction was confirmed in a female patient in her 30s who suffered from migraine with aura.
PO109
Comparing colleges’ of pharmacy didactic migraine education to the US headache consortium’s evidence-based migraine treatment guidelines

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Objectives: Evaluate the academic year 2008/2009 Doctor of Pharmacy (Pharm.D.) candidates’ didactic migraine training.

Background: Year-after-year a complaint of “headache” ranks as a leading reason people seek a pharmacist’s assistance, up to 53,000 times daily. Yet the quality of pharmacists’ training to treat headache, particularly migraine, remains unknown.

Table. Survey responses

<table>
<thead>
<tr>
<th>Question</th>
<th>Written handout (%)</th>
<th>Verbally conveyed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the US Headache Consortium’s evidence-based migraine treatment guidelines discussed?</td>
<td>55</td>
<td>77</td>
</tr>
<tr>
<td>Is the concept of stratified-care explained?</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>Is the concept of step-care explained?</td>
<td>65</td>
<td>74</td>
</tr>
<tr>
<td>Is information regarding the reason(s) for the selection of over-the-counter agents (OTC) versus prescription agents explained?</td>
<td>49</td>
<td>70</td>
</tr>
<tr>
<td>Is the patient counseling point of limiting acute therapy use to two days or less per week explained?</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Are the goals of acute migraine therapy explained?</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Are the goals of preventive migraine therapy explained?</td>
<td>75</td>
<td>81</td>
</tr>
<tr>
<td>Are the indications of preventive migraine therapy explained?</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>Are patient counseling points for preventive therapy explained?</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>Is the need for patients to maintain a headache diary discussed?</td>
<td>70</td>
<td>87</td>
</tr>
<tr>
<td>Are non-drug treatments discussed (eg. biofeedback)?</td>
<td>73</td>
<td>81</td>
</tr>
<tr>
<td>Are butalbital-containing products recommended for acute migraine attacks?</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Are any tools that assess migraine-related debilitation discussed?</td>
<td>20</td>
<td>32</td>
</tr>
</tbody>
</table>

"percentages indicates % of programs responding "Yes" to the question

Methods: Self-administered survey sent to all 90 Accreditation Council for Pharmacy Education (ACPE)-approved Pharm.D. programs assessing information conveyed to students via their therapeutics’ course migraine lecture’s written handout and verbally conveyed by the instructor. Survey questions are based on the US consortiums’ guidelines’ recommendations.

Results: Seventy-seven programs responded (77/90 = 86%). Sixty nine usable surveys were identified and are tabulated in Table I. A total of eight programs were excluded from analysis because this study’s lead author provided two programs’ migraine lecture, four programs do not provide a migraine lecture, and two programs are “student self-directed learning”, thus lack a formal migraine lecture. A total of 49 lecture handouts were returned and evaluated.

Conclusions: Opportunities exist to improve Pharm.D. candidates’ didactic migraine education. Particular attention is needed regarding 1) expanded dissemination of evidence-based care, 2) the rationale to select OTC versus prescription products, 3) avoiding butalbital-containing products, and 4) tools to assess migraine-related debilitation.

PO110
Imaging study for patients with headache at the emergency department

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Objectives: A purpose of this study is to assess an importance of imaging study for a diagnosis of headache at the emergency department.

Background: Headache is one of the most common symptoms at the emergency department. Taking a history about headache is most important for a diagnosis of headache. It’s also important to exclude headache caused by organic lesions.

Methods: In serial 447 patients (199men, 248women, average44.3 years) who visited the Emergency Room, Kawakita General Hospital between March 2008 and August 2009 because of headache were evaluated. Information about clinical characteristics, history about headache, imaging study and diagnosis of headache were obtained from medical records. Correlation between headache and imaging study was closely evaluated.

Results: One hundred and seventy-four of 447 patients (38.9%) underwent brain imaging. The majority of neuroimaging were brain CT (98.9%), and remains were brain MRI (1.1%). Patients with imaging were significantly younger (53.3 years) than patients without imaging (38.5 years). Headache was an only symptom in 23 of 174 (13.2%) patients with imaging, and in 24 of 273 (8.8%) patients without imaging. Onset of headache and clinical course of headache were not described in many patients. Most of patients with imaging were febrile, although about a half of patients without imaging were febrile. More than half of patients with imaging were hypertensive, although more than half of patients without imaging were normotensive. Level of consciousness was alert in more than half of patients with imaging. In most of patients without imaging, level of consciousness was not described. There were one or more focal neurological findings in 53 of 174 (30.5%) patients with imaging, and in 18 of 273 (6.6%) patients without imaging. In 174 patients with imaging, 24 (13.8%) had diagnosed having primary headache (Migraine 11, Tension-type headache 11, Cluster headache 2), 85 (48.9%) had diagnosed having secondary headache (cerebral or cranial vascular disorder 42, non-vascular intracranial disorder 4, infection 24, attributed to disorder of homeostasis 10, disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures 2, psychiatric disorder 3), and remains (37.3%) had not diagnosed. In 273 patients without imaging, 28 (10.3%) patients had diagnosed having primary headache (Migraine 6, Ten-
sion-type headache 21, Cluster headache 1), 188 (68.9%) patients had diagnosed having secondary headache (non-vascular intracranial disorder 6, a substance or its withdrawal 2, infection 171, disorder of homeostasis 1, psychiatric disorder 8), and remains (20.8%) had not diagnosed.

Conclusions: At our emergency department, 38.9% of patients with headache underwent imaging study, and most of them were brain CT scan. Patients with imaging were older, more hypertensive, and a febrile compared with patients without imaging. Many patients could not be diagnosed by only an imaging study, except for patients with headache attributed to cranial or cervical vascular disorder.

PO111
Abstract withdrawn

PO112
Difficulties for diagnosing and treating migraine among general practitioners
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Objectives: Our aim was to analyse the actual knowledge of the local general practitioners (GPs) in migraine diagnosis.

Background: Headache in general, and particularly migraine, is the main reason for consultation to neurology services from the GPs.

Methods: Unselected GPs from two provinces in Spain were asked main reason for consultation to neurology services from the GPs.

Results: Of the 105 GPs who were consulted, 46 (44%) diagnosed migraine correctly, 41 (39%) diagnosed the patient as tension-type headache, 17 (16%) as 'mixed' headache and one GP was unable to diagnose the patient. With only two exceptions, all recommended NSAIDs as symptomatic treatment. Triptans were recommended by 67 GPs (including 15 of the 41 who had diagnosed the patient as tension-type headache). Regarding preventive treatment, it was not considered by 30 GPs. A total of 66 GPs would prescribe beta-blockers (13 out of the 41 giving the diagnosis of tension-type headache), 35 amitriptyline (23 of those who had diagnosed as tension-type headache) and the remaining nine other treatments.

Conclusions: More than half of the GPs made diagnostic mistakes and more than one-third treatment mistakes. In conclusion, there is a need for a better teaching in primary headaches, the first reason for neurological consultation for the GPs.

PO113
Livening and Latham: induction, deduction, and the Cambridge connection
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Objectives: To investigate the origins of the important contributions of the 19th century physician Edward Liveing and Peter Wallwork Latham to the development of theories of migraine.

Background: The major 19th century British contributions to theories of migraine pathogenesis were Edward Liveing’s theory of nerve storms and Peter Wallwork Latham’s vascular theory, based on contemporary understanding of the function of the sympathetic nervous system. Both Liveing and Latham studied mathematics and medicine at the University of Cambridge in the 1850s, developed their theories of migraine in the 1860s, and published their work in the 1870s. How, then, did their theories come to differ so radically? This paper suggests that to understand the origins of their theories one must understand their different institutional backgrounds at that University.


Results: Liveing’s connection with the elite physicians based at Caius College and his subsequent successful metropolitan practice in London put him firmly within the tradition of inductive clinical science by which general laws were supposed to be developed from analogies drawn from wide clinical experience. Liveing’s theory therefore puts migraine within a general category of paroxysmal disorders that includes many conditions, such as asthma, that are no longer regarded as at all neurological. Latham, on the other hand, was educated at Downing College, where he became assistant to (and ultimately succeeded) the Downing Professor of Medicine William Webster Fisher. In the 1840s and 1850s Webser was in the vanguard of British clinical neuroanatomy, publishing well-regarded papers on the sympathetic nervous system. Latham’s deductive approach to the development of a theory of migraine rests upon observations made in his role as Webster’s assistant in the 1860s, and an approach to medical science that was beginning to prioritise information derived from the laboratory.

Conclusions: While Liveing’s name is now better known by historians of migraine, Latham’s theory was more in tune with prevailing views of migraine throughout the century following its publication. With our current understanding of migraine as a neurovascular disorder, both are now regarded as prescient pioneers, and their inductive and deductive approaches are still relevant in advancing knowledge in the field.

PO114
Improving the management of migraine sufferers: focus on pain-free interval and comorbidity
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Objectives: Objectives of the study were to evaluate quality of life (QoL) out of M attacks and to reveal clinical and psychopathological factors which determine QoL in pain-free interval in M subjects.

Methods: Well established diagnostic algorithm of migraine (M) is mainly focused on the characteristics of attacks and attack-related quality of life (QoL) which present only ‘the top of an iceberg’. Less attention is being given to the QoL of M patients in headache-free intervals.

Results: The study included 320 M patients (m. age 37.9 ± 10.3, F-85%, M-15%; u. illness duration. 20.8 ± 11.1 years; MO-70%, MA-15%). Methods: clinical interview with focus on comitant/ comorbid conditions, VAS (%), West Haven-Yale Multidimensional Pain Inventory with QoL Inventory (as a part of WHYMPI) focused on different QoL dimensions out of attacks, State-Trait Anxiety Inventory (STAI), Beck’s Depression Inventory (BDI).

Results: In a total M group QoL was reduced by 33%; satisfactory level (reduction <30%) was seen only in 36% of subjects; 64% had low QoL level (reduction by 30–40% in 34% of subjects, ≤40% – in 30%). Further analysis was based on the comparison of two ‘opposite’ groups of patients: with good (reduction <30%) and low (reduction >40%) QoL levels. The analysis of main clinical characteristics of M attack (frequency, severity and duration) has shown that significant (003) difference existed only for the parameter ‘attack dur-
Adherence with pharmacologic prophylaxis for migraine

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Objectives: To examine real-world adherence with pharmacologic prophylaxis for migraine.

Background: Persons with frequent and/or severe migraines often receive selected antidepressants, antiepileptics, or beta blockers as prophylaxis against migraine. Information is limited on adherence with these therapies in real-world clinical practice.

Methods: Using a US health insurance claims database spanning the period 1/1/2003 to 12/31/2005, all migraine patients who initiated treatment with selected antidepressants (tricyclics [TCAs], selective-serotonin reuptake inhibitors [SSRIs], bupropion, mirtazapine, trazodone, venlafaxine), antiepileptics (carbamazepine, divalproex sodium/sodium valproate, gabapentin, topiramate), or beta blockers (atenolol, metoprolol, nadolol, propranolol, timolol) were identified. Date of initial receipt of these agents was designated the ‘index date’. Patients with <6 months of complete data preceding and following this date (‘pretreatment’ and ‘follow-up’, respectively) were dropped from the study sample, as were those without evidence of migraine during pretreatment. Patients with evidence of depression were excluded from analyses of antidepressants; those with epilepsy, from analyses of antiepileptics; and those with hypertension or heart failure, from analyses of beta blockers. An assessment of the number of prescriptions for – and therapy-days with – prophylaxis over 6 months was assessed. Adherence with prophylaxis was examined using a medication possession ratio (MPR); patients with MPR < 80% were designated non-adherent.

Results: A total of 1166 migraine patients who began treatment with TCAs; 696 with SSRIs; 493 with other antidepressants; 1896 with antiepileptics; and 936 with beta blockers were identified. On average, patients received slightly less than three prescriptions for migraine prophylaxis over 6 months (range: 2.6 [TCAs] – 3.2 [SSRIs]), comprising about 100 days of therapy (range: 80.5 [TCAs] – 114.6 [SSRIs]). Relatively few patients were adherent (MPR ≥ 80%) with prophylaxis at 6 months, ranging from 15% for TCAs to 28% for SSRIs (Figure). Approximately one-half of all adherence failures occurred within one month of therapy initiation. Mean (SD) MPR was 42.8% (31.8%) for TCAs, 59.2% (33.8%) for SSRIs, 51.8% (34.3%) for other antidepressants, 50.8% (33.7%) for antiepileptics, and 50.6% (34.9%) for beta blockers.

Conclusions: Adherence with pharmacologic prophylaxis for migraine is poor, albeit slightly better for SSRIs than other medications. These findings suggest that adherence with current treatment options remains challenging.

Prevalence of migraine in a population based sample in Germany: results of the GHC study

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Objectives: To estimate a 1-year prevalence of migraine (MIG) and associated risk factors in the general population in Germany.

Background: Large population-based studies in Germany assessing the prevalence of MIG are scarce.

Methods: A random sample of 16,500 participants (5,500 each in Essen, Münster in North Rhine-Westphalia in the western part and Siegen in the southern part of Germany) was screened by using a previously validated questionnaire.

Results: The response rate was 60.4% (9968 of 16,500), mean age 43 ± 13.1, 5234 (52.5%) of them were women. The 1-year prevalence of migraine was 9.2% (95% confidence interval: 8.5–9.9%). The 1-year prevalence of MIG was 2.5% (95% confidence interval: 2.1–2.9%). The prevalence of MIG was higher in women (3.4%) than in men (1.7%). The prevalence of MIG was higher among participants with lower education, higher BMI, and lower socio-economic status. The prevalence of MIG was higher in participants with a higher number of comorbid conditions. The prevalence of MIG was higher in participants with a higher number of comorbid conditions. The prevalence of MIG was higher in participants with a higher number of comorbid conditions.

Conclusions: The prevalence of MIG in the general population in Germany is lower than in other European countries. The prevalence of MIG is associated with lower socio-economic status, lower education, and higher number of comorbid conditions.

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Conclusion: The prevalence of migraine estimated as 16.4% in this study was similar to one of previous population based study done on 15–55 years old households. However, in present study, women/men ratio (2.89) was higher than before. Lower rates of migraineurs on prophylactic treatment than expected was remarkable.

PO117
Prevalence of migraine in Turkey: a nationwide home-based study
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Objective: To describe the impact of migraine in Turkey by estimating its prevalence and analyzing its clinical features as well as demographic and socio-economic characteristics of the participants by a population based study.

Background: Migraine prevalence differs from one to another country and even in the same country depending upon the methodology. In 1998, migraine prevalence was estimated as 16.4% in Turkey among 15 to 55 years old Turkish people by a population based study using ICH-I criteria.

Methods: This nationwide, home based prevalence study was done in 21 cities presenting all geographical regions of Turkey. Total 5323 households, aged between 18–65 years, were interviewed by using a structured interview form and examined for headache by specially trained 33 physicians. Interview form included diagnostic questions based on ICH-2 criteria for migraine, features of headache and associated symptoms, demographic and socio-economic information, information about previous physician visits for headache, previous headache diagnoses, acute and prophylactic medication for headache, and access to headache medication.

Results: Of 5323 participants, 48.8% were women and 51.2% were men. Mean age was 35.9 ± 12 years. Of all participants, 2376 reported having headaches during last one year and 871 were diagnosed as migraine. Migraine prevalence was estimated as 16.4% (8.5% in men and 24.6% in women). In migraineurs, mean headache frequency was 5.9 ± 6 per month, mean attack duration was 35.1 ± 72 hours and mean number of headache days per month was 6.2 ± 6. Of 871 migraineurs, 68.3% had three or more migraine attacks in a month, 54.2% of all had severe, 39.0% moderate and 6.0% mild headaches. 70.6% of migraineurs had admitted to physician for their headaches. Of migraineurs, 42.0% had been diagnosed as migraine by first admitted physician, 14.3% reported ergotamine use and 2.9% reported triptan use, 4.9% were on prophylactic treatment. MIDAS scores revealed moderate or severe disability in 25.3% of migraineurs.

PO118
Migraine and allergy – a significant comorbidity
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Objective: To document allergic inflammations triggering migraine attacks (allergic migraine) and vice versa (migrainous allergy).

Background: Molecular mechanisms of peripheral sensitization of nociceptors could be identical for painful and pruritic disorders. Therefore, therapeutic approaches for pain treatment may also be beneficial for allergic inflammations. Montelukast, cyproheptadine, bromfenac, ketorolac and corticosteroids are found to be very effective in both migraine and allergy.

Methods: Prospective study spanning 5 years (April 2004–March 2009), 10,240 migraine patients (ICHD II 1.1, 1.2, 1.6), aged 10 to 50 years were questioned about various allergic manifestations. Different migraineurs were diagnosed using a headache questionnaire based on ICHD II diagnostic criteria.

Results: 7995 (78%) were suffering from various allergic disorders either at the time of presentation or sometime in the past. Nasal allergy was the commonest 6396 (80%). Ocular allergy diagnosed in 4797 (60%). Bronchial allergy in 3198 (40%) and skin allergy in 640 (8%). Food allergy (71) and drug allergy (63) were the other allergies diagnosed. 1439 were getting all three allergies (naso-ocular-bronchial). 52% reported migraine and 48% reported allergy as the first manifestation in life. 102 patients reported getting migraine headpain during or immediately after the allergic inflammatory process (Allergic migraine) and in 21, migraine triggered an allergic inflammation (Migrainous allergy).

Conclusion: Migraine increased the risk for allergic disorders and allergic disorders increased the risk for migraine. This bidirectional association immensely helps the clinician to explain the causative molecular mechanisms and genetic origin of these two disorders in the most simple way to their patients. In addition, this significant relation influences the choice of therapy, giving opportunity to treat both the conditions with a single drug. Moreover, identification of this association should yield better insight into the pathophysiology (mast cell activation) of both diseases.

PO119
Employment and work impact of headache among episodic and chronic migraine sufferers: results of the American migraine prevalence and prevention (AMPP) study
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Objective: To compare the work productivity and employment status of chronic migraine sufferers to those migraineurs with less frequent headaches.

Background: Chronic migraine (CM) has been recognized as significantly more disabling than episodic migraine (EM), but the work impact of chronic migraine has yet to be quantified.

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Methods: In 2005, we mailed questionnaires to 24,000 severe headache sufferers identified from a previous US population survey. Data were from 11,624 respondents defined as having ICHD-2 migraine who completed the employment questions were analyzed. Four groups were compared—CM (ICHD-2 migraine with 15 or more days of headache/month, n=640); high-frequency EM (HFEM) (ICHD-2 migraine with 10–14 days of headache/month, n=587); moderate-frequency EM (MFEM) (ICHD-2 migraine with 4–9 days of headache/month, n=3715); and low-frequency EM (LFEM) (ICHD-2 migraine with 0–3 days of headache/month, n=6682). Lost Productive Time (LPT) was defined as the sum of missed hours plus reduced productivity hour equivalents. The cause of LPT was self-defined by the respondent. Employment status was self-reported as working full or part time, unemployed, on medical leave, or one of several other options.

Results: Headache-days were directly related to employment status. Compared to those with LFEM, the adjusted prevalence ratio (PR) for working for pay full or part time was 0.86 (95% CI = [0.77, 0.97]) for those with HFEM and 0.80 (95% CI = [0.71, 0.90]) for the CM group. Among employed individuals with migraine, the average LPT per worker/week was specifically due to headache was 4.5 hours for those with CM compared to 1.2 hours/worker/week for those with LFEM. LPT due to non-headache causes was similar among headache frequency groups. The 9.1% of employed migraine sufferers with HFEM and CM account for 34.7% of the overall LPT.

Conclusions: Among headache frequency groups. The 9.1% of employed migraine sufferers with HFEM and CM account for 34.7% of the overall lost work time.

PO120

Headache prevalence and characteristics of a socially active population working in the Tokyo metropolitan area


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Objectives: This study aimed to clarify headache prevalence among socially active people working in the Tokyo metropolitan area and clinical characteristics of headache sufferers in this population.

Background: It has been not clear what extent the impacts of migraine affect social activities in the productive and active population in this area.

Methods: We conducted a survey concerning headache prevalence and headache characteristics of 7917 people at four institutions located in the metropolitan area around Tokyo, which consist of a university hospital, a department store, an insurance company, and a computer manufacturing company. The items in the questionnaire included demographic parameters (age, gender, occupation, etc.), headache prevalence, headache characteristics, the frequency with which they sought medical attention because of headache, and the relationship of headache frequency and severity with the burden of work.

Results: Of all respondents, 46% were female. Headache prevalence was 64.7% of the entire population. Migraine was present in 8.9%, and women exhibited higher prevalence of migraine (15% vs. 3.7%). As for the difference of headache prevalence among occupations, headaches were most common in nurses working at the university hospital, such that migraine and tension-type headache were identified in 17.3% and 23.7%, respectively. The influence of migraine on social activities was remarkable, as witnessed by the fact that 22.4% of the migraineurs had been obliged to be absent from work because of headache several times during a year. Among the migraineurs, 2.0% could not go to work once a month. Nevertheless, as much as 59.4% of the migraineurs had never consulted with a physician about their headaches. Moreover, 24.6% of the migraineurs was not in touch with any physician at the time of survey. The most common reason why they had stopped visiting their physician was that they had been told that their headaches were not fatal, followed by inability to get adequately advised about their headaches by their physician. These findings underscore a need to inform the public of migraine more thoroughly to encourage migraine sufferers currently medically unattended to seek medical attention with a headache specialist. In comparison, tension-type headache sufferers were less affected in terms of restrictions of social activities, because there had been no impact of headache on their work in 89.9%. However, there was a clear correlation between the headache severity and the duration at which they worked using a personal computer (PC). Working with a PC for more than 8 hours a day appeared to increase the development of tension-type headache in our population. As regards how headache sufferers managed their headaches, more people used OTCs than drugs prescribed at hospitals irrespective of their headache types.

Conclusions: The present survey has uncovered that migraine poses a problem about social activities and has revealed that a considerable proportion of migraine sufferers fail to seek necessary medical attention.

PO121

Cutaneous allodynia — a predictor of migraine chronification: a longitudinal population-based study

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Objectives: To explore the relationship between cutaneous allodynia (CA) and new onset chronic migraine (CM) in individuals with episodic migraine (EM).

Background: CA is a marker of increased excitability of central nociceptive neurons, i.e. central sensitization. CA is more prevalent in CM than EM. It is unclear if CA is the risk factor for or the consequence of the development of CM.

Methods: This study is a part of American Migraine Prevalence and Prevention study. A population sample of 24,000 individuals was sampled in 2005 to identify those with EM. Migraineurs completed Allodynia Symptom Checklist (ASC), assessing the frequency of CA symptoms during headache. Each of 12 items was scored on a three point scale corresponding with response options were never / rarely (0), less than 50% of the time (1), 50% of the time or more (2). Total ASC score ≥ 3 indicated presence of CA. ASC included questions, which could identify three subtypes of CA: thermal, mechanical static and mechanical dynamic. Subscales for thermal, dynamic, and static mechanical allodynia were not dichotomized and instead used as continuous predictors. Repeated measures logistic regression was used to model the probability of new-onset of CM in 2006 and 2007. Odds ratios were adjusted for depression, anxiety, body mass index, disability (assessed by MIDAS), income, sex, age.

Results: Of 11,388 individuals with EM at baseline in 2005, 160 met criteria for CM in 2006 while 162 met criteria in 2007. Consequently, there were a total of 322 individuals who transformed from EM in a preceding year to CM in a subsequent year in this sample. Episodic migraineurs with total (all subtypes) CA (OR = 1.74, 95% CI = 1.32–2.28, P < 0.001) were at increased risk of CM at follow-up. Thermal (OR = 1.07, 95% CI = 1.01–1.13, P = 0.017),
PO122
Migraine, headache and survival in the Reykjavik study
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Objectives: To estimate the relative risk of overall and cardiovascular disease (CVD) related death in headache sufferers compared to others.

Background: In recent years numerous studies have shown that migraine is a risk factor for cardiovascular disease. Few results have been published on migraine in relation to cardiovascular- and/or all-cause mortality, with somewhat contradictory findings, depicting migraine as a risk factor, neutral or a protective factor.

Methods: Migraine and headache was defined from a questionnaire in the Reykjavik Study (n=18882) a population-based cohort study, aged 33–81. Those with headache once or more per month were included in the analyses. Hazard ratio was used to estimate the relative risk of death after adjusting for demographics and baseline CVD risk factors.

Results: Compared to those without headache (n = 13176), risk of overall mortality was higher in those with migraine: RR 1.14 [1.07–1.22] (n = 2051) but not MO (1.02 [0.90–1.15]; n = 635). Risk was not elevated for those with non-migraine headache. Average follow-up was 25.9 years (0.1–40.2 years) in all 474448 person years. We used Cox proportional hazards to estimate the relative risk of death after adjusting for demographics and baseline CVD risk factors.

Conclusions: Men and women with migraine in particular those with MA were at increased risk of all-cause and CVD mortality.

PO123
Disability status of chronic and episodic migraineurs globally
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Objectives: To examine the impact of CM compared to EM on headache-related-disability, absenteeism, and presenteeism globally.

Method: Cross-sectional data was collected via a web-based survey in five countries: US, Canada, Germany, UK, and France. Respondents were classified as CM (ICHD-2 diagnosis of migraine and ≥15 headache days/month) or EM (ICHD-2 diagnosis of migraine with <14 headache days/month). Minimum of fifty CM patients per country were targeted. Productivity was measured by the Migraine Disability Assessment Questionnaire (MIDAS) which captures headache-related disability over the preceding 3 months and categorizes respondents into four grades of severity of disability. Data was also gathered on work absenteeism and presenteeism due to headache over the preceding 4 weeks. An analysis of covariance (ANCOVA) model predicted rank-order MIDAS scores by migraine group when adjusted for country, age, gender, race, education, and comorbidities.

Results: Panelists were contacted (n = 30,200), 13,050 responded, of which 6,258 had migraine and were eligible for survey. Of invitees: 1.1% had CM (n = 325); 18.4% had EM (n = 5541). Respondents were mostly female (86.8%) with an average age for CM and EM 44 (± 12) and 42 (± 11), respectively. Across countries, more CM respondents had MIDAS grade IV, indicating severe disability due to migraine. EM respondents were more evenly distributed across the four MIDAS disability grades. Both CM and EM respondents reported headache symptoms affecting ability to work; however, productivity was affected more for CM. CM respondents (86.6 ± 84.1, mean ± SD) had significantly higher MIDAS scores than EM (18.5 ± 27.3) across countries (P < 0.0001), after adjusting for demographic covariates and comorbidities.

Conclusions: In this global population, CM had significantly more severe migraine-related-disability and impact on productivity when compared to EM. Country-specific cost impact for this loss in productivity should continue to be explored.
PO124

Temporomandibular symptoms, migraine and chronic daily headaches in the population

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Objectives: To explore the relationship between headache types and TMD, as well as number of TMD symptoms.

Background: Migraine is a chronic-recurrent disorder that sometimes progresses into chronic migraine, a subtype of the chronic daily headaches (CDH). Most risk factors for CDH (including TMD) have been assessed as a dichotomous variable (present or not). More important is to measure if magnitude of exposure increases risk.

Methods: This questionnaire-based population study estimated prevalence rates of TMD symptoms and of primary headaches in 1230 individuals representative of an urban population. Primary headache syndromes (HA) were classified based on the International Classification of Headache Disorders. Five questions focusing on TMD symptoms were asked, based on the recommendation of the the American Academy of Orofacial Pain. The χ² test and odds ratio - 95% Confidence Interval (CI) was applied and the significance level adopted was 5%.

Results: From 1230 individuals surveyed (51.5% women), 1148 presented any type of HA. Individuals with TMD were more likely to have any form of HA as compared to individuals without TMD symptoms (P < 0.001). Taking the no headache group as a reference (27.7% had TMD symptoms), the prevalence ratio (PR) of TMD symptoms were significantly higher in individuals with ETTH (PR = 1.48, 95% CI = 1.20–1.79), migraine (PR = 2.10, 95% CI = 1.80–2.47) and CDH (PR = 2.41, 95% CI = 1.84–3.17). Incremental TMD symptoms yielded increased relative odds of all other headaches. Table 1 shows that taking the no headache group as the reference, when 1 and 2 symptoms of TMD were present, the magnitude of increase was higher in the CDH group, intermediate for migraine and non-significant for ETTH; when >3 symptoms were present, odds were significantly increased for all headache groups.

Table 1. Relative risk of headache types as a function of number of symptoms suggestive of TMD.

<table>
<thead>
<tr>
<th>Headache type</th>
<th>No TMD</th>
<th>1 TMD symptom</th>
<th>2 TMD symptoms</th>
<th>&gt;3 TMD symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMD</td>
<td>N (%)</td>
<td>N [%], OR (95%CI)</td>
<td>N [%], OR (95%CI)</td>
<td>N [%], OR (95%CI)</td>
</tr>
<tr>
<td>No</td>
<td>489 (72.3%)</td>
<td>120 (17.8%)</td>
<td>39 (5.8%)</td>
<td>28 (4.1%)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>ETTMH</td>
<td>118 (90.9%)</td>
<td>46 (22.0%)</td>
<td>17 (8.5%)</td>
<td>21 (10.5%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>100 (41.3%)</td>
<td>61 (25.3%)</td>
<td>27 (11.2%)</td>
<td>51 (22.0%)</td>
</tr>
<tr>
<td>CDH</td>
<td>11 (19.2%)</td>
<td>13 (42.4%)</td>
<td>6 (19.2%)</td>
<td>4 (12.0%)</td>
</tr>
</tbody>
</table>

TMD, temporomandibular disorder; OR = odds ratio; CI, confidence interval; ETT, episodic tension-type headache; CDH, chronic daily headache.

Conclusions: We found that TMD is associated with migraine and CDH. Since most individuals with CDH evolve from migraine, the finding is biologically plausible and the presence of TMD symptoms in migraineurs could increase the risk for migraine chronication.

PO125

Economic burden of chronic daily headache in France

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Objectives: The aim of this study was to determine the economic burden of chronic daily headache (CDH) in France.

Background: Epidemiologic evidence indicates that chronic daily headache (CDH) is a major health problem. While the clinical and the humanitarian burden of CDH is increasingly recognized, few researches have been conducted on the economic impact of CDH. So, we have utilized data from the GRIM study to evaluate the impact of CDH on health care resource utilization, medication use, and productivity loss.

Methods: From a representative general population sample of 10 585 individuals aged ≥15 years in France in 1999, 1486 individuals experiencing headaches of whom 151 with CDH were identified and interviewed (face-to-face) regarding healthcare resource consumption in the previous 6 months. By applying unit costs to the resource data, annual costings were determined for physician consultations, hospitalization, medication use and diagnostic/laboratory tests, and evaluated from a healthcare system perspective. Based on these data, we have estimated the total direct costs associated with CDH. In addition, an evaluation of indirect costs was performed considering information on work absenteeism and lost productivity derived from the items one and two of the Migraine Disability Assessment Score (MIDAS) questionnaire. Finally, direct and indirect costs induced by CDH were compared with those induced by non migraine and migraine episodic headaches.

Results: Total annual direct healthcare cost were estimated to be €1322 per individual with CDH, corresponding to €1900 million when extrapolated to all individuals experiencing CDH and aged ≥15 years (French CDH prevalence determined to be 3% in GRIM study). Around two-thirds (€1181 million) of this extrapolated cost were induced by hospitalization, whereas physician consultations, medications use and diagnostic/laboratory tests corresponded to €341, €241 and €137 million respectively. The total annual direct cost of episodic headaches was much lower at €28 per individual with non migraine episodic headache and €128 per individual with episodic migraine. Regarding MIDAS data, the mean number of days lost to work absenteeism and reduced productivity over 3 months were 0.73 [2.79] and 0.83 [5.37] respectively. These values were > 1.4-fold higher in the individuals classified as having CDH compared with those with episodic migraine and more than > 3-fold compared with those with non migraine episodic headache.

Conclusions: CDH exacts a significantly higher economic toll on health care system compared with episodic headaches. Our findings are important to evaluate cost-effectiveness of emerging treatments developed to provide appropriate management and treatment of CDH.

PO126

Health care resource utilization patterns among individuals with chronic migraine (CM) and episodic migraine (EM)

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Objectives: To evaluate the health resource use patterns of individuals with CM and EM across countries.
Background: Migraine is a prevalent condition requiring care by a health care professional (HCP). Examination of health resource utilization among migraineurs provides insight into the CM management compared to that of EM in a usual care environment.

Methods: Cross-sectional data were collected via a web-based survey in five countries: US, Canada, Germany, UK, and France. Respondents were classified with CM (ICHD-2 diagnosis of migraine and ≥15 headache days/month) or EM (ICHD-2 diagnosis of migraine with ≤14 headache days/month). Minimum of 50 CM patients per country were targeted. Data was gathered on health care resource utilization for treatment of headaches or migraines over the preceding three months. Logistic regression models predicted resource use by migraine group, with and without adjustment for country, age, gender, race, education, and comorbidities.

Results: Panelists were contacted (n = 30,200) and 13,050 responded, of which 6,258 had migraine and were eligible for survey. Of all invitees: 1.1% had CM (n=325); 18.4% had EM (n=5,541). Most respondents were female (86.8%) with an average age for CM and EM being 44(±12) and 42 (±11), respectively. CM respondents reported higher rates of consulting HCP for headache than EM.CM respondents had significantly more frequent visits to medical care providers, and emergency room/urgent care clinics than EM across countries (all P < 0.0001), after adjusting for other variables.

Table 1. Resource utilization for headache for pooled countries

<table>
<thead>
<tr>
<th>In the past 3 months:</th>
<th>odds ratios* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted model</td>
</tr>
<tr>
<td>Primary care physician/nurse</td>
<td>2.5† (1.9,3.3)</td>
</tr>
<tr>
<td>Neurologist/headache specialist visits</td>
<td>2.3† (1.5,3.4)</td>
</tr>
<tr>
<td>Emergency room/urgent care clinic visits</td>
<td>1.9† (1.2,3.1)</td>
</tr>
<tr>
<td>Hospital admissions/overnights</td>
<td>2.2† (1.0,4.9)</td>
</tr>
</tbody>
</table>

Conclusions: Evidence from this study suggests that the global economic burden of CM due to health service utilization is substantial and significantly greater than health service utilization of respondents with EM.

PO128
Headache or neck pain the day before: impact on migraine treatment outcome
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Objectives: To determine if the presence of headache or neck pain on the day preceding migraine is related to 2-hour pain free response.

Background: We have previously shown that neck pain is exceedingly common in migraine and is more often present at the time of migraine treatment than is nausea. We have also shown that neck pain at the time of migraine treatment negatively impacts achievement of 2-hour pain free status. Finally, we've shown neck pain to be predictive of migraine-related disability independent of headache.
frequency and severity. The purpose of this study is to explore the possible influence of headache or neck pain occurring on the day prior to migraine onset on treatment outcomes.

Methods: In this prospective cross-sectional cohort study of 127 migraineurs, subjects kept daily diaries in which they recorded headache and neck pain at prescribed times throughout the day. Details of all migraineurs were recorded over the course of at least one month and until six qualifying migraineurs had been treated. Potential subjects were screened by Headache Medicine specialists to exclude cervicogenic headache and fibromyalgia. Four groups were identified based on data recorded on the day preceding migraine onset: 1) no headache or neck pain; 2) headache only; 3) neck pain only; 4) both headache and neck pain. If the day preceding migraine was also a migraine day (i.e., consecutive migraine days), all subsequent sequential migraine days were excluded from analysis. Primary endpoint was 2-hour pain-free rates relative to the presence of headache or neck pain on the day preceding migraine treatment.

Results: Subjects recorded 762 migraineurs, the majority of which were treated in the moderate pain stage. Compared to the no headache or neck pain group, those with neck pain \((P < .0001)\) and those with headache \((P < .03)\) on the day preceding migraine were less likely to achieve pain-free status. While the headache only group had better outcomes than those experiencing both headache and neck pain \((P > .01)\), the neck pain group had comparable pain-free outcomes as the combined headache/neck pain group \((P = .85)\). Those with neck pain tended to have poorer outcomes than those with headache \((P < .08)\).

Conclusions: Presence of neck pain on the day preceding migraine is associated with poorer treatment response. Neck pain before migraine is a better predictor of adverse treatment outcome than headache.

PO129
How closely can migraine patients predict their next migraine attack?
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Objectives: To determine migraine patients’ ability to predict several attributes of their next migraine attack.

Background: Migraine attacks vary both between and within patients. Little is known about how accurately migraineurs can predict their next attack.

Methods: Physician-diagnosed migraineurs were recruited from a previously-assembled migraine patient panel. Participants completed an on-line survey at study baseline and were asked to predict three attributes of their next migraine: when the attack would occur (calendar day), the time of day it would strike (while asleep, before breakfast, between breakfast and lunch, between lunch and dinner, or between dinner and bedtime), and where they thought they would be (at work, at home, in transit, or another public place). They completed the follow-up survey within 48 hours of resolution of their next migraine.

Results: Of 1,519 migraineurs enrolled, 877 (mean age 44.4; 78.8% females) completed the follow-up survey. Only 21.4% correctly predicted their next migraine within 3 calendar days. More participants accurately predicted the time of day of attack onset and their location (46.6% and 70.7%, respectively). However, when the three variables were evaluated together, only 9.2% foretold all three attributes of their next migraine attack. In univariate analysis, correct predictions were not associated with migraine frequency, severity, menstruation, or gender. Age, education, marital and employment status were associated with prediction about the location of migraine.

Conclusions: In general, migraine patients could not predict their next migraine with good precision. With few exceptions, migraine profiles and demographic characteristics were not associated with accuracy of prediction.

PO130
Excessive daytime sleepiness increases with headache frequency. The Akershus sleep apnea project
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Objectives: To evaluate the importance of excessive daytime sleepiness (EDS) in relation to headache and migraine.

Background: Both migraine and headache patients often complain of sleepiness, a symptom with high clinical and public health importance due to increased risk for accidents, decreased productivity and impaired quality of life.

Methods: This is a cross-sectional population-based survey. A random age and gender stratified sample of 40,000 persons aged 20–80 years old were drawn by the National Population Register. The participants were residing in Akershus, Hedmark or Oppland County, Norway. The single questions of headache and migraine were not asked in the survey. The overall one year prevalence of headache was 84.0% in women and 69.6% in men, while the lifetime prevalence of migraine was 34.1% in women and 18.1% in men. EDS significantly increased among participants with migraine with an adjusted odds ratio of 1.30 (1.16–1.46) in women and 1.35 (1.15–1.60) in men with normal sleep time duration compared to non-migraineurs. The probability for EDS increased with the headache frequency. The adjusted odds ratios for EDS in infrequent, frequent and chronic headache were 0.94 (0.76–1.17), 1.36 (1.09–1.70) and 2.67 (1.79–3.98) in women without migraine. In men without migraine, the corresponding relationship was only significant in those without depression. The adjusted odds ratios for EDS in infrequent, frequent and chronic headache were 1.33 (1.12–1.57), 2.08 (1.72–2.51) and 3.21 (1.93–5.35).

Conclusions: The probability for EDS increased significantly with the headache frequency. The literature reports association of EDS with several other pain conditions. Thus, it may be the pain rather than the specific type of pain that is associated with EDS.
PO131
Rates and predictors of remission from chronic migraine to episodic migraine: results from the American migraine prevalence and prevention (AMPP) study
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Objectives: To estimate rates and potential predictors of remission from chronic migraine (CM) to episodic migraine (EM).

Background: Each year, approximately 2.5% of EM sufferers develop CM. Though predictors of migraine progression have been studied, data are limited on the rates and predictors of CM remission and persistence.

Methods: In 2005, questionnaires were sent to 24,000 severe headache sufferers identified in a previous US population survey and followed over the next three years. Participants with CM (defined as an ICHD-2 diagnosis of migraine with ≥15 headache days/month) were identified in 2005 and had to have 3 consecutive years of follow-up. To assess potential predictors of remission, two migraine groups were identified: persistent CM (those who met CM criteria in every year from 2005–2007) and remitted CM (those who met CM criteria in 2005 but had low frequency EM [LFE]: 0–9 headache days/month in 2006–2007). Demographic variables, body mass index (BMI), depression, allosthenia, medication utilization and headache-related disability were examined as potential predictors by assessing both between and within group effects.

Results: The subject pool included 432 individuals with CM in 2005 who contributed 3 years of data. Of those, 52.7% (n = 238) had CM in at least one year of follow-up and 64.6% (n = 292) had either CM or high-frequency EM (HFEM: 10–14 headache days/month) in at least one year of follow-up. Approximately 20% (n = 90) had CM in all 3 years (i.e., persistent CM) while 35.4% (n = 160) did not meet criteria for CM or HFEM in 2006 and 2007 (i.e., remitted CM). With regard to predictors of remission, all models were adjusted for age, sex, race, population density, geographic region and household income. Exploratory analyses suggested that none of the study variables significantly predicted remission.

Conclusions: Over 3 years of follow-up, the majority of those with CM remained with either CM or HFEM. CM is a complex headache disorder, which is reflected in the lack of clear predictors of disease remission. Longitudinal diary studies may be more sensitive to assess individual predictors of remission.

PO132
Long-term evolution of chronic daily headache with analgesic overuse in the general population after diagnosis and therapeutic intervention
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Objectives: Our aim was to investigate the long-term efficiency of an intervention protocol for the management of chronic daily headache (CDH) with analgesic overuse (AO) in an unselected cohort of subjects taken from the general population.

Background: The high prevalence numbers and the negative influence in daily life of CDH with AO call for public health interventions. There are no studies testing such a potential intervention in the general population.

Methods: The 72 subjects meeting CDH and AO criteria coming from an epidemiological study in the general population (Neurology 2004; 62: 1338–42) were offered follow-up and standard treatment for 1 year and then discharged to their GP with general treatment recommendations. Four years after the diagnosis these subjects were interviewed again to check for their headache status. They were asked to fill in the headache diary for one month and the SF-12 test.

Results: At the end of the first year and according to the diary, 46 (64%) of the 72 subjects did not fulfill AO criteria while 26 (36%) were still overusing. After 4 years, 68 subjects could be contacted. Within these 48 subjects and according to the new diary, 38 (58%) did not meet the criteria for CDH with AO, while the remaining 30 (44%) still had AO. Among those 38 subjects who did not meet AO criteria, six had headache more than 15 days per month for more than 4 hours. Therefore, they fulfilled CDH criteria in spite of having given up AO. Age, gender, civil status, socioeconomic situation and type of CDH were not significantly different in the group with AO versus those without AO. The consumption of NSAIDs and/or triptans as symptomatic treatment was significantly higher in subjects without CDH and AO, while the use of ergotamine-containing medications and/or opioids was significantly higher in those patients who still meet CDH with AO criteria. In spite of our recommendations, preventative treatment was being received by only 6 (20%) of those subjects still fulfilling CDH with AO after four years. QoL was numerically better in those subjects who did not meet overuse criteria.

Conclusions: After 4 years, almost 60% of subjects did not fulfill CDH with AO criteria and their QoL was also improved. This justifies public health interventions which should include recommendations on a judicious use of symptomatic medications together with an early use of preventive medications.

PO133
Chronic migraine is rare in the general population.
The Akershus study of chronic headache
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Objectives: To investigate the prevalence of chronic migraine in the general population, according to the International Classification of Headache Disorders (ICHD) II and ICHD II revised criteria.

Background: The prevalence of chronic headache is about 3% in industrialized countries. Controversies start when the discussion is related to the prevalence of chronic migraine. In the USA it is thought that chronic migraine is quite common among those with chronic headache, while in Europe many think that chronic migraine is rare, since the majority of those with chronic headache have chronic tension-type headache.

Methods: A cross sectional epidemiological survey of 30,000 persons, aged 30–44 years from the general population of Akershus County, Norway received a posted questionnaire. A 2nd and 3rd questionnaire was posted to non-responders. Those with self-reported chronic headache, i.e. ≥215 days within the last month and/or ≥180 days within the last year were included into the study. The interview, physical and neurological examination was conducted by either of two neurological residents. The criteria of ICHD II and relevant revisions were applied.

Results: The questionnaire response rate was 71% and the participation rate of the interview was 74%. Chronic migraine classified according to the ICHD II and ICHD IIIR is rare. It occurs in 1 of 3,000 persons or 1 of 500 persons from the general population depending on the criteria used. This corresponds to chronic migraine occurring in 0.8–5.3% of those with chronic headache, i.e. one of 125 person with chronic headache or one of 19 person with chronic headache.

Conclusions: Chronic migraine is rare in the general population.
PO134

Age, sex and prophylaxis dependent differences of premonitory symptoms in migraine patients

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Objectives: To explore how the number and profile of premonitory symptoms (PS) depend on sex, age, migraine subtype, attack frequency and use of acute/ preventive medication.

Background: In the premonitory phase of migraine a variety of symptoms provides a potential early warning signal for the migraine attack. In PS, neurological, neuropsychological, gastrointestinal and general domains can be distinguished, which 12–87% of migraineurs experience 1–48 hour prior to a migraine attack. It is not fully known, however, whether the number and profile of PS depends on patient’s age or gender, and whether the profile depends on use of anti migraine medication. Such data may be helpful in elucidating the premonitory phase as initiation phase of the migraine attack and understanding its possible relation with prophylactic medication.

Methods: Via the LUMINA website self-reported migraineurs could participate in an extended web-based questionnaire study which included questions on a variety of PS. The algorithm’s accuracy in diagnosing migraine subtypes has been validated previously with a semi-structured telephone interview. A multiple regression model was used to assess the number of PS symptoms, after controlling for age, age of onset, gender, migraine subtype (migraine with [MA] or without aura [MO]), use of prophylactic and acute medication. A regression model was also used to predict the effects of different patient characteristics on PS domains.

Results: Data from 2,290 migraine patients was included of which 1,958 (86%) were female, 1,383 (60%) were migraine without aura patients and mean age [SD] was 43.0 [11.9] years. 95% of patients reported at least 1 PS and mean number of PS [SD; range] was 1.9 [3.9; 0–17]. The multiple regression model showed that the number of PS was higher in females (P < 0.001), earlier age of onset of migraine (P < 0.001), and use of prophylaxis (P < 0.001) respectively. Migraine subtype, attack frequency and use of acute anti migraine medication did not influence number of PS. Of reported PS 20% were general symptoms, 25% neurological, 37% neuropsychological and 18% digestive. The regression model showed that general PS increased (P < 0.001) and neurological PS (P = 0.002) decreased with female gender. Neuropsychological PS increased with age (P = 0.066) and MA subtype (P = 0.025). Gastro-intestinal PS increased with earlier age of onset (P = 0.004), age (P = 0.003), and MO subtype (P = 0.014).

Conclusions: PS are very common among migraineurs and the number of PS primarily depends on patient’s gender, age, age of onset, and use of prophylactic medication. General PS are more common in women, neurological PS in men. Older and MA patients report more neuropsychological PS, and older and MO patients report more gastro-intestinal PS. Use of prophylaxis does not seem to influence the clinical PS profile in this population.

PO135

Global impact of chronic migraine (CM) compared to episodic migraine (EM) on health-related quality of life (HRQoL), depression and anxiety

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Objectives: To examine the impact of CM compared to EM on HRQoL, depression, and anxiety across countries.

Background: US population-based studies have demonstrated that CM has a greater burden than EM in terms of health-related disability, productivity, and comorbidities including depression and anxiety, but these differences across multiple countries have yet to be examined.

Methods: Cross-sectional data were collected via web-based survey in five countries: US, Canada, Germany, UK, and France. Respondents were classified as CM (ICHD-2 diagnosis of migraine and ≥15 headache days/month) or EM (ICHD-2 diagnosis of migraine with ≤14 headache days/month). Minimum of fifty CM patients per country were targeted. The Migraine-Specific Quality of Life Questionnaire v2.1 (MSQ) measures impact of migraine on HRQoL in 3 domains: Role Restrictive (RR), Role Preventive (RP) and Emotional Functioning (EF); higher scores indicating better HRQoL. Patient Health Questionnaire (PHQ-4) screens for depression and anxiety; higher scores indicating a greater likelihood of disorder. Analysis of covariance (ANCOVA) models predicted MSQ and PHQ-4 by migraine group and adjusted for country, age, gender, race, education, and comorbidities.

Results: Panelists were contacted (n = 30,200), and 13,050 responded, of which 6,258 had migraine and were eligible for survey. Of invitees: 1.1% had CM (n = 325); 18.4% had EM (n = 5541). Their average age was 44 ± 12 and 42 ± 11, respectively. Respondents were largely female (86.8%). Across all countries, individuals with EM had better HRQoL than CM (P < 0.05). Respondents with CM had significantly higher PHQ-4 scores than CM across countries (P < 0.001)

Table 1: MSQ ≥1 and PHQ-4 Model Adjusted Means by Migraine Group and Country

<table>
<thead>
<tr>
<th>Country</th>
<th>RR</th>
<th>RP</th>
<th>EF</th>
<th>PHQ-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>56.2*</td>
<td>58.0*</td>
<td>44.0</td>
<td>7.8*</td>
</tr>
<tr>
<td>Canada</td>
<td>57.3*</td>
<td>52.6*</td>
<td>73.3*</td>
<td>5.4*</td>
</tr>
<tr>
<td>Germany</td>
<td>46.3*</td>
<td>54.3*</td>
<td>56.1*</td>
<td>3.9</td>
</tr>
<tr>
<td>UK</td>
<td>54.6*</td>
<td>54.6*</td>
<td>57.5*</td>
<td>4.9*</td>
</tr>
<tr>
<td>France</td>
<td>43.3*</td>
<td>57.7*</td>
<td>47.7*</td>
<td>5.4*</td>
</tr>
<tr>
<td>Pac1</td>
<td>50.5*</td>
<td>56.1*</td>
<td>63.1*</td>
<td>2.1*</td>
</tr>
<tr>
<td>Pac2</td>
<td>52.9*</td>
<td>62.1*</td>
<td>58.3*</td>
<td>3.0*</td>
</tr>
</tbody>
</table>

*P < 0.05, TP < 0.01, TP* = 0.001 for comparison between US means for migraine.

Conclusions: Worldwide, patients with CM have significantly worse HRQoL than those with EM, even after controlling for other variables. CM patients are also more likely to have anxiety and depression, further contributing to the burden of the disease.

PO136

High prevalence of migraine in women in a south Indian coastal population

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Objectives: To estimate the prevalence of migraine in a south Indian coastal state.
Background: To date no migraine epidemiological study has been done in India. Lifting the burden, Global campaign against headache has just initiated such work in countries like India. Recent migraine prevalence studies based on ICHD 2 show a clear increase in prevalence.

Methods: Accompanying persons of patients presenting to an Eye Centre and a multispeciality hospital with complaints other than pain (head or eye pain) were interviewed. 8000 women and 4000 men aged 15 to 60 years were included. Diagnosis mostly based on ICHD 2 criteria and a special headache questionnaire suit- ing to this region. The results obtained from women were compared with the data collected from six nurses hostels comprising 824 inmates.

Results: 30.8% (2464) were suffering from ICHD2, 1.1 and 1.2, and 20.4% (1632) with 1.6 making the overall prevalence to show a shocking 51.2%. No significant headache in 18% (1439). Episodic tension type headaches only in 6% (478). Another 18.4% (1472) were diagnosed as 2.1, 2.2 and 2.4 based on first interview but re-diagnosed as mild to moderate migraine attacks (bilateral activity affected throbbing headaches lasting less than 2 hours with no diagnostic associated features. Only phono or photo reported by 203), migraineous disorder (bilateral or unilateral activity not affected throbbing, less than 2 hours, no diagnostic associated features, only phono or photo in 174) were more convincing to the patients and relatives as all of them were getting these aches when exposed to two common migraine triggers in this region. (exposure to sunlight and bus travelling) and a family member (first or second degree relative) suffering from migraine with same triggers. In another 137, ETTH was re-diagnosed as migraine trait (unilateral or bilateral activity not affected, variable duration throbbing, no associated features or only phono or photo, occasional common migraine triggers, no tension anxiety situations but positive family history of migraine. These diagnoses were considered according to ICHD2 recommendation of considering all other available information when patients fulfill part of both criteria (1.6 and 2.4). 1.8% (144) reported migraine in the past (years ago). Chronic migraine (27%), chronic tension type headaches (4) and other primary headaches (4) were less than 0.5%. The rest were secondary headaches (fasting, hypertension, sinus, refractive etc) or headache not elsewhere classified (14.1). The data collected from nurses hostels also showed comparable results regarding migraine and tension. In men, 69% (2761) reported no headache. 13.6% (544) were suffering from ICHD2, 1.1, 1.2 and 1.6. Episodic tension type headaches in 4.6% (183). Past history of migraine (years ago) in 3.2% (128). Headache fulfilling 2.1, 2.2 and 2.4 with a differential diagnosis of mild to moderate migraine attacks, migraineous disorder or migraine trait in 8.8% (352). The rest were secondary headaches or headache not elsewhere classified.

Conclusions: This study, carried out in a South Indian coastal state, mostly based on ICHD2 diagnostic criteria, shows a shocking very high migraine prevalence in women and considerably more in men than that reported in the west.

PO137
Impact of migraine occurrences on work productivity
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Objectives: This study seeks to assess migraine characteristics in relation to work as well as the impact of migraine on work productivity, considering both absenteeism and presenteeism.

Background: The impact of migraine on lost work productivity has been well researched through clinical trials and survey instruments. Previous research has demonstrated that presenteeism is a greater contributor to lost work time than absenteeism, however, quantifying these differences remains controversial.

Methods: This prospective study included a baseline survey and three follow-up, 48 hour post-migraine surveys that collected data on respondents’ next three migraine attacks. Inclusion criteria were: US residency and citizenship, minimum age of 18, employed full-time, self-reported healthcare provider diagnosis of migraine, average of 2–8 migraines per month with fewer than 15 headache days per month, and treatment with prescription or over-the-counter oral migraine medications. Data were weighted to be representative of adults in the US who are diagnosed with migraines. Nominal p values are reported. Logistic regression analysis was used to evaluate predictors of absenteeism and linear regression analysis was used to evaluate predictors of presenteeism. This study was IRB approved

Results: A total of 509 migraineurs participated in the study, resulting in 1,527 migraine attacks. Sixty-four percent (64%) of migraines occurred on a workday. Thirty-two percent (32%) of migraines began prior to work (up to 5 hours), 40% began while at work, and 28% occurred after work. Twenty-eight percent (28%) of workday migraines resulted in absenteeism. Eleven percent (11%) resulted in a full day of work lost, 5% led to a late arrival, and 12% led to leaving work early. Workday migraines beginning before or during work hours accounted for 974 total hours lost due to absenteeism, or 1 hour and 24 minutes lost per migraine. Presenteeism was observed in 62% of workday migraines, resulting in an average of 25% work productivity loss. A total of 1301 hours were lost due to presenteeism. Presenteeism accounted for 57% of total work time lost. To explore factors contributing to absenteeism and presenteeism, regression analyses were performed. Regression analysis for migraine episodes occurring on a workday and completing before the start of the survey uncovered three primary factors contributing to absenteeism: pain severity at onset, pain severity at peak, and vomiting, and two primary contributors to presenteeism: pain severity at peak and number of symptoms experienced.

Conclusions: Migraines occurring on a work day resulted in substantial lost work productivity as a result of both absenteeism and presenteeism. Our research supports previous findings that presenteeism leads to more lost work time than absenteeism. Pain severity at peak was a key contributor to both of these work-related consequences of migraines. Addressing these and other migraine-related issues that impact work productivity will help migraineurs to better manage their condition, improve their ability to get to work or stay at work, and to function better while at work.

PO138
Allergy modulates the frequency, but not the prevalence of migraine headache
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Objectives: To determine if the degree of atopy (number of positive allergy tests) modulates the prevalence or frequency of migraine headache in patients with allergic rhinitis.

Background: Several studies have suggested that migraine headaches are more common in patients with allergic rhinitis, but the exact relationship between allergy and headache disorders is currently unknown.

Methods: Consecutive patients between the ages of 18–65 presenting to an allergy practice that received a rhinitis diagnosis and had ≥ 1 positive allergy test (e.g. skin prick or Immunocap) were enrolled in this study. All participants underwent a structured verbal headache diagnostic interview and were later assigned a headache diagnosis by a headache specialist blinded to the rhinitis diagnosis based on 2004
International Classification Headache Disorder (ICHD-2) diagnostic criteria. Migraine headache was defined as an ICHD-2 diagnosis of 1.1–1.6. The frequency of migraine headache days was ascertained by patient self-report during the diagnostic interview. Patients were categorized into low and high atopic groups based on the number of skin prick or Immunocap allergy tests that were positive. Low atopy was defined as 1–9 and high atopy as 10–20 positive allergy tests. Analyses were performed to determine if the number of positive allergy tests modulated the prevalence and frequency (days/month) of migraine headache within the high and low atopic groups. Age and sex were controlled within the analyses.

Results: Four hundred and forty-eight allergic rhinitis patients (60% female, mean age 41) participated in the study. One hundred and forty-five patients were diagnosed with migraine headache (32%). The prevalence of migraine was not altered by increasing numbers of positive allergy tests within the high or low atopic groups. Female gender was a risk factor for migraine prevalence (RR = 2.0 [1.28, 3.39; 95%CI]), independent of age and number of positive allergy tests. In patients <40 years of age, fewer migraine headache days occurred in the low atopic group with higher numbers of positive allergy tests (RR = 0.87 [0.78, 0.97; 95% CI]) while higher numbers of positive allergy tests led to more migraine headache days in the high atopic group (RR = 1.36 [1.08, 1.72; 95% CI]). There was no effect of degree of atopy on the frequency of migraine headache in those >40 years of age.

Conclusions: The degree of atopy does not affect the prevalence of migraine headache in allergic rhinitis patients. The frequency of migraine headache does appear to be modulated by the number of positive allergy tests with low to intermediate degrees of atopy being protective and high degrees being provocative for migraine headache in those <40 years of age. This suggests that atopy may be a modulating rather than a causative factor for migraine headache.

PO139

Employed US migraineurs: migraine attack characteristics and treatment patterns

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Objectives: The goal of this study was to better understand the characteristics of migraineurs and current treatment patterns in employed US migraineurs.

Background: Understanding migraine and its impact on employee work productivity is fundamental to minimizing the effects of migraine in the workplace.

Methods: This prospective study included a baseline survey and three follow-up, 48 hour postmigraine surveys that collected data on respondents’ next three migraines. Inclusion criteria were: US residency and citizenship, 18 years of age or older, employed full-time, self-reported healthcare provider migraine diagnosis, average of 2–8 migraines per month with fewer than 15 headache days per month, and acute migraine treatment using prescription or over-the-counter oral medications. Data were weighted to be representative of adults in the US who are diagnosed with migraines. Nominal p-values are reported. This study was IRB approved.

Results: Survey data on 1,527 migraine attacks across 509 respondents were collected. Approximately two-thirds (64%) of these migraine episodes occurred on a work day while nearly half (46%) were ‘awakening migraines’. Fifty-eight percent (58%) of all migraines began with moderate pain, while only a quarter, (26%) were classified as mild pain at onset. Average migraine duration was 10 hours (9.02 S.D.), with 9% of migraines lasting less than 2 hours and 10% lasting more than 24 hours. The majority (63%) of attacks were treated within 1 hour, 13% within 2 hours, 17% after 2 hours, while 7% did not treat at all. Those migraine episodes treated within 1 hour were significantly shorter on average than those treated after 1 hour (9.1 hours vs. 12.3 hours) (P < 0.05). Notably, workday migraines were significantly more likely to go untreated than day-off migraines (9% vs. 4%) (P < 0.05). The primary reason cited for delayed or non-treatment was ‘I did not have my migraine medication with me so I had to wait.’ OTC medication was the most frequently reported first line treatment (44%) followed by oral triptan (30%), another prescription medication (14%), and combination therapy (4%). Rescue treatment was reported in 57% of attacks, which was most commonly a second dose of the first line of treatment. The majority of OTC (69%) and another prescription (55%) treated attacks required rescue while only 39% of first line triptan attacks required rescue.

Conclusions: With nearly two out of three migraines occurring on a workday, it is clear that migraines have a significant impact on the employed US population. This study suggests that nearly half of migraine attacks begin during sleep and that the majority of attacks begin with moderate or severe pain. Findings also indicate that treatment within one hour of migraine onset may reduce their duration. While this study did not seek to compare effectiveness of migraine treatments, it is notable that migraines treated with triptans are least likely to require rescue. These studies clearly show the need for and impact that proper migraine treatment and additional education could have on migraine outcomes.

PO140

Migraine and cardiovascular disease: a systematic review and meta-analysis

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Objectives: To evaluate the association between migraine and cardiovascular disease (CVD), including stroke, myocardial infarction (MI), and CVD death.

Background: A meta-analysis from 2005 reported an increased risk for ischemic stroke in migraine. Recent large studies suggest that the association may be limited to migraineurs with aura. In addition, migraine may also be associated with other ischemic vascular events.

Methods: Systematic review and meta-analysis of studies published until January 2009 using electronic databases (PubMed, EMBASE, Cochrane Library) and reference lists of included studies and reviews on the topic. We included case-control and cohort studies investigating the association between overall migraine or specific migraine subtypes and cardiovascular events. Two investigators independently assessed eligibility of the identified studies in a two-step approach. Disagreements were resolved by consensus. Studies were grouped according to strict a priori categories regarding migraine and CVD. Two investigators extracted relevant data and pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Results: Studies were heterogeneous with regard to the characteristics of investigated subjects and definition of CVD. Nine studies investigated the association between any migraine and ischemic stroke (pooled RR = 1.73, 95% CI 1.31–2.29). This association reached significance only among migraineurs with aura (pooled...
Methods: Hypothyroidism. Thyroid function and manifest multiple symptoms compatible with assumed 'normal,' however, this may represent considerable loss of triples, it may remain well within the reference range and will be mely low, but if it is disproportionately low, yet within the reference range. Dysfunction may be manifested by laboratory features consistent with central hypothyroidism (low TSH and low thyroid function). However, central hypothyroidism (low TSH and low thyroid function) is not obtained. Endocrinology textbooks demonstrate in migraine. Thus, it is likely that hypothalamic dysfunction characterized by hypothalamic activation and abnormal secretion of melatonin, cortisol, and prolactin has been demonstrated in migraine. Therefore, TSH should be used as a screening test for thyroid function. Unfortunately, TSH has somehow become the gold standard and is the single test ordered most commonly to assess thyroid function. However, central hypothyroidism (low TSH and low thyroid hormones) can occur and the diagnosis will be missed if T4 (tetraiodothyronine) and T3 (triiodothyronine) are not obtained. Hypothalamic dysfunction characterized by hypothalamic activation and abnormal secretion of melatonin, cortisol, and prolactin has been demonstrated in migraine. Thus, it is likely that hypothalamic dysfunction may be manifested by laboratory features consistent with or suggestive of central hypothyroidism. TSH may not be extremely low, but if it is disproportionately low, yet within the reference range, it will be presumed 'normal.' Or worse, if the TSH doubles or triples, it may remain well within the reference range and will be assumed 'normal,' however this may represent considerable loss of thyroid function and manifest multiple symptoms compatible with hypothyroidism.

Methods: Records from a random sample of headache clinic CM patients seen from 5/1-08 to 5/1-09 were reviewed regarding demographics and thyroid function tests.

Results: There were 69 women and nine men, mean age 47.1 years, mean migraine onset 16.6 years. TSH range 0.25–32.697 (reference range: 0.4–4.5 mIU/l), mean 2.15, median 1.48, 2/74 (2.7%) < 0.4, and 3/74 (4.0%) > 4.5. Total T4 range 2.5–13.2 (reference range: 4.5–12.5 mcg/dl), median 8.4, 1/60 (1.7%) < 4.5 and 1/60 (1.7%) > 12.5 (neither patient had a TSH outside the reference range). Free T4 range 0.6–3.5 (reference range: 0.9–1.8 ng/dl), median 1.1, 9/64 (14.1%) < 0.9 and 5/64 (7.8%) > 1.8. Total T3 range 90–253 (reference range: 97–219 ng/dl), median 135, 5/51 (9.8%) < 97 and 2/51 (3.9%) > 219. Free T3 range 184–424 (reference range: 230–420 pg/dl), median 285, 2/59 (3.4%) < 230 and 1/59 (1.7%) > 420. TSH was ≤ 1.0 in 17/74 (23%) of patients. However, when TSH was ≤ 1, mean total T4 8.3, mean free T4 1.3, mean total T3 135, and mean free T3 301, thus all thyroid hormone levels were within the reference range.

Conclusions: Migraine is associated with a two-fold increased risk for ischemic stroke, which is only apparent among migraineurs with aura. Risk was magnified for migraineurs aged < 45, smokers, and women using oral contraceptives. We did not find an overall association between any migraine and MI or CVD death. Too few studies are available to reliably evaluate the impact of modifying factors, such as migraine aura, on the association of migraine on MI and CVD death.

PO141
Disproportionately low thyroid stimulating hormone in chronic migraine
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Objectives: The purpose of this study was to determine whether low or relatively low thyroid stimulating hormone (TSH) levels occurred in chronic migraine (CM) sufferers, perhaps as evidence of hypothalamic dysfunction, and consequently was a poor predictor of thyroid function in this population.

Background: Studies show that 30% of patients presenting with hypothalamic dysfunction have headache. Additionally, new daily persistent headache (NDPH), when associated with hypothalamic dysfunction, may respond to thyroid hormone replacement. Endocrinology textbooks recommend that TSH should be used as a screening test for thyroid function. Unfortunately, TSH has somehow become the gold standard and is the single test ordered most commonly to assess thyroid function. However, central hypothyroidism (low TSH and low thyroid hormones) can occur and the diagnosis will be missed if T4 (tetraiodothyronine) and T3 (triiodothyronine) are not obtained. Hypothalamic dysfunction characterized by hypothalamic activation and abnormal secretion of melatonin, cortisol, and prolactin has been demonstrated in migraine. Thus, it is likely that hypothalamic dysfunction may be manifested by laboratory features consistent with or suggestive of central hypothyroidism. TSH may not be extremely low, but if it is disproportionately low, yet within the reference range, it will be presumed 'normal.' Or worse, if the TSH doubles or triples, it may remain well within the reference range and will be assumed 'normal,' however this may represent considerable loss of thyroid function and manifest multiple symptoms compatible with hypothyroidism.

Methods: Logs from a random sample of headache clinic CM patients seen from 5/1-08 to 5/1-09 were reviewed regarding demographics and thyroid function tests.

Results: There were 69 women and nine men, mean age 47.1 years, mean migraine onset 16.6 years. TSH range 0.25–32.697 (reference range: 0.4–4.5 mIU/l), mean 2.15, median 1.48, 2/74 (2.7%) < 0.4, and 3/74 (4.0%) > 4.5. Total T4 range 2.5–13.2 (reference range: 4.5–12.5 mcg/dl), median 8.4, 1/60 (1.7%) < 4.5 and 1/60 (1.7%) > 12.5 (neither patient had a TSH outside the reference range). Free T4 range 0.6–3.5 (reference range: 0.9–1.8 ng/dl), median 1.1, 9/64 (14.1%) < 0.9 and 5/64 (7.8%) > 1.8. Total T3 range 90–253 (reference range: 97–219 ng/dl), median 135, 5/51 (9.8%) < 97 and 2/51 (3.9%) > 219. Free T3 range 184–424 (reference range: 230–420 pg/dl), median 285, 2/59 (3.4%) < 230 and 1/59 (1.7%) > 420. TSH was ≤ 1.0 in 17/74 (23%) of patients. However, when TSH was ≤ 1, mean total T4 8.3, mean free T4 1.3, mean total T3 135,
Clinically, these patients often ascribe their neck pain to the cumulative effect of daily stresses or activities. In contrast to this attribution, we hypothesize that neck pain is part of the migraine process; its prevalence should then parallel that of headache present on awakening.

Methods: In this prospective cross-sectional cohort study of 113 migraineurs, subjects were examined by Headache Medicine specialists to exclude cervicogenic headache and fibromyalgia. They were divided into three groups based on review of their diary entries: those with episodic patterns for both headache and neck pain frequency (E/E), those with chronic patterns for both headache and neck pain (C/C), and those with a mixed pattern of either episodic headache/chronic neck pain or chronic headache/episodic neck pain (EC/CE). Primary endpoint was prevalence of headache and neck pain present on awakening.

Results: In this cohort of migraineurs, chronification was associated with increasing prevalence of neck pain present on awakening.

Conclusions: In migraineurs, neck pain present on awakening parallels the prevalence of headache present on awakening; both increase with chronification. Possible explanations include that: 1) neck pain represents an alternate location of pain in the acute migraine process; and/or 2) neck pain occurring between migraine attacks may be associated with chronification.

PO144
Public headache care: the impact of a collective effort in the Brazilian National Headache Day
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Objectives: The aim of this study is to present the results of a collective effort to assist headache patients in the 2008 Brazilian National Headache Day.

Background: The headaches are among the 10 main causes for seeking medical consultations. In Fortaleza, Brazil, a three million inhabitants city, there are only two public headache clinics. This way, the Municipal Health Office estimated that there are more than two thousand and five hundred patients needing specialized consultation for headache in our city. In 2008, as an activity related to the Brazilian National Headache Day, we decided to do a collective effort to assist patients with requested consultations for headache that still had not been assisted.

Methods: For three consecutive days, announcements and interviews on newspapers, radios and televisions called people with headaches to seek The First Collective Effort on Headache. In the Collective Effort day, the patients were submitted to MIDAS questionnaire and had a consultation with a neurologist. After the consultations, the patients had their headaches classified, exams requested (if necessary) and was established a therapeutic plan. All the data (demographics and headache characteristics) were compiled in a Epi-Info spreadsheet and statistically analyzed.

Results: Of the 142 patients that attended (119 women and 23 men) the majority suffers recurrent headaches for more than 15 years and was waiting for a consultation for more than two years. The media that more attracted patients was the television. The most common diagnoses were: migraines (85%), tension-type headache (7%) and trigeminal-autonomic cephalalgias (3%). No secondary headache was diagnosed. The disability assessment was evaluated by the MIDAS questionnaire in 111 patients. The disability was severe in 102 (91.9%), moderate in 5 (4.5%), mild or infrequent in 2 (1.8%) and minimal or infrequent in 2 (1.8%). Approximately a fifth of the patients (22%) had already used some prophylactic treatment.

Conclusions: Our experience demonstrates that collective efforts can be an effective way to enlarge and get better assistance to patients with headache in places with few available public resources.

PO145
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Objectives: The objective of the study is to assess the prevalence of headache in the United States population.

Background: Headache (Cephalgia) is one of the major disabilities posing a burden for the population in the United States and all over the world. The burden on the economy due to the use of over the counter drugs is also a concern for estimation of the magnitude of the problem. There is a worldwide estimation of 46% for all types of headache according to the study conducted in 2007 by major non-governmental headache organizations along with the WHO.

Methods: National Health and Nutritional Examination Survey (NHANES) 2003–2004 provided the source population, who were selected from the non institutionalized population of the United States. Data was collected by using personal interviews, physical examinations and blood sample tests. Participants were asked the following question to define the headache. ‘During the past 3 months did you have severe headache or migraine? Statistical analysis was done by using proc survey methods with SAS 9.1 version statistical software.

Results: The overall age adjusted prevalence of headache in the population above 20 years was 21.85% (Standard error (SE) of 1.07%), suggesting that 61.49 million suffers from headache. The age adjusted prevalence of headache among women were 29.12(SE 1.07%) and men were 14.25% (SE 1.01%) respectively. By projecting this to US population, 41.75 million females and 19.67 million males also suffers from headache. When stratified by race, Caucasians had a prevalence of 22.05% (SE 1.54%), African Americans 23.14% (SE 1.68%), Hispanics 20.17% (SE 1.48%) and other races 21.45% (SE 3.67%). Prevalence among smokers were 25.22%(SE 1.23%) and non smokers were 20.57%(SE 1.34%). Prevalence of headache was higher among married people compared to unmarried. 23.14% (SE 0.96%) of the married people had headache while only 21.19% (1.62%) of the unmarried people had complained of headache.

Conclusions: Our research showed that the prevalence of headache continues to be a burden on the population. The issue of concern with headache is not that it poses any risk contributing to the mortality and fatality but that it seriously affects the productivity and quality of an individual. So this calls for the development of various primary preventive methods to combat with the headache of all types. All this should aim at giving the population a better ‘quality of life’.
PO146
Migraine and probable migraine prevalence and clinical characteristics in Korea: a nationwide population-based survey
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Objectives: To investigate prevalence and clinical characteristics of migraine and probable migraine in Korea.

Background: Since ICHD-II announced in 2004, migraine and probable migraine prevalence was studied in several western countries. However no population-based study on prevalence and clinical characteristics of both migraine and probable migraine was available in Korea or Asian countries.

Methods: Among Koreans of 20 years old or more, we randomly selected 1,500 target population by stratified random sampling with clustering, regarding area, age and gender. The survey was conducted by semi-structured interview using 12-item questionnaire. The questionnaire was constructed to sort out headache and migraine based on ICHD-II.

Results: A total of 1,506 participants were included in this survey. Migraine prevalence for last 12 months was 6.0% and mean attack frequency was 3.5 ± 5.8 per months. Twenty four (26.4%) migraine suffers complained of absence or reduced activity at work or school by headache. Migraine sufferers usually reported nausea (69.2%), vomiting (30.8%), photophobia (45.1%), phonophobia (59.3%) and dizziness (49.5%). Probable migraine prevalence was 11.5% and mean attack frequency 3.1 ± 4.9 per month. Thirty five (21.0%) probable migraine suffers complained of absence or reduced activity at work or school by headache. Some probable migraine suffers reported nausea (58.0%), vomiting (41.9%), photophobia (44.9%), phonophobia (61.7%) and dizziness (55.0%). The diagnosis of probable migraine was made most commonly by not fulfilling adequate headache duration (82.0%). Not fulfilling adequate headache characteristics was followed the next (16.8%).

Conclusions: Migraine prevalence was similar to previous reports in Korea and probable migraine prevalence was somewhat higher than previous reports in western countries.

PO147
A study on indirect costs in acute migraine treatment with Aspirin and/or Frovatriptan
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Objectives: Looking at the socio-economic burden of headache disorders, the issue of costs represents an important part of the problem in terms of both direct and indirect costs. Direct costs concern mainly drugs expenses.

Background: The annual cost of migraine treatment in US ranges around 15 billion dollars, of which one tenth ($1.5 billion) goes for medication. Triptans represent the main portion of such rate ($1.18 billion). The present 1-year open study aimed at analysing indirect cost of a migraine population with low-medium frequency of attacks, treated with two different drugs (Frovatriptan 2.5 mg; Aspirin 500 mg; or both).

Methods: We evaluated 120 migraine patients without aura (MWA) (88 F, 32 M; age 45.7 ± 9.1 years; illness duration 20.4 ± 5.0 years) with 18 crises per month. Patients changed the treatment group (A, B, C) every 4 months according to the following protocol: A) Frovatriptan 2.5 mg; B) Aspirin 500 mg; C) Frovatriptan 2.5 mg + Aspirin 500 mg. The following parameters for indirect costs have been calculated in our migraine population sample following a previously reported methodology (1):

1. Bedridden days per year (BDY).
2. The total number of migraine-related missed workdays (TMWD) per year.
3. Impaired work performance (NWDM) has been calculated according to the number of working days with migraine (NWDM) and reduced work efficiency during attacks.
4. Lost working days equivalent (LWDE) due to impaired work performance.
5. Economic loss due to reduced productivity (TELM).

Results: The main results of the study are summarized in Table 1.

Table. Indirect costs in migraine without aura (MWA) acute treatment

<table>
<thead>
<tr>
<th>MWA (n = 120)</th>
<th>Treatment</th>
<th>BDY</th>
<th>TMWD</th>
<th>NWDM</th>
<th>LWDE</th>
<th>TELM (€ p/p/y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>Aspirin 500 mg</td>
<td>25</td>
<td>6.0</td>
<td>12.6</td>
<td>8.8</td>
<td>5.566</td>
</tr>
<tr>
<td>Group B</td>
<td>Frovatriptan 2.5 mg</td>
<td>25</td>
<td>5.5</td>
<td>11.9</td>
<td>11.5</td>
<td>7.434</td>
</tr>
<tr>
<td>Group C</td>
<td>Aspirin 500 mg + Frovatriptan 2.5 mg</td>
<td>10</td>
<td>3.2</td>
<td>8.1</td>
<td>6.7</td>
<td>6.132</td>
</tr>
</tbody>
</table>

Each group = 40 MWA patients; € p/p/y = € per patient/year

Conclusions: The analysis of obtained data evidenced that migraine-related costs can be well reflected in terms of both bedridden days and restricted activities. Economic analyses reveal that indirect costs (TELM per/patient) could be reduced through the use of low-cost drugs, such as aspirin instead of triptans like frovatriptan. The contemporary intake of both drugs reduces migraine’s indirect costs further. However, direct costs represent a small portion of migraine’s societal costs. Analyses should therefore concentrate on indirect costs.

PO148
Migraine and migraines of specialists: perceptions and management
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Objectives: The objectives of this study were to describe perceptions of migraine by neurologists, to compare perceptions between neurologists who suffered from migraines themselves and those that did not, and to describe treatments used.

Background: Awareness of migraine has increased over the past two decades due to the availability of standardised diagnostic criteria, introduction of effective treatments and publication of treatment guidelines. In spite of this, migraine headaches remain under-diagnosed and under-treated in France and elsewhere. For this reason, we have performed a survey of neurologists’ perceptions of migraine, in order to identity potential barriers to optimal care.

Methods: This was an observational epidemiological study conducted in hospital- and community-based neurologists in France. An anonymous self-administered questionnaire was proposed to 1260 of
PO149
Temporomandibular disorders are associated with increased headache severity and frequency
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Objectives: The aim of this study was explore the relationship between headache types and TMD in a clinical well controlled study.

Background: Temporomandibular disorders (TMD) are considered to be comorbid with migraine headaches. Limited evidence suggests that TMD may also be a risk factor for migraine progression.

Methods: This was a clinic-based study focusing on the association of episodic and chronic daily headaches (CDH) and TMD. Individuals were evaluated for primary headache syndromes (HA) based on the International Classification of Headache Disorders. TMD was classified according to RDC/TMD an instrument that evolve dual-axial approach to measurement of physical findings (Axis I) and psychosocial status including chronic pain severity, depression, other physical symptoms and mandibular functioning limitations (Axis II). We identified 271 individuals that had TMD and/or HA. The control group was composed by 29 individuals free of HA and TMD. The \( \chi^2 \) test and odds ratio – 95% Confidence Interval (CI) was applied and the significance level adopted was 5%.

Results: From our sample, 247 individuals had any form of TMD. Of them, 58.3% had mixed TMD (myofascial and articular origin), 16% had myofascial TMD and 8% had articular TMD. As for headaches, 65 (21.7%) had no headaches, 43 (14.3%) had episodic tension-type headache (ETTH), 104 (44.4%) had migraine and 88 (29.3%) had CDH. Individuals with HA, were more likely to have any type of TMD than the No HA group. Prevalence of TMD on No HA group was 55.4%, 86% on ETTH group, 83.7% on migraine group and 98.8% on CDH group. When myofascial TMD was present, the magnitude of increase was higher in the CDH group (OR = 70.1, 95% CI = 9.19–534.4) and very similar for migraine (OR = 4.1, 95% CI = 2.0–8.4) and ETTH (OR = 4.9, 95% CI = 1.8–13.3); all groups differed from controls. When mixed TMD were present, odds were significantly increased for all headache groups following the same pattern observed on myofascial TMD. For CDH group, the OR was 93.9, 95% CI = 12.0–731.7; for migraine: OR = 5.1, 95% CI = 2.3–11.1; and for ETTH: OR = 5.2, 95% CI = 1.8–15.2. Presence of articular TMD did not increase the odds for any type of HA. Greater TMD grade was associated with increased prevalence for migraine (\( \chi^2 \) Test for Independence= 13.054; \( P = 0.0045 \) and CDH (\( \chi^2 \) Test for Independence= 24.471; \( P < 0.0001 \), but not for ETTH (\( \chi^2 \) Test for Independence=1.134; \( P = 0.7688 \)). Also, positive and statistically significant association was found among frequency of HA and grade of TMD chronic pain (\( \chi^2 = 53.844; P < 0.0001 \)).

Conclusions: HA and TMDs are associated. Both myofascial and mixed TMD increased the risk for CDH, migraine and ETTH. Since a positive and statistically significant association was observed among grade of TMD and HA prevalence, as well as HA frequency, our results can confirm that TMD may be an aggravating factor for HA and risk factor for it chronification. Accordingly, simultaneously evaluation and treatment of HA and TMD is the great importance for both positive prognosis.

PO150
Association of migraine with temperature and humidity
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Objectives: The aim of the study was to investigate the relationship between specific weather parameters and the onset and intensity of migraine attacks.

Background: Migraineurs frequently describe an association between weather changes and the onset of their migraine attack. Scientific evidence which support this relationship remains scarce and inconclusive.

Methods: To determine a link between migraine and weather, headache diaries of 20 randomly selected migraineurs of our headache outpatient department were retrospectively analyzed. Data were collected for 12 consecutive months and correlated with barometric pressure, temperature and relative humidity. We analyzed absolute values of the specific weather parameters as well as their relative changes within the preceding 24 hours. Statistical analysis used the data in 4-hour time frames in analogy to the patients’ diaries.

Results: Descriptive analysis revealed that migraine attacks started most frequently at 4 am. and reached their maximum intensity between 4 am. and 8 am. A slight dependency could be detected in relation to calendar month, whereas an association to a specific day of the week was not found. The highest migraine frequency was observed in January and the lowest in August. In six out of 20 patients analysis revealed an association between specific meteorological variables and the onset or migraine attacks. In these patients the onset of a migraine attack as well as headache intensity were correlated to lower temperature and higher humidity. An association between migraine onset or migraine intensity and barometric pressure could not be found.
Conclusions: Our results indicate that a subgroup of migraineurs is highly sensitive to specific weather changes.

PO151
Cervicogenic headache in the general population. the Akershus study of chronic headache
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Objectives: The objective was to study the prevalence of cervicogenic headache (CEH) in the general population.

Background: The prevalence of CEH varies considerably, depending on the applied diagnostic criteria.

Methods: An age and gender stratified random sample of 30,000 persons aged 30–44 years received a mailed questionnaire. Those with self-reported chronic headache were interviewed by neurological residents. The criteria of the Cervicogenic Headache International Study Group and the International Classification of Headache Disorders were applied.

Results: The questionnaire response rate was 71% and the participation rate of the interview was 74%. The prevalence of CEH was 0.17% in the general population, with a female preponderance. 50% had co-occurrence of medication overuse and 42% had co-occurrence of migraine. The pericranial muscle tenderness score was significantly higher on the pain than non-pain side (P < 0.005). The cervical range of motion was significantly reduced compared to healthy controls (P < 0.005). The mean duration of CEH was 8 years. Greater occipital nerve (GON) blockade and cryotherapy was effective in 90% of those whom had this procedure, while other treatment alternatives were less effective.

Conclusions: CEH is rare in the general population. The headache is chronic, and usual pharmacological management is not effective, while GON blockade/cryotherapy seems to be effective. The nuchal onset of pain, reduced cervical ROM, ipsilaterality of the pain and pericranial muscle tenderness score and the efficacy of GON blockade and cryotherapy suggest that local factors in the neck are responsible for pain in CEH. Whether this mechanism is involved in other types of headache can not be concluded from our study.

PO152
Primary chronic headache; medication use and utility of health services – the Akershus study of chronic headache
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Objectives: To investigate physician contact pattern and medication overuse in people with primary chronic headache from the general population.

Background: Most current knowledge about primary chronic headache is from selected specialised clinics. Patients with primary chronic headache seen in specialised headache clinics, general practices and in the general population may vary. This information is important for health economics, for planning studies in primary health care and interpreting studies from other than specialised clinic settings. Knowledge of pattern of medication use and use of alternative treatment strategies may also be of importance.

Methods: An age and gender stratified cross-sectional epidemiological survey included 30,000 persons aged 30–44 years from the general population. A posted questionnaire screened for chronic headache. Those with self-reported chronic headache were interviewed by neurological residents. The International Classification of Headache Disorders was used. Participants were asked about previous physician contacts, hospital admission and medication usage. The Severity of Dependence Score (SDS) was used in relation to headache medication. Those with primary chronic headache were included.

Results: The questionnaire response rate was 71%, the interview participation rate 74%. Of those with primary chronic headache, 19% had never consulted a physician, 63% had consulted their GP, and 17% consulted both their GP and a neurologist due to headache. Those with chronic tension-type headache (CTTH) and medication-overuse headache (MOH) had similar consultation pattern, while co-occurrence of migraine significantly increased consultation with GP and neurologist. Main overused medications were simple and combination analogesics. 63% had used alternative treatment, most commonly physiotherapy, acupuncture and chiropractic. Use of alternative treatment differed between different physician contact levels. The SDS score was significantly higher in those with MOH than those with CTTH for all levels of physician contact. Primary chronic headache subjects in contact with physicians had significantly higher SDS than those without such contact.

Conclusions: The spectrum of primary chronic headache, medication use and use of alternative treatments differ between GPs and neurologists settings.
PO154
Disability impact upon remission from chronic migraine to episodic migraine: results from the American migraine prevalence and prevention (AMPP) study
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Objectives: To assess the impact of chronic migraine (CM) remission on headache related disability.

Background: The clinical course of migraine can be conceptualized as transitions among three states: low frequency episodic migraine (LFEM) [ICHD-2 diagnosis of migraine with ≤ 9 headache (HA) days/month], high frequency EM (HFEM) [ICHD-2 diagnosis of migraine with 10–14 HA days/month] and chronic migraine (CM) [ICHD-2 diagnosis of migraine with ≥ 15 HA days/month]. Treatment of CM is intended to facilitate the transition from CM to EM or complete remission, but the benefits of these changes in state have not been quantified.

Methods: In 2005, questionnaires were mailed to 24,000 severe headache sufferers identified in a previous US population survey. Respondents were followed annually over the following three years. Participants must have met criteria for CM in 2005 and have 3 consecutive years of follow-up data. Two groups were contrasted: persistent CM (those who met CM criteria every year from 2005–2007) and remitted CM (those who met CM criteria in 2005 but had LFEM in 2006–2007). Within group effects were assessed by examining change in MIDAS score from 2005 to 2007 among CM sufferers with persistent disease and among those who remitted. Between group effects were assessed by contrasting MIDAS scores for those with persistent CM to those with remitted CM. In addition, interaction effects were assessed by examining differences between remitted and persistent CM on mean change in MIDAS between baseline and follow-up.

Results: The subject pool included 452 individuals with CM in 2005 who contributed 3 years of data, of which 19.9% (n = 90) had CM in all 3 years (i.e., persistent CM) and 35.4% (n = 160) had CM in 2005 but did not meet criteria for CM or HFEM in 2006 and 2007 (i.e., remitted CM). The overall within group effect for MIDAS scores was significantly different between 2005 and 2007 assessments (P = 0.04). Comparing mean MIDAS scores from baseline (2005) to follow-up (2007), in 2005, persistent CM had a mean score of 51.1 that increased to 64.3 (Δ = 13.2) in 2007; while remitted CM had a 2005 baseline mean score of 50.4 that decreased to 12.8 in 2007 (Δ = -37.6). The differences between remitted and persistent CM in mean change MIDAS scores was also significant (95% CI = -48.6 (-62.4–-34.9), P = 0.001).

Conclusions: Those with persistent CM experienced increasing disability over 2 years of follow up. Those with remitted CM had substantial decreases in disability. Treatments for CM should substantially reduce headache related disability if they result in CM remission.

PO155
Headache during late Ramadan month: a controlled study
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Objectives: The aim is to study the characteristics of headache attacks in fasting subjects during the last two days of Ramadan month (after 20 consecutive days of fasting) compared to age and gender matched controls.

Background: The headache of the first day of Ramadan fasting or Yum Kippur is well documented, however little is known about the nature and patterns of headache during the subsequent days of Ramadan. As Muslims continue to practice fasting-abstinence from food and water from dawn to sunset-for 30 consecutive days.

Methods: This cross-sectional study was carried on 93 fasting subjects, 97 non-fasting controls during the 4th week of Ramadan month, subjects were asked to fill a self-administered headache questionnaire based on the 2nd edition of the diagnostic criteria of the international headache society; to report any headache within the last day, besides; information about trigger factors, sleep, work, drugs, health conditions as well as demographic data were also sought.

Results: Fifty two (53.1%) fasting subjects experienced an attack of headache in the previous day, compared to 41 (44.6%) controls (X2 = 2.11, P = 0.02). The attacks were only severe in eight fasting subjects compared to 13 controls (X2 = 2.11, P = 0.05); seven subjects had difficulty maintaining their routine activities. Most of the attacks (78%) were short in duration (less than 4 hours). The attacks were distributed throughout the day with only seven subjects reporting headache close to breakfast time, which refute the common belief that end of day headache is the most common in Ramadan. The headache was not related to number of working hours, smoking, and amount of coffee, tea taken per day or sleep disturbances. 36 (38.7%) fasting subjects recalled having severe first day headache. The diagnosis suggested a migrainous attack in nine subjects. Patients should not take oral medications because of fasting; although Islamic rules permit people who are in severe pain to stop fast, none of the interviewed subjects saw the pain severe enough to stop fasting.

Conclusions: Except for the first day in Ramadan month, headache in Ramadan is mostly mild, of short duration; most of the attacks are of tension type headache and is not more frequent in fasting subjects than controls.

PO156
Secondary headaches in adults with down syndrome: case series and literature review
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Objectives: To determine the prevalence and etiologies of secondary headaches in adults with Down syndrome (DS).
Background: DS, the most commonly identified cause of mental retardation, occurs in about one in 750 births. One of the most frequently occurring chromosomal abnormalities, DS affects people of all ages, races and economic levels. The life expectancy of these individuals has been increasing from an average of 9 years of age in 1929, to 12 years of age in 1949, to 35 years of age in 1982, to 55 years of age or older currently. Over the past 50 years, the life expectancy for people with DS has increased by an average of 0.94 life years per calendar year, compared to the 0.23 life years per calendar year for the general United States population. These differential increases in life expectancy would suggest that, within the next generation, people with DS will be living as long as the general population. As a result, the medical, psychological and social needs of adults with DS are receiving greater attention. These individuals have an increased prevalence of medical disorders that affect virtually every organ system. Knowledge of the many medical problems found in individuals with DS enables clinicians to provide rational medical monitoring.

Methods: The charts of all adult patients with DS who presented to a hospital based DS center for their annual physical examination between May 22, 2006 and May 31, 2007 were reviewed. Diagnosis of a secondary headache was made on the basis of International Headache Society (IHS) standard diagnostic criteria.

Results: Four hundred patients had attended the clinic for their annual physical examination; 228 male patients (average age 39; 46.9% living in residential facilities) and 172 female patients (average age 39; 56.4% living in residential facilities). Of the 400 patients, 7 (1.7%) were found to have secondary headaches: two were cervicogenic headaches from atlantoaxial instability; two were attributed to intracranial hypertension secondary to hydrocephalus; one was a chronic post traumatic headache; one was attributed to intracerebral hemorrhage; and one was attributed to posttraumatic stress disorder. As we previously reported, no primary headache disorders were found in this group of patients.

Conclusions: Secondary headaches in adults with DS are uncommon and usually are severe in nature. We discuss the etiologies of secondary headaches in adult DS patients with a review of the literature.

PO157
Diagnosing migraine using a web-based questionnaire: report from the lumina (Leiden University migraine neuro analysis) group
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Objectives: To validate the use of a self-reporting, web-based questionnaire to diagnose migraine headache and migraine aura.

Background: For current genetic research aimed at identifying migraine gene variants using genome-wide association studies (GWAs), large numbers of cases are needed. Self-administered web-based questionnaires represent an attractive alternative for a direct interview in diagnosing migraine because they are less time consuming, but may lead to the inclusion of false positive cases.

Methods: We recently launched a LUMINA website as a portal to recruit migraine patients and informed the public nationwide via the lay press. Self-reported migraineurs could participate in a web-based extended questionnaire study after having fulfilled screening criteria on the website, using screening questions that were validated previously in a population-based study [Launer et al., Neurology 1999]. After completion of the extended questionnaire, an algorithm based on IHS criteria was run and individual diagnosis was determined. A semi-structured telephone interview was used as a golden standard to validate the algorithm diagnosis with specific attention to migraine aura. Interviews were performed by the principle study physicians (WPJoV, CMW, AHS), who are experienced in diagnosing migraine patients, and by well-trained medical students that were supervised by them. A final diagnosis was always made after the interview. In case of ambiguous symptoms, a headache specialist (GMT) was consulted. Patients were asked to participate in genetic research.

Results: From April 2008 until April 2009, the questionnaire was completed by 2,397 subjects. 1,038 out of 1,067 (97%) randomly selected subjects were reached for semi-structured telephone interview. Age, gender or algorithm diagnosis did not differ between selected and non-selected subjects, or between subjects reached and not reached. 982 subjects were diagnosed with migraine headache and 488 with migraine aura. The algorithm for migraine headache had a sensitivity of 73% (721/982), specificity of 68% (38/56), positive predictive value (PPV) of 98% (721/739), negative predictive value (NPV) 13% (38/299), positive likelihood ratio (LR+) of 2.28 and negative likelihood ratio (LR-) of 0.40. The algorithm for migraine aura had a sensitivity of 45% (221/488), specificity of 95% (520/530), NPV 88% (221/251), PPV 66% (520/787), LR+ of 9.00 and LR - of 0.58. Accuracy of aura subtype classification: visual (PPV 93%; LR + 16.50), sensory (PPV 56%; LR + 8.75), dysphasia (PPV 46%; LR + 5.18) and motor aura (PPV 24%; LR + 10.33). A logistic regression model containing the best predictors for migraine diagnosis and migraine aura will be presented.

Conclusions: The LUMINA web-based questionnaire predicts migraine headache and migraine aura accurately in a population of self-reported migraineurs, which makes it a valuable tool for diagnostic ascertainment for genetic studies.

PO158
Validating use of the headache impact test (HIT-6) among migraine patients
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Objectives: This study was to provide evidence for reliability and validity of the six-item Headache Impact Test (HIT-6) across the types of migraine to further assist its practical use in clinical research and practice for detecting and monitoring functional impact due to headaches.

Background: The HIT-6 is a reliable and valid questionnaire, developed in samples of headache sufferers. It has been used among different types of headache patients, including migraine. Validation study is needed for the ability of the HIT-6 in differentiating the functional impact across the types of migraine.

Methods: Data came from two sources of adult participants with headache complaints: 1) the National Survey of Headache Impact (NSHI); and 2) the HIT-6 Validation (HIT6-V) study. An epidemiological migraine screener (ID Migraine) was used for identifying participants with migraine. Migraine participants with 15 or more headache days per month (HDPM) were considered as having chronic migraine (CM); 10–14 HDPM as high-frequency episodic migraine (HEM); and less than 10 HDPM as low-frequency episodic migraine (LEM). HIT-6 was analyzed for internal consistency and test-retest reliability and convergent validity among migraineurs, and discriminant validity across participants with various types of headaches using criteria measures.

Results: A total of 994 participants (48.5% out of 2,049) were identified having migraine (53.5% from NSHI) with 6.4% CM; 5.9% HEM; 36.3% LEM; and rest 51.5% non-migraine headache. HIT-6 scores (mean ± SD) across four groups were: 62.5 ± 7.8; 62.2 ± 6.7; 59.9 ± 7.9; and 49.1 ± 8.7, respectively. Among migraineurs, internal consistency (Time1/Time2) was 0.830/0.87 for the NSHI; 0.82/0.92 for the HIT6-V; 0.83/0.90 for the total sample; and test-retest reliability of HIT-6 observed among migraineurs was 0.77 (intra-class correlation between Time1 and Time2 of the HIT6-V).
scores correlated significantly \( (P < 0.0001) \) with SF-8 (HIT6-V only) Physical Component Summary \( (r = -0.27) \) and Mental Component Summary \( (r = -0.19) \); as well as with the total Migraine Disability Assessment Scale score \( (r = 0.56) \) and number of HDPM \( (r = 0.29) \). Using the logic of known groups for discriminant validity, mean HIT-6 scores differed significantly \( (F = 332.95, \ P < 0.0001) \) across CM, HEM, LEM, and non-migraine headache participants in the hypothesized direction, with the exception of comparison between CM and HEM \( (P = 0.9565) \).

**Conclusions:** The psychometric evaluation in this study demonstrated that the HIT-6 is highly reliable and valid, and it differentiates the functional impact due to headache between CM/HEM and LEM, non-migraine headache sufferers.

**PO159 Interactions between alcohol flushing, drinking frequency and migraine/tensions-type headache in Japanese**

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**Objectives:** To evaluate interactions among alcohol flushing, alcohol drinking, and migraine/tension-type headache.

**Background:** Our previous cross-sectional survey of 12,988 subjects receiving health checkups at a Tokyo clinic showed that headache sufferers of both genders reported less alcohol consumption (Yokoyama M et al. J Headache Pain 2009). Alcohol consumption of Japanese is inhibited by the presence of Asian inactive aldehyde dehydrogenase-2 (ALDH2), whose carriers are sensitive to alcohol flushing responses including headache. A questionnaire asking current and past facial flushing after drinking a glass (180 ml) of beer can indentify inactive ALDH2 with the sensitivity/specificity of 90% among both genders (Yokoyama T, et al. Cancer Epidemiol Biomark Prev 2003;12:1227–33).

**Methods:** We conducted a cross-sectional study in 5408 subjects (M/F; 2778/2630) receiving health checkups at the Tokyo clinic by using a headache questionnaire designed to diagnose headache type according to the ICHD-II criteria, a drinking questionnaire, and the flushing questionnaire.

**Results:** 2577 subjects (M/F; 1018 [36.6%]/1559 [59.3%]) who completed items related to drinking and the flushing questionnaire reported to have ever experienced headache except cold and alcohol hangover. Migraine was diagnosed in 419 (M/F; 75 [1.4%]/344 [13.1%]) subjects, and tension-type headache, 613 (249 [9.0%]/364 [13.8%]) subjects. 1545 (694 [25.0%]/851 [32.4%]) subjects were classified as other headaches, which tended to be less frequent and milder than migraine and tension-type headache. In comparison with subjects with other headaches, both male and female migraineurs and men with tension-type headache significantly less frequently drink alcohol. According to the flushing questionnaire, 45.6% of the 2577 subjects were predicted to have inactive ALDH2. When the drinking frequency was classified as none, sometimes or less than 3 days/wk, 4–6 days/wk, or every day, the decreasing trend in migraine risk according to the category of drinking frequency was significantly more marked in men with inactive ALDH2 than in those with active ALDH2 (age-adjusted ORs [95% CIs] per + 1 category increment of drinking frequency were 0.43 [0.28–0.74] and 0.92 [0.61–1.38], respectively; \( P = 0.039 \) for difference in OR). The decreasing trend in migraine risk according to the category of drinking frequency was marginally significant in women with inactive ALDH2 (0.75 [0.56–1.01], \( P < 0.06 \)), and the decreased trend in risk of tension-type headache were not significant regardless of gender and ALDH2.

**Conclusions:** Migraineurs and men with tension-type headache less frequently drink alcohol than subjects with other headaches in Japan. Interactions between the ALDH2 activity assessed by the flushing questionnaire, drinking frequency, and headache prevalence differ according to the headache classification. Migraineurs with inactive ALDH2, who are more vulnerable to severe alcohol-induced headache than those without it, may be more likely to avoid alcohol drinking.

**PO160 Population-based survey of primary headache disorders in Russia: validation of questionnaire and methodology**

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**Objectives:** The first population-based survey of primary headache disorders in all Russia is being conducted within Lifting the Burden: the Global Campaign to Reduce the Burden of Headache Worldwide.

**Background:** In the pilot phase we validated the methodology and a Russian-language diagnostic questionnaire for migraine and tension-type headache (TTH).

**Methods:** Trained non-medical interviewers made door-to-door visits, randomly selecting one respondent per household. They surveyed 501 subjects in four large cities (Smolensk: \( n = 41 \); Tver: \( n = 75 \); Chelyabinsk: \( n = 72 \); Nizhny Novgorod: \( n = 76 \)) and three rural areas (Tula region: \( n = 85 \); Tver region: \( n = 81 \); Samara region: \( n = 71 \)). Of these, 190 (143 with headache and 47 without) were randomly selected and re-interviewed, by telephone, by a headache specialist.

**Results:** Response rates were 72.9% in the cities and 80.1% in the rural settlements. Of the 501 respondents, 301 (60.1%) reported headache ‘not related to flu, hangover, cold or head injury’ at least once in the previous year, including 79 (26.2%) claiming more than one headache type. Diagnosed by questionnaire, 43 of the 501 had migraine (1-year prevalence 8.6%), and a further 51 (10.2%) had probable migraine; 41 (8.1%) had TTH and a further 93 (18.6%) had probable TTH. Since the diagnostic algorithm excluded TTH before diagnosing probable migraine, and excluded migraine and probable migraine before diagnosing probable TTH, the probable cases were included with the definite cases for this validation (migraine: 18.8%; TTH: 26.7%). By comparing questionnaire diagnoses with specialist diagnoses, we calculated sensitivities and specificities of the questionnaire: 87.3% (95% CI: 76.8–93.7) and 69.4% (57.3–79.5) respectively for migraine; 86.2% (74.8–93.1) and 73.1% (61.6–82.2) for TTH. Headache on > 15 days/month was reported by 61 respondents (12.2%). This high prevalence was confirmed in telephone interviews.

**Conclusions:** The questionnaire and survey methodology were therefore acceptably reliable, and valid to collect data on headache in the general population. The main survey will study 2,000 respondents in 20 of the 22 regions of Russia.
PO161
Modern approaches to care providing optimization in headache patients
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Objectives: Assessment and improvement of health-care solutions for headaches in Russian Federation (RF).

Background: Headache represents global health problem in RF. It ranks among the most common complaints in primary care system and can cause substantial level of disability and productivity loss. The reason for this is low effectiveness of care providing in Public Health system in RF. This highlights the need for improvement of headache treatment and prophylactics.

Methods: The organization of care-providing for headache patients in Moscow city out-patient clinics, in-patient clinics and two specialized headache centers was assessed by means of complex expert evaluation.

Results: The study revealed significant defects in treatment organization, accessibility and effectiveness. Many patients are not satisfied with care-providing level in out-patient clinics. Among their complaints are the following: 64% are displeased with long waiting period (due to lines), 54% assess the facilities as very poor, 21% note low qualification of medical staff in headache diagnosis and treatment. The study also proved the need for specialized centers for headache diagnosis and treatment in RF. The care-providing system in such centers showed to be more convenient and effective comparing this with the out-patient units. Life-quality after treating headache in specialized centers is significantly higher, mainly due to social, emotional and psychological rehabilitation. But the existing amount of specialized headache centers in RF is obviously insufficient (there are only two of them, both localized in the Central Federal District).

Table 1. The desirable amount of centers in various RF regions

<table>
<thead>
<tr>
<th>RF regions</th>
<th>Amount of centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central federal district</td>
<td>2</td>
</tr>
<tr>
<td>Northwest</td>
<td>1</td>
</tr>
<tr>
<td>South</td>
<td>1</td>
</tr>
<tr>
<td>Volga federal district</td>
<td>1</td>
</tr>
<tr>
<td>Ural federal district</td>
<td>1</td>
</tr>
<tr>
<td>Siberian federal district</td>
<td>1</td>
</tr>
<tr>
<td>Far east</td>
<td>2</td>
</tr>
<tr>
<td>Total in RF</td>
<td>9</td>
</tr>
</tbody>
</table>

Conclusions: Our study revealed lack of effectiveness of the existing headache treatment system in RF. This should be solved by making the problem a national priority and demonstrating global burden of headaches. Public health policy should contain special section regarding set of measures for headache diagnosis and treatment accessibility and effectiveness. The amount of specialized multidisciplinary centers, implementing highly sophisticated headache diagnosis and treatment should be increased (see Table 1). Their tasks should include: interdisciplinary headache diagnosis and treatment, complex evaluation with life quality assessment, clinical and economical trials of headache prophylactics and treatment methods, healthy life propaganda. Multidisciplinary approach suggests coordinated work of various specialists. In every RF region it is essential to elaborate a unique system of care providing to address local conditions. Crucial for system optimization is interacting of different care providing levels, from primary care physician to specialized multidisciplinary center team. Information support of headache problem via Internet is also essential.

PO162
Episodic tension type headaches or mild to moderate migraine attacks – learning from triggers and family history
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Objectives: To alter a diagnosis of ICHD 2 ETTH (2.1 and 2.2) to mild to moderate migraine attacks.

Background: ICHD2 ETTH can be difficult to distinguish from migraine without aura in patients with atypical features. Both the diagnostic criteria have overlapping statements. Some experts have hypothesized that migraine and tension might represent a continuum rather than two distinct entities.

Methods: 5 year prospective study of 1041 patients aged 10 to 50 years. All presented with ICHD2 eth diagnostic features with two common migraine triggers (exposure to sunlight and travelling by bus) precipitating their headpain and family history (first or second degree relative) with migraine origin pain (1.1,1.2,1.6) precipitated by the same triggers. Exclusion criteria – if no family history of migraine origin pain and ETTH resembling atypical migraine episodes (recurrent throbbing pain) not precipitated by known or common migraine triggers.

Results: A total of 827 patients reported activity not affected (mild to moderate pain intensity) bilateral throbbing pain and 214 with non throbbing pain. 424 had only phonophobia and 83 with phonophobia only to certain sounds. 101 reported only photophobia. 433 reported neither phonophobia or photophobia. Family history showed 813 with maternal and 228 with paternal first or second degree relative with migraine origin pain (1.1,1.2,1.6) precipitated by the same triggers. Patients with throbbing headaches were provisionally diagnosed as most probably migraine or migraine-like disorder and those with non throbbing pain were diagnosed as borderline migraine or migraine trait.

Conclusions: This study concludes that patients presenting with ICHD2 ETTH features or atypical migraine features (bilateral activity not affected throbbing pain and no diagnostic associated features) to be diagnosed as mild to moderate migraine attacks if known migraine triggers other than tension anxiety situations are precipitating these headaches and if one family member is suffering from migraine origin pain precipitated by same triggers. Patients, parents and other family members were more convinced when the diagnosis was altered from ETTH to mild to moderate migraine attacks. Follow up revealed significant improvement in their recurrent head pain episodes when common and known migraine triggers were avoided completely.

PO163
Temporomandibular disorders and cutaneous allodynia are associated in individuals with migraine
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Objectives: To estimate and contrast the occurrence of ictal and inter-ictal cutaneous allodynia (CA) in individuals with migraine with and without temporomandibular joint disorders (TMD).

Background: Both TMD and CA are common in migraine and may be associated with migraine transformation from episodic into a chronic form. Herein we hypothesize that TMD contributes to the development of CA and to more severe headaches.
Methods: In a clinic-based sample of individuals with episodic migraine, the presence of TMD was assessed using the Research Diagnostic Criteria (RDC) for myofascial or mixed (myofascial and arthralgic) TMD. Ictal CA was quantified using the validated Allodynia Symptom Checklist (ASC-12). The ASC-12 measures CA over the preceding month by asking 12 questions about the frequency of allodynia symptoms during headaches. Interictal CA was assessed in the domains of heat, cold and mechanical static allodynia using quantitative sensory testing.

Results: Our sample consists of 55 individuals; 40 (73%) had TMD (23 with myofascial TMD and 17 with the mixed type). Allodynia scores, as measured by ASC-12 are presented in Figure 1. CA of any severity (as assessed by ASC-12) occurred in 40% of those without TMD (reference group), 86.9% of those with myofascial TMD (P = 0.041, RR = 3.2, 95% CI = 1.5–7.0) and in 82.3% in those with mixed TMD (P = 0.02, RR = 2.5, 95% CI = 1.2–5.3) Table 1.

Figure 1

Table. Presence and severity of headache-related allodynia, as measured by the ASC-12.

<table>
<thead>
<tr>
<th>Allodynia Categories</th>
<th>Myofascial</th>
<th>Mixed</th>
<th>Myofascial vs. no</th>
<th>Mixed vs. no</th>
<th>Myofascial vs. mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>TMD (N%)</td>
<td>TMD</td>
<td>(P value)</td>
<td>(P value)</td>
<td>(P value)</td>
</tr>
<tr>
<td>No</td>
<td>8 (33.3%)</td>
<td>3 (3%)</td>
<td>0.042</td>
<td>0.028</td>
<td>0.4048</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Myofascial</td>
<td>Mixed</td>
<td>Myofascial vs. no</td>
<td>Mixed vs. no</td>
<td>Myofascial vs. mixed</td>
</tr>
<tr>
<td>(N%)</td>
<td>(N%)</td>
<td>(N%)</td>
<td>(P value)</td>
<td>(P value)</td>
<td>(P value)</td>
</tr>
<tr>
<td>No</td>
<td>8 (33.3%)</td>
<td>3 (3%)</td>
<td>0.042</td>
<td>0.028</td>
<td>0.4048</td>
</tr>
<tr>
<td>Allodynia</td>
<td>(53.3%)</td>
<td>(13.04%)</td>
<td>(17.64%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>2 (5%)</td>
<td>2 (2%)</td>
<td>0.004</td>
<td>0.003</td>
<td>0.006</td>
</tr>
<tr>
<td>Allodynia</td>
<td>(13.3%)</td>
<td>(21.73%)</td>
<td>(11.76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (2%)</td>
<td>2 (2%)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (20%)</td>
<td>7 (10%)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Allodynia</td>
<td>(33.3%)</td>
<td>(30.43%)</td>
<td>(50.82%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Individuals with TMD were more likely to have moderate or severe CA associated with their headaches. Interictally (QST), thresholds for heat and mechanical nociception were significantly lower in individuals with TMD. Cold nociceptive thresholds were not significantly different in migraine patients with and without TMD. TMDs were also associated with change in extra-cephalic pain thresholds. In logistical regression, TMD remained associated with CA after adjusting for aura, gender and age.

Conclusions: TMD and CA are associated in individuals with migraine.
PO165
Migrade: development of a grading system for migraine patients
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Objectives: To develop a clinically and scientifically applicable grading system for determining the clinical significance, the degree of impact and response to treatment.

Background: Migraine is a common disorder, but can vary greatly in the degree of impact and response to treatment from consistent simple analgesics to extensive multidisciplinary treatment requiring both pharmacological and non-pharmacological intervention. Attempts have been made to address this problem using headache indexes and disability assessment. A global assessment of headache grade, as has been developed for other disorders, has not been possible. The spectrum of secondary chronic headache differs between GPs and neurologists. Knowledge of pattern of medication overuse and use of alternative medications in different settings is important for health economics, for planning and interpreting studies in other than specialised clinic settings.

Methods: A scoring system was developed combining headache characteristics (frequency, severity, duration, associated features including allostynia, and the presence of aura), disability and impact, co-morbid conditions, and treatment utilized and the response to the treatments. Points were developed for each feature and the system applied to a detailed computer database of well-characterized headache patients. A binomial distribution was observed and a 5 level grading system derived.

Results: Based on the features assessed, a scoring range of 0 to 61 was possible. From database screening, a score from 3383 subjects were measured (mean 15.36 ± 5.68, range 1 to 35) with complete data available on 474 subjects (mean score 18.83 ± 5.86, range 3 to 35). Based on the scoring range and standard deviation, a grade was assigned – Grade I (0–6), Grade II (7–12), Grade III (13–18), Grade IV (19–24), and Grade V (> 25). Applying these grades to the subjects with complete data, the distribution was maximal for Grade III (13–18) and Grade IV (19–24). The contacts with different physician levels for headache patients were as follows: chronic posttraumatic cervicogenic headache 14%, chronic posttraumatic cervicogenic headache 33%, chronic rhinosinusitis headache cervicogenic headache 33%, chronic rhinosinusitis headache cervicogenic headache 26%, chronic rhinosinusitis headache cervicogenic headache 30%.

Conclusions: Using a combination of headache features, disability and treatment response, a comprehensive system was developed that had a binomial distribution of scores allowing for the development of a migraine grade – MiGrade. Further validation in headache specialty and general practices needed to be performed to assess the wide applicability of this grading system.

PO166
Secondary chronic headache; medication use and utility of health services – the Akershus study of chronic headache
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Objectives: To investigate physician contact pattern and medication overuse in people with secondary chronic headache from the general population.

Background: Secondary chronic headaches, chronic posttraumatic headache, chronic headache attributed to whiplash injury, cervicogenic headache, headache attributed to chronic rhinosinusitis) are associated with high intake of medication and frequent use of alternative treatment. Patients in specialised headache clinics, general practices and in the general population differ. Knowledge of pattern of medication overuse and use of alternative medications in different settings is important for health economics, for planning and interpreting studies in other than specialised clinic settings.

Methods: An age and gender stratified epidemiological survey included 30,000 persons aged 30–44 years from the general population. A posted questionnaire screened for chronic headache. Those with self-reported chronic headache were interviewed by neurological residents. The International Classification of Headache Disorders was used with additional definitions for chronic rhinosinusitis and cervicogenic headache. Participants were asked about physician contacts, alternative treatments and medication. The Severity of Dependence Score (SDS) was used for headache medication. Those with secondary chronic headache were included.

Results: The questionnaire response rate was 71%, the interview participation rate 74%.

Medication overusers were more commonly in contact with neurologists, those without overuse more often had no physician contact. 73% had used alternative treatment, mostly physiotherapy, acupuncture and chiropractic. Use of alternative treatment differed between different physician levels. Those with chronic rhinosinusitis headache had more psychologist contact and less physiotherapy. For other secondary diagnoses there was no difference in use of alternative treatments. The SDS score was higher in medication overusers than in non-overusers.

Table 1. The contacts with different physician levels for headache were as follows:

<table>
<thead>
<tr>
<th>Level of physician contact</th>
<th>Chronic posttraumatic headache</th>
<th>Chronic whiplash cervicogenic headache</th>
<th>Chronic rhinosinusitis headache</th>
<th>All secondary headaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14%</td>
<td>33%</td>
<td>33%</td>
<td>26%</td>
</tr>
<tr>
<td>GP only</td>
<td>28%</td>
<td>33%</td>
<td>38%</td>
<td>46%</td>
</tr>
<tr>
<td>Neurologist</td>
<td>59%</td>
<td>38%</td>
<td>29%</td>
<td>28%</td>
</tr>
</tbody>
</table>

Conclusions: The spectrum of secondary chronic headache differs between GPs and neurologist settings.
PO167
Development, reliability and validity of the chronic daily headache–computer assisted telephone interview (CDH-CATI)
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Objectives: To develop and validate a telephone interview for the diagnosis of chronic daily headache (CDH), episodic migraine (EM), and chronic migraine (CM).

Background: There are no valid telephone screening tools for the diagnosis of CDH, EM, and CM available. Such an instrument would facilitate the assessment of the prevalence of these disorders.

Methods: We developed the CDH-CATI based on a previously validated CATI and self-administered questionnaire. We administered the CDH-CATI to 95 patients identified from a specialty headache center. Participants completed the CDH-CATI, and provided information about headache characteristics and frequency at two time points: current and ‘past’ (about two years prior). Diagnoses were assigned by a headache expert using both Silberstein-Lipton and ICHD-2 criteria and current and past diagnoses were extracted from medical records. A researcher blinded to their clinical diagnosis assigned the CDH-CATI diagnoses, for ‘current’ and ‘past’.

Results: Using the clinical diagnosis as the ‘gold standard’, 31/41 individuals with current CDH (sensitivity = 0.76) and 53/54 (specificity = 0.98) without current CDH were correctly classified; corresponding positive predictive values (PPV = 0.97) and negative predictive values were high (NPV = 0.84). The questionnaire identified 54/55 patients with EM (sensitivity = 0.98; specificity = 0.75; PPV = 0.84, NPV = 0.97), and 9/14 patients with CM (sensitivity = 0.64; specificity = 0.96). Similar results were found for ‘past’ CDH, EM, and CM diagnoses. Test-retest reliability was very good (current CDH and EM: Kappa = 0.78; past CDH and EM: Kappa of 0.66).

Conclusions: The CDH-CATI demonstrated excellent operating characteristics for identifying individuals with current and past diagnoses of CDH, CM, and EM in a clinic-based sample.

PO168
Can information and communication technology improve the management and the outcome of medication overuse headache? The challenge of the ‘COMOESTAS project’
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Objectives: An innovative informatic tool for the diagnosis and the follow-up of patients with Medication Overuse Headache (MOH) – a common condition and a major cause of disability in the frame of chronic neurological disorders – is being tested in a multicentre controlled trial. The objective of the trial is to demonstrate that the proposed system may improve the management and the outcome of MOH.

Background: Information and communication technologies have been used only sparsely in the field of headache, but it seems likely that a system favouring close monitoring would be helpful in the monitoring of MOH patients.

Methods: The tool is an innovative ICT (Information and Communication Technology) system designed to provide MOH patients with continuous and personalized treatment, thereby making the patients themselves a key node of the entire process (Patient-centric Health Care System). The system is based on an Interactive Electronic Patient Record (IEPR), which incorporates five main features: Minimum Data Set, which receives and elaborates the patient’s basic clinical data, producing a preliminary automated diagnosis, screening patients to be enlisted for the detoxification procedure and, subsequently, for the follow-up program. Electronic Patient Record, which collects and stores the complete set of patient’s clinical data and relevant indicators. MOH Electronic Diary: the electronic version of the classic headache diary on paper currently used in the most advanced European Headache Centres. Filling in this diary allows physicians to continuously monitor patient’s follow-up and to receive alerts and warnings, should selected parameters exceed given thresholds. Second opinion features, incorporating tools for booking, videoconferencing, chat, structured mail that allow physicians to ask for a second opinion to their colleagues within the Consortium and also to promote direct internet based contact between physicians and patients. Business logic: the informatic engine that manages monitoring, alerts and supports physician’s decisions, diagnosis and treatment, fostering interoperability between communication technologies and ICT systems.

Results: The IEPR software has been released and is currently being tested in two centres. Preliminary results suggest that it is well accepted by patients and easy to use.

Conclusions: Application of an ad hoc alert and monitoring system seems a feasible possibility in MOH following withdrawal from over-used drugs. The system may improve the early detection of relapses or help preventing them.
PO169

A pilot study to assess the responsiveness of the headache impact test (HIT-6)

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Objectives: To investigate whether the Headache Impact Test (HIT-6) can detect clinically relevant changes.

Background: The HIT-6 is a short comprehensive questionnaire measuring the impact of headache on patients quality of life. To evaluate treatment outcome it needs to be responsive and the clinically relevant difference expressed in points needs to be determined.

Methods: Headache sufferers were recruited in an open population and asked to complete the HIT-6 twice with a six weeks interval. In this period no treatment was started nor changed. A general headache questionnaire was used to make an inventory of clinical patient characteristics such as headache frequency and intensity. HIT-6 responsiveness was assessed via Minimal Detectable Change and by optimal cut off points on ROC-curves. Global Perceived Effect (GPE) was used as external criterion.

Results: A total of 91 headache sufferers completed the HIT-6 twice. Mean HIT-6-score at both measuring moments was 62.13 points ± 6.34 points and 60.29 points ± 7.18 points, respectively.

After 6 weeks, nine patients perceived their headache to be improved, 82 perceived no change or deterioration. Using GPE as the external criterion, the Minimal Detectable Change was 4.06 points. The Area Under the Curve was 0.79. A cut off value of 4.50 points corresponded with a sensitivity of 0.71 and a specificity of 0.81.

Conclusions: These results suggest that the HIT-6 is a responsive tool. The values of the 4.06 points and 4.50 points can be used to identify clinical relevant changes in daily practice.

PO170

Abstract withdrawn

PO171

High pulse pressure is associated with a decreased prevalence of headache in adolescents. Cross-sectional data from an epidemiological study

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Objectives: The objective of the present study was to provide data on the association between blood pressure and headache prevalence in an adolescent population.

Background: Cross-sectional epidemiological data in adults have indicated an inverse relation between blood pressure levels and prevalence of headache and chronic pain.

Methods: Data from a large population-based survey with 5847 adolescents were used to evaluate the association between blood pressure (systolic, diastolic, mean arterial and pulse pressure) and migraine and tension-type headache.

Results: Analysing boys and girls together, increasing pulse pressure was inversely related to headache, both tension-type and migraine (P-trend analysis, P = 0.001). This was also the case for systolic blood pressure, even though for migraine the results were only borderline significant (P = 0.05). These findings were also present after adjustment for age. There was also a weak negative correlation between headache frequency and both pulse pressure and systolic blood pressure (P ≤ 0.02).

Conclusions: High pulse pressure has previously been found inversely related to migraine and tension-type headache in an adult population. This inverse relationship has now been demonstrated also among adolescents with BP values considered to be well within the normotensive range. The findings can be explained by hypertension-associated hypalgesia, indicating an interaction of brainstem centres involved in cardiovascular control and pain modulation.

PO172

Headache outcome measured with the HIT-6 scale in a cohort of patients attending a headache unit: intrapatient evolution

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Objectives: When we began this study, we wanted to know if the patients who got into our Headache Unit had actually any benefit from it or not.

Background: There are several types of headache patients and the outcome could be different from one headache type to other. Other questions to answer were: which kind of headache type gets greater benefit attending the Headache Unit? Are there headache types without benefit?

Methods: In order to evaluate the headache outcome we have used the HIT-6 scale which has a great power to compare the intrapatient evolution of headache. All the patients attending the Headache Unit since January, 2007 till October, 2008 were requested to self-fill the HIT-6 scale before each visit. In this paper we review the HIT-6 evolution of patients attended for the first time in the unit, prospectively. Data analysed includes: age, sex, 2004’s International Headache Classification headache type, acute treatment used and symptomatic treatment used (if used). Patients were treated following the national and international standard recommendations from headache treatment guides. In Medication Overuse Headache patients an outpatient drug withdrawal was made and preventive treatment used since the first visit.

Results: Two hundred and sixty four patients came to the unit for the first time in the analysed period, and we have evolutive data from 94 of them. At their first visit, these 94 patients had a 65.45 score in HIT-6. Prospectively the rate lowered -5.8 points to 59.65. 18 patients had an increased score, +3.89 (62.44 at the beginning); 11 patients remained the same rate, +/-0 (65); and 65 patients improved in HIT-6 score,-9.45 (62.44 at the beginning). All the headache types improved in HIT-6 scores, but the greater improvement was found in Medication Overuse Headache patients (n = 10), with-13.4 (66.1 points at their first visit to 52.7). Also secondary headaches (n = 8) had better outcome: -10.1 (68.25 at the beginning). The rest of headache types have poorer improvement. We also found a significant change in the pattern of acute treatments used: less ergots, metaramizol and simple analgesics and more triptans. Patients using preventive treatment were 12% at their first visit and 68% prospectively.

Conclusions: Patients attended in the Headache Unit got a clear significant benefit in terms of HIT-6 scale scores. The use of preventive treatment and the change in the pattern of acute medications used seem to influence this good outcome. Medication Overuse Headache patients have the better outcome when treated in a Headache Unit.
PO173
Prevalence of migraine diagnosis using ID migraine among university students in Thrace area of Turkey
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Objectives: Migraine is a significant health problem due to its frequency and accompanying morbidity, which includes disability and loss of performance especially young people.

Background: We aimed to determine the prevalence of migraine headaches using a questionnaire, including ID Migraine, for university students in Edirne, a Turkish city.

Methods: The study was designed cross-sectionally and a questionnaire was applied to 4,645 students. The questionnaire consisted of questions related to demographic, social, curriculum, housing and headache characteristics of the subjects. Three-item screening questions of the ID Migraine test were included at the end of the questionnaire aimed at migraine diagnosis.

Results: The mean age of 4,645 students (529 females and 727 males) enrolled in the study was 19.20 ± 1.58 (18–25 years). Migraine-type headache was detected in 231 subjects (6.19%) based on the ID Migraine evaluation.

Conclusions: As a conclusion, the questionnaire appears like an useful, fast and easy method for the evaluation of diagnosis of migraine in populations groups.

PO174
Characteristic analysis of primary headaches applying the new IHS criteria: the West China headache outpatient study (WCHOS)
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Objectives: To analyze the characteristics of patients with primary headaches referred to outpatient neurology clinics in the West China Hospital.

Background: Headache occurs worldwide, but documentation on the study of headache in developing countries, especially in West China, is quite limited.

Methods: All data were collected in face-to-face interviews from December 1st to December 31st, 2008. Self-administered questionnaires were used, applying standardized methods. Headache diagnosis was made according to the second edition of The International Classification of Headache Disorders (January 2004) (ICHD-II).

Results: The questionnaire response rate was 71.2%. A total of 632 patients with primary headache were included in the study. The average age was 37.4 ± 13.6 years and suffers were predominantly women (64.9%). The most frequent diagnosis was tension-type headache (TTH) (55.2%); other types in descending order of frequency were: migraine (41.6%), cluster headache (1.7%) and other primary headaches (1.4%). The percentages of probable migraine and probable TTH were 0.4% and 6.0%, respectively. Most patients complained of repeated pain localized in unfixed regions (44.3%), while 25.5% and 25.0% subjects selected unilateral and bilateral headache option in their questionnaires. Fifty five point seven percent patients had experienced some accompanying symptoms. And about 67.6% of all reflected that their headaches have indeed affected their work and lives.

Conclusions: The results agree with most reported constituent ratio of primary headaches. Patients referring to the neurology clinics were greatly affected by their headache disorders. So it is important to provide suitable and effective treatment to them in order to minimize their sufferings.

PO175
A survey of headache care experiences in rural American migraineurs
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Objectives: Gather historical information from subjects in rural United States who suffer from migraine regarding experiences with headache care including healthcare utilization and medication usage.

Background: Migraine has a negative impact on biopsychosocial aspects of individuals as well as creates a significant social burden of medical costs and productivity loss. Migraine, affecting 12% of the US population, has an increased incidence in lower socioeconomic groups, and chronic migraine risk factors include obesity and use of certain medication types. West Virginia, entirely encompassed in Appalachia, is likely to be significantly adversely affected by migraine.

Methods: This survey study of West Virginia residents (native or long-term residents) seen as new patients in the West Virginia University Headache Center includes collection of historical data of headache complaints, number and types of providers seen, diagnostic procedures performed, diagnoses given, and current and past medications tried. It includes ICHD-2 based diagnostic impressions, and results are tabulated quantitatively as the objectives of this study are descriptive only.

Results: 26 subjects who were native or long-term West Virginia residents completed surveys and were diagnosed with migraine with or without aura. 14 (%) had Chronic Migraine, and 10 (%) had probably medication overuse headache. In subjects with migraine, mean age was 42.2 years with mean of 17.5 years of headaches. Subjects reported a mean of 3.9 providers seen for headaches – see figure 1 for detailed breakdown. 16 subjects were aware of a previous diagnosis of migraine, six reported a diagnosis of sinus headache, seven a diagnosis of tension headache, and nine reported no previous diagnosis given. Eight subjects were currently using opiates and 11 had previously used opiates for headaches. Triptans were currently used by 9 subjects and previously used by 16. Eight subjects were currently using opiates and/or butalbital without also using triptans.
Conclusions: 1. Rural migraneurs have a high incidence of Chronic Migraine and Medication Overuse Headache. 2. Migraneurs have heavily utilized healthcare resources including providers and diagnostic procedures. 3. Migraneurs currently and historically use multiple non-specific therapies, including opiates and barbiturates. 4. Evaluation is needed to determine factors leading to these utilization patterns, including patient expectations, physician education, and healthcare access.

PO176
Chronic daily headache
Ailani J and Silberstein SD
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Objectives: 1. To determine if patients with chronic daily headache (CDH) have continuous headache or moments of headache relief. 2. To determine the length of time that patients with non-continuous CDH are headache free.

Background: CDH prevalence ranges between 3–5% worldwide. Point five percent of patients with CDH experience severe headaches. Approximately 80% of CDH patients ‘transformed’ from an episodic headache disorder into a daily headache pattern. Often, this transformation is due to the overuse of medication. It is unknown what percentage of patients with CDH have continuous headache vs. moments of headache freedom, and whether or not this difference is related to treatment strategy, or the natural history of the disease.

Methods: Retrospective chart review of 62 patients over age 18, who were seen during an initial or routine follow-up visit, diagnosed with chronic migraine (CM), chronic tension type headache (CTTH), new daily persistent headache (NDPH), or chronic post traumatic headache (CPTH) (ICHD-2). Patients were asked a series of questions about their headaches, and their responses were recorded in their medical record.

Results: Sixty-two patients who fulfilled criteria for CM, NDPH, CPHTH, or CTTH were evaluated. 72.6% of patients in the study had headache every day (HED) (45 of 62 patients). The average age of patients with HED was 55.5 years of age; the majority were women, and the most common diagnosis was CM (31 of 45 patients/68.9%). 60% of patients with HED had continuous headache (27/45), and 40% had non-continuous headache (18/45). 11.1% of patients with non-continuous headache had a day of headache relief, 72.2% had hours of headache relief, and 11.1% had minutes of headache relief.

As expected, the majority of patients in this study had CM. In patients with CM, 36.9% had continuous headache. In patients with NDPH, 66.6% had continuous headache. In patients with CPHTH, 50% had continuous headache. Our study included one patient with CTTH, and that patient had continuous headache. Medication overuse was present in 17.7% of patients with HED at the time of data collection (11 of 62 patients).

Table 1.

<table>
<thead>
<tr>
<th>Headache Type</th>
<th>Total Patients</th>
<th>Headache Every Day</th>
<th>Continuous</th>
<th>Non-Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>CM</td>
<td>46 (74.2%)</td>
<td>31 (67.4%)</td>
<td>17 (36.9%)</td>
<td>14 (30.4%)</td>
</tr>
<tr>
<td>NDPH</td>
<td>9 (14.5%)</td>
<td>8 (88.9%)</td>
<td>6 (66.6%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>CPHTH</td>
<td>6 (9.7%)</td>
<td>5 (83.3%)</td>
<td>3 (50%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>CTTH</td>
<td>1 (1.6%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Conclusions: Most patients with HED have continuous headache. For patients with non-continuous HED, the majority have hours of headache free time, independent of medication use for pain control. This study did not demonstrate if HED that is continuous indicates worse prognosis. Further studies should evaluate if HED that is continuous is predictive of refractoriness, requiring a more aggressive management approach.

PO177
HLA-DQB1*02 allele and risk to allodynia in patients with migraine
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Objectives: The purpose of this study was to investigate the relationship between allodynia and HLA-DQB1 polymorphism in migraine patients with allodynia.

Background: Cutaneous allodynia is defined as the perception of pain or discomfort generated by a non-noxious stimulus to normal skin. Approximately two thirds of patients with migraine complain of allodynia during headache attacks, usually referred to the periorbital area.

Methods: Twenty three (33.8%) of sixty eight migraine patients, recruited from a Headache Service in a private clinic, complained of allodynia during headache attacks. The diagnosis was made according to the International Headache Society criteria. Additionally, 129 ethnically matched controls from the same geographical area were enrolled in the study. Characterization of HLA variants was done using Dynal RELI SSO HLA-DQB1 Typing Kits. Frequencies were determined by direct counting. The statistical significance of allele frequency was estimated by Fisher’s exact test. Odds ratio (OR) with corresponding 95% confidence intervals (95% CI) were calculated to measure the strength of associations.

Results: The frequency of the DQB1*02 allele is significantly increased in migraine patients with allodynia compared to healthy individuals (50% vs. 19.37%, OR = 3.1; P = 0.013). Also, this allele was observed significantly increased among patients with exploding headache and allodynia compared to healthy individuals (46.15% vs. 19.37%, OR = 2.79; P = 0.048).

Conclusions: The results suggest an influence of DQB1 polymorphism in the incidence of allodynia during migraine attacks.

PO178
Genome-wide association study of migraine with aura in a large international consortium sample
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Objectives: The objective of this study was to identify genetic variants linked to migraine susceptibility.
Background: Despite a well-established genetic component for migraine and numerous studies, no variants influencing migraine susceptibility have been convincingly identified. Recently, large-scale multinational collaborations for genome-wide association (GWA) studies have yielded many successes by revealing new genes and pathways in many complex diseases. In order to recruit sufficient numbers of patients to reach statistical power considerably higher than in previous studies, we formed the International Headache Genetics Consortium. Currently, seven top-tier migraine centres are participating in the Consortium.

Methods: In this study, we have performed a genome-wide analysis of 2,900 cases and 9,500 controls, roughly equally distributed between Finland, Germany and the Netherlands. All cases have extensive phenotype information available and have been interviewed by a migraine specialist. For genotyping, we used the Illumina 610 k and 550 k GWA chip platforms, and obtained population-matched controls from other studies (Health2000 from Finland, ERGO from the Netherlands, and KORA, PopGen and HNR from Germany) and genotyped on the same chips. Association analyses were performed using the PLINK and Haploview software.

Results: Here, we present the results of these large-scale analyses, including both population-specific and across-population findings. Furthermore, we demonstrate the added power of the previously-published trait component approach in detecting these associations.

Conclusions: In this presentation we detail the first statistically robust and consistent genetic associations in migraine genetics, as the first step to quantify the genetic background of migraine.

PO179
A role of the TREX1 gene in disorders that are comorbid with migraine?

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Objectives: To investigate the role of the TREX1 gene in various brain disorders in which migraine can be part of the phenotype.

Background: TREX1, the main mammalian 3'-5' DNA exonuclease, was identified as the cause of Retinal Vasculopathy with Cerebral leukodystrophy (RVCL). RVCL is mainly characterized by progressive blindness and can be associated with various neurological manifestations such as cognitive disturbances and depression. Migraine and Raynaud’s phenomenon are part of the RVCL syndrome, especially in a large Dutch RVCL family. TREX1 mutations have been identified in patients with Systemic Lupus Erythematosus (SLE) in which migraine and Raynaud’s phenomenon also can occur. The role of TREX1 in migraine and various brain disorders, which are often associated with migraine-like symptoms, has not been studied.

Methods: By direct sequencing, we investigated the role of the TREX1 gene in patients with CADASIL. (n = 50), neuropsychiatric SLE (n = 60), or migrainous infarct (n = 28) for high-penetrant mutations in the TREX1 gene. In addition, we studied whether low-penetrant DNA variants in TREX1 are associated with migraine in a large genetic isolate in the Netherlands (migraine cases: 360, controls: 1291), using genetic association analysis.

Results: We identified a causal p.Arg128His TREX1 mutation in a patient with neuropsychiatric SLE, severe migraine-like headache and white matter hyperintensities. No TREX1 mutations were identified in CADASIL patients or in patients with migrainous infarct. Our genetic association study in the genetic isolate did not show evidence for an association of TREX1 with migraine.

Conclusions: We could show a role of the TREX1 gene in neuropsychiatric SLE (with migraine-like headache). Although, migraine is associated with TREX1 in certain RVCL families, we were unable to demonstrate that TREX1 is a major migraine susceptibility gene.

PO180
A-fodrin as a candidate gene closely related to migraine pathophysiology


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Objectives: Migraine is a complex disorder of the peripheral and central sensitization of pain perceptive systems. However, the pathophysiology is not fully understood. Then, in this study, we investigate a causative gene and key molecule related to migraine pathophysiology.

Background: We previously reported that dysfunctions in the autonomic nervous systems of patients with migraines occur not only in the brain, but throughout the whole body. Serotonin and neuropeptides are also known to have important roles in the pathophysiology of migraine. With this background in mind, we analyzed human lymphoblast cell lines from migraine with aura (MwA) patients to investigate the pathophysiology of migraine.

Methods: Lymphocytes were used to establish Epstein-Barr virus (EBV)-immortalized lymphoblast cell lines, which were then analyzed using a differential cRNA microarray analysis. The gene expression results were validated using real-time polymerase chain reaction.

Results: Gene expression profiling identified 15 genes as being differentially expressed in lymphoblasts originating from patients diagnosed as having migraine with aura (MA). One-fifth of these genes were associated with cytoskeletal proteins. The expressions of seven genes increased significantly by more than 50% of the value in the controls, while the expressions of eight genes decreased significantly by more than 50% of the value in the controls. We also verified that the expression of α-fodrin, which was 1 of the 15 genes that were differentially expressed in lymphoblasts originating from patients with MA, increased after cortical spreading depression in an animal model.

Conclusions: α-fodrin might play an important role in the pathophysiology of migraine, possibly serving as a migraine biomarker.

PO181
MTHFR 677C>T and ACE D/I polymorphisms and migraine attack frequency in women

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Objectives: To evaluate the association of the MTHFR 677C>T (rs1801133) and ACE D/I (rs1799752) polymorphisms with migraine attack frequency.

Background: Data on the association between the MTHFR 677C>T and ACE D/I polymorphism and migraine, including aura status, are conflicting. This may in part be due to the broad clinical spectrum and heterogeneous phenotypes among migraineurs. Using migraine attack frequency as a marker of migraine severity in addition to aura status may help to establish more homogeneous migraine categories. Gene variants may reveal specific associations with certain attack frequency categories.
PO182
Shared genetic factors in migraine and depression
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Objectives: To investigate the co-occurrence of migraine and depression and assess whether shared genetic factors may underlie both diseases.

Background: There is a bidirectional comorbidity of migraine and depression of unknown etiology. Shared genetic factors may underlie this bidirectional comorbidity. Dissecting molecular pathways leading to this comorbidity may help to unravel the etiology of both disorders.

Methods: Subjects were 2,652 participants of the Erasmus Rucphen Family (ERF) genetic isolate study. Migraine was diagnosed using a validated three-stage screening method that included a telephone interview. Symptoms of depression were assessed using the Centre for Epidemiologic Studies Depression (CES-D) scale and the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D). The contribution of shared genetic factors in migraine and depression was investigated by comparing heritability estimates for migraine with and without adjustment for symptoms of depression, and by comparison of the heritability scores of depression between migraineurs and controls.

Results: We identified 360 migraine cases, 209 had migraine without aura (MO) and 151 had migraine with aura (MA). Odds ratios for depression in migraine patients were 1.29 (95% CI 0.98–1.70) for MO and 1.70 (95% CI 1.28–2.24) for MA. Heritability estimates were significant (P < 0.001) for migraine (0.56), MO (0.77), and MA (0.96), and decreased after adjustment for symptoms of depression or use of antidepressant medication, in particular for MA. Comparison of the heritability scores for depression between migraine patients and controls showed a genetic correlation between the HADS-D score and MA.

Conclusions: There is a bidirectional association between depression and migraine, in particular MA, which can be explained, at least partly, by shared genetic factors.

PO183
A genome-wide linkage analysis of migraine in the descendents of the bounty mutineers implicates the 13q chromosomal region
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Objectives: The aims of the present study were to characterise the demographics and molecular genetics of migraine in a large pedigree derived from a known population isolate, Norfolk Island. We also aimed to determine the heritability, the impact of ancestry on affection status and lastly, perform genome-wide linkage screening to localise regions that may potentially harbor susceptibility genes in this unique population.

Background: Norfolk Island is a small volcanic land mass, situated in the South Pacific Ocean approximately 1,500 km southeast of Brisbane, Australia. The island was settled in 1856 by Pitcairn Islander’s descended from a limited number (< 20) of English Bounty mutineer and Tahitian founders. To this day, approximately 80% of the permanent adult residents inhabiting Norfolk possess ancestral lineages to the original population founders. Previous epidemiological and genetic studies of cardiovascular risk traits and linkage disequilibrium suggest that the Norfolk population may be of particular use in investigating complex multifactorial disorders, including migraine.

Methods: DNA samples from two-thirds of the permanent adult population have been prepared and phenotypes relating to migraine obtained. Most of these individuals fit within a single large, 12-generational (~6500 individuals) pedigree extending back to the original population founders. Previous epidemiological and genetic studies of cardiovascular risk traits and linkage disequilibrium have been determined and linkage disequilibrium investigated. We have also undertaken a full microsatellite genome scan using this population. Results were analysed using non-parametric variance component linkage methods.

Results: Migraine was diagnosed in accordance with International Headache Society guidelines. Using a combined migraine with (MA) and without aura (MO) phenotype, the cohort was observed to have an overall migraine prevalence of 24%, with approximately 33% of women and 12% of men affected. Admixture analysis indicated that Polynesian ancestry had no significant effect on migraine status (P = 0.70). Heritability screening of the MA/MO phenotype estimated a genetic liability of 42% (P < 0.05). Linkage analysis identified a peak signal on chromosome 13q33.1 (point-wise P-value = 0.006). To further investigate this locus, we chose to stratify this peak finding using trait component analysis. Results revealed suggestive evidence of linkage also to the chromosome 13 for a combined photophobia and/or phonophobia phenotype (LOD = 2.11; P = 0.0009).

Conclusions: Migraine has an elevated prevalence in the descendents of the Bounty Mutineers and heritability estimates support a significant genetic component in this population. Results from a genome wide linkage analysis in this population replicate linkage previously detected on chromosome 13 in a Dutch cohort. Our population isolate results thus support the involvement of 13q in migraine susceptibility.
PO184
Regulatory effect of inflammation on cytokines in rat trigeminal ganglia
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Objectives: The present study was designed to investigate the hypothesis that cytokines are up-regulated in rat trigeminal ganglia following inflammation. Furthermore, it was studied if CGRP and CGRP in combination with the MEK/ERK blocker U0126 could modify the cytokine response.

Background: Inflammation is the immune systems response to harmful stimuli and as such considered involved in primary headaches. Calcitonin gene related peptide (CGRP) is a major constituent in the trigeminovascular pathway, and putatively plays a part in inflammation. The inflammation is most likely associated with an increase in expression of various ‘common’ cytokines such as Interleukin 6 (IL6) and Leukemia inhibitory factor (Lif). The overall cytokine involvement in trigeminovascular inflammation is still unclear but these chemical regulators are thought to be involved in migraine attacks.

Methods: To study the hypothesis, a quantitative RT-PCR assay was designed to study up/down regulation of common cytokines (SABiosciences part#21) was used. The studies were carried out in fresh rat trigeminal ganglia (TG) functioning as controls and in organ culture (OC) of rat TG. The effect of 24 hour OC, 24 hour OC + CGRP (1 μM) and 24 hour OC + CGRP (1 μM) + U0126 (1 μM) have been studied.

Results: The results show that OC for 24 hour alone massively up-regulate the pro-inflammatory cytokines IL6 and Lif. Furthermore, Interleukin 1 receptor antagonist (IL1rn) and Interleukin 10 (IL10) both inflammatory inhibitors are slightly up-regulated by 24 hour OC, perhaps to be on the ready to counter the inflammatory effects of the former. Addition of CGRP (1μM) to 24 hour OC reveals a further up-regulation of IL6. While Lif show decreased up-regulation when compared to organ culture alone. IL10 and IL1rn are both further up-regulated after addition of CGRP to the OC (see table). Addition of the MEK/ERK inhibitor U0126 (1 μM) to the CGRP 24 hour OC mix, still have IL6 up-regulated but Lif is only slightly up-regulated with the MEK/ERK blocker present. IL10 is further up-regulated when compared to the CGRP condition whereas IL1rn shows a decreased up-regulation.

Table 1.

<table>
<thead>
<tr>
<th>Interleukin/ treatment</th>
<th>OC 24 hour</th>
<th>OC + CGRP</th>
<th>OC + CGRP + U0126</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL6</td>
<td>427</td>
<td>492</td>
<td>399</td>
</tr>
<tr>
<td>Lif</td>
<td>246</td>
<td>150</td>
<td>33</td>
</tr>
<tr>
<td>IL10</td>
<td>6</td>
<td>19</td>
<td>41</td>
</tr>
<tr>
<td>IL1rn</td>
<td>11</td>
<td>33</td>
<td>16</td>
</tr>
</tbody>
</table>

Cytokine RNA up-regulation compared to control group (fresh TG).

Conclusions: The data suggests that organ culture treatment itself induces inflammation in rat trigeminal ganglia with a marked up-regulation of the pro-inflammatory cytokines IL6 and Lif. Addition of CGRP has only little effect on further up-regulation of the studied cytokines. The up-regulation of Lif can be quenched by a specific MEK/ERK inhibitor, indicating that this cytokine perhaps is regulated downstream in the MAPK pathway.

PO185
A long-term follow-up study of 18 patients with sporadic hemiplegic migraine
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Objectives: To study the long-term prognosis of sporadic hemiplegic migraine (SHM).

Background: The long-term prognosis of sporadic hemiplegic migraine (SHM) is unknown. Attacks of SHM are clinically identical to attacks of familial hemiplegic migraine (FHM), suggesting a shared pathophysiological basis. Since SHM and FHM, at least in part, share a similar genetic background, we hypothesised that a clinical follow-up study of SHM patients will show that SHM may turn into FHM.

Methods: We performed a longitudinal follow-up study in 18 patients who were diagnosed with SHM between 1993 and 1996. Follow-up time between the first and second survey ranged from 9 to 14 years. These patients have been included as part of the genetic study in which we systematically analysed the role of the three known FHM genes (de Vries et al. Neurology 2007 69:2170–6).

Results: In 12 patients the diagnosis remained unchanged. In two patients the attacks were no longer associated with hemiplegia. One had an ATP1A2 gene mutation (E120A). In four patients the diagnosis was changed into familiar hemiplegic migraine (FHM), because a family member developed hemiplegic migraine since the initial diagnosis was made. Two of these four patients had a mutation in the CACNA1A (R834Q) and ATP1A2 (R834X) gene.

Conclusions: This study shows that the diagnosis of SHM changes into FHM in a considerable percentage (4/18) of patients, almost a decade after the initial diagnosis. This indicates that a careful follow-up of SHM patients and their family is advisable for optimal care and counselling. Diagnostic screening of FHM-genes in SHM patients can be of value, as we could identify a gene mutation in half of the patients that changed from SHM to FHM. Our genetic and clinical follow-up studies reinforce the evidence that FHM and SHM are part of the same spectrum of migraine.

PO186
Association of the H3 receptor a280V polymorphism and migraine
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Objectives: The aim of this study was to investigate the possible association between H3 receptor A280V polymorphism and the risk of migraine.

Background: Activation of histamine H3 receptors blocks the release of vasoactive peptides responsible for headache. We studied the A280V polymorphism of the H3 receptor, found in the third axon and responsible for the replacement of valine by alanine.

Methods: Our study analyzed the possibility of A280V polymorphism contributing to the development of migraine in the Mexican population. We evaluated the frequency of the A280V genotypes and allelic variants of rH3 in 147 migraine patients and 186 healthy controls using a PCR-RLFP method.

Results: The frequency of the A280V genotypes and allelic variants did differ significantly between migraine patients and controls.

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Migraine and coronary artery disease: an open study on the genetic polymorphism of the 5, 10 methylenetetrahydrofolate (MTHFR) and angiotensin I-converting enzyme (ACE) genes

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Objectives: The aim of the our study is evaluate the incidence of ACE and MTHFR polymorphism in a consecutive series of migraineous patients and of patients affected by myocardial infarction.

Background: Genetic factors that increase susceptibility to oxidative stress, endothelial dysfunction and, possibly, stroke include angiotensin-converting enzyme gene deletion polymorphism (ACE-DD) and the methylenetetrahydrofolate reductase (MTHFR) C677-TT polymorphism. The relationship of ACE-DD genotype to ischemic stroke and cardiovascular disease is controversial, but it has been independently linked to lacunar infarction, in the absence of carotid atheroma. Lea et al. (2005) reported that the ACE DD genotype acts in combination with the MTHFR T/T genotype to increase migraine susceptibility, with the greatest effect in those with aura. The ‘TT’ polymorphism is also associated with an increased risk of migraine with aura, independent of other cardiovascular risk factors.

Methods: We studied a series of 90 migrainous patients (1) aged 35.7 years +/- 16.2 (18 MWA and 72 MwA, ICHDII-2004 criteria) and of 80 patients (2) affected by Acute Myocardial Infarction (AMI). The analyse was based on Polymerase Chain Reaction (PCR) and on reverse-hybridization.

Results: MTHFR (C677T): 58 patients (64.4%) (1) and 47 (58.7%) (2) were heterozygous; 2 patients (2.2%) (1) and 5 (6.2%) (2) were mutated. MTHFR (A1298C): 47 patients (52.2%) (1) and 40 (50%) (2) were heterozygous; 2 patients (2.2%) (1) and 5 (6.2%) (2) were mutated. ACE: 36 patients (40%) (1) and 43 (53.7%) (2) had an DD genotype; 44 (48.8%) (1) and 31 (38.7%) (2) had a ‘TT’ genotype. Conclusions: The results of our study confirm the high incidence in the genetic polymorphisms ACE and MTHFR in migraineur. These data are confirmed in the sample of patients affected by myocardial infarction. This gives evidence of a strong relationship between migraine and major vascular diseases and let us hypothesize an important role of ACE and MTHFR system in the pathogenetic model of migraine for its capability to interfere with the endothelial regulation tone. Once an effective role in the genesis of migraine and in the increased risk of migrainous patients to evolve into an ischemic pathology has been obviously assigned to this genetic mutation, future researches must aim through wider and more controlled casis-tics also to clarify the role that drugs acting on these systems may have on the resolution of these diseases.

PO189

Does migraine as a partly inflammatory disease increase the inflammatory markers of the patient during a migraine attack?

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Objectives: To compare the levels of inflammatory markers between a group of migraineurs before, during and after a migraine episode, with a control group of non-migraineurs; to determine the extent of such increases; and which markers might be more sensitive.

Background: Migraine is a neurological-vascular disease, but is clinically diagnosed on a combination of symptoms. Inflammation of brain tissue as a result of neuronal activity and the subsequent release of inflammatory markers such as C-reactive protein (cRP)
occurs during migraine, as does calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and Substance P.

Methods: Twenty-seven subjects with a history of migraine were enrolled in the study for three visits, during which five samples were gathered: serum and salivary cRP; salivary CGRP, VIP and Substance P. The 2nd visit occurred during a migraine episode, and a third, 30 days following a migraine attack. Ten subjects with no history of migraine were recruited to serve as a control group. Samples of this latter group were collected during two visits, baseline and 2–4 weeks after baseline.

Results: CGRP, VIP, Substance P and cRP levels remained constant for control subjects, and cRP fold values only favored a non-statistically significant trend in migraineurs. However, migraineur levels of CGRP, VIP and Substance P levels and fold values, demonstrated a significant increase during an attack, and remained elevated at 30 days post attack. CGRP data and fold values are depicted in graphs 1 and 2. VIP levels for migraineurs, (pmol/mg total protein) were 150.39 at visit 1, 492.14 during a migraine episode, and 326.27 30 days post migraine; and their fold values were 1.00, 3.3 and 2.56. VIP control levels were 86.01 at visit 1 and 79.51 at visit 2; and their fold values were 1.00 and 1.14. Substance P results for migraineurs were 36.88, 69.47 and 45.81 for respective visits, with fold values of 1.00, 4.14 and 2.41. For the control group, levels were 25.21 and 21.9, with fold values of 1.00 and 1.00. The CGRP graphs are highly representative of all data, and the findings from VIP and Substance P data strongly correlate to them.

Conclusions: Although all markers were higher in migraine subjects when compared to the control group, and were elevated even further during a migraine episode, the data in this study suggest that CGRP, VIP and Substance P levels for migraineurs demonstrate statistically significant results as indicators, and all were more sensitive than cRP samplings.
sample was collected at study entry, immediately processed, and stored at -80°C for the genetic study.

Results: Of the 480 patients, 288 (60%) were diagnosed with episodic migraine, of these (37.2%) had aura, predominantly visual. Patients with chronic migraine suffered from aura (37%), although 8.85% mentioned it to be occasional. Most of migraineurs suffered from sleep disorders (72.7%), had a normal BMI (54.7%) and had a college education level (61%) with no differences among groups. The clinical characteristics found to be more frequent in chronic migraineurs were the presence of an anxiety-depression syndrome (P < 0.05), history of head trauma (P < 0.05), and presence of maternal family inheritance (P < 0.05). Presence of allostynia was not seen to be different between patients (49.6%). The scales revealed that chronic migraineurs were more disabled (MIDAS and HIT-6), had a severe anxiety status (STAI), a higher score on the Visual Analogue Scale (VAS), and a higher dysfunction in their perceived health status (SF-36v2) (P < 0.001). Triptans alone and in combination with NSAIDS were used more by chronic than episodic migraineurs (P < 0.05).

Conclusions: As patients were recruited from a specialized Headache Unit, the proportion of chronic migraine is higher than described in the general population. Episodic and chronic migraineurs have similar sociodemographical features. Presence of maternal migraine history, anxiety-depressive syndrome and head traumaism were found to be risk factors for developing chronic migraine, whereas obesity, sleep disorders and the presence of allostynia, were not. The differences seen in the impact of migraine and the clinical characteristics found are a warrant for the quality of the phenotypic description of patients for future genetic studies.

PO192
Exploding-imploding headaches: DQB1 polymorphism
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Objectives: The purpose of this study was to investigate the relationship between migraine and HLA-DQB1 polymorphism in Venezuelan patients recruited from a Headache Service in a private clinic.

Background: Migraine is a syndrome characterized by a moderate to severe, throbbing type headache, associated with photophobia, phonophobia, nausea and vomiting. The etiology of migraine is still unknown but several studies support a strong genetic basis for the disease.

Methods: Sixty eight migraine patients were involved in the study. The diagnosis of migraine was made according to the International Headache Society criteria. Based on their testimonies, the patients were divided into those with exploding headache (n = 34) and those with imploding headache (n = 34). Frequencies were determined by direct counting. The statistical significance of allele frequency was estimated by Fisher’s exact test and p values were corrected according to Bonferroni. Odds ratio (OR) with corresponding 95% confidence intervals (95% CI) were calculated to measure the strength of associations.

Results: A statistically significant frequency difference was found present between migraine patients and controls for DQB1*03 (46.32% vs. 29.06%, OR = 2.11, P = 0.00025; pc = 0.003). Likewise, the DQB1*02 allele was observed significantly increased among patients with exploding headache compared to patients with imploding headache (22.05% vs. 7.35%, OR = 3.56; P = 0.0013; pc = 0.039).

Conclusions: The results suggest an influence of DQB1 polymorphism in the occurrence and the clinical features of migraine.

PO193
Familial hemiplegic migraine – relevance to the common types of migraine
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Objectives: Familial hemiplegic migraine (FHM) is a rare, dominantly inherited subtype of migraine with transient hemiplegia during the aura phase. Mutation screening of families with FHM has revealed a range of different mutations in genes coding for ion homeostasis proteins. Animal and cellular studies of the mutated FHM genes revealed a lowered threshold for cortical spreading depression. None of the mutations have, however, been found in migraine with or without aura. Hypersensitivity to migraine provoking substances is a fundamental trait in patients with migraine with (MA) and without aura (MO).

Background: We have therefore studied whether FHM mutations are associated with hypersensitivity to two known migraine provoking substances; nitric oxide (GTN) and calcitonin gene-related peptide (CGRP) which could indicate common migraine mechanisms in FHM, MA and MO.

Methods: We recruited 16 FHM patients with a known mutation (eight FHM-1 and eight FHM-2 patients) from a Danish population based cohort and one patient from an Italian partner institution. We used the human in vivo model of experimental headache and conducted three separate controlled provocation studies. GTN and CGRP were given intravenously and headache characteristics were recorded.

Results: We found that both GTN and CGRP failed to trigger more migraine headache in FHM patients than in healthy controls. FHM-1 and FHM-2 gene mutations apparently do not confer hypersensitivity to NO and CGRP, as characteristically seen in MO and MA patients.

Conclusions: Given that both GTN and CGRP trigger migraine-like attacks in the common types of migraine, the absence of a robust migraine response in FHM patients indicates that FHM patients do not share the hypersensitivity to migraine-inducing substances known from MO and MA patients. The present data thus suggest that pathophysiological pathways underlying migraine headache in FHM-1 and FHM-2 may be different from the common types of migraine.

PO194
Effect of coexisting migraine on the sensitivity to nitric oxide in patients with familial hemiplegic migraine
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Objectives: In the present study we used the GTN model of migraine in FHM patients without known genetic mutations. We hypothesised that a migraine eliciting effect of GTN might be linked to coexisting migraine with (MA) and without aura (MO) rather than to the pure FHM phenotype.

Background: Experimental studies have shown that FHM-1 or FHM-2 mutations do not confer hypersensitivity to activation of the NO-cGMP pathway, as characteristically seen in patients with MA and MO. However, FHM patients reacting with a migraine-like attack after pharmacological provocation tended to suffer from coexisting MO/MA. It is therefore important to distinguish between
FHM patients with the pure FHM phenotype and FHM patients who also have MO/MA.

Methods: The study design was balanced and single-blinded provocation study. 23 FHM patients (12 with pure FHM; 11 with coexisting migraine with and without aura) and 11 healthy controls received a continuous intravenous infusion of 0.5 μg/kg/min GTN over 20 minutes.

Results: Patients with co-existing migraine with and without aura, 55% (6 out of 11), reported more migraine attacks than patients with FHM, 8.3% (1 out of 12) (P = 0.02). Compared to healthy controls more FHM patients with co-existing migraine (55%; 6 out of 11) reported migraine-like attacks than controls (P = 0.03), whereas the FHM group with the pure FHM phenotype did not.

Conclusions: These data suggest that neurobiological pathways responsible for triggering migraine headache in FHM patients might be linked to co-existing migraine with and without aura, whereas the pure FHM phenotype is not related to the NO – cyclic GMP molecular pathway.

PO195
Location of primary headache of outpatients using new modified meridian and acupuncture points of Korean hand therapy
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Objectives: One diagnostic criteria of primary headache is location which has been underestimated. The decision of location is very important for diagnosis and non-pharmacological treatment such as acupuncture or botulinum injection.

Background: There are limited literatures concerning lateralization. That might be due to some problems because the complained location is not well described such as various or diffuse points. We need to develop specific method. There is New Modified Meridian of East-Asian Acupuncture which is developed in Korean Hand Therapy (KHT). New modified acupuncture points are well documented. It is easy and practical to decide the location of tenderness using such Meridian and acupuncture points on the head and neck.

Methods: This study was performed during one part of physical examination at department of neurology, Pusan National University Hospital from March 2006 to Feb. 2008. The 600 patients with primary headache without other neurological or systemic diseases were included. The patients were classified based on the international headache classification. On physical examination using tip probe of roller stimulator made by KHT, we palpated both sides of head along New Modified Acupuncture points on Gallbladder Meridian such as CM-1 to CM-10 and Urinary Bladder such as CI-1 to CI-8. The symbol of alphabet and numbers was designated in KHT such as C means Korean, M means Gallbladder meridian, I means Urinary Bladder meridian. Number signified the order of meridian as C means Korean, M means Gallbladder meridian, I means Urinary Bladder meridian.

Results: The locations of tenderness of 600 primary headache patients are various patterns as followings.

The migraine patients showed tenderness as followings. The number of only right side of Modified Gallbladder Meridian and Acupuncture points (CM) is 136, of only left side of CM is 110, both side of CM is 48, right side of CM and Modified Urinary Bladder Meridian and Acupuncture points (CI) is 20, right side CM and left side CI is 40, left side CM and CI is 16, left side CM and right side CI is 30. There are several patterns in migraine patients group such as pure Gallbladder Meridian involved or Gallbladder and Urinary Bladder Meridians involved.

Tension type headache patients showed tenderness as followings. The numbers of only right side of CI is 67, only left side of CI is 105, both sides CI is 28. Comparing migraine headache, tension type headache showed only Urinary Bladder Meridian is involved.

Conclusions: It is very difficult to decide the location of headache. For accurate diagnosis and treatment, we need time to palpate the tender point carefully along the New Modified Meridian system which is simple comparing with traditional East Asian Meridian. New modified KHT Meridian system is useful to decide the location of headache. We can save the time on physical examination and treat effectively with acupuncture or botulinum injection for primary headache.

PO196
Riboflavin status in 12 pediatric migraine patients is analyzed using the erythrocyte glutathione reductase level activation test (EGR-A)
Sabo TM
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Objectives: Exploration of utility and clinical use of the EGR-A to assess Riboflavin Stores in our selected population.

Background: Riboflavin (B2) and Co-Enzyme Q 10 are ‘assistess’ and involved intracellularly within the energy pathways of the mitochondrial system. Riboflavin has been studied in adult migraine studies with suggestive results of possible treatment efficacy. A recent pediatric study failed to show positive treatment outcomes when migraine patients (n = 544) were supplemented with high dose Riboflavin (200 mg) versus placebo. No riboflavin status was analyzed in the trial. Riboflavin serological levels are thought to be unreliable and not necessarily a good indicator of true bioavailable status. The Erythrocyte Glutathione Reductase Activation (EGR-A) value is thought to be a more accurate representation of riboflavin status. Low values of the EGR-A indicate adequate Riboflavin stores, while high EGR-A reflect low bioavailable stores.

Methods: The EGR-A was completed using the RANDOX invitro diagnostic assay. The ‘normal ranges’ of the EGR-A are thought to be 4–13.2 U/g Hb. There is no pediatric reference range for this assay. Patients aged 5–18 with migraine (with or without aura) based on IHS criteria, with headaches for at least a 6 month period of time. The patients represented primarily are from the Denver central or suburban areas. All patients were thought to have adequate nutrition and access to nutritional resources. Patients were excluded if they had significant GI, renal or any other systemic medical condition. Patients were told to withhold vitamin supplementation 1 month prior to the assessment of the lab draw and to maintain a typical diet.

Results: Twelve subjects with one or more EGR-A measures were analyzed. The range of EGR-A at baseline measurement for this group was between 4.2 and 16.9 with mean (SD) of 9.5 (3.8). 33% of the subjects had the EGR-A level above 12. This value is above or within upper 10% (suggesting Riboflavin deficiency) of the suggested reference ranges by our lab.

Conclusions: In a small group of pediatric migraine patients, Riboflavin status was evaluated using a laboratory test which most laboratories would be able to run (the EGR-A). It may possible that if migraine patients have singly (one-hit) or in combination (two-hit) deficiency or alteration of Riboflavin and/or Co-Enzyme Q 10 stores, there may be more prominent expression of migraine. Nutritional correction or supplementation may thus augment the expression of migraine and may prove to be single or dual treatment options for patients suffering from migraine. The diagnostic, therapeutic and prognostic values of EGR-A will be investigated in the future.
PO197
Does estrogen withdrawal affect gene expression of CGRP and its receptor components RAMP1 and CLR?
Link AS and Messlinger K
Institute of Physiology & Pathophysiology, University of Erlangen-Nuremberg, Erlangen, Bavaria, Germany

Objectives: This study was performed to investigate a potential effect of estrogen withdrawal on the gene expression of calcitonin-gene related peptide (CGRP) and its receptor components calcitonin receptor-like receptor (CLR) and receptor activity-modifying protein 1 (RAMP1) in trigeminal ganglion cultures of immature female C57BL/6 mice.

Background: Migraine is up to three times more likely to affect women than men during the reproductive years. Approximately half of the female migraineurs suffer from perimenstrual migraine attacks, which are considered to be more severe, disabling and less responsive to acute treatment compared to non-menstrual migraine attacks. An abrupt fall in estrogen levels before menstruation has been clinically identified as a potential trigger for menstrual migraine. However, the molecular mechanisms of how estrogen withdrawal can lead to migraine have not yet been clarified. CGRP and its receptor are considered to play a key role in migraine pathophysiology. Especially RAMP1 has attracted attention as it was recently suspected to be rate limiting for the function of the CGRP receptor. A potential up-regulation of RAMP1 may thus increase CGRP-mediated actions and facilitate nociceptive transmission.

Methods: Estrogen withdrawal was mimicked by treating trigeminal cell cultures with 17β-estradiol (10 nM) for 24 hours before it was completely removed. RNA was isolated either immediately, 30 minutes, 2, 4, 6, 16, 24 or 72 hours after that. The amount of mRNA of CGRP, RAMP1, CLR and estrogen receptor-alpha (ERα) was then assessed relative to the reference gene ribosomal protein L13A (Rpl13a) by performing real time PCR.

Results: Compared to the mRNA levels after 24 hours of estrogen treatment, RAMP1 levels increased about 3.5-fold while CGRP expression decreased approximately 4.5-fold after 72 hours. The amount of CLR and ERα mRNA did not change substantially within that period of time. Immediately after estrogen removal, the amount of CLR mRNA was about 70 times higher than that of RAMP1 mRNA. After 72 hours, the expression of RAMP1 had increased to such an extent that there was only ten times more CLR mRNA compared to RAMP1 mRNA.

Conclusions: The gradual decrease of CGRP expression may reflect a recovery of the cells from the stress caused by cell culture procedures. However, the rising levels of RAMP1 mRNA after estrogen withdrawal may in fact point to a potential formation of more functional CGRP receptors. Assuming that the increase in RAMP1 mRNA levels is reflected in protein levels, an elevated number of RAMP1 proteins could assemble with CLR proteins and form functional CGRP receptors. Menstrual migraine attacks might thus be triggered by increased CGRP effects mediated by a higher number of CGRP receptors.

PO198
Ovarian hormones and migraine headache: in search of the holy grail
Martin VT1 and Houle T2
1Internal Medicine, University of Cincinnati, Cincinnati, OH, USA; 2Anesthesiology, Wake Forest University, Winston Salem, NC, USA

Objectives: To determine the utility of models of hormonal variables in the prediction of migraine headache in women and to ascertain which hormonal variables (e.g. levels, rates of change or ratios of estrogen and progesterone) have the greatest modulatory effect.

Background: Menstrual migraine is thought to be triggered by estrogen withdrawal, but very little is known of the specific hormonal changes that trigger migraine headaches throughout the menstrual cycle.

Methods: Participants included twenty-three female migraineurs who participated in the medical oophorectomy in migraine study. They recorded the severity of headache (0-10 rating scale) three times per day for three consecutive menstrual cycles. Participants also collected urine each morning that was later assayed for estrone glucuronide and pregnandiol glucuronide (e.g. estrogen and progesterone metabolites). Individual time-series regression models were conducted for each of the migraine patients. The three daily headache ratings were summed and two headache indices were calculated: a dichotomous rating of the presence (headache sum > 0) or absence (headache sum = 0) of headache on that day, and a headache sum representing the sum of the day’s pain ratings. Using generalized estimating equations (GEE), two types of regression models were separately conducted using either the dichotomized rating (logit link function) or the headache sum (log link function). Predictors in the models included various representations of the hormonal series: estradiol levels (E), progesterone levels (P), estrogen change (dE = absolute value of [Next Day E – Same Day E]), progesterone change (dP = absolute value of [Next Day P- Same Day P]), and the ratio between P and E (P/E).

Results: The top 10 best fitting models for each participant were determined by the models that had the lowest BIC score (i.e., the simplest models that accounted for the most variance in the outcome). The R² values of these models for predicting the sum of headache severity ranged from 0.01% to 39% while the AUC for predicting the presence or absence of headache ranged from 0.46 to 0.87. The predictors from the top 10 models and their percentage inclusion were: dP (in 83% of individuals), dE (74%), E + dE (70%), E + dP (65%), and P + dE (65%).

Conclusions: Hormonal models were modestly predictive for migraine headache in our study population. To our knowledge this is the first study to prove that both E and P can modulate migraine headache not just during perimenstrual time periods, but throughout the menstrual cycle. Interestingly dP and dE were more frequently represented in the best fitting models than E, P or P/E. These data could suggest that changes of ovarian hormones are more important than absolute levels in the provocation of migraine headache.

PO199
Disturbances of hormonal status in women of reproductive age with chronic tension headache
Kristina D and Speransky V
Central Laboratory for Science, Bashkir State Medical University, Ufa, Bashkortostan, Russian Federation; Central Laboratory for Science, Bashkir State Medical University, Ufa, Bashkortostan, Russian Federation

Objectives: Tension-type headache is the most prevalent of the primary headache disorders. Both the chronic and episodic forms of the disorder are more common in women than in men.

Background: 100 women with chronic tension headache and 30 women with episodic tension headache have been examined. Women who took oral contraception, with pregnancy and chronic diseases were excluded from the study.

Methods: The study techniques include: neurological examination and radioimmunometrical methods.

Results: The investigation results of possible pathogenic correlation of tension headache and functional status of hypophysial-ovarian system in women of reproductive age have been represented. It has
been demonstrated that in case of chronic tension headache the marked imbalance of sex hormones and cortisol dependent on the phase of menstrual cycle occurs. In patients with chronic tension headache in phase I: FSH (follicle-stimulating hormone) (8.2 ± 0.7 IU/L), estradiol (274.37 ± 25.3 pg/ml), LH (luteinizing hormone) (16.8 ± 1.9 IU/L), progesterone (20.42 ± 2.6 n mole/L), testosterone (2.1 ± 0.3 ng/mL), cortisol (755.4 ± 34.5 n mole/L), prolactin (10.8 ± 0.8 ng/mL); in phase II: FSH (7.5 ± 0.7 IU/L), estradiol (311.2 ± 27.1 pg/ml), LH (11.1 ± 1.4 IU/L), progesterone (36.3 ± 3.6 n mole/L), testosterone (2.4 ± 0.4 ng/mL), cortisol (817.2 ± 35.6 n mole/L), prolactin (13.5 ± 1.5 ng/mL).

Significant deviations have not been revealed in women with episodic tension headache in phases I, II of menstrual cycle.

**Conclusions:** On the basis of the obtained data pathogenic correlation of chronic tension headache and hormonal deviations is taken into account.

**PO200**

**Distinct vascular sensitivity to calcitonin gene-related peptide in cranial and peripheral arteries from males and females**

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Division of Pharmacology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

**Objectives:** To investigate the vasodilatory responses to CGRP in human isolated meningeal arteries obtained perioperatively from both male and female subjects. As a control we also studied a peripheral blood vessel, namely human coronary artery segments that were obtained from heart valve donors.

**Background:** The prevalence of migraine in females is 2–3 times higher than in males and the changes in migraine frequency and severity are associated with menarche, pregnancy and menopause. Migraine pathophysiology most likely involves cranial vasodilatation caused by neuropeptides such as calcitonin gene-related peptide (CGRP). Increased relaxations to CGRP in intracranial meningeal arteries in females as compared to those in males may be an important determinant for the higher prevalence of migraine in females. Alternatively, it is feasible that not the sensitivity to CGRP is increased in females, but that the amount of CGRP that is released during a migraine attack is larger in females.

**Methods:** Segments of human middle meningeal (10 M, 12 F) and coronary (22 M, 25 F) artery were mounted in Mulvany myographs. The artery segments were precontracted with 30 mM KCl and cumulative concentration response curves to α-CGRP were constructed.

**Results:** The maximal responses to CGRP in middle meningeal artery were not different between males (Emax 91 ± 3%) and females (Emax 84 ± 3%), whereas the pEC50 values tended to be slightly higher in segments obtained from males (8.64 ± 0.24) than in those obtained from females (8.07 ± 0.20, P = 0.076). In contrast, in human coronary artery segments, CGRP induced higher relaxant responses obtained from females (Emax 93 ± 2%) than in those obtained from males (Emax 85 ± 3%, P = 0.008).

**Conclusions:** During a migraine attack, CGRP is released from perivascular nerves innervating the meningeal artery. In view of the higher prevalence of migraine in females, a higher CGRP release in females could lead to a desensitization of the CGRP receptor on the meningeal artery in females. Such a desensitization may explain the lower apparent pEC50 value of CGRP in meningeal arteries that we obtained from females. A larger CGRP release from cranial peri-vascular nerves in females is supported by our previous animal study, where periarterial electrical stimulation induced a larger vasorelaxation (induced by endogenous CGRP release) in ovariectomized rats treated with 178-estradiol compared to the response in ovariectomized rats treated with placebo (Gupta et al., Headache 2007; 47:225–35). As the coronary artery is obviously not innervated by cranial nerves, this mechanism will most likely not affect the responses to CGRP in the coronary artery. Thus, the higher maximal responses to CGRP in the coronary artery will be caused by a distinct mechanism, possibly a higher density of CGRP receptors, unrelated to the decreased sensitivity in the middle meningeal artery in females.

**PO201**

**Pressure pain thresholds in craniocervical muscles in women with migraine, chronic migraine, and with no headaches**

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1Department of Biomechanics Medicine and Rehabilitation of the Locomotor Apparatus, University of Sao Paulo, School of Medicine, Ribeirão Preto, Sao Paulo, Brazil; 2Department of Neurology Psychiatry and Medical Psychology, University of Sao Paulo, School of Medicine, Ribeirão Preto, Sao Paulo, Brazil; 3Department of Neurology, Albert Einstein College of Medicine, Global Directors for Scientific Affairs-Neuroscience-Merck Research Laboratories, Bronx, NY, USA

**Objectives:** To assess and compare the pressure pain threshold (PPT) of cranio-cervical muscles in women with migraine (M) (n = 15), chronic migraine (CM) (n = 14), and no headaches (C) (n = 15).

**Background:** Muscular tenderness is often reported as a symptom in primary headache syndromes.

**Methods:** The PPT was obtained by pressure algometry method, in 10 points bilaterally marked on the frontal, temporalis, masseter, trapezius, and sternocleidomastoid muscles.

**Table 1. Mean and standard deviation values of ptt (kg/cm2) obtained for the craniocervical muscles in the m, cm and c groups for both the right and left sides of the face**

<table>
<thead>
<tr>
<th>Muscles</th>
<th>Right side</th>
<th>Left side</th>
<th>Right side</th>
<th>Left side</th>
<th>Right side</th>
<th>Left side</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC</td>
<td>M (n = 15)</td>
<td>M (n = 15)</td>
<td>C (n = 15)</td>
<td>C (n = 15)</td>
<td>M (n = 15)</td>
<td>M (n = 15)</td>
</tr>
<tr>
<td>Frontal</td>
<td>2.19 ± 0.64</td>
<td>2.01 ± 0.67</td>
<td>2.17 ± 0.52</td>
<td>2.08 ± 0.69</td>
<td>2.79 ± 0.71</td>
<td>2.84 ± 0.71</td>
</tr>
<tr>
<td>Anterior</td>
<td>2.44 ± 0.79</td>
<td>2.40 ± 0.73</td>
<td>2.69 ± 0.81</td>
<td>2.50 ± 0.61</td>
<td>2.97 ± 0.74</td>
<td>2.80 ± 0.67</td>
</tr>
<tr>
<td>M (n = 15)</td>
<td>2.53 ± 0.75</td>
<td>2.32 ± 0.63</td>
<td>2.62 ± 0.76</td>
<td>2.53 ± 0.78</td>
<td>2.89 ± 0.65</td>
<td>2.89 ± 0.62</td>
</tr>
<tr>
<td>posteri or</td>
<td>2.72 ± 0.89</td>
<td>2.60 ± 1.00</td>
<td>3.17 ± 0.79</td>
<td>3.24 ± 1.03</td>
<td>3.36 ± 0.72</td>
<td>3.34 ± 0.84</td>
</tr>
<tr>
<td>temporalis</td>
<td>M (n = 15)</td>
<td>M (n = 15)</td>
<td>C (n = 15)</td>
<td>C (n = 15)</td>
<td>M (n = 15)</td>
<td>M (n = 15)</td>
</tr>
<tr>
<td>Masseter</td>
<td>1.56 ± 0.54</td>
<td>1.49 ± 0.39</td>
<td>1.82 ± 0.45</td>
<td>1.70 ± 0.41</td>
<td>1.99 ± 0.55</td>
<td>1.79 ± 0.50</td>
</tr>
<tr>
<td>-origin</td>
<td>1.63 ± 0.46</td>
<td>1.43 ± 0.37</td>
<td>1.87 ± 0.43</td>
<td>1.67 ± 0.48</td>
<td>2.04 ± 0.45</td>
<td>1.78 ± 0.58</td>
</tr>
<tr>
<td>-buccal</td>
<td>1.82 ± 0.62</td>
<td>1.57 ± 0.48</td>
<td>1.98 ± 0.49</td>
<td>1.79 ± 0.52</td>
<td>2.20 ± 0.54</td>
<td>1.99 ± 0.45</td>
</tr>
<tr>
<td>-insertion</td>
<td>2.26 ± 0.94</td>
<td>2.28 ± 0.70</td>
<td>2.63 ± 0.87</td>
<td>2.46 ± 0.81</td>
<td>2.91 ± 0.88</td>
<td>2.89 ± 0.74</td>
</tr>
<tr>
<td>Trapezius</td>
<td>2.69 ± 1.00</td>
<td>2.54 ± 0.93</td>
<td>2.96 ± 0.95</td>
<td>2.66 ± 0.84</td>
<td>3.49 ± 0.83</td>
<td>3.32 ± 0.96</td>
</tr>
<tr>
<td>-upper</td>
<td>2.12 ± 0.71</td>
<td>1.97 ± 0.74</td>
<td>2.23 ± 0.45</td>
<td>2.03 ± 0.53</td>
<td>2.48 ± 0.64</td>
<td>2.50 ± 0.61</td>
</tr>
</tbody>
</table>

ANOVA two-way (F = 112.25; P < 0.000001), Difference in relation to control group, *SCM: sternocleidomastoid muscle*
Results: Contrast to controls, individuals with M had significantly decreased PPT (kg/cm²) for the following muscles: left frontal (2.01 ± 0.67 vs. 2.84 ± 0.71), right and left posterior temporalis (2.72 ± 0.89 vs. 3.36 ± 0.72) and (2.60 ± 1.00 vs. 3.34 ± 0.84), and right and left upper trapezius (2.69 ± 1.00 vs. 3.49 ± 0.83) (2.54 ± 0.93 vs. 3.32 ± 0.96). CM individual also had reduced PPT, relative to controls, on the right frontal muscle (2.17 ± 0.52 vs. 2.79 ± 0.71), left anterior temporalis muscle (2.30 ± 0.61 vs. 2.72 ± 0.89) and left upper trapezius muscle (2.66 ± 0.84 vs. 3.32 ± 0.96). No significant differences were found between the M and CM groups for any of the points.

Conclusions: We conclude that PPT is reduced in both the episodic and chronic forms of migraine, as contrasted to controls. The fact that no statistical differences were found between CM and M lead to two possibilities: 1) The differences between muscular involvement in both conditions are small and our study was underpowered to see them; 2) Muscular tenderness arises as part of the migraine spectrum, and is not a function of headache frequency.

PO202

How often women use headache as an excuse to avoid sex?

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Objectives: The aim of this work is to study the impact of migraine attacks in women marital and sexual lives and how often they, even not having headache, use headache as an excuse to avoid sex.

Background: Migraine occurs disproportionately in women. Many have their lives strongly affected by recurring migraine attacks and, additionally, have their complaints discredited by relatives, friends and even doctors. The excuse, ‘not tonight, I have a headache,’ to avoid a sexual relationship is a cliché that frequently have been imputed to women. This, partly, derive of being intuitive the incompatibility between sexual activity and headache and partly by the socially attributed role of women in sex.

Methods: Sixty women were interviewed. They were divided in two groups: group A (30 women) with patients in regular headache clinic appointments for migraines (types 1.1 and 1.2 of the ICHD-II); and group B (30 women) with patients without migraine that sought the hospital for consultations for other reasons. The demographic data, migraines characteristics (group A), the impact of headache in their marital and sexual lives and how often they, even not having headache, use headache as an excuse to avoid sex, were annotated. The data were compared and statistically analyzed.

Results: In group A, women were, on average, 44 years (± 10 years) old and 37% were single, 57% married, 3% widows and 3% divorced. In group B, the mean age was 48 years (± 14 years) and 25% were single, 59% married, 13% widows and 3% divorced. In both groups the women sexual relationship mean frequency of was seven times a month. Among migraine patients, 20% affirmed that recurring migraines attacks interfere in her marital life, 67% affirmed that they interfered negatively in her sexual activity but only 24% said that already have interrupted a sexual relationship because of headache. Only three women (10%) of the group A and nine women (30%) of the group B already had used headache as an excuse to avoid sex, even not having headache. All patients with migraine, but one (96%) said that their partners always respected them in these occasions. The treatment had a positive impact in the sexual life of 60% of the migraine patients.

Conclusions: A minority of women uses headache as an excuse for not having sex. This behavior, although without statistical significance, is less common among migraine suffers. Migraine affects the sexual life of the majority of women suffers and this impact that can be reduced with treatment.

PO203

Results from an international observational study of pregnancy outcomes following exposure to sumatriptan, naratriptan or treximet

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Objectives: To determine the risk of major birth defects (MBDs) associated with exposure to sumatriptan or naratriptan or Treximet (sumatriptan/naproxen) during pregnancy.

Background: The prevalence of migraine peaks in women of childbearing age. The sporadic nature of migraine attacks, coupled with a high proportion of unplanned pregnancies, makes inadvertent exposure to anti-migraines in pregnancy likely. The Sumatriptan and Naratriptan Pregnancy Registry (S (N)PR) was established to monitor the risk of MBDs following in utero exposure.

Methods: The SPR was established in 1996 as an international registry monitoring pregnancy outcomes for MBDs. Exposures to naratriptan and treximet have been monitored since 2001 and 2008 respectively. Physicians report exposure during pregnancy and subsequent outcomes on a voluntary basis. Prospective reporting (prior to any knowledge of the pregnancy outcome) early in pregnancy is encouraged. MBDs are classified according to criteria of the Metropolitan Atlanta Congenital Birth Defects Program and are reviewed by a paediatrician, and an obstetrician/clinical geneticist. The percentage of MBDs is calculated by drug and trimester of exposure. There is no internal control group. Conclusions are developed by an independent scientific advisory committee.

Results: Through October 2008, the SPR prospectively enrolled 828 pregnancies exposed to sumatriptan. Analyzable data were available for 599 pregnancies with 31 (3.7%) pregnancies not yet due to deliver and 199 (24.0%) lost to follow up. Of 599 pregnancies with outcome data, 479 represented first trimester exposure including 16 live infants, one stillbirth and three induced abortions, with birth defects. The proportion of first trimester exposures with birth defects (n = 16/433, excluding spontaneous pregnancy losses and fetal deaths and induced abortions without birth defects) was 4.6% (95% Confidence Interval 2.9–7.2%). There was no consistent pattern of birth defects. There were fewer data on naratriptan: Among 50 first trimester exposures there was one major defect reported in a live infant also exposed to sumatriptan in the first trimester. No pregnancy outcome data are currently available for Treximet. Six additional observational studies with internal control groups were identified for sumatriptan from the literature. All failed to observe an increased risk of birth defects in infants exposed in utero to sumatriptan. The largest study in the Swedish Medical Birth Registry reported over 2000 first trimester sumatriptan exposures with a birth defect risk (both major and minor) of 3.6%, identical to the risk reported for the general Swedish population.

Conclusions: While the sample sizes of individual studies remain too small to draw definitive conclusions about the safety of sumatriptan use in pregnancy, this registry and six additional studies, using different methodologies, suggest no signal for major teratogenicity. Continued registration of new exposures in the SNPPr early in pregnancy will continue to enhance the statistical power of the registry.

PO204

Abstract withdrawn
PO205
Pattern of migraine during pregnancy and postpartum
Hoshiyama E1, Tatsumoto M1, Iwanami H1, Saisu A1, Watanabe H2, Inaba N2 and Hirata K1
1Neurology, Dokkyo Medical University, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi, Japan; 2Obstetrics and Gynecology, Dokkyo Medical University, Kitakobayashi 880, Mibu, Shimotsuga, Tochigi, Japan

Objectives: The aim of this study was to investigate prospectively the course of migraine during postpartum in a case of migraine from an obstetrics department.

Background: Several past studies have determined that migraine disappears in most women during pregnancy. However, there are a few reports on the course of migraine during postpartum.

Methods: We studied migraine patients from a postnatal ward during the first postpartum week asking about features of headache before and during pregnancy and their possible modification or recurrence. Subsequent examinations were performed at the first month and 3 month and 6 month after delivery. Complete cessation of attacks was defined as remission. The presence of migraine was investigated according to the ICHD-II. At the postpartum examination, information was also gathered on the delivery, the type of feeding. The study was approved by institutional review boards appropriate for each investigator.

Results: The cases were 60 patients (median age 31 years) affected by migraine (migraine without aura; n = 53, migraine with aura; n = 7). The remission was recognized within the first trimester (63%), increased during the second trimester (83%), and continued throughout the third period, a pregnancy in which almost 85% of the women were migraine free. Furthermore, no women experienced a worsening of headache during pregnancy. Twenty-four women (60%) had normal deliveries, 36 (60%) underwent pathological deliveries (promotion delivery, vacuum extractor delivery, cesarean section). We found a considerable rate of migraine recurrence 63% within the first month and 75% within the 3 month and 78% within the 6 month following childbirth. Migraine was seen to recur in 50% of breast feeding sufferers during the first month after delivery in 65.8% during the 3 month and in 71.1% during the 6 month, while recurrence was attained by 86.4%, 90.9%, and 95.5% of the bottle feeding, respectively.

Table. Characteristic of migraine and pregnancy

<table>
<thead>
<tr>
<th>Parity</th>
<th>Total</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Remission</td>
<td>No remission</td>
<td>Remission</td>
<td>No remission</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>37</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>Parity</td>
<td>72</td>
<td>28</td>
<td>82</td>
<td>8</td>
</tr>
<tr>
<td>Primigravid</td>
<td>57.1</td>
<td>42.9</td>
<td>74.3</td>
<td>25.7</td>
</tr>
</tbody>
</table>

Table. Migraine recurrence during postpartum in relation to patient characteristics

<table>
<thead>
<tr>
<th>Parity</th>
<th>Total</th>
<th>First month after delivery</th>
<th>Third month after delivery</th>
<th>Sixth month after delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrence</td>
<td>No recurrence</td>
<td>Recurrence</td>
<td>No recurrence</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>37</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Delivery</td>
<td>62.5</td>
<td>37.5</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Normal</td>
<td>39</td>
<td>61</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Delivery</td>
<td>50</td>
<td>50</td>
<td>65.8</td>
<td>34.2</td>
</tr>
<tr>
<td>Pathological</td>
<td>Bottle feeding</td>
<td>86.4</td>
<td>13.6</td>
<td>90.9</td>
</tr>
</tbody>
</table>

PO206
Orthostatic headache in postural tachycardia syndrome (POTS)
Khurana RK
Division of Neurology, Union Memorial Hospital, Baltimore, MD, USA

Objectives: i. To examine the relationship between POTS and headache ii. To increase awareness and knowledge of these co-morbidities.

Background: POTS, a form of orthostatic intolerance, causes dizziness, palpitations, fatigue, panic-like symptoms and heart rate increase ≥ 30 bpm (Khurana, 1995 & 2006). It may afflict 500,000 Americans (Robertson, 1999). Mokri and Low (2003) reported orthostatic headache without CSF leak in four POTS patients. However, there is no systematic study of headache in POTS.

Methods: Twelve consecutive POTS patients (nine women, three men; age range, 20–47 years) prospectively underwent a structured verbal diagnostic interview. They were asked about preexisting headache, autonomic symptoms, and effect of posture on headache. They were assigned a headache diagnosis based on the International Classification of Headache Disorders (ICHD-II). Sudomotor, cardiovagal and adrenergic functions were assessed using thermoregulatory sweat test, heart rate response to deep breathing, the Valsalva maneuver and head-up tilt (HUT) test (Neurology 1996). The results were compared with historic controls from our laboratory. Occurrence of orthostatic headache was queried during the HUT.

Results: All 12 patients had orthostatic intolerance exceeding 6 months. Four out of 12 displayed distal anhidrosis. Cardiovagal functions were normal. HUT revealed orthostatic hypertension (diastolic BP > 90 mmHg) in 9 patients. All patients demonstrated exaggerated heart rate increase (range, 30 to 65 bpm; normals, 18.79 ± 2.27 bpm). Five women had preexisting migraine without aura, with POTS aggravating migraine in three. One developed migrainous symptoms with the onset of POTS. Headache was precipitated upon standing during daily activities in 3/9 women. Six of nine women developed headache during HUT; four showed improvement upon attaining horizontal position, but headache persisted for 2–24 hours in two patients. None of the three men had headache preexisting, during daily activity, or during HUT.

Conclusions: Orthostatic headache was frequent among women with POTS. Patients with complaint of orthostatic headache should be evaluated for orthostatic intolerance and orthostatic tachycardia.

PO207
Treatment of premenstrual syndrome with B6 vitamin: clinical responses and estimate of peripheral neurotoxicity risk
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Objectives: To evaluate the clinical and electromyography responses in PMS after using of B6 vitamin in dose of 600 mg/day from fourteen day until the first day of next cycle, for four consecutive menstrual cycles.

Background: Premenstrual syndrome (PMS) reaches a great part of feminine population. The trigger for menstrual migraine is the decline in serum estradiol levels that occur shortly before and during

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the peri-menstrual period. Menstrual migraine, as defined by the IHS, has two subtypes well described as attacks of *menstrually related migraine without aura* must have an onset during the peri-menstrual time and attacks of *pure menstrual migraine without aura*. However, PMS headache has not been properly characterized. Despite many drugs to PMS treatment, challenges to abolish the disagreeable symptoms stay in doubt. B6 vitamin has been used like one of the therapeutic options; but the ideal dose was not still established. B6 vitamin probable acts in PMS with the following properties: interfere in pain conduction from motor to sensitive fibers; has diuretic action and improves the serotonin and melatonin metabolism.

**Methods:** This study was descriptive and serial cases, with pattern of thirty five women attended in the Clinical Hospital of the Federal University of Pernambuco. All women were fertile, having at least one year of PMS symptoms, including headaches that occurred exclusively in the menstrual period. All patients claimed to be in good health, without other medical conditions that could interfere in the study.

**Results:** The response to B6 vitamin was evaluated through the observation of symptoms like discouragement, inability to concentration, depression, anxiety, irritability, insomnia, somnolence, discomfort and distension abdominal, lumbar pain, oliguria, breast edema and breast tenderness, pain and edema in the legs, all these parameters were monthly compared with the values before treatment, by McNemar test, for four consecutive menstrual cycles and statistical significant differences occurred since the first cycle of treatment. The patients with headache related to PMS obtained significant improvement after use of B6 vitamin. The probable tension type of headache occurred monthly in 11 women (31.4%), 2–4 days before to 2–3 days after the onset of menstruation and 90.9% (*P = 0.003*) improved after treatment. Migraine without aura related to peri-menstrual period was verified in 14 women (40%), 1–3 days before to 3–4 days after the onset of menstruation and 85.7% (0.001) had improvement of this headache. Attacks of *pure menstrual migraine* without aura were only presented in three women, and after use of four cycles of B6 vitamin, two patients had reduction of this headache. The amplitude of sensitive potential and sensitive conduction velocity of sural nerves by electromyography, before and after using B6 vitamin did not showed significant differences.

**Conclusions:** We concluded that B6 vitamin in dose of 600 mg/day for four consecutive menstrual cycles is efficient and security in PMS treatment, including headaches, and do not induce peripheral neuropathy.

**PO208**

**Headache and migraine during pregnancy and puerperium**

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**Objectives:** The main purpose of the present study was to describe in detail the course of migraine and headache in general during pregnancy and puerperium and to explore migraine’s relation to various factors, in particular the relation to breastfeeding.

**Background:** Migraine is a disabling disorder which most frequently affects women, and it poses a particular challenge for women during pregnancy and puerperium due to scarcity of treatment options in this period. Most women experience an improvement of their migraine during pregnancy and a recurrence of migraine post partum. The effect of breastfeeding on the course of headache and migraine post partum is not yet established.

**Methods:** In the MIGRA-study, carried out at a university Hospital and local hospital in 1997 and 1998, more than 2000 pregnant women answered three questionnaires, Q1, Q2 and Q3, concerning the time before, during and after pregnancy respectively. In addition,

**Figure 1**

208 of these women with migraine kept a headache diary during the last half of pregnancy and the first two months of the puerperium.

**Results:** In general, headache and migraine improved gradually during pregnancy. Very few had headache or migraine on the day of delivery, but in the days after there was a prominent peak in the incidence (Figure 1). Migraine and headaches during pregnancy or puerperium showed no significant relationship to parity, and headaches in the puerperium were not influenced by breastfeeding.

**Conclusions:** The study confirms previous studies showing that headache and migraine tend to improve during pregnancy. There is an increase in headache right after delivery, but overall the headache incidence in the first 8 weeks of the puerperium is almost as low as in pregnancy. Breastfeeding the baby or not does not seem to influence the headache pattern. These data may be of importance for advising pregnant women with headache about the likely prognosis and for unravelling the complex pathophysiologic relation between headache and female hormones.

**PO209**

**The influence of gender and estrogens on nitroglycerin-induced Fos expression in the rat brain**

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**Objectives:** In the present study we evaluated the influence of gender and estrogen treatment on NTG-induced neuronal activation in the rat brain.

**Background:** Nitroglycerin (NTG) administration is recognized experimental model of migraine. NTG is indeed capable of inducing migraine-like attacks in migraine sufferers. In the rat, systemic administration of NTG induces hyperalgesia and activates neurons located in nuclei involved in nociceptive transmission, regulation of baroreception, and neuroendocrine and autonomic functions.

**Methods:** Intact and castrated male and female rats, and castrated female rats treated with placebo or estrogen replacement (50 μg/kg for 3 weeks) were injected with NTG (10 mg/kg, i.p.) and sacrificed after 4 hours. Animals were anesthetized and then perfused; their brains were removed and processed for the immunocytochemical detection of Fos protein, a marker of neuronal activation.

**Results:** Experimental data showed a reduced expression of NTG-induced Fos protein in brain areas of male rats in the paraventricular nucleus (PVH), supraoptic nucleus (SON) and nucleus trigeminalis caudalis (NTC) in comparison with intact animals, in PVH, SON, central nucleus of the amygdala (AMi), nucleus tractus solitarius (NTS), area postrema (AP) and NTC. In castrated male rats, Fos expression was reduced uniquely in the NTC. Chronic administration of estrogen restored Fos protein expression in PVH, SON, AMi, NTS, AP and NTC in castrated female rats.
Conclusions: The present data point to a sexual dimorphism in NTG-induced neuronal activation and suggest that estrogens significantly influence the cerebral structures implicated in the pathophysiology of migraine.

PO210 Childhood maltreatment and migraine: emotional abuse as a risk factor for headache chronification

Tietjen GE1, Brandes J2, Peterlin BL3, Ellof A4, Dafer R5, Stein M6, Drexler E7, Martin V8, Hutchinson S9, Aurora S10, Recober A11, Herial NA1, Utley C1, White L1 and Khuder S1

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Objectives: To assess in a headache clinic population the relationship of childhood abuse and neglect to migraine characteristics, including type, frequency, disability, allodynia and age of migraine onset.

Background: Childhood maltreatment is prevalent and has been associated with recurrent headache. Maltreatment is associated with many of the same risk factors for migraine chronification, including depression and anxiety, female sex, substance abuse, and obesity.

Methods: Electronic surveys were completed by patients seeking treatment in headache clinics at 11 centers across the US and Canada. Physician-determined data included the primary headache diagnosis based on the ICHD-2 criteria, average monthly headache frequency, and whether headaches transformed from episodic to chronic if headaches were continuous. Analysis includes all persons with migraine with aura, and migraine without aura. Questionnaire collected information on demographics, social history, age at onset of headaches, migraine-associated allodynic symptoms, headache-related disability (HIT-6), current depression (PHQ-9), and current anxiety (BAI). History and severity of childhood (< 18 years) abuse (sexual, emotional, and physical) and neglect (emotional and physical) was gathered using the Childhood Trauma Questionnaire.

Results: A total of 1348 migraineurs (88% women) were included in this study (mean age 41 years). Diagnosis of migraine with aura was recorded in 40% and chronic headache (≥ 15 days/month) was reported by 34%. Transformation from episodic to chronic was reported by 26%. Prevalence of current depression was 28% and anxiety was 56%. Childhood maltreatment was reported as follows: physical abuse 21%, sexual abuse 25%, emotional abuse 38%, physical neglect 22% and emotional neglect 38%. In univariate analyses, physical abuse and emotional abuse and neglect were significantly associated with chronic migraine and transformed migraine. Emotional abuse was also associated with continuous daily headache, severe headache-related disability, and migraine-associated allodynia. Adjusting for sociodemographics, and current depression and anxiety, only emotional abuse was associated with chronic migraine (OR = 1.77) and with transformed migraine (OR = 1.89). Childhood emotional abuse was also associated with younger median age of headache onset (16 vs. 19 yo, P = .0002).

Conclusions: Our findings suggest that physical abuse and emotional abuse and neglect may be risk factors for development of chronic headache, including transformed migraine. The association of maltreatment and headache frequency appears to be independent of depression and anxiety, which are related to both childhood abuse and chronic daily headache. The finding that emotional abuse was associated with an earlier age of migraine onset may have implications for the role of stress responses in migraine pathophysiology.

PO211 Childhood maltreatment and migraine: association with comorbid pain conditions

Tietjen GE1, Brandes J2, Peterlin BL3, Ellof A4, Dafer RM5, Stein MR6, Drexler E7, Martin VT8, Hutchinson S9, Aurora SK10, Recober A11, Herial NA1, Utley C1, White L1 and Khuder S1

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Objectives: To evaluate in a headache clinic population the relationship of childhood maltreatment and the prevalence of pain conditions comorbid with migraine.

Background: Childhood maltreatment is prevalent and has been associated with recurrent headache. The relationship of maltreatment and pain has, however, been a subject of some debate.

Methods: Cross-sectional data on self-reported physician-diagnosed pain conditions were electronically collected from persons with migraine (diagnosed according to ICHD-2), seeking treatment in headache clinics at 11 centers across the US and Canada. These included irritable bowel syndrome (IBS), chronic fatigue syndrome (CFS), fibromyalgia (FM), interstitial cystitis (IC), arthritis, endometriosis (EM), and uterine fibroids. Other information included demographics, migraine characteristics (frequency, headache-related disability), remote and current depression (PHQ-9), and remote and current anxiety (BAI). Patients also completed the Childhood Trauma Questionnaire regarding sexual, emotional, and physical abuse, and emotional and physical neglect under the age of 18 years old. Statistical analyses accounted for the survey design and appropriate procedures in SAS such as surveymeans, surveyfreq, and surveylogistic were applied to the weighted data.

Results: A total of 1348 migraineurs (88% women) were included in this study (mean age 41 years). Based on physician diagnosis or validated criteria, 32% had IBS, 16% had CFS, and 10% had FM. Diagnosis of IC was reported by 6.5% and arthritis by 25%. Uterine fibroids were reported by 14% and EM by 5%. At least one comorbid pain condition was reported by 57%, two conditions by 15%, and three or more by 8%. Childhood maltreatment was reported by 58% of the patients. Emotional abuse was associated with increased prevalence of IBS, CFS, arthritis, and physical neglect with arthritis. In women, physical abuse was associated with EM and physical neglect with uterine fibroids. Emotional abuse, and physical abuse and neglect (P < .0001 for all) were also associated with increased total number of comorbid conditions. In ordinal logistic regression models, adjusted for sociodemographics and current depression (prevalence 28%) and anxiety (prevalence 56%), emotional abuse (OR = 1.60, 95% CI: 1.14–2.25) and physical neglect (OR = 1.63, 95% CI: 1.14–2.35) were independently associated with an increased number of pain conditions. The cohort of women, similarly, had associations of emotional abuse (OR = 1.89, 95% CI: 1.34–2.66) and physical neglect (OR = 1.83, 95% CI: 1.28–2.62) with an increased number of pain comorbidities.
Conclusions: The findings suggest that in migraineurs childhood maltreatment may be a risk factor for development of comorbid pain disorders. The association of emotional abuse and physical neglect was strongest in those reporting multiple pain comorbidities.

PO212
Temporal relationship of onset of migraine and comorbid conditions: migraine first
Tietjen GE1, Brandes JL2, Peterlin BL3, Eloff A4, Dafer RM5, Stein MR6, Drexler E7, Martin VT8, Hutchinson S9, Aurora SK10, Recober A11, Herial NA1, Utley C1, White L1 and Khuder SA1
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Objectives: To compare the age of onset of migraine and comorbid conditions in a headache clinic population.

Background: There has been mounting interest in migraine comorbidities, but there is a paucity of data evaluating the age of onset of these conditions, relative to migraine.

Methods: Electronic surveys were completed by patients seeking treatment in headache clinics at 10 centers across the US and Canada. Physician-determined data for all participants included the primary headache diagnoses based on the ICHD-2 criteria, and average monthly headache frequency. The questionnaire collected information on demographics, social history, and age at onset of migraine and a number of other conditions, suspected of being comorbid with migraine. These included anxiety, depression, irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), interstitial cystitis (IC), postural orthostatic tachycardia syndrome (POTS), asthma, Raynaud’s disease, hypothyroidism, sleep apnea, hypertension, diabetes mellitus, myocardial infarction or angina, stroke or transient ischemic attack (TIA), arthritis, and endometriosis (EM), and uterine fibroids.

Results: A total of 1348 surveys were completed by patients (88% women) diagnosed with migraine. The mean onset age of all conditions is given in the figure, and the conditions were arranged in the order of increasing age at condition diagnosis or symptom onset. By participant report, migraine onset was the first of all the conditions (except for asthma, which overlapped in onset), appearing at the age of 19 years. When evaluating individual temporal onset reports, in only 7% to 32% of the cases did the onset of a comorbid condition precede onset of migraine. There were no differences between migraine with and without aura in the mean age at onset of comorbid conditions. Women were significantly younger than men at the time of diagnosis with depression (mean age: 27 vs. 31 years, \( P = .021 \)), interstitial cystitis (24 vs. 45 years, \( P = .001 \)), and stroke/TIA (34 vs. 46 years, \( P = .004 \)).

Conclusions: In the vast majority of participants, the onset of migraine preceded the onset other comorbid conditions. This suggests that early diagnosis of migraine affords an opportunity for prevention of the development of related disorders. In this context, identification of risk factors, such as childhood maltreatment, becomes particularly germane.

PO213
The neurobiology of sexual orientation – total medical evidence presentation
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Objectives: Improved understanding for the neurobiology of sexual orientation.

Background: Homosexuality is a constantly debated issue as to whether it is determined at birth or a choice (nature vs. nurture). The works of the Kinsey Reports and Dr. Evelyn Hooker published in the 1950s resulted in the removal of homosexuality from the DSM4 in 1973. Since then, it has been mentioned as an illness only in the context of being a putative exacerbating factor in anxiety states. Recent studies reveal a clear cut neurobiology to sexual orientation.

Methods: Neurobiologist Simon LeVay conducted a study of brain tissue samples from 41 human autopsies performed at several hospitals in New York and California. He found a significant size difference in the interstitial nuclei of the anterior hypothalamus between the brains of homosexuals and heterosexuals. He also found significant cerebral size differences between homosexual men and heterosexual women. Amygdala connectivity differences were found. Sexual participants. Amygdala connectivity differences were found to be statistically significant and provided evidence towards sexual dimorphism between homosexual and heterosexual men.

Results: In addition, Dr. Ivanka Savic-Berglund and Dr. Per Lindstrom of the Karolinska Institute, Stockholm, performed fMRI and PET measurements of cerebral blood flow. Using volumetric studies, they found significant cerebral size differences between homosexual and heterosexual subjects; the brains of homosexual men resembled heterosexual women and homosexual women resembled heterosexual men. Pheromonal studies also have added to the scientific knowledge of sexuality. Sex-atypical connections were found among homosexual participants. Amygdala connectivity differences were found to be statistically significant and provided evidence towards sexual dimorphism between homosexual and heterosexual subjects. Extensive controls were performed during testing to exclude analytical variability.

Conclusions: A totally evidence-based medicine presentation will provide current data regarding homosexuality showing differences, or similarities, between the brains of homosexuals and heterosexuals.
PO214
Effect of migraine, the menstrual cycle, and perimenstrual estradiol supplements on urinary 5HT, 5HIAA and tryptophan in women with menstrual migraine

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Objectives: To provide information on urinary 5HT, 5HIAA & tryptophan across natural menstrual cycles in women with menstrual migraine (MM) and assess the effects of perimenstrual estradiol supplements. The hypothesis was that changes in urinary 5HT, 5HIAA and tryptophan parallel changes in urinary estradiol metabolites.

Background: Experimental and physiological studies suggest a relationship between 5HT and menstrual cycle hormones. This association may be important to our understanding of the pathophysiology of MM.

Methods: A previous study using perimenstrual estradiol gel for prevention of MM was undertaken in 38 women.1,2 Early-morning urine samples were collected daily across three untreated cycles and six treated cycles (three estradiol, three placebo) and assayed for 5HT, 5HIAA and tryptophan differences between (i) migraine and non-migraine days, (ii) placebo and estradiol gel days and (iii) the three days just before and after the first full day of menstruation. All urine samples were assayed only 1/10th of the urine samples available, assaying the E1G (0.4). Otherwise there were no clear changes of 5HT, 5HIAA & tryptophan across the menstrual cycle.

Results: There was no evidence that levels of 5HT, 5HIAA and tryptophan differed between (i) migraine and non-migraine days, (ii) placebo and estradiol gel days and (iii) the three days just before and just after the first full day of menstruation. There was a moderate association between 5HIAA and E1G (0.33), and tryptophan and E1G (0.4). Otherwise there were no clear changes of 5HT, 5HIAA and tryptophan across the menstrual cycle.

Table. Relationship between each of 5HT, 5HIAA & tryptophan, and E1G & PDG

<table>
<thead>
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<th>Patient ID</th>
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<th>14</th>
<th>20</th>
<th>38</th>
<th>40</th>
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<td>0.23</td>
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<tr>
<td>PDG</td>
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<td>-0.16</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5HIAA with E1G</td>
<td>0.35</td>
<td>0.35</td>
<td>0.41</td>
<td>0.21</td>
<td>0.31</td>
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<tr>
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<td>0.09</td>
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</tr>
<tr>
<td>Tryptophan with E1G</td>
<td>0.56</td>
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<td>0.28</td>
<td>0.36</td>
<td>0.54</td>
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</tr>
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</tr>
</tbody>
</table>

*Spearman’s rank correlation coefficient for each woman pooled over 5 observations

Conclusions: These preliminary results suggest a moderate association between 5HIAA & E1G, and tryptophan & E1G. Since we assayed only 1/10th of the urine samples available, assaying the remaining samples could confirm or refute this finding.

References:

PO215
Migraine outcome in postmenopausal patients: looking for possible predictive factors

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Objectives: It is well known that migraine characteristics may widely change after menopause. The possibility to predict the outcome of the illness in this phase of women’s life could be very useful. Aim of this study was to identify the existence of factors influencing the outcome of the illness.

Background: Throughout reproductive life cycle, as hormonal levels are changing, many women experience significant headache changes. Although migraine prevalence decreases with advancing age, migraine can either regress or worsen or remain unchanged at menopause. Up to now, no certain data exist, predicting the illness’ outcome after the onset of menopause. In a previous study we observed that the outcome of migraine after menopause in the majority of cases follows the one of the patients’ mothers. In order to find out some other predictive factor about the development of the illness, we studied the course of postmenopausal migraine focalizing the attention on the existence of a possible link between the evolution of migraine after menopause and particular features during reproductive life.

Methods: 215 post-menopausal women (age 35–78 years) suffering from migraine according to ICHD-II criteria, referring for the first time to Turin University Headache Centre, in the years 2003–2005, were studied. They were asked if and how the characteristics of migraine changed after menopause, if before menopause their migraine attacks were in some way correlated to the menstrual cycles, if they had ever suffered from dysmenorrhea, if they had ever used Combined Oral Contraceptives (COCs) and if they had pregnancies and their eventual number.

The data were statistically analyzed using the y2 test.

Results: In 34 (15.08%) patients migraine improved after menopause, in 129 (60%) worsened, while in the remaining 52 (24.2%) of them migraine remained unchanged. 32 (94.1%) of the 34 patients whose migraine improved after menopause had migraine attacks correlated to the menstruation, while only 95 (73.6%) of the patients whose migraine worsened after menopause and 40 (76.9%) of the patients whose migraine remained unchanged had this correlation (P = 0.05). 73.33% of the patients whose migraine improved after menopause suffered from dysmenorrhea, while only 59.25% of the patients whose migraine worsened after menopause and 55.0% of the patients whose migraine remained unchanged showed this correlation (pns). The number of pregnancies and the use of COCs do not show any link with the outcome of migraine after menopause.

Conclusions: On the basis of these data correlation of migraine attacks with menstruation during reproductive life seems to predict a migraine improvement after menopause. No one of the other three factors studied shows such a predictive value, even if dysmenorrhea seems to be more frequent in the patients whose migraine improves after menopause than in the others. Since at present there are little or no data on this particular aspect of the illness, more studies are needed to assess this tendency. If these data will be confirmed this will be a very useful indication for many women approaching the menopausal period.
PO216
Childhood maltreatment and migraine: prevalence and adult revictimization
Tietjen G1, Brandes J2, Peterlin B3, Elhoff A4, Dafer R5, Stein M6, Drexler E7, Martin V8, Hutchinson S9, Aurora S10, Recober A11, Herial N, Utley C1, White L1 and Khuder S1
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Objectives: To examine the prevalence of childhood maltreatment and adult revictimization in migraineurs and the association with sociodemographic factors, depression and anxiety.

Background: Population and practice-based studies have demonstrated an association of childhood abuse and headache in adults, although details on headache diagnoses, characteristics, or comorbid conditions are lacking. There is mounting data suggesting substantial impact of early maltreatment on adult physical and mental health.

Methods: Electronic surveys were completed by patients seeking treatment in 11 headache centers across the US and Canada. Physicians determined the primary headache diagnoses based on ICHD-2 criteria and average monthly headache frequency. Self-reported information on demographics (including BMI), social history, and physician-diagnosed depression and anxiety was collected. Survey also included validated measures for current depression (PHQ-9) and anxiety (BAI). History and severity of childhood (< 18 years) abuse (sexual, emotional, and physical) and neglect (emotional and physical) was gathered using the Childhood Trauma Questionnaire. Adult physical and sexual abuse, including age of occurrence was queried.

Results: A total of 1348 migraineurs (88% women) were included (mean age 41 years). Diagnosis of migraine with aura was recorded in 40% and chronic headache (≥ 15 days/month) was reported by 34%. Prevalence of childhood maltreatment types was as follows: physical abuse 21%, sexual abuse 25%, emotional abuse 38%, physical neglect 22% and emotional neglect 38%. Nine percent reported all three categories of abuse (physical, sexual and emotional) and 17% reported both physical and emotional neglect. Overlap between maltreatment types ranged between 40% and 81%. Of those reporting childhood abuse, 43% reported abuse in adulthood, but infrequently (17%) over the age of 30 years. In logistic regression models adjusted for sociodemographics, current depression was associated with physical (P = .003), sexual (P = .007), and emotional abuse (P < .001), and physical and emotional neglect (P = .001 for both). Current anxiety was also associated with all childhood abuse and neglect types (P < .001 for all). A graded relationship was observed between number of maltreatment types and remote or current depression and anxiety. Migraineurs reporting three or more types of childhood trauma were more likely to have received diagnoses of both depression and anxiety (OR = 6.91), or either depression or anxiety (OR = 3.66) as compared to those without childhood abuse or neglect.

Conclusions: Reports of childhood maltreatment, especially emotional abuse and neglect, are prevalent in outpatients with migraine. There is extensive overlap of maltreatment types and a high rate of revictimization in adulthood. All types of childhood abuse and neglect are strongly associated with remote and current depression and anxiety, and the relationship strengthens with increasing number of maltreatment types.

PO217
Menstrual migraine in the general population. the Akershus study of menstrual migraine
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Objectives: To investigate the prevalence of menstrual migraine in the general population.

Background: Premenstrual fall in estrogen concentration seem to be a trigger attacks of menstrual migraine.

Methods: An age and gender stratified sample of 30,000 persons, 30–44 years old and residing in the eastern Akershus County received a postal questionnaire.

Results: The study included 11,123 women. The questionnaire response rate was 77%. The prevalence of self-reported migraine was 35.9%, and 18.8% of the migraineurs had self-reported menstrual migraine, i.e. 7.1% had pure menstrual migraine and 11.8% had menstrually related migraine. This corresponds to a prevalence of pure menstrual migraine and menstrually related migraine of 2.5% and 4.2% in the general population, respectively.

Conclusions: Menstrual migraine is common in the general population.

PO218
The impact of physical abuse on headache disorders differs in adolescents
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Objectives: To investigate the impact of physical abuse on headache disorders in a non-referred sample of adolescents.

Background: Physically abused adolescents experience a greater risk of a wide variety of psychosocial and behavioral problems. Relatively little information is available on the link between physical abuse and headaches in adolescents.

Methods: The questionnaire included three parts: 1) A validated headache questionnaire for adolescents used for headache diagnoses; 2) Adolescent Depression Inventory (ADI) for depression symptoms and 3) Self-report physically abuse. The frequency of physical abuse was graded as: rarely, sometimes, and often.

Results: A total of 3,955 students completed the study with a response rate of 93%. Overall, 2,461 students had at least one headache in the past three months; of whom, 926 students (37.6%) had migraine with or without aura or probable migraine; 1092 (44.4%) had tension-type headache (TTH) and 443 (18.0%) were classified as having other headaches. Physical abuse was reported by 945 (23.9%) students, classified for frequency as: rarely in 762 (19.3%) students, sometimes in 143 (3.6%) and often in 40 (1.1%). As shown in Table 1, the students with headaches showed increasing mean ADI scores and headache frequency, and higher proportions of severe headache intensity and migraine diagnosis in relation to the frequency of physical abuse. After controlling for gender, age and ADI scores, the students with ‘often’ physical abuse had higher headache frequency compared with those without physical abuse among students with migraine (general linear regression model, estimated difference = 2.5 days per month, P = 0.014) but not among those with non-migraine headaches. In contrast, physical abuse was an independent predictor for severe headache intensity among students.
with TTH (OR = 2.2,  P = 0.017) but not among those with migraine.

Table. The comparison of ADI scores and headache profiles by different frequency of physical abuse among 2461 students having headaches within 3 months prior to the survey

<table>
<thead>
<tr>
<th>Physical Abuse</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>Rare</td>
</tr>
<tr>
<td>ADI scores*</td>
<td>9.4 ± 6.3</td>
</tr>
<tr>
<td>Headache frequency (days/month)*</td>
<td>2.8 ± 3.3</td>
</tr>
<tr>
<td>Severe headache intensity§</td>
<td>5.1%</td>
</tr>
<tr>
<td>Migraine diagnosis§</td>
<td>35.3%</td>
</tr>
</tbody>
</table>

ADI: Adolescent Depression Inventory, *: one way analysis of variance test, §: Chi-square for trend test

Conclusions: Physical abuse had impacts on headache profile in patients with headache disorders; however, the impact differed between migraine and TTH. A history of physical abuse should be elicited from adolescents in treatment for headache.

PO220
Prevalence and epidemiological profile for adolescent chronic migraine: results of a US national survey of chronic daily headache

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Objectives: To describe the epidemiologic profile of CM in adolescents including age-adjusted prevalence rates.

Background: The epidemiology of CM in adolescents has rarely been studied, in part because of uncertainty regarding optimal diagnostic criteria.

Methods: This was a 3-stage, population-based panel study. In Stage 1, questionnaires were mailed to 63,500 households with residents 12–19 years of age selected to be representative of the US adolescent population. The questionnaires identified headache sufferers and assessed attack frequency. In Stage 2, all chronic daily headache sufferers and a random sample of episodic headache sufferers were invited to participate in a computer assisted telephone interview (CATI). The CATI included validated questions assessing potential diagnosis, disability assessment and allodynia as well as patterns of healthcare utilization. Because there are no diagnostic criteria for CM in adolescents, CM was diagnosed using proposed revised adult CM criteria (International Classification for Headache Disorders [ICHD-2R]). Results were benchmarked to the 2004 US census data using a two-step weighting method to account for selective participation (ie. noncoverage and nonresponse). Prevalence rates and demographics from Stage 1 and 2 for adolescents 12–17 years old are presented.

Results: A total of 24,712 adolescents (28.7%) completed the mailed questionnaire and 750 (88%) selected respondents completed Stage 2 CATI. Responders and non-responders differed statistically in both Stage 1 and 2. The one-month period prevalence rate for adolescent CM was 0.76% (95% CI: 0.05–1.48) with rates higher among teenage females [1.39% (95% CI: 0.00–2.87)] than in males [0.15% (95% CI: 0.05–0.26)]. Prevalence rates of CM increased with age from 12–13 years 0.09% (95% CI: 0.00–0.19), 14–15 years 0.22% (95% CI: 0.06–0.38) and 16–17 years 2.02% (95% CI: 0.00–4.71). The vast majority (99%) of CM adolescents reported their race as Caucasian and none reported having Spanish origin.

Conclusions: Using an adult CM definition, adolescent CM is rare, with an overall prevalence of less than 1%. From ages 12 to 17 years, the prevalence of CM is higher in females than in males and increased with age.

PO221
Basilar-type migraine with coma aura: report of three cases

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Background: Basilar-type migraine (BTM) is a rare subset of migraine with aura. Decreased level of consciousness is rare in migraineurs. Coma, as an aura, rarely lasted for a long time.

Methods: We report the first three cases of adolescent BTM in China with coma as an aura symptom.

Results: Case 1 A 15-year-old boy complained a 5-year history of migraine lasting 4 to 6 hours occurring once per 2–3 months and associated with symptoms of recurrent coma, flashing lights, nausea, photophobia, dysphasia, phonophobia and dizziness. Coma lasted 5
to 30 minutes. EEG showed focal slow wave and higher electrical power. MRI and other laboratory examinations were normal. Treatment included sodium valproate, amitriptyline. In the next 10 days under treatment, headache occurred again without coma when he was in a crowded train but was released in 2 hours after he took domperidone and rizatriptan. No headache reported in the next 6 months. Case 2 A 13-year-old girl has a 5-year history of migraine which happened every month and progressed to 10 times per month in the last two years. Throbbing headaches often triggered by cold frequently and located in the temples or frontal head regions associated with dizziness, vomiting, diplopia, ataxia, imbalance and transient hearing loss. She became unconscious for about 10 minutes to 2 hours for at least 5 times these years. Physical and auxiliary examinations were unremarkable. We prescribed sodium valproate, amitriptyline for prophylactic agent. Three days after this visit, an attack occurred without coma but was released in 2 hours after taking a pill of rizatriptan. No attack reported in the following 4 months. Case 3 A 13-year-old girl presented to our hospital with complaints of recurrent headache with dizziness, blurred vision, and coma in the last 5 years. These symptoms were triggered by chocolate or coffee, occurred 0–3 times per month. She became confused for about one hour during two attacks a day, and was admitted to hospital last year and diagnosed as migraine without any special treatment. One day before this visit, she suffered a headache and was unconscious for 1.5 hours. On admission, she had normal general and neurological examinations. Usual laboratory examinations, CT, MRI, AEEG, as well as ambulatory electrocardiograph test were normal. Prophylactic treatment with sodium valproate and rizatriptan for acute treatment were proven successful in the next 3 months.

Conclusions: Basilar-type migraine is mainly occurred in adolescents. Differential diagnosis is difficult and diverse especially when coma associated. Sodium valproate as a preventive treatment was proven effective. Adolescent migraine can be impaired successfully with abortive or prophylactic treatment on accurate diagnosis.

PO222
Under recognition of abdominal migraine
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Objectives: Our goal was to assess the population of children referred to the GI clinic with ‘recurrent abdominal’ pain to determine if AM is under diagnosed and/or an example of diagnostic substitution.

Background: The International Classification of Headache Disorders (ICHD-2004) included Abdominal Migraine (AM) among its ‘periodic syndromes of childhood that are precursors for migraine’. Infrequently diagnosed in the US, AM is an idiopathic disorder characterized by attacks of midline, moderate to severe abdominal pain lasting 1–72 hours with vasomotor symptoms, nausea and vomiting.

Methods: Retrospective chart review of children presenting to GI clinic with complaint of recurrent abdominal pain applying ICHD 2004 criteria to identify subsets of children fulfilling criteria for AM. Demographics, diagnostic evaluation, treatment regimen and outcomes were collected.

Results: From an initial cohort of 450 children (ages 1–18; 57% females, 43% males) with recurrent abdominal pain, 111 (24.7%) were excluded on the basis of their ultimate GI diagnosis. 339 met inclusion criteria, of whom 287 (84.6%) did not meet criteria for AM. 15 (4.4%) met formal criteria for AM and another 37 (11%) had documentation consistent with AM, but fell short on at least 1 criteria (probable AM).

Conclusions: Of children with idiopathic recurrent abdominal pain, Abdominal Migraine represents about 4–15%. Given the spectrum of available treatment modalities now available for pediatric migraine, increased awareness of cardinal features of AM by pediatricians and pediatric GI clinics may result in improved diagnostic accuracy and early institution of both acute and preventative migraine specific treatments.

PO223
Prevalence of regulatory t-cells in pediatric migraine
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Objectives: The goal of our study was to investigate the prevalence of the regulatory T-cells and the lymphocyte subpopulations controlled by the regulatory T-cells as well as natural killer cells in pediatric migraine patients.

Background: Migraine headaches can be framed as the brain communicating with the trigeminal nerve and its central projections, with meningeal tissues, with circulating substances and the immune system. The regulatory T-cells have a pivotal role in the cell mediated adaptive immune response. The altered functioning of the regulatory T-cells are in close association with the secretion of several cytokines by influencing lymphocyte subpopulations.

Methods: Seventy-nine patients 7–17 years old, diagnosed according to ICHD-II were included. Patients were classified as migraine without aura: 40, migraine with aura: 24, hemiplegic migraine: 14. The controls consisted of 16 healthy probands. Periferal blood samples were taken in the headache-free intervals. The prevalence and ratio of the lymphocyte subpopulations; the CD4+, CD8+, Th1 and Th2 cells as well as the prevalence of the regulatory T cells and the natural killer cells: NK, NKT, iNKT were determined by using flow cytometry method. Statistical comparisons were performed using the Mann-Whitney U test.

Results: In the prevalence and ratio of the CD4+, CD8+, Th1, Th2 cells and in the prevalence of the NK, NKT, iNKT cells no difference was found neither between the migraine groups and the controls, nor between the different migraine subtypes. A marginally significant decrease in the prevalence of the regulatory T-cells in all of the migraine subtypes compared to the control group was observed. The ratio of the Th1 / Th2 cells were tendentially lowered and the prevalence of the Th2 and iNKT cells were increased in the migraine patients.

Conclusions: According to our study no significant alteration in the functioning of the immune cells was observed in pediatric migraineurs in the headache-free period. However, the decreased regulatory T-cell prevalence could be interpreted as a potential over response of the immune system. It is speculated that the tendentious lowering of the Th1 / Th2 lymphocyte ratio and the increased Th2 and iNKT cell prevalence indicate a contribution to this hypothesis.

PO224
Low dosage of topiramate in children and adolescent migraine prevention
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Objectives: The objective of this study was to evaluate the efficacy of low dosage of TMP for the prevention of pediatric migraine.

Background: Migraine is a significant problem for recurrent headache children. Some reports show that topiramate (TPM) has been effective for the prophylaxis of migraine in adults, but there is not enough data in children and adolescents.

Methods: Children with frequent migraine attacks were prescribed low dosage of TPM for prophylaxis with the rage of 0.33 to 2.5 mg per weight (kg) at bedtime for preventive treatment. Frequency, severity, and duration of headaches were checked and headache
impact test-6 (HT-6) score also were measured. They were groups as low dosage group (L-TPM), usual dosage group (U-TPM).

Repeated measured data were analyzed with methods of generalized estimating equations (SPSS 16).

Results: Totally 66 children were treated with TPM. Their age were 12.3±2.6 year-old and sex ratio was 34:62 (male: female). They were consisted of chronic daily headache (CDHA) 8 (12.1%), basilar-type migraine (BTM) 11 (16.77%), migraine with aura (MWA) 14 (21.2%) and migraine without aura (MWOA) 33 (50.0%). L-TPM was effective at MWOA, MWA but BM, CDHA (p < 0.05). There was no statically difference between L-TPM and U-TPM (P = 0.649).

With frequency of headache and HT-6 scales, scores were reduced to 85.7% in BTM, 85.7% in MWA and 91.75% in MWOA.

Conclusions: Low dosage of topiramate is an effective prophylactic medication for children with frequent migraine.

PO225
Prophylactic treatment of headaches in adolescents with riboflavin
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Objectives: To determine whether high-dose riboflavin (vitamin B2) prophylaxis can improve various types of chronic headaches in adolescents age 14 to 20 years old.

Background: Open-label and randomized placebo-controlled clinical trials have demonstrated the efficacy of prophylactic high-dose riboflavin (B2) in adults with episodic migraine. B2 is commonly recommended for prophylactic treatment of migraine in children and adolescents as well, but no reports have been published of its efficacy.

Methods: We retrospectively reviewed charts of all new adolescent patients, aged 14 to 20 years, who presented for treatment at our Center in the last 2 years. Inclusion criteria: 1). Had been prescribed B2 400 mg/day as their only prophylaxis for headache. 2). Duration of treatment ≥ 6 weeks. 3). Had been compliant with dosing and with keeping daily headache diaries. 4). Had kept ≥ 1 follow-up appointment. We analyzed each daily headache diary for headache days and headache intensity score for the 14 days following initiation of treatment (baseline) compared to the last 14 days of a six-week treatment interval. The headache intensity score was calculated from 14 days of daily intensity scores, based on the 0-10 visual analog diary previously reported. Results were stratified by headache type and reported as percent of responders (> 50% reduction in headache days or headache intensity score), as well as percent of patients with any improvement in these indices.

Results: We had evaluated 89 new adolescent patients in the last 24 months, of which 32 met all inclusion criteria. There were 25 girls, 7 boys, aged 14 to 20. The largest group (N = 15, 47%) of patients carried the pretreatment diagnosis of chronic migraine, with 8 (25%) diagnosed with New Daily Persistent Headaches, 6 (19%) with episodic migraine with or without aura, and one patient each with chronic posttraumatic headache, occipital neuralgia and primary stabbing headache. Single patients with chronic posttraumatic headache and primary stabbing headaches showed little or no reduction in headache days and headache intensity score. A single patient with occipital neuralgia, however, had 96% reduction of headache intensity score, but continued to have very mild pain daily, so headache days did not decrease.

Table. Improvement with riboflavin 400 mg/day, adolescents, % of total (n = 32)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>% of Total N</th>
<th>% with Improvement ≥ 50%</th>
<th>#/% with Any Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine with Aura</td>
<td>6</td>
<td>19%</td>
<td>5/6 (83%)</td>
<td>5/6 (83%)</td>
</tr>
<tr>
<td>Chronic Migraine</td>
<td>15</td>
<td>47%</td>
<td>2/15 (13%)</td>
<td>2/15 (13%)</td>
</tr>
<tr>
<td>NDPH</td>
<td>8</td>
<td>25%</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
</tr>
</tbody>
</table>

Conclusions: In this retrospective study of prophylactic B2 400 mg/day, adolescents with episodic migraine improved more frequently than previously-reported adults. Adolescents with chronic migraine improved very well in 20%, with some response seen in 73%. Although adolescents with NDPH mostly did not improve with B2, about 2/3 had some reduction in their usually-refractory daily headaches. Although other types of headache were represented by only single patients in this study, it appears that occipital neuralgia might be quite sensitive to B2 treatment in some patients.

PO226
Chronic daily headache, obesity, and medication overuse in a pediatric headache clinic population
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Objectives: The objectives of this study are to 1) identify the prevalence of chronic daily headache (CDH) in our Pediatric Headache Clinic Population, 2) identify the proportion of those CDH patients with medication overuse headache, 3) investigate the degree of disability associated with the various types of CDH (chronic migraine, chronic tension, and medication overuse headache), and 4) investigate the frequency of overweight in the CDH Population as compared to the population of patients with episodic migraine and the pediatric population in general.

Background: Primary CHD in adults has received attention as a public health priority because of prevalence and associated disability. There has been effort to further define CDH in cpediatrics. A study completed in 2001 evaluated a Pediatric Headache Clinic population and found that 34.6% of 577 children evaluated had headache greater than 15 days per month. CDH can have a negative impact on daily functioning and quality of life in children and adolescents as in adults. There has also been recent attention to the association between migraine headache and obesity in children and adults (Hershey et al, 2009). We undertook this retrospective study to further evaluate characteristics of the CDH population in our Pediatric Headache Clinic.

Methods: We completed this retrospective study by reviewing the existing data base of Pediatric Headache Clinic patients seen for initial evaluation between 7/13/2004 and 7/30/2008. We reviewed data for patients with the following diagnoses: chronic migraine, chronic tension headache, medication overuse headache, episodic migraine with and without aura. (ICHHD-2 criteria). Data was reviewed on patients carrying these diagnoses for the following information: demographics, PedMDIAS score (disability score), body mass index (BMI), current and past preventive medications, and reported response to treatment with headache diary. BMI was plotted on the standard CDC growth curve and assessed at risk for overweight (85-95%) or overweight (> 95%). Data was analyzed statistically with ANOVA for differences between group.

Results: 942 pediatric headache patients were identified during a 4 year time period. Incomplete data noted in 17 patients was excluded from final data analysis for a final n = 925. 252 (27%) had CDH,
PO227

Childhood short lasting headaches

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Objectives: i. To report the characteristics of SLH. ii. To examine whether SLH in children would fit to specific diagnostic categories.

Background: Short lasting headaches (SLH) have been studied infrequently in children and it is not known whether the main categories of primary headaches of this type in adults are applicable to children.

Methods: Consecutive children referred with headaches were assessed in respect to the SLH. Children with epilepsy, learning difficulties, febrile headaches, and systemic illnesses were excluded. Headache diagnosis was based on the IHCS 2004.

Results: SLH was diagnosed in 15/770 (2%) children (10 females; seven ethnic minorities; age range = 8–15.2 years). Headache history ranged from few days to 5 years (mean = 0.9 years). Other headache characteristics included the duration of the attacks (few seconds to about ½ hour), frequency from 1/month–daily attacks, intensity from mild (2); moderate (1) and severe (12). None of our patient’s headaches were related to sexual activities, physical activities, cough or sleep. Associated autonomic features were found in 6/15 (40%) children (five cluster headaches, 1 SLH with unilateral facial oedema and tingling). SUNCT was suspected in a patient with unilateral conjunctiva tears (masked by the tearful painful crying). 1/15 with acute lymphoblastic leukaemia (ALL) was diagnosed with methotrexate toxicity. Psychosocial issues were found in 2/15 (parental worries). MRI brain was normal in 14/15 patients. Brain MRI/CTS showed low signal in the deep white matter of the patient with ALL.

Conclusions: SLH, as we have demonstrated in 53% of our patients, did not have autonomic associations and did not fit to a specific diagnostic category. Our findings highlight the need for further studies to examine childhood SLH and reconsider its classification.

References

2. The International Classification of Headache Disorders. 2nd ed.; Cephalalgia 2004; 24 suppl 1: 1–160.
Outcome of biofeedback therapy for children with recurrent headaches
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Objectives: To determine which factors are associated with a favorable response to biofeedback therapy for children with recurrent headaches.

Background: Chronic headaches (HA) cause significant disability for many children. Population-based studies have found that 6% of children have frequent or severe HA. Biofeedback therapy (BFT) is one option for management of recurrent pediatric HA, but we do not know which children are most likely to benefit from BFT.

Methods: We examined the records of 84 children referred to a pediatric BFT clinic for recurrent HA between 2004 and 2008. These files include information about HA’s, demographic data, and patient anxiety and depression. BFT was designed to include 8 visits with training in hand warming, pulse regulation, and relaxation. The outcomes we examined included: 50% decrease in HA days/week, 50% decrease in HA hours/week, and 3 point decrease in HA severity. Responders were defined as those with 50% reduction in number of HA days/week, 50% decrease in HA hours/week, or 3 point decrease in HA severity at visit four. We analyzed associations between characteristics and outcome using Fisher’s exact or Mann-Whitney U tests.

Results: Of 84 children referred for BFT, 62 attended at least one BFT session, 55 attended at least 4 sessions, 30 attended eight sessions. At visit four, the response rate to BFT was 50% overall, 61% for those with initial HA = 7 days/week and 35% for those with initial HA = 7 days/week.

<table>
<thead>
<tr>
<th></th>
<th>Total % n = 84</th>
<th>Non-Responders % n = 25</th>
<th>Responders % n = 25</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>Caucasian</td>
<td>84</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Mother College Grad</td>
<td>60</td>
<td>59</td>
<td>74</td>
</tr>
<tr>
<td>Migamious HA</td>
<td>72</td>
<td>72</td>
<td>68</td>
</tr>
<tr>
<td>≥4 HA days/week</td>
<td>48</td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td>Missed School</td>
<td>74</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Modified School</td>
<td>23</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>Sleep Problems</td>
<td>56</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td>Fam. Hx of HA</td>
<td>56</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>55</td>
<td>62</td>
<td>56</td>
</tr>
<tr>
<td>Preventive Meds. 1</td>
<td>28</td>
<td>29</td>
<td>32</td>
</tr>
<tr>
<td>2+</td>
<td>30</td>
<td>38</td>
<td>24</td>
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<tr>
<td>Alternative Therapies</td>
<td>40</td>
<td>48</td>
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<tr>
<td>Supplements</td>
<td>35</td>
<td>39</td>
<td>32</td>
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<tr>
<td>Overweight</td>
<td>25</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Subjective Improvement</td>
<td>77</td>
<td>68</td>
<td>83</td>
</tr>
</tbody>
</table>

**STAI: Anxiety screen** CDI: Depression screen * P < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Non-Responders</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>13 (12–16)</td>
<td>14 (13–16)</td>
<td>12 (11.5–14)</td>
</tr>
<tr>
<td>Initial HA days/week</td>
<td>3.8 (2–7)</td>
<td>7 (2–7)</td>
<td>3 (1.5–7)</td>
</tr>
<tr>
<td>STAI Pt</td>
<td>41 (30–50)</td>
<td>45 (30–53)</td>
<td>32.5 (29–41)*</td>
</tr>
<tr>
<td>STAI Parent</td>
<td>31 (39–58)</td>
<td>34 (30–60)</td>
<td>40.5 (38–51)*</td>
</tr>
<tr>
<td>CDI Pt</td>
<td>7 (4–11)</td>
<td>10 (7–13)</td>
<td>4 (2.7–5.5)*</td>
</tr>
<tr>
<td>CDI Parent</td>
<td>9 (4–14)</td>
<td>12 (9–18)</td>
<td>7.5 (4–10)*</td>
</tr>
<tr>
<td>School Days Missed</td>
<td>7 (0–15)</td>
<td>8 (0–25)</td>
<td>7.5 (0–14)</td>
</tr>
</tbody>
</table>

**PO233**

Abdominal migraine and probable abdominal migraine – a South Indian study
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Objectives: To diagnose abdominal migraines and to document abdominal migraines lasting less than one hour duration in children.

Background: Abdominal migraines in children are not well documented in the Indian subcontinent and probable abdominal migraines are not currently recognized by ICHD2.
Methods: 87 children and adolescents aged 6 to 15 years with ICHD2 migraine headache (1.1, 1.2, 1.6) reported abdominal pain with normal abdominal examination (renal and GIT) were studied over a period of 5 years. All were examined by senior pediatricians and surgeons and ruled out other causes.

Results: All of them had central or periumbilical pain which made them motionless (activity affected) during the pain period. Only six were diagnosed as IHS 1.3.2 with a duration of more than one hour and the rest reported less than one hour (brief or probable abdominal migraines). 68 had nausea and vomiting and 19 had nausea and pallor. Anorexia was not considered diagnostic as the episodes were very short in the majority. 56 reported no triggers and 31 had triggers like hunger, certain food ingestion, exercises, bus travelling and tension anxiety situations. 88% reported family history of migraine.

Conclusions: This study concludes that in Indian subcontinent, brief abdominal migraines of less than one hour duration are more common than ICHD 2, 1.2, 3. Either probable abdominal migraine to be included in the childhood periodic syndrome diagnostic criteria or if the duration is less than one hour, known or common migraine triggers precipitating abdominal pain in migraineurs to be considered diagnostic of abdominal migraine.

PO232
Idiopathic intracranial hypertension in children with learning difficulties
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Objectives: To describe two cases of Idiopathic Intracranial Hypertension (IIH) found in children presenting to a paediatric headache clinic with chronic daily headache and learning difficulty.

Background: To our knowledge only a few previous studies have looked at an association between IIH and any form of cognitive impairment, only one of these studies was specifically in children and all looked at a population of IIH and then sought evidence of cognitive dysfunction retrospectively. The majority of the studies identified demonstrated improvements in both the headache and cognitive symptoms after treatment of IIH.

Methods: We looked at a population of 773 patients attending a paediatric headache clinic (receiving referrals from GP’s and other local general and community paediatricians) over a 4 year period and identified two patients with both IIH and learning difficulty.

Results: Of the 773 patients, 4 (0.5%) had a diagnosis of IIH, two of which (50%) had a learning disability. In total six patients from the 773 had a learning disability, 2 (33%) of whom had their headache explained by a diagnosis of IIH. The two cases appeared to show both headaches and quality of life (subjectively reported by the parents but not formally tested) to have improved after the lumbar puncture (LP), removal of CSF to a normal pressure and commencement of oral acetazolamide. Both patients had a long delay in diagnosis. One of the patients was an 8-year-old boy with spastic cerebral palsy secondary to extreme prematurity who presented with a 4 year history of headaches. MRI Brain showed periventricular leptomeningitis but was otherwise normal; delay in diagnosis was partly due to photosensitivity making fundoscopy very difficult, difficult communication and treatment attempts at differentials including migraine and analgesic overdose. Diagnosis was only made after LP. The Second patient was a 13-year-old girl with Aspergers syndrome, right sided convergent squint and extreme hypermetropia. She presented with a 1.5 year history of daily headaches following a head injury secondary to a fall which was initially believed to be the cause of the headaches. Difficulty in communication again appeared to play a part in the delay in diagnosis. MRI Brain was normal.

Conclusions: Although the numbers are too small to draw conclusions it is of interest that 1/3 (2 out of 6) of the patients with learning difficulty attending the headache clinic were found to have IIH and 1/2 (2 out of 4) of the patients with IIH had learning difficulties. Previous studies have shown an improvement in cognitive function with IIH treatment. In our series both patients were reported by parents to have an improved quality of life but no formal cognitive testing was undertaken. Communication difficulties played a part in delay in diagnosis in both cases. We believe that further research is warranted to ascertain whether children with learning difficulty without the ability to communicate symptoms of headache or with asymptomatic IIH may benefit from fundoscopy to rule out the diagnosis.
PO234
Determining the pattern of response to preventative therapy in pediatric patients with chronic daily headaches

Objectives: To determine whether preventative treatment of CDH will have a predictable time course of response by evaluating the duration of treatment before a maximal response is achieved.

Background: The prevalence of chronic daily headache (CDH) is a significant problem in the pediatric population as a major cause of disability affecting school performance and personal relationships. There are open-labeled reports on the use of preventative medications, but these are conflicting and there is insufficient evidence to determine the efficacy of preventative therapy. Thus, there are currently no standardized criteria for responses to treatment of CDH.

Methods: Over 1,400 children ≤ 18 years referred to the Headache Center at the Cincinnati Children’s Hospital Medical Center were retrospectively evaluated. Using standardized questionnaires and a semi-structured interview process, headache characteristics and response to treatment were tabulated, including headache frequency (headaches per month) and disability (PedMIDAS). Frequency reduction, defined as a 50% or greater reduction in headache frequency from initial to follow-up visits was evaluated. Follow-up evaluations were examined in 30 day intervals from 30 to ≤ 600 days. Analysis compared the fraction with a 50% or greater reduction of headache frequency in individual 30 day intervals, with all subjects seen within that same interval to determine when the response to therapy reached a plateau.

Results: At 30 days from initial visit, 33% of patients reported a 50% or greater frequency reduction. By 180 days, 64% of patients reported a 50% or greater frequency reduction. Beyond 180 days, further reductions were minimal towards additional response to preventative treatment.

Conclusions: A time course of response to preventative treatment was able to be identified. There is a trend toward progressive reduction in headache frequency over time for up to 180 days. After 180 days of preventative therapy, there is a trend towards no further reduction in headache frequency out to 600 days. This has significant implications in the identification of refractory headache patients.

PO235
Quantitative caffeine intake of adolescents upon referral to tertiary headache center
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Objectives: To attempt to quantify the amount of caffeine intake of adolescents upon referral to a headache specialty clinic and to determine if primary evaluators address the issue of caffeine.

Background: Caffeine has been used in treatment for acute headaches yet chronic ingestion of caffeine is known to cause not only withdrawal headaches but is also implicated in the development of chronic daily headache (CDH), even though the exact minimum dose to induce CDH from caffeine is unknown.1-2 A small study showed that when adolescents with CDH ingesting at least 1.5 L of cola per day have their caffeine intake tapered, all subjects’ headaches ceased or became infrequent.3 There is little to no data examining the amount of caffeine ingested amongst adolescents with headaches of all classifications. Studying not only the amount of caffeine but also whether or not the issue of caffeine use was addressed in the primary evaluation may lead to identifying factors early in the course of headache that could interfere with improvement of pain before it becomes medication overuse headache or caffeine withdrawal headache.

Methods: A survey was administered to subjects 12–17 years old upon first visit to headache center for any type of headache. Questions were asked about exact types of beverages and medications that contain caffeine including brand names of various coffee purveyors, teas, energy drinks, soft drinks, and over-the-counter pain relievers. Also assessed were the types and amount of physicians seen prior to visit as well as if they addressed the issue of caffeine. Caffeine content of items reported was researched on one website that contains all available beverages with caffeine. Categorical measures were described using frequencies and percentages. Continuous measures were summarized using means and standard deviations, as well as the median and range.

Results: Of 34 patients surveyed on first visit, the mean amount of caffeine intake was 108.4 mg/day (range 0–825 mg/day). Nineteen of these patients were diagnosed with chronic daily headache and had a mean amount of 156.9 mg/day of caffeine. The most popular form of caffeine intake was soda pop. There were a total of 60 prior medical evaluations of all 34 patients with the most common being a pediatrician (55% of all visits; 33/34 patients). The average number of prior evaluations per patient was 1.76. Only 26.5% of all prior evaluations addressed the issue of caffeine.

Conclusions: Adolescents from this study were ingesting an equivalent of what is equal to the amount of caffeine needed to induce caffeine withdrawal headache, and possibly CDH. Though caffeine as a risk factor for chronic daily headache is well known, there is still a lack of awareness of primary evaluators of headache to address the important issue of caffeine. Ideally, larger studies evaluating caffeine intake with comparison to controls would need to be completed to elucidate a minimal amount of caffeine required to induce CDH.

References:

PO236
Headache and psychiatric comorbidity in children and their mothers: a correlational study
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Objectives: Main aim is investigating the presence of psychiatric comorbidity in pediatric primary headaches and the contemporary presence of psychopathology in mothers. Secondary aim is to verify whether differences are headaches-specific and what are mothers’ perceptions of children’s problems.

Background: The genetic transmission of migraine in at least a half of cases (mainly in maternal line) is no matter of debate, such as the comorbid association of headache and anxiety/mood disorders both in children and/or adolescents and adults.

Methods: Clinical sample: 55 subjects range of 8–18 (average age 13.19) and 55 respective mothers. Thiryt-one migraineurs (19M, 12F, m.a.13.14); 21 frequent episodic tension-type headache (3 M, 18 F, m.a.13.1) and three had tension-type headache plus migraine (2 M, 1 F). Control group: 76 subjects in a range age of 8–18 (34M, 42F, M.A.12.63) and 76 respective mothers. Diagnoses according to ICHD-II and DSM-IV criteria by standard diagnostic protocol. Psychometric tools: SAFA-Psychiatric Scale for children and adolescents 8–18 years (Anxiety and Depression scales); CBCL-Child Behavior Checklist 4–18 years; MINI-Mini International Neuropsychiatric Interview (Current Major Depression (CMD), Past Major Depression (PMD), Recurrent Major Depression (RMD), non-Melancholic Major Depression (nMMD), Generalized Anxiety disorder (GAD)) (mothers). Comparisons between the two groups of frequency for MINI’s scales and sub-scales have been made by Chi-Square Test. Correlation test by R of Pearson coefficient.
Results: Most psychopathology was related to Anxiety (SAFA A $P = .039$) and Depression (SAFA D $P = .0003$), internalizing (CBCL INT $P = .001$) and externalizing problems (CBCL EST $P = .009$) in clinical sample vs controls. Results showed that the presence of disorders in patients (SAFA A;SAFA D) and the perception by their mothers (CBCL INT; CBCL EST; CBCL TOT) was associated to maternal psychopathology more in the clinical than in the control group: MINI CMD-CBCL TOT $P = .007$; MINI PMD-CBCL TOT $P = .006$; MINI RMD-CBCL TOT $P = .000$; MINI nMMD-CBCL TOT $P = .000$; MINI GAD-CBCL TOT $P = .006$. The most significant comparisons between psychopathology in mothers and their children were: MINI CMD-SAFA A TOT $P = .011$; MINI CMD-SAFA D TOT $P = .000$; MINI RMD-SAFA A TOT $P = .043$; MINI GAD-SAFA A TOT $P = .003$; MINI GAD-SAFA D TOT $P = .010$. Data showed that mothers belonging to clinical group agree more with what their children express about themselves compared to those of the children belonging to the control group (CBCL INT-SAFA A TOT $P = .01$; CBCL INT-SAFA D TOT $P = .008$). Headache children’s mothers would be more aware of their children’s problems. The presence of psychopathology in mothers and children seems to be reciprocally related, in a way not related to headache diagnoses.

Conclusions: It has been confirmed the presence of psychiatric comorbidity with internalizing and externalizing disorders in headache patients and the correlation of maternal and children’s psychopathology. The relation is not headache specific.

PO237
Evolution of chronic daily headache in children and adolescents: a 10-year follow-up study
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Objectives: Aim of the present study is to analyse the clinical evolution of Chronic Daily Headache (CDH) in a ten-year follow-up.

Background: CDH with onset in children and adolescents represents a challenge in diagnosis, etiopathogenesis and therapy. The prevalence of CDH in childhood and adolescence ranges from 0.2 to 0.9% in the general population, rising to 20–30% of all patients referring to third level centres both in adult and pediatric age.

Methods: In 1998, we enrolled 91 CDH patients (54F, 27M; m.a.11.6, SD = 2.58) according to IHS criteria (1988). In 2008, we interviewed 37 (25F, 12M; m.a.21.8, SD = 2.96) of them, according to ICHD-II criteria. The presence of medication overuse has been accurately evaluated in the first and second clinical interview.

Results: We found an overall improvement in 86.5% (32/37), a worsening in 8.1% (3/37) and unchanged in 5.4% (2/37). Sixteen patients were headache-free (43.2%), 8 (21.6%) had frequent episodic tension-type headache, 7 (18.9%) infrequent episodic tension-type headache, 5 (13.5%) chronic tension-type headache, 1 (2.7%) had migraine without aura. Most of patients improved or remitted within one-year from the first referral. No-one of patients had medication overuse in the first and second clinical interview.

Conclusions: CDH with onset has an overall good prognosis in the short period following the first visit to third level centre, with low relapsing rate over a period of ten years. Many factors may explain the good trend over time: from the global kind of intervention (medical and psychological) characterising our centre to a better prognosis for chronic headache with onset in children than adults. Further studies are compelling to look for risk factors of headache chronification and the implementation of the best treatment for such a kind of patients. Of interest the absence of medication overuse as factor involved in pediatric CDH.

PO238
Profile of pediatric headache at a tertiary-level hospital in India
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Objectives: To describe the characteristics of headache disorder among pediatric patients attending a ‘Headache clinic’ at a tertiary level pediatric hospital in India.

Background: Data on headache disorder is lacking from developing countries. This is especially true for data on pediatric headache from India.

Methods: A retrospective chart review was done for all patients attending the clinic from September 2005 (when the clinic started) to March 2007. The data was entered in a pretested structured form. Children were diagnosed as per ICHD II criteria and managed as per standard guidelines. Patients were followed monthly for initial 3-months and then 3-monthly. Performa was updated at each follow-up visit.

Results: A total of 134 new patients were evaluated during the period and follow-up data till June 2007 was analyzed. Of these 50 were excluded (irregular follow-up/did not return 28, non-compliance with headache diary 17, non-compliance with treatment/using other modalities 5) and data is presented for the remaining 84 patients [47 females; median age 8.5 years (range 3.5 years to 12 years) with at least 6 months of follow-up (median 12 month, range 6–18 month). Of these, 41 (48.8%) had migraine with/without aura (three with childhood periodic syndromes), 30 (35.7%) had TTH, seven had other primary headache disorders, and six had secondary headaches (neurocysticercosis in 3). Majority (58%) of the referrals were from pediatricians, 11 from ophthalmology, five from ENT, two from dentistry, and 17 were self-referrals. There was only one emergency-room visit for headache. Propanolol was the only drug used for prophylaxis and showed favorable results. At 6-month follow-up, headache frequency/severity was lower in 22 (28%).

Conclusions: The profile of pediatric headache was studied at a tertiary hospital in India and found to be similar to that reported from other countries.

PO239
Pet therapy: study of effectiveness on childhood headache
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Objectives: The goal of this work is to evaluate the salient features of headache patients, to whom the Pet Therapy had long-lasting benign effect.

Background: Pet Therapy effectiveness studies are rarely found in international publications, although in the common practice, also outside clinical environment, there exist very high statistics of well responding patients. Our group has been using for several years the Pet Therapy as child’s headache first choice Therapy. In several works we authored, we noticed a reduction of headache-defining parameters, as well as of associated psychological markers.

Methods: All patients which underwent Pet Therapy in 2006 have been contacted and questioned. Out of the 74 patients, 65 patients have been reached; out of the group of questioned 65, 55 patients declared to not show anymore headache symptoms. Data from 2006 clinical charts of the responding 55 patients have been reanalyzed.
PO240
Clinical presentation and morphology of the cerebral venous system in headaches precipitated by cough, exercise or sexual activity: a French multicentric study
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Objectives: We proposed a systematic exploration with a MR venography (MRV) of headaches provoked by cough, physical exercise and sexual activity.

Background: Headaches provoked by cough, physical exercise and sexual activity are included in the fourth group of the other primary headaches in the ICHD-II. These headaches have been recently studied clinically and radiologically by Pascual et al. (J Headache Pain. 2008 Oct; 9(5):259–66). The authors suggest a separation between cough headache versus headache due to physical exercise and sexual activity, and confirm that these two latter headaches are clinical variants of the same entity. Moreover, the role of cerebral venous system has been recently suggested as a pathophysiological mechanism for exertional headache (Cephalalgia. 2008 Nov; 28(11):1201–3). We proposed a systematic exploration with a MR venography of headaches provoked by cough, physical exercise and sexual activity.

Methods: Cerebral MRI and MRV were performed for all patients. Two neuroradiologists (PL, OL.), unaware of clinical data, realized an evaluation of MRV imaging in this population and gave description of the venous morphology. The transverse sinus and jugular veins were scored using the following grading system: normal, stenosis < 50%, stenosis > 50%, thrombosis.

PO241
Classification of abrupt onset chronic daily headache (CDH): revised criteria for new Daily-Persistent Headache (NDPH)
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Objectives: To compare patients with abrupt onset primary CDH of long duration meeting ICHD-2 criteria for NDPH with those who have too many migraine features to qualify.

Background: NDPH is a form of primary CDH with an abrupt onset as its hallmark. ICHD-2 requires headache that ‘is daily and unremitting from onset or from <3 days from onset’ (B) with the pain features of tension-type headache (C) and no more than one of photophobia, phonophobia and mild nausea (D). This defines NDPH as the abrupt onset of unremitting headache similar to chronic tension-type headache. In clinical practice many patients with abrupt onset CDH have migraine features, making classification difficult.

Methods: Retrospective case series in a tertiary headache center. Patients were diagnosed with NDPH using ICHD-2 criteria. An additional group that met criteria A, B and E but not both C and D were also identified (NDPH-minus). We compared NDPH and NDPH-minus groups in demographics, clinical features and prognosis. Three prognostic groups were included: (1) persistent form with continuous headache from onset, (2) remitting form with <5 days of headache per month for >3 months and (3) relapsing-remitting form with periods of continuous headache interspersed with remissions.

Results: Of 70 patients with primary CDH of abrupt onset 42.9% (n = 39) fulfilled ICHD-2 criteria while 57.1% (n = 40) met criteria for NDPH-minus. Both NDPH and NDPH-minus usually began in adulthood (mean onset age: 35.3 vs. 26.9 years) and were more common in women (60.0% vs. 82.5%) and Caucasians (83.3% vs. 77.5%). A positive family history of frequent headache in a 1st degree relative (53.3% vs. 45.0%), ability to recall the precise onset date (46.7% vs. 40.0%) and a specific onset trigger (43.3% vs. 50.0%) were also similarly common. Coexisting anxiety and depression were more common in NDPH-minus (anxiety: 40.0% vs. 23.3%, depression: 45.0% vs. 20.0%). In NDPH-minus, 20.0% were missing just criterion C, 40.0% were missing just criterion D and 40.0% were missing both criteria. NDPH and NDPH-minus had similar distribution of outcomes: persistent form (76.7% vs. 75.0%), remitting form (13.3% vs. 17.5%) and relapsing-remitting form (10.0% vs. 7.5%). In the persistent form, NDPH-minus had a longer median duration than NDPH (31 months vs. 18 months).
Conclusions: Of our patients with abrupt onset primary CDH, less than half met ICHD-2 NDPH criteria. The NDPH-minus group has migraine-like features that prevent classification. The NDPH and NDPH-minus groups were similar in demographic profile and prognosis. The NDPH-minus group had higher rates of coexisting anxiety and depression, possibly suggesting a biological link to migraine. To improve understanding of abrupt onset primary CDH we recommend: 1) expanding the NDPH criteria to include individuals with and without migraine features and 2) exploring subtypes defined by the presence and absence of migraine features, treatment response, comorbidities, prognosis and family history.

PO242
Prognosis in new daily-persistent headache: persistent, remitting, and relapsing-remitting subforms
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Objectives: To assess the long-term prognosis of new daily-persistent headache (NDPH) and identify subforms in patients presenting to a tertiary headache center.

Background: NDPH is a form of chronic daily headache, initially thought to be a self-limited disorder. Subsequent clinical experience has demonstrated that the prognosis is variable and that some patients are refractory to treatment.

Methods: Retrospective case series in a tertiary headache center. Patients were diagnosed with NDPH-minus if they met criteria A, B and E of the 2nd edition of the International Classification of Headache Disorders (ICHD-2). We identified 3 temporal profiles for NDPH: 1) a persistent form with continuous headache from the onset, 2) a remitting form with either a complete remission of the continuous headache or with residual headache occurring less than 5 days per month for at least 3 months, and 3) a relapsing-remitting form, defined by periods of continuous headache interspersed with pain-free periods.

Results: Of 70 patients fulfilling criteria for NDPH-minus, the persistent form was most common (n = 53, 75.7%), with a median duration of continuous headache of 24 months. Remission occurred in 15.7% (n = 11), at a median interval of 21 months, and 63.6% of remissions occurred within 2 years. A relapsing-remitting pattern occurred in 8.6% (n = 6), with a median time to first remission of 5.5 months. None of the patients with the relapsing-remitting subform and 90.9% of the remitting subform were on preventive medications when their continuous headache pattern broke.

Conclusions: NDPH patients can be divided into three prognostic subsets: persistent, remitting, and relapsing-remitting. The majority of NDPH patients seeking care at a tertiary headache center have the persistent subform, although around 24% will have either relapsing-remitting or remitting subforms. Patients with NDPH who do not remit within months of onset can be counseled that remission may occur within 2 years. Predictors of prognosis for these three subgroups will be performed in future studies.

PO243
The prevalence of typical aura without headache in Japan: a questionnaire study
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Objectives: The aim of study is to investigate the prevalence and characteristics of TAWH in a setting of ophthalmology clinics in Japan.

Background: Typical aura without headache (TAWH) has been diagnosed according to the operational diagnostic criteria of The International Classification of Headache Disorders (ICHD-II). It is reported that the prevalence of TAWH was 0.2%. However, it is not known prevalence and characteristics of TAWH in Japan.

Methods: This study was conducted from April 2007 to June 2008 at seven ophthalmology clinics, one University Hospital and six ophthalmology clinics in Kanto area in Japan. The study was performed by questionnaire according to ICHD-II. The study was approved by institutional review boards appropriate for each investigator. We distributed a self-report questionnaire comprising seven (ID migraine screener Japanese version and additional six questions) items that could be used for classification of headaches according to ICHD-II for all patients, and collected their responses. The additional items included questions for the presence or absence aura of headache, its frequency, duration and past history of cerebrovascular disease.

Results: Of 1,914 cases, the numbers of the valid answers were 1,063 cases (55.5%). There were 1063 outpatients including 348 male and 715 female patients. There were 81 patients of 1063 outpatients were positive and 982 patients were negative in ID migraine screener Japanese version. Among negative cases, 356 cases have aura. There were 35 patients (3.2%) who were diagnosed TAWH. Of these, as for the age, 23–87 years old, the median age were 47 years old with 12 males, 23 females. There were 67 patients (6.3%) who were diagnosed migraine with aura (MWA), there were nine males and 58 females, aged 22–89 years, and the median age was 42 years old.

Conclusions: In our data the prevalence of TAWH was 3.2% in ophthalmology clinics in Japan. In addition, the numbers of patients with TAWH showed two peaks in the age distribution. These data suggest that TAWH is not rare headache type in clinics especially in a setting of ophthalmology clinics, and MWA may transform to TAWH by aging.
PO244
Normal visual evoked potentials habituation in chronic daily headache with medication overuse
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Objectives: We test here, for the first time, in a group of MOH patients the habituation of the visual evoked potentials, reflecting bioelectrical activity of the visual cortex, an area unrelated to pain matrix.

Background: Episodic migraineurs during the interictal phase are characterized by lack of habituation during stereotyped stimulus repetition with different sensory modalities. We recently observed that migraine patients evolved in chronic daily headache due to medication overuse (MOH; ICHD-II 8.2) showed a lack of habituation in somatosensory cortex.

Methods: We recorded VEPs (600 sweeps, 15 minute of arc checker-board, 3.1 reversal rate, 80% contrast) in 11 healthy subjects and in 14 age and gender matched MOH patients. Habituation of the visual EPs was defined as the % change of the N1-P1 amplitude between the 1st and 6th block of 100 averaged responses.

Results: No significant differences were observed in single block amplitudes and latencies. Moreover, during the continuous stimulation VEPs habituated normally across the six consecutive blocks in both groups (mean percentage amplitude change -12.8 in HS and -12.5% in MOH).

Conclusions: These results are not in favour of a lack of habituation of the visual cortical responses in medication overuse headache patients. Whether this normal behaviour is due to daily headache of the visual cortical responses in medication overuse headache (MOH).

Conclusions: These findings provide neurophysiological evidence showing that excessive medication overconsumption induces normalization of the cortical motor inhibitory neurons underactivation found in episodic migraine interictally.

PO246
Physician diagnosis of probable migraine after education and use of a structured interview
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Objectives: To assess physician diagnosis of probable migraine without aura (ICHD-II 1.6.1) following education and use of a structured interview.

Background: Probable migraine (PM) is a prevalent and disabling migraine sub-type which meets all but one of the four major criteria: frequency, duration, pain features, or associated symptom features (ICHD-II 1.6.1). PM is under-diagnosed and under-treated, even in individuals who have access to medical care [Bigal, 2006].

Methods: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating subjects with ≥6 months of moderate to severe PM lasting ≥4–72 hours was conducted in 53 centers (~ equal ratio of headache specialists to PCPs). Investigators participated in ICHD-II Diagnostic Criteria educational sessions on epidemiology of and impact of PM, delineation of PM from tension-type headache and migraine using diagnostic criteria, and review of case histories. Investigators were also trained to use a structured headache (HA) history interview (duration, frequency, severity, and symptomatology assessment) to allow for consistent evaluation. Subjects were excluded if they had a previous or current migraine diagnosis, or had ever used a triptan or an ergot. Eligible subjects were randomized to SumaRT/Nap or placebo, provided study drug and an electronic diary (e-Diary), and were instructed to treat their next PM. Data was entered in the e-Diary each time the subject thought the HA may be PM to determine whether it was a qualifying HA, i.e. a moderate-to-severe PM without aura.

Results: Using a structured interview, 679 subjects were diagnosed with PM without aura at screening. Based on a review of features reported in the clinical assessment 675 of 679 (99%) were correctly diagnosed (4 misclassified: 1 migraine, 3 “likely tension”). Most subjects described their PM as a “tension/stress” HA (54%) or “sinus” HA (24%). One “likely tension” subject (1/443 of the ITT Population) took study drug. At screening, subjects characterized their HAs with PM lasting 4–72 hours was conducted in 53 centers (~ equal ratio of headache specialists to PCPs). Investigators participated in ICHD-II Diagnostic Criteria educational sessions on epidemiology of and impact of PM, delineation of PM from tension-type headache and migraine using diagnostic criteria, and review of case histories. Investigators were also trained to use a structured headache (HA) history interview (duration, frequency, severity, and symptomatology assessment) to allow for consistent evaluation. Subjects were excluded if they had a previous or current migraine diagnosis, or had ever used a triptan or an ergot. Eligible subjects were randomized to SumaRT/Nap or placebo, provided study drug and an electronic diary (e-Diary), and were instructed to treat their next PM. Data was entered in the e-Diary each time the subject thought the HA may be PM to determine whether it was a qualifying HA, i.e. a moderate-to-severe PM without aura.

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Conclusions: Probable migraine, a sub-type of migraine, may go unrecognized by clinicians. Undiagnosed patients with probable migraine may receive suboptimal care for this disabling and prevalent form of migraine. These data suggest that education on probable migraine diagnostic criteria and the utilization of a structured interview enabled both specialists and non-specialists to successfully diagnose subjects with probable migraine. Headache diaries provided useful confirmation and diagnostic refinement after the initial patient evaluation.

PO247
New daily persistent headache in the general population. The Akershus study of chronic headache
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Objectives: To investigate the prevalence of new daily persistent headache (NDPH) in the general population, and compare the clinical characteristics of NDPH and chronic tension-type headache (CTTH).

Background: There is need for population-based studies on NDPH. A population based cross-sectional study. A random sample of 30,000 persons aged 30–44 years was drawn from the population of eastern Akershus County, Norway. A postal questionnaire screened for chronic headache, 633 with self-reported chronic headache (≥15 days) within the last month and/or year were invited to an interview and examination by a neurological resident. A follow-up interview was conducted after 1 1/2 to 3 years. The headaches were diagnosed according to the International Classification of Headache Disorders, 2nd edition 2004 (ICHD-II) and relevant revisions.

Results: The response rate of the questionnaire was 71% and the participation rate of the interview was 74%. Four persons, three men and one woman had NDPH. The overall one-year prevalence of NDPH was 0.03%. The clinical characteristics of NDPH and CTTH were similar, except for the sudden onset in NDPH. Three of the four persons with NDPH had medication overuse. The follow-up disclosed that the symptomatology of NDPH improved in two persons.

Conclusions: NDPH is rare in the general population and is often associated with medication overuse.

PO248
Mood disorders of medication-overuse headache in Japanese patients
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Objectives: The aim of the present study was to evaluate and characterize psychiatric comorbidity in patients with medication-overuse headache (MOH).

Background: The importance of psychiatric comorbidity in migraine has long been recognized. There is a growing body of evidence that these psychiatric comorbidities share diverse epidemiological properties, pathophysiological mechanisms, and treatment response. The prevalence of psychiatric comorbidities is high in patients with MOH.

Methods: This prospective study included 30 patients [mean age 41.5 ± 16.5 (mean ± SD) years (range, 41–71)]. MOH was diagnosed based on new appendix criteria open for a broader concept of chronic migraine in all subjects. The first control group consisted of 15 patients diagnosed with endogenous depression. The second control group consisted of 70 patients diagnosed with migraine without MOH (migraine with aura migraine without aura). For the diagnosis of depression associated with MOH and second control group, we used the MINI based on the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV). Based on the results, we determined the &SH#12456; each prevalence rate of depression, and also determined each risk factor (age and gender) of MOH-related depression in MOH as markers of MINI. In addition we estimated the depression of migraine without MOH by same procedure in MOH. Furthermore we examined Hamilton Depression Scale (HAM-D17) for Group of MOH-related depression and group of endogenous depression (first control group), and we compared MOH-related depression and depression using items of HAM-D17 to evaluate these character differences.

Results: According to use of these neuropsychological tests, the prevalence of Depression was 60% and females were at higher risk of than males in MOH. On the other hand, only 3% of patients with migraine without MOH had depression. The characteristic of MOH-related depression and endogenous depression was almost common, but “anxiety, somatic” was tended to be stronger in MOH-related depression. These results suggested that mood disorders in MOH are similar to those in endogenous depression but different from those of secondary mood disorders associated with other diseases. Suspicion of depression and intervention are essential for providing medical care for patients with MOH.

Conclusions: Affective disorders diagnosed in migraine patients might later progress to MOH. In contrast, migraine patients without MOH had similar prevalence of mood disorders in the healthy subjects.

PO249
Hemicrania continua and unilateral chronic migraine indometacin negative: A clinical comparison study
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Objectives: The aim of this study was to perform a clinical comparison between patients with hemicrania continua and those with unilateral chronic migraine, in order to identify any clinical pointers to differentiate the diagnoses.

Background: HC is an uncommon primary headache characterized by unilateral continuous pain responsive to indometacin. Migrainous features are common in HC and the differential diagnosis between HC and unilateral chronic migraine can be challenging.

Methods: Patients with unilateral head pain were identified at the National Hospital for Neurology and Neurosurgery from 1995 to 2008 and attended the outpatient department between 2004 and 2008. The data were obtained from the clinical notes and by information received by direct interview and/or by telephone. Clinical features of 27 patients with HC were compared with those of 27 age- and sex-matched with CM. The study was approved by the Ethics Committee.

Results: Eight patients were male and 19 were female. In the CM, 20 (74%) had throbbing pain. 24 (89%) had one or more cranial autonomic symptoms with exacerbations. Cranial autonomic features included 15 (55%) forehead/facial flushing, bilateral in 8 (53%), 13 (48%) lacrimation, bilateral in 4 (30%), 12 (44%) ptosis, bilateral in 1 (8%), 11 (40%) forehead/facial sweating, bilateral in 8 (72%), 10 (37%) conjunctival injection, bilateral in 4 (40%), 9 (33%) peri-orbital swelling and gritty eye, bilateral in 2 (22%), 8 (30%), rhinorrhea and sense of aural fullness, 7 (26%) nasal congestion. Phonophobia in 24 (89%), unilateral in 10 (41%), photophobia in 21 (78%), unilateral in 8 (38%), nausea/vomiting in 17 (63%) and
Response of primary stabbing headache to Occipital Nerve Stimulation (ONS)

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Objectives: Finding support for novel therapies for medically intractable primary stabbing headache.

Background: Primary stabbing headache is a neurological disorder that can be very disabling. In a considerable number of patients it coexists with other primary headache conditions. Pharmacological therapy is mainly limited to Indomethacin, which is not universally effective, or may cause unacceptable side effects, or both. Stimulation of the Greater Occipital Nerve is a relatively novel therapy showing promising efficacy results, good tolerability and low risk profile. Its effects have been reported in a number of primary headache syndromes, for patients failing drug therapies.

Methods: The response to ONS was recorded in four patients with primary stabbing headache, to whom the therapy was initially offered for co-existing primary headache conditions (two patients with hemicrania continua and two patients with migraine), as part of clinical trials. The treatment was administered via three different types of neurostimulation devices, ipsilateral to the pain (two patients) or bilaterally (two patients).

Results: Following ONS therapy the primary stabbing headache markedly improved (one patient with migraine) or stopped (three patients). The headaches reoccurred in all patients at times when the neurostimulation was interrupted deliberately or due to device malfunction. In one patient with bilateral migraine pain receiving optimal ONS only on the side ipsilateral to the primary stabbing headache, the stabbing pain almost ceased on the stimulated side, eventually being noted on the contralateral side, where it had never been reported prior to neurostimulation. No improvement of the migraine headache was noticed for this patient. The two patients with coexisting ipsilateral hemicrania continua did not experience any primary stabbing headache attacks on the non-stimulated side.

Conclusions: Our observations indicate that ONS may be a promising therapeutic approach for certain patients with primary stabbing headache, which can be effective even when coexisting headache conditions are not equally well controlled by the ONS. It is also possible that the primary stabbing headache is side-locked when occurring ipsilaterally to another headache condition in which side variation is unlikely; however when occurring in patients with coexisting non-side-locked headache conditions (such as migraine) the pain may migrate to the untreated side; further work will be required to support and understand better these potential characteristics and the interaction between ONS and primary headaches.

PO251
Four patients with occipital neuralgia with trigeminal autonomic activation

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Objectives: Case report of four patients with occipital neuralgia (ON) with trigeminal autonomic activation at the same side. This association has not been described in the literature.

Background: Occipital neuralgia (ON) is a paroxysmal jabbing pain in the distribution of the greater or lesser occipital nerves or of the third occipital nerve, sometimes accompanied by diminished sensation or dysesthesia in the affected area. It is commonly associated with tenderness over the nerve concerned. Cranial autonomic symptoms such as lacrimation, conjunctival injection, nasal congestion, rhinitis, eyelid oedema, ptosis and miosis, reflect excessive cranial parasympathetic cranial autonomic reflex activation and sympathetic dysfunction, associated with the stimulation of trigeminal cervical complex, and they are the clinical mark of the “Trigeminal Autonomic Cephalalgias” (TACs). According to the IHS classification/2004, the Trigeminal Neuralgia is the only cranial neuralgia which presents with autonomic activation (lacrimation) after a paroxysmic neuralgic pain. We report four cases with concomitance of ON and ipsilateral trigeminal autonomic symptoms, which is not found in the literature. We also discuss briefly the clinical features of these curious entities, as well the possible pathophysiology involved in the autonomic activation of these patients.

Methods: Retrospective analysis from a total of 1800 outpatients in our headache clinic. 14 patients with diagnosis of ON according to IHS-2004 diagnostic criteria. 4 patients with ON and trigeminal autonomic activation.

Results: Four patients in the outpatient clinic headache with occipital neuralgia and trigeminal autonomic activation that clinical and neurological examinations were normal. Cranial and cervical spine magnetic resonance imaging were normal.

Conclusions: Kerr and Olafson were the first to suggest a convergence between trigeminal and cervical afferents; however a direct coupling between meningeal afferents and cervical afferents was not described in animal model until recently and further extended to human data. It was shown that a population of nociceptive second-order neurons in the C2 dorsal horn receives convergent synaptic input from the trigeminal innervated supratentorial dura mater and from cervical afferents within the greater occipital nerve3. The ON not secondary to structural process still is a intriguing entity and few studies have been made about it. Maybe ON have been subdiagnosed or not always remembered. We believe that association between ON symptoms and cranial autonomic activation present an important anatomic role in the ON physiopathology.

PO252
Chronic headaches: clinical features and treatment outcome at 1-year follow-up

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Objectives: The aim of our study was to compare clinical characteristics of chronic headaches and treatment outcome at 1-year follow-up...
PO253

Subject recognition of probable migraine
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Objectives: To assess subject recognition of probable migraine without aura after investigator diagnosis, to describe the characteristics of probable migraine, and to assess diary influence on overall diagnostic evaluation.

Background: Probable Migraine (PM) is a prevalent and disabling migraine subtype which meets all but one of the four major criteria: frequency, duration, pain features, or associated symptom features (ICHD-II 1.6.1). Contrary to what many patients seeking medical care believe, episodic, disabling headache is typically migraine or probable migraine (Tepper 2004). Recently, it was reported that submucosal and naproxen sodium (SumaRT/Nap) was efficacious and generally well-tolerated in probable migraine (Silberstein 2007).

Methods: A multicenter, randomized, double-blind, placebo-controlled, 6-month parallel-group study of subjects with 26 months of moderate to severe PM lasting 24–72 hours, was conducted. Subjects were excluded if they had a previous or current diagnosis of migraine (ICHD-II 1.1 or 1.2), or had ever been prescribed a triptan or an ergot derivative. Subjects’ headaches were diagnosed using a structured interview, and eligible subjects were randomized to SumaRT/Nap or placebo and educated on PM and on headaches that should not be treated. Subjects were instructed to enter data into an e-Diary for headaches they thought were PM and treat the first headache and provided post-treatment data (Intent-to-Treat Population; ITT). For subjects who entered any diagnostic data, 87% (451/517) were able to recognize an attack meeting criteria for PM, with 75% (386/517) doing so on the first or second attempt. ITT subjects characterized their headaches at treatment baseline as pulsating/throbbing or pounding pain (66%), bilateral pain (59%), moderate intensity (69%) and absent nausea/vomiting (95%), photophobia (77%) or phonophobia (74%). Sixty-six subjects (13%) were unable to identify a PM attack. E-Diary data for these subjects showed that 80% (53/66) had migraine, 14% (9/66) had tension-type headaches; and 6% (4/66) had both migraine and tension-type headaches.

Conclusions: These data suggest that patient education can result in successful recognition and treatment of probable migraine and that headache diaries may serve as educational tools, as well as to confirm and refine diagnosis. Further, these results support previous findings that “pure” tension-type headache is rare in the clinic and over-recognized by patients. Physician and patient education, with periodic monitoring of diaries, is recommended to most accurately diagnose and treat probable migraine.
PO255
Nummular headache: a case series from a district general hospital
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Objectives: To highlight that nummular headache may not be as rare as previously thought and is not infrequently referred to outpatient neurology. Improved knowledge of the features of nummular headache may improve diagnostic certainty.

Background: Nummular headache is thought to be a rare primary headache disorder characterised by pain and sensitivity in a localised area of the scalp, possibly representing sensitivity of terminal trigeminal nerve fibres.

Methods: I report a retrospective series of 11 new cases seen over a 14 month period at a district general hospital neurology clinic. Data was obtained from outpatient hospital records.

Results: Nummular headache occurred in 8 men and 3 women. Mean age of onset 48 years, mean diameter of area of pain 4cm. Most patients described a background mild pain with exacerbations lasting from seconds to days triggered by factors ranging from stress to cold wind and brushing hair. In 6 patients the pain was in a unilater al parietal area, 2 midline over the vertex, 1 occipital, 1 temporal and 1 frontal. 7 had altered sensation, typically hyperaesthesia, over the painful area.

Conclusions: Nummular headache may be more common than previously thought and may be an underdiagnosed entity commonly presenting to outpatient neurology.

PO256
Primary pain on the vertex: successful treatment with botulinum toxin A
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Objectives: Our interest lies in the effective treatment tools for primary POV as well as pathophysiologic mechanisms related to POV. The present study was designed to investigate the effectiveness and the safety of botulinum toxin type A (BTX-A) in the treatment of primary POV.

Background: Pain on the vertex (POV) is a commonly presented symptom in headache clinics. However, as far as we know, there have been few studies on this type of headache. POV was observed in several primary headaches including migraines and tension-type headaches. POV related to primary headache was optionally classified as the primary POV for convenience. We found that several underlying factors had roles in the development of primary POV. These included sleep deprivation, stress, anxiety, depression, cold beverages, scalp traction, scalp compression, and others. POV can also develop secondarily with underlying primary disorders such as vertex meningioma, sphenoidal sinusitis, cervical disorders, sickle cell disorders, angina pectoris, epidermal hematomas, subdural hematomas, brain tumors, pseudoaneurysms of the occipital artery, Chiari type 1 malformation, occipital condyle syndromes, primary calvarial menigiomas, Paget’s disease of the skull, scalp malformations, hemi-modalities, and others.

Methods: This open-labelled study was designed to investigate the effectiveness of BTX-A for the treatment of primary POV. Forty-four patients with primary POV were enrolled. 100 Units of BTX-A (Dysport) were injected at 6 distinct points of the vertex once a month for 3 months.

Results: Thirty-five out of 44 (79.5%) cases showed moderate to dramatic improvements after 3 months of consecutive treatments. Two patients complained about post-injection pain; however, these symptoms resolved themselves within a few days.

Conclusions: This study showed that BTX-A was a safe and effective treatment for primary POV.

PO257
Benign paroxysmal vertigo accompanied with migraine in adult
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Objectives: Although paroxysmal vertigo in childhood is well known to change to migraine by age, similar vertigo in adult has not been examined in much detail. We report such 10 cases.

Background: Totally 10 cases; one male and 9 females. The age ranged from 29 to 77 years old with the mean of 55.5 ± 14.8. The affected period of migraine was from 9 to 52 years with the mean of 35.1 ± 13.2.

Methods: We examined these patients mainly about vertigo clinically.

Results: The appearance of vertigo was from 7 to 49 years with the mean of 29.1 ± 11.2 years after the onset of migraine. The frequency of vertigo was from 2 to 6 times per year. The severity of vertigo was strong, and all patients were forced to keep lying down. The vertigo was episodic and continued from 8 to 72 hours. All patients showed photophobia and phonophobia upon a vertigo attack. Prognosis was gradual decrease in the frequency and stopped with aging in 3 cases.

Conclusions: Such vertigo was episodic and accompanied with photophobia and phonophobia, and almost an equal duration of attacks of both headache and vertigo. We thought these patients could be diagnosed as paroxysmal vertigo in adulthood.

PO258
Exploration of the relationship between presence or absence of aura to response and tolerability after treatment with Sumatriptan 85 mg formulated with RT Technology/Naproxen Sodium 500 mg (SumaRT/Nap) for the early intervention treatment of migraine
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Objectives: To evaluate the relationship between presence or absence of aura to responsiveness and tolerability to early intervention treatment of migraine with SumaRT/Nap.

Background: While the efficacy and tolerability of many migraine treatments have been heavily studied, far less research has focused on factors predictive of treatment response. Diener (2004) and colleagues evaluated possible predictors of response to sumatriptan and found that the association of aura with a treated attack was a predictor of lower 2 hour pain-free response. Given this, it is plausible that the presence or absence of aura may impact response to, and/or tolerability of, SumaRT/Nap.

Methods: The relationship between the presence or absence of aura during an attack and tolerability/response to treatment was evaluated using a dataset encompassing eight early intervention SumaRT/Nap trials including: TRX101998, TRX101999, TRX103632, TRX103635, TRX106571, TRX106573, TRX105850, and TRX105852. Response to treatment was assessed using 2 hour pain-free or 2–24 hour sustained pain-free outcomes. Tolerability was evaluated using “percent of subjects with at least one drug-related AE”, “percent of subjects with at least one adverse event (AE)”, “percent of subjects with at least one drug-related AE”, and “percent of subjects with at least one severe AE”. For trials treating multiple attacks, only data from the first treated attack were included. Statistical significance was set at P ≤ 0.05; P-values were not adjusted for multiple comparisons.

Results: Across the 8 studies, 2204 subjects provided information as to the presence or absence of aura for a treated attack. For subjects whose attacks were associated with aura, 40% (170/420) were pain-free at 2 hours after treatment as compared to 48% (863/1784) of subjects whose attacks were not associated with aura. This difference was statistically significant (P = 0.002). For sustained pain-free, 32% of subjects (136/420) whose treated attacks were associated with aura
achieved pain-freedom from 2–24-hours, as compared to 37% (668/1784) for those whose attacks were not associated with aura. This difference was statistically significant (P = 0.043). The percentage of subjects with at least one AE (12% vs. 13%, with and without aura, respectively), with at least one drug-related AE (9% vs. 10%), and with at least one severe AE (1% vs. 2%) were similar among the groups.

Conclusions: Findings from the current analysis support those of Diener et al. and suggest that the presence or absence of aura associated with a migraine can impact SumaRT/Nap response, although not tolerability. These findings may provide insight into the pathophysiology of migraine with aura and may also be useful to know when prescribing an acute migraine medication treatment.

PO259
CGRP and CGRP receptor distribution in the human trigeminal ganglion
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Objectives: We designed this study to evaluate the localization of CGRP and its receptor components calcitonin like receptor (CLR) and receptor amplifying peptide 1 (RAMP1) in the human trigeminal ganglion.

Background: The trigeminal ganglion contains the cell bodies for the bipolar neurons that project peripheral to the intracranial vasculature and central to the trigemino-cerebral complex in the brain stem with Ad- and C-fibers; this constitutes an essential part of the pain pathways activated in migraine attacks. A large part of these fibers contain calcitonin gene-related peptide (CGRP) as neuronal messenger. The recent development of CGRP antagonists has opened a new option in migraine therapy. However, it remains unclear where the CGRP signaling mechanisms are located in the human trigeminal system.

Methods: The indirect immunofluorescence method with antibodies against human CGRP, CLR and RAMP1 was used and the number of cells expressing each was measured. Double immunolabelling was performed to evaluate neurons that express CGRP and the CGRP receptors parts. In addition, the majority of cells in the trigeminal ganglion are glial (>90%); the relation to these were studied using a marker for glial cells.

Results: We observed immunoreactivity for CGRP, CLR and RAMP1 in the neurons. There were a high number of CGRP-expressing neurons while the expressions of the receptor parts were less. There were no CGRP immunoreactions in the glial cells; however, some glial cells showed CGRP receptor elements.

Conclusions: We conclude that the human trigeminal neurons store CGRP, CLR and RAMP1. Our results indicate the possibility of CGRP signaling in the human trigeminal ganglion involving both neurons and glial cells; this suggests a possible site of action for the novel CGRP receptor antagonists in migraine therapy.

PO260
Parameters for light aversive behavior and initial neuroimaging studies in a murine migraine model sensitive to CGRP
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Objectives: To evaluate new parameters of light aversive behavior and develop neuroimaging techniques to identify important brain regions involved in the light aversion of a transgenic mouse sensitive to CGRP.

Background: In migraine, the underlying pathophysiology is poorly understood; however, a significant role for calcitonin gene-related peptide (CGRP) is emerging. In two key clinical studies, peripheral injection of CGRP induced a delayed migraine-like headache in migraineurs, but not in non-migraineur subjects. This suggests that migraineurs may be more sensitive to CGRP. As a key neuropeptide in the trigeminovascular system, CGRP is involved in nociception, vasodilation, and neurogenic inflammation. The CGRP receptor is an unusual receptor consisting of the receptor activity modifying protein 1 (RAMP1) subunit, which is required for CGRP binding. To study the effects of heightened CGRP sensitivity, we used a tissue specific Cre-mediated inducible strategy to generate transgenic mice that overexpress human RAMP1 (hRAMP1) in the nervous system. Previous work has established that hRAMP1 transgenic mice demonstrate enhanced light aversive behavior and mechanical allodynia in response to CGRP. These behaviors reflect photophobia and sensitivity to touch, which are common migraine symptoms.

Methods: In the light aversive behavior assays, mice are subjected to a light/dark box, which is an open field divided into two zones, thirty minutes after intracerebroventricular CGRP administration. Initial characterization of the light aversive behavior focused on time spent in the light. We have now conducted further analyses and studies that allow for evaluation of several additional parameters including: transition between zones, latency to enter a zone distance traveled, and average velocity. To identify the neuronal regions responsible for the light aversive behavior, we have conducted preliminary neuroimaging using microPET, microMRI, and autoradiography.

Results: Previous work has established that hRAMP1 mice spend less time in light in response to CGRP. Analysis of new parameters demonstrates that, in response to CGRP, hRAMP1 mice showed fewer transitions between the zones and delayed reentries into the light after initially entering the dark. Preliminary analysis of PET images suggests that hRAMP1 mice have an overall decrease in fluorodeoxyglucose (FDG) uptake in the brain following CGRP.

Conclusions: Results from these new parameters confirm the robust light aversive phenotype of the hRAMP1 mice. It is unclear whether the decrease in FDG uptake reflects a functional decrease in brain metabolism or decrease in blood flow due to CGRP induced vasodilatation. However, additional imaging should provide regional targets for future studies and potential correlations with clinical findings. Behavioral and preclinical imaging results will begin to elucidate the mechanisms underlying the CGRP-induced light aversion.

PO261
Common denominator in chronic migraine and fibromyalgia
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Objectives: To explore the central mechanisms of chronic pain such as chronic migraine (CM) and Fibromyalgia (FM), using a novel approach – adapted diffusion tensor imaging (aDTI).

Background: There has been a focus on exploring the central mechanisms of chronic pain such as chronic migraine and Fibromyalgia in current research and new medication development. aDTI is a novel approach that detects neural activity in the white matter fiber tracts in the brain. Although DTI is best known as a white matter structural imaging tool, we have been able to expand its capabilities in functional brain imaging. aDTI allows us to map baseline neural activity in brain white matter. It is fundamentally different from fMRI that relies on blood flow as an indirect measure of brain activation. In contrast, aDTI determines axonal conduction of neural impulses by capturing changes in water diffusion through channel proteins, a phenomenon that accompanies the ion flux of the action
PO263
Chemical activation or inactivation of the Dopaminergic A11 cell group affects neuronal transmission in the trigeminocervical complex
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Objectives: To investigate the effect on trigeminovascular transmission of chemical activation or inactivation of the A11 nucleus in the rat.

Background: It is thought that activation of primary afferents to the spinal trigeminal nucleus is involved in migraine pain, and that dopamine may play a modulatory role in this. The A11 nucleus, located in the posterior hypothalamus, provides the only known source of descending dopaminergic innervation for the spinal grey matter. We have previously found that electrical stimulation in the A11 region inhibited nociceptive evoked firing of the trigeminal nerve, whilst electrical lesioning of the A11 facilitated nociceptive and non-nociceptive trigeminal evoked firing. We aimed to further understand the physiology of the A11 nucleus by performing chemical analyses, in which the A11 was modulated by microinjection of specific drugs into the nucleus.

Methods: Extracellular recordings were made in the trigeminocervical complex (TCC), in response to electrical stimulation of the middle meningeal artery (15V, 0.3–0.5ms, 0.5Hz), and cutaneous receptive field characterisation of the ophthalmic dermatome. After recording baseline firing, the following drugs were microinjected into the A11, and the effect on firing determined: L-glutamate (5 mM; pH 7.4; 250 nL), GABA (10 mM; 250 nL), GABA\(_A\) agonist muscimol (10 nmol; 250 nL) or orxsin 1 antagonist (1 mM; 420 nL).

Results: Microinjection into the A11 of L-glutamate and orxsin A significantly inhibited dural MVA and cutaneous noxious pinch evoked firing of neurons from the TCC. L-glutamate inhibited MVA evoked firing by 27 ± 3% (F\(\_2,5\)\(,\)12\(,\)6 = 5.01; P < 0.05; n = 6) from 5 to 40 minutes, and noxious pinch evoked firing by 24 ± 3% (F\(\_2,9\)\(,\)14\(,\)6 = 2.57; P < 0.05; n = 6) from 10 to 30 minutes. Orexin A inhibited MVA evoked firing from 10 to 40 minutes by 20 ± 3% (F\(\_2,4\) = 2.46; P < 0.05; n = 8), and noxious pinch evoked firing from 5 to 40 minutes by 16 ± 2% (F\(\_4,6\)\(,\)4 = 2.32; P < 0.05; n = 8). Microinjection into the A11, of lidocaine and orexin1 antagonist significantly facilitated MVA, noxious pinch and innocuous brush evoked firing of neurons in the TCC. Lidocaine facilitated MVA evoked firing by 12 ± 3% (F\(\_3,4\)\(,\)16\(,\)5 = 4.98; P < 0.05; n = 6), noxious pinch by 37 ± 3% (F\(\_2,6\)\(,\)13\(,\)0 = 4.11; P < 0.05; n = 6) and innocuous brush by 51 ± 7% (F\(\_2,11\)\(,\)2 = 3.04; P < 0.05; n = 6) over a 40 minute period. Orexin 1 antagonist facilitated MVA evoked firing by 27 ± 5% (F\(\_2,4\) = 2.51; P < 0.05; n = 8) from 10 to 40 minutes, noxious pinch by 29 ± 4% (F\(\_3,3\)\(,\)1 = 2.23 P < 0.05; n = 8) from 10 to 30 minutes, and innocuous brush by 34 ± 5% (F\(\_3,3\)\(,\)3 = 2.85; P < 0.05; n = 8) from 20 to 40 minutes. GABA, muscimol and orexin B had no significant effects when microinjected into the A11.

Conclusions: The data demonstrates that modulation of neurons in the A11 dopaminergic nucleus affects trigeminovascular traffic, and that inputs to the A11 may be glutamatergic and/or orexinergic. We also propose that the A11 nucleus may act tonically in the modulation trigeminal nociceptive transmission.

PO264
Brainstem and thalamic projections from a craniovascular sensory nervous center in the rostral cervical spinal dorsal horn of rats
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Objectives: Ascending projections from the spinal dorsal horn have been extensively examined in different species using high-resolution anterograde tracers; however, no study has specifically addressed the
ascending projections from the cranial blood vessel-receptive area in the rostral cervical spinal dorsal horn. We therefore traced the brainstem and thalamic projections from this area, using BDA as anterograde tracer.

**Background:** The expression of pain in primary headaches is associated with activity in intracranial perivascular sensory nerve fibers, which originate in the trigeminal ganglion and project to the trigemino-cervical complex in the brainstem. To understand the mechanisms of head pain in the pathogenesis of headaches, it is important to identify the CNS regions that process nociceptive information from the trigeminovascular system.

**Methods:** We injected biotinylated dextran amine (BDA) into the ventrolateral dorsal horn of segments C1 and C2, a region previously demonstrated to receive input from sensory nerves in cranial blood vessels in rats deeply anesthetized with chloral hydrate. Following a laminectomy 10% BDA was BDA was injected iontophoretically into different lamina at the C1 and C2 levels. After 1–3 weeks the animals were anesthetized with sodium pentobarbital and terminated by transcardial perfusion; the brain stem fixed in paraformaldehyde, sectioned and processed for BDA visualization.

**Results:** Following injections into laminae I–II, BDA-labeled terminations were found bilaterally in several nuclei in the pons and the midbrain, including the pontine reticular nucleus, the parabrachial nuclei, the cuneiform nucleus, and the periaqueductal gray. In the diencephalon, terminations were confined to the contralateral side and evident foremost in the posterior nuclear group, especially its triangular part, and in the ventral posteromedial nucleus. Following injections extending through laminae I–IV, anterograde labeling was more extensive.

**Conclusions:** Some of the above regions are likely to be involved in the central processing of noxious signals of craniovascular origin and therefore putatively involved in mechanisms associated with primary headaches.

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**PO265**

**Time course of phosphorylation of ERK, p38 and Akt (protein kinase B) in PC12 cells after TRPV1 activation**

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**Objectives:** The purpose of the present study is to clarify whether phosphorylation of Extracellular Signal-Regulated Kinase (ERK), p38, and Akt (protein kinase B) can be observed following TRPV1 (transient receptor potential vanilloid-type 1) activation *in vitro*.

**Background:** The activation of the meningeal nociceptors is considered to play an important role in migraine. We reported the occurrence of the TRPV1 receptor, a major nociceptive receptor, in the dura matter of the rat. The increase in pERK at 1 and 3 min following capsaicin application (1 min following capsaicin application, and phosphorylation of ERK returned to the original level before the capsaicin stimulation. There was no increase in ERK phosphorylation in the control. The phosphorylation of p38 and Akt showed a similar time course to that of ERK.

**Conclusions:** The time course of ERK phosphorylation in PC12 cells after capsaicin application was similar to ERK phosphorylation in trigeminal ganglion by noxious stimuli. The results indicate the possibility that phosphorylation of ERK is a useful biological marker of the activated nociceptive systems.

**PO266**

**Relation of orexin system and NO in the pathophysiology of migraine**

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**Objectives:** To elucidate the role of orexinergic system and NO in the pathophysiology of migraine, we investigated the distribution of orexin A and nNOS in the trigeminovascular system of the rat.

**Background:** The orexin system is known that it has several physiological functions, sleep, feeding, nociception, autonomic system and so on. And it is also known that orexinergic fibers project from neurons of lateral hypothalamus area (LH) to central nervous system, including PAG, dorsal raphe, locus coeruleus, spinal cord, which involve in the trigeminal pain transmission and pain control system in migraine attack. We have shown the lower value of plasma orexin-A concentration in migraine patients. Also we could observe that orexinergic fiber is distributed in the trigeminovascular system. NO has many physiological roles in the pathomechanism of cerebral ischemia and migraine headache.

**Methods:** A total of 10 Sprague-Dawley rats, weighing 350–450 g, were perfused with Zamboni’s fixative. The dura mater, the trigeminovascular system, the hypothalamus, the periaqueductal gray, the medulla oblongata and autonomic ganglia (superior cervical ganglion, otic ganglion, sphenopallarine ganglion) were dissected. The specimens were sectioned in 10 μm thick and the pial arteries and dura mater were processed as the whole mount preparation. Immunofluorescence staining method was utilized to examine the expression of orexin-A and orexin-1 receptors, nNOS microscopically.

**Results:** In the PAG and trigeminal spinal tract, orexin-A immunoreactive (ir)-fibers and nNOS ir-neurons and fibers were closely expressed. The orexin system is known that it has several physiological functions, sleep, feeding, nociception, autonomic system and so on. And it is also known that orexinergic fibers project from neurons of lateral hypothalamus area (LH) to central nervous system, including PAG, dorsal raphe, locus coeruleus, spinal cord, which involve in the trigeminal pain transmission and pain control system in migraine attack. We have shown the lower value of plasma orexin-A concentration in migraine patients. Also we could observe that orexinergic fiber is distributed in the trigeminovascular system. NO has many physiological roles in the pathomechanism of cerebral ischemia and migraine headache.

**Conclusions:** Morphologically we have shown that the orexinergic nerve fibers are expressed that near the nNOS positive neurons and fibers. It is suggested that orexin system modulates nNOS activity in the migraine-related structure in the brain.

**PO267**

**Event-related fMRI activation in spontaneous trigeminal neuralgia attacks**

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**Objectives:** To identify activation patterns in spontaneous trigeminal neuralgia attacks using event-related functional magnetic resonance imaging (fMRI).
PO269

Involvement of pro-nociceptive 5-HT$_{2A}$ receptor in the pathogenesis of medication-overuse headache

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Objectives: To determine the involvement of 5-HT$_{2A}$ receptor in the process of trigeminal plasticity induced by chronic analgesic exposure and in the process of inflammatory-induced thermal hyperalgesia.

Background: Derangement in 5-HT$_{2A}$ serotonin receptor has been reported to implicate in pathogenesis of medication-overuse headache. No clear explanation concerning the precise roles of these receptors in the process.

Methods: Wistar rats were daily administered with paracetamol (200 mg/kg) for thirty days. On the next day, ketanserin, a 5-HT$_{2A}$ antagonist, or saline was given prior to cortical spreading depression (CSD) induction. Electrocorticogram, cortical blood flow, Fos and 5-HT$_{2A}$-immunoreactivity in cortex and trigeminal pathway were studied. In the other experiment, complete Freund’s adjuvant was injected into the rat hind paw to induce tissue inflammation. Three days later, ketanserin was given and noxious heat was applied to both inflamed and non-inflamed paws. The response between two sides was compared by measuring paw withdrawal latency.

Results: Chronic paracetamol exposure led to an increase in CSD frequency and CSD-evoked Fos expression in cerebral cortex indicating the increase in neuronal excitability. Prolonged medication exposure also facilitated trigeminal nociception as evident by an increase in CSD-evoked Fos expression in trigeminal nucleus caudalis. The expression of 5-HT$_{2A}$ receptor in cerebral cortex and trigeminal ganglia was enhanced by chronic paracetamol administration. Pretreatment with ketanserin significantly attenuated these effects. The second experiment showed that ketanserin was able to lengthen the paw withdrawal latency in the inflamed side but did not alter nociceptive response in the non-inflamed side.

Figure 1

Conclusions: These findings suggest that up-regulation of pro-nociceptive 5-HT$_{2A}$ receptor is an important step in the process of cortical hyper-excitation and nociceptive facilitation induced by chronic analgesic exposure.

PO270

Calcitonin gene-related peptide differentially regulates gene and protein expression in trigeminal neurons and glia cells: findings from array analysis

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Objectives: The goal of this study was to use array analysis to identify proteins and genes in trigeminal neurons and glia that are regulated by calcitonin gene-related peptide (CGRP).

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Background: CGRP is a neuropeptide found at elevated levels during migraine attack. Trigeminal ganglia are comprised of neurons found in close association with satellite glial cells and both cell types express functional CGRP receptors. Activation of trigeminal nerves can cause release of CGRP from the cell bodies of neurons within the ganglion. However, a comprehensive analysis of pro-inflammatory genes and proteins expressed in trigeminal ganglion neurons and glial cells regulated by CGRP has not been performed.

Methods: Primary trigeminal cultures enriched for neurons or glia were treated with 1 μM CGRP for 2, 8, or 24 hours. Protein, mRNA, and oligo arrays were used to study the temporal and cell specific expression of proteins and genes regulated by CGRP (n = 3). Statistical analysis was performed using Student’s t-test with significance considered when P ≤ 0.05.

Results: RayBio Cytokine Protein Arrays: The maximum amount of cytokines secreted from glial cells was seen 8 and 24 hrs after addition of CGRP. A smaller number of cytokines were increased in neurons in response to CGRP treatment but the magnitude of some increases was up to >50 fold over non-stimulated control levels.
SA Bioscience Rat MAP Kinase Signaling Pathway Arrays: CGRP caused >3 fold upregulation of 22 genes in neurons but caused increased expression of 68 different genes in glia. Several of these genes are known to modulate the activity of ion channels or p38 Sigma Panorama Ab Cell Signaling Microarrays: The majority of proteins with increased expression were initially observed in neuronal cells at 2 hours and in glial cells at 8 hours.
SA Bioscience Rat Signal Transduction Pathway Finder Arrays: CGRP increases expression of 89 transcription factors in neuronal cells and 62 in glial cells. It is of interest that the number of genes increased in neuronal cells at the 2 hour time point is greater than that observed at 8 hours.

Conclusions: A significant novel finding from this study is that CGRP increased gene and protein expression of many known pro-inflammatory genes in trigeminal ganglion glial cells. Our data support an important role of CGRP in modulating glial activity within trigeminal ganglion and ultimately, affecting the excitability state of trigeminal neurons. Interestingly, while the stimulatory effects of CGRP were observed more quickly in neurons, the stimulatory effects on glial cells were sustained for a longer time. Based on our data, we predict that CGRP functions as a neuronal-glial modulator within the trigeminal system that likely contributes to peripheral sensitization.

PO271
Abstract withdrawn

PO272
Intact neurovascular coupling during executive function in migraine without aura: interictal near-infrared spectroscopy study
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Objectives: We aimed to investigate neurovascular coupling during mental task interictally in patients with migraine without aura by near-infrared spectroscopy (NIRS). We hypothesised that migraineurs would show altered vasoreactivity, oxyhemoglobin and deoxyhemoglobin during stroop task in migraine without aura patients interictally.

Background: Migraine is proposed to be an uncoupling disorder where the neuronal activity induced metabolic demand such as oxygen or glucose is unmet by vascular supply. Cortical spreading depression (CSD) impairs neurovascular coupling and induces relative hypoxia and glucose depletion. CSD is a pathophysiological correlate of migraine aura and has recently been put forward to lead to also migraine attacks without aura.

Methods: Twelve migraineurs and 12 healthy controls were included. Using NIRS, we recorded the magnitude and latency of cortical changes in oxyhemoglobin (HbO2) and deoxyhemoglobin (Hb) during the colour-word matching stroop test via 16 channels covering the forehead.

Results: We found no differences in the magnitude responses between migraineurs and healthy subjects in the incongruent stroop task subtracted by the neutral stroop task on either side of the frontal cortex for HbO2 (Left: P = 0.984; right: P = 0.406) and Hb (left: P = 0.689; right: P = 0.406) values. No differences in error rate (P = 0.611) and reaction time (P = 0.936) were found between healthy subjects and MO patients for incongruent tasks.

Conclusions: We conclude that neurovascular coupling during a mental task as measured with NIRS is intact in migraine without aura patients between attacks.

PO273
Gender-dependant effect of acute dietary tryptophan depletion on sensitivity to cortical spreading depression in rats
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Objectives: To determine the effect of acute dietary tryptophan depletion on KCl-induced CSD in rats and search for gender differences.

Background: Migraine is sexually dimorphic (male/female ratio 1:3) and thought to be a “low 5-HT” condition. Reduced serotonergic transmission might be responsible for deficient pain control and for changes in cortical excitability. In migraineurs, dietary tryptophan depletion decreases 5-HT levels and worsens migraine symptoms. Brain depletion of 5-HT by PCPA in male rats enhances cortical spreading depression (CSD) a likely cause for the migraine aura.

Methods: Adults males and females Sprague-Dawley rats receive, after 18 hours food deprivation, two oral administrations of a gelatin-based protein–carbohydrate mixture (Solugel® with Trp+ group) or without (Trp- group) L-tryptophan (0.0112 g/kg). Control rats are not food deprived and received two oral administrations of NaCl. Plasma Trp depletion is verified by HPLC measurement in independent groups 4 hours after the first oral treatment. CSD are elicited 4 hours after the first oral treatment under chloral hydrate anaesthesia by applying 1 M KCl over the occipital cortex with a cotton ball. The electrocorticogram is recorded ipsilaterally (DC-100 Hz) with parietal and frontal electrodes for 1 hour.

Results: Our results show that tryptophan depletion induces a decrease of plasmatic tryptophan level (-49% in females and -44% in males) 4 hours after the first oral treatment. Surprisingly, tryptophan depletion significantly decreases the frequency of CSD in females (control vs. TRP+: -56% CSD/hour, P = 0.04) while a slight tendency is observed in males (control vs. TRP+: -19% CSD/hour). By contrast, administration of the same preparation supplemented with tryptophan significantly reduces CSD occurrence in male rats (control vs. TRP+: -41% CSD/hour, P = 0.01) while it has only a modest inhibitory effect in females (control vs. TRP+: -22% CSD/ hour).

Conclusions: These preliminary results show a sexual dimorphism of the effect of tryptophan depletion on CSD occurrence. They suggest a complex interplay between 5-HT, sex hormones and cortical excitability. Translated to migraine (with aura), they might indicate that 5-HT is not a crucial factor for the increased susceptibility to CSD.
PO274
Differences in short-term primary motor cortex plasticity as assessed by repetitive transcranial magnetic stimulation in migraine with and without aura
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Objectives: To find out more about glutamatergic and gabaergic transmission in migraine, in this study we investigated glutamate-dependent short-term plasticity and GABA-dependent inhibitory cortical interneuron excitability as assessed by 5-Hz repetitive Transcranial Magnetic Stimulation (rTMS) delivered over primary motor cortex (M1) (MEP facilitation and CSP shortening) in migraine patients with (MA) and without aura (MwoA) and healthy controls.

Background: Several lines of evidence indicate that migraine, like epilepsy, fundamentally arises from altered neuronal excitability. Unlike single-pulse TMS, a technique that investigates global M1 excitability and paired-pulse TMS, which investigates facilitatory and inhibitory interneuron interactions within M1, 5-Hz rTMS gives insights into mechanisms of glutamate-dependent short-term plasticity in humans resembling those described in animals.

Methods: We studied 19 patients with MA, 18 patients with MwoA and 19 HC. 5-Hz rTMS was delivered at 120% resting motor threshold to the hand motor area of the left hemisphere with the target muscle at rest and during contraction. Three of the patients with MA were also tested at the end of visual aura during a spontaneous migraine attack.

Results: ANOVA showed that the MEP significantly increased in size and CSP significantly shortened during 5-Hz rTMS in the three groups tested. The 5-Hz rTMS induced MEP facilitation significantly being highest in the group of patients with MA aura. In the three patients tested both icatally and interictally the MEP increased during the interictal session but remained unchanged when the visual aura ended.

Conclusions: Our study shows that the neurophysiological feature that differentiates patients with MA from patients with MwoA and HC is an abnormal M1 susceptibility to 5-Hz rTMS both outside and during the attack suggesting that glutamate-dependent short-term M1 cortical plasticity patterns differ in MA and MwoA. Our interictal neurophysiological findings might help to explain the clinical finding that MA is probably never completely clinically silent even outside the attacks. Ictal data, in keeping with altered glutamate-mediated cortico-cortical projections to M1 when the visual aura ends, deserve confirming in larger studies.

PO275
Functional-MRI (f-MRI) evaluation in chronic migraine with medication overuse
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Objectives: The aim of the study is to submit a group of patients suffering from chronic migraine (CM) and medication overuse to withdrawal and to evaluate by functional MRI the presence of specific cerebral functional patterns before withdrawal.

Background: CM and medication overuse needs particular management. Recent studies confirmed that particular findings of personality of these patients are similar to those of subjects addicted (alcohol, or different kind of drugs) and these characteristics may be predictive for a therapeutic success or not, moreover some neuro-imaging studies showed that abnormalities revealed in these patients are related to a specific cerebral pattern and that they can return to the normal state after withdrawal.

Methods: Ten patients suffering from CM and medication overuse and seven healthy controls entered the study and were scanned on a 1.5 T MR system (Siemens Magnetom Avanto). All subjects were submitted to an initial psychophysical testing session. Mechanical pressure stimuli of 3 sec in duration were applied to the middle and index fingers of the left hand to determine threshold for just noticeable pain (level 2), moderate pain (level 4) and strong pain (level 6) on visual analogue scale (VAS) ranging from 0 to 10. The participants were exposed at the three intensity levels determinate during the previous psychophysical test during the f-MRI performed with SS-EPI. Pressure stimuli (duration of each stimulus = 6 seconds) were pseudo-randomly presented in 18 s blocks interspaced with 18 s no stimuli periods over two functional scans. At the first scan, subjects had to draw their attention to noxious stimulus; at the second one they had to indicate the felt level of the pain stimuli on the response box. Pre-processing and statistical analysis of the f-MRI data were conducted with the Statistical Parametric Mapping software (SPM5, Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). Functional-MRI data were realigned and resliced to correct for subject's movements. Then data were normalized to a reference space according to the MNI template of SPM5.

Results: No difference in the level of pain perception between CM and controls was found by means of a two sample t-test. f-MRI analysis showed significant activations in both groups bilaterally in the middle frontal gyrus, in the insula, in the superior and inferior parietal lobe, in the supramarginal and in the angular gyri and in the anterior and middle cingulum and in the right superior and inferior frontal gyrus between pain and rest condition as expected from the literature. A significant decreased activation was found in the right supramarginal gyrus and in the right inferior and superior parietal cortex in the chronic migraine patients compared with controls.

Conclusions: Functional-MRI seems to be a useful technique to obtain information on particular neuronal changes of the pain network involved in this type of patients. The activated areas are congruent with some data of the literature. More subjects are needed to evaluate the possible changes after withdrawal.

PO276
Comparison of L/N-Type Ca\(^{2+}\) channel blocker and L-Type Ca\(^{2+}\) channel blocker in migraine model rat
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Objectives: Cilnidipine is a Ca\(^{2+}\) channel blocker (CCB) with suppressive effects on L- and N-type Ca\(^{2+}\) channels and used to treat hypertension. It is known that N-type Ca\(^{2+}\) channels are localized at the presynaptic terminals of the neurons. Ziconitide, which act only on N-type Ca\(^{2+}\) channel, is used in treatment of severe chronic pain but its indication is limited. In this study, we compare two types of CCB, cilnidipine (L/N-type CCB) and nifedipine (L-type CCB), to clarify the role of N-type Ca\(^{2+}\) channel in migraine.

Background: The pathogenesis of migraine is still unclear, but cortical hyperexcitation with subsequent cortical spreading depression (CSD) is thought to have important role on the pathogenesis of migraine with aura. At present, some drugs such as antiepileptic drugs (valproate, topiramate), antidepressants (amitriptyline), beta blockers (propranolol) are used to prevent migraine attack. CCBs (flunarizine, lomerizine) are also known to have the potential of migraine prophylactic drug. But the mechanism of their action in migraine treatment is not fully understood.

Methods: Ten male Sprague-Dawley rats, weighing 350–500 g, were anesthetized with isoflurane, and ventilated mechanically with 30% O\(_2\). Parietal cortical blood flow (CoBF) was continuously monitored.
with the Laser-Doppler flowmeter. A hydrogen electrode was placed in the open parietal cranial window to measure direct current potential (DCP) next to Laser-Doppler flowmeter. CSDs were triggered with an application of 0.1 M KCl solution with the volume of 3 μl through another open cranial window. DCP and CoBF were measured to detect CSD after application of KCl for 60 min under intra-peritoneal injection of 2.0 ml saline followed by cilnidipine (100 μg/kg in 2.0 ml saline) or nifedipine (100 μg/kg in 2.0 ml saline). The CSD data were analyzed by paired-T test.

**Results:** Cilnidipine significantly attenuated the number of CSD from 6.2 to 5.0 (P < 0.05). Conversely, nifedipine did not attenuate the number of CSD.

**Conclusions:** Only L/N-type CCB attenuated the number of CSD after KCl application in rat. Our results indicate that N-type Ca2+ channel have a role in migraine attack and it might be related to an attenuation of synaptic transmission in trigeminal nerve terminal.

**PO277**

Modulation of human trigeminal and extracranial nociceptive processing transcranial direct current stimulation (tDCS) of the motor cortex

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**Objectives:** We aimed to investigate the modulation of the trigeminal and extracranial nociceptive processing induced by transcranial direct current stimulation (tDCS) of the human motor cortex.

**Background:** Transcranial direct current stimulation has previously been used to modulate human pain perception in different chronic pain conditions. Underlying pathophysiology is not fully understood.

**Methods:** Nineteen healthy volunteers were stimulated three times each, using cathodal, anodal (both 1 mA) or sham tDC for 20 minutes. Trigeminal pain processing was assessed by recording pain related potentials (PREP) and nociceptive blink reflex (nBR) following the nociceptive electrical stimulation of the contralateral forehead and the extracranial nociceptive transmission using the PREP elicited from the contralateral hand. The electrophysiological recordings were performed before, immediately after, 20 and 50 minutes after stimulation.

**Results:** Cathodal tDCS resulted in an inhibition, anodal tDCS in an excitation of mainly cranial but also, even though less pronounced in extracranial pain processing. Influences of the BDNF Val66Met gene polymorphism will be evaluated.

**Conclusions:** The results of the study suggest that both, trigeminal and extracranial human nociceptive systems can be modulated by tDC stimulation of the motor cortex.

**PO278**

An acute reduction of the endocannabinoid-hydrolase FAAH is coupled with an improvement of the facilitation of the nociceptive pathways in medication-overuse headache after withdrawal treatment

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**Objectives:** Our study is aimed to investigate 1) a possible relationship between the functional activity of the endocannabinoid system (ES) and the facilitation of pain processing in migraine patients with medication-overuse headache (MOH) and 2) the effect of the withdrawal treatment (WT) on both the ES metabolism and the pain processing.

**Background:** The ES has been demonstrated to play a role in the antinociception also by the prevention of the central sensitization processes of nociceptive pathways. The sensitization of cephalic and extracephalic pain pathways has been demonstrated to play a pivotal role in the development and maintaining of chronic form of migraine, including MOH. In MOH patients, recently emerged a defective functioning of the ES expressed as a down-regulation of the biochemical mechanisms degrading endocannabinoids.

**Methods:** We used the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) as an objective method to explore the spinal cord pain processing and the platelet activity of the enzyme fatty acid amide hydrolase (FAAH) to detect the functional state of the ES. In 21 (12 F; 9 M; mean age 42.8 ± 12.0) MOH and 8 (5 F; 3 M; mean age 41.4 ± 12.9) healthy subjects the TST of the NWR, the subjective painful sensation and the FAAH activity were measured, before and after 7 and 60 days after a standard withdrawal treatment (WT).

**Results:** Both a significant facilitation in pain processing (reduced TST and increased painful sensation) and a reduction in FAAH activity was found in MOH before WT when compared with controls. A significant FAAH activity reduction coupled with a significant improvement in facilitation of spinal cord pain processing (increased TST and reduced pain sensation) was found in MOH patients before WT when compared with MOH patients 7 and 60 days after WT.

**Conclusions:** We hypothesized a chronic reduction in endocannabinoid tone in MOH patients before WT when compared with controls as consequence of an adaptive response induced by chronic pain and which could act in favour of a facilitation of the pain processing. Furthermore, the acute reduction of the FAAH activity coupled with an improvement of the facilitation in pain processing immediately after WT and its persistence 60 days after WT could represent the consequence of a mechanism devoted to acutely reduce the degradation of endocannabinoids and aimed to increase the activity of the ES which results in an anti-nociceptive effect.

**PO279**

A mouse model to study the effects of obesity on chronic migraine

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**Objectives:** To develop a mouse model to study the effects of obesity on progression of migraine-like symptoms from episodic to chronic.

**Background:** Obesity has recently been identified as risk factor for increasing the frequency of migraine attacks. Our long-term goal is to identify the mechanisms by which obesity may induce the transformation of migraines from episodic to chronic. We hypothesize that inflammatory state associated with obesity increases susceptibility to central sensitization and by that mechanism leads to progression from episodic to chronic pain. We will characterize behavioral and biochemical features of migraine in obese versus lean mice. In the current study we examined light aversion and trigeminal mediated pain, as surrogates for photophobia and head pain.

**Methods:** C57BL/6 mice of both sexes were placed on a high fat (45%) or standard diet at 4–6 weeks of age. After 14 weeks, the weights were significantly different, so behavioral testing commenced. To assess light aversion we used a natural conflict based assay. Mice were tested individually in a chamber with two compartments, half enclosed and dark and half open and brightly lit, joined by a small opening in the center. Total time spent in the light was measured. To assess thermal nociception we used the hot plate assay and an operant facial pain assay. In the hot plate test, nociception is assessed by measuring the latency to lick the hindpaw in response to a thermal stimulus. In the operant facial pain assay, mice are trained...
to lick a palatable solution while placing their faces against a heated surface. Number of licks and duration of facial contacts with the aversive stimulus are quantified, and a decrease of these parameters indicates pain.

Results: In the light aversion test, there was no effect of obesity on time spent in the light. In the hot plate assay, there was no effect of obesity on thermal nociception and mice on both diets exhibited a typical decrease in latency to lick the hindpaw with increasing temperature. In the operant facial pain assay, there was no significant difference in reward licks with a 32°C stimulus, indicating that diet does not enhance or diminish motivation for the milk reward. Duration of facial contacts was similar in both groups at 32°C and 43°C. Obese mice had 45% fewer licking events than lean mice with a 43°C stimulus ($P = 0.011$).

Conclusions: Our preliminary results suggest that obesity may have a selective effect on trigeminal mediated pain, but is not sufficient to induce photophobia. More intense thermal stimuli may be required to detect differences in nociception between obese and lean mice. Based on the current results we conclude that diet induced obesity does not affect response to acute nociceptive stimuli. We plan to use the nitroglycerine induced headache model to investigate this hypothesis. We will also examine the effect of obesity on biochemical marker associated with migraine, such as CGRP and TNF-alpha, and on activation of second order neurons in the trigeminal nucleus caudalis.

PO280
Prevalence of patent foramen ovale and MRI white matter lesions in migraine with aura: a cross-sectional study
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Objectives: To evaluate in migraine with aura (MA) the prevalence of a right-left shunt (R-Ls) by contrast transcranial doppler sonography (cTCD) and of MRI white matter lesions (WML) and infarcts and to search for possible correlations.

Background: The precise role of patent foramen ovale in migraine remains unclear.

Methods: We enrolled 129 consecutive patients who attended our headache clinic with an ICHD-II diagnosis of migraine with aura (1.2.1) (MA). Fifty patients had strictly visual auras, 79 had visual and sensory aura symptoms. There were 98 females and 31 males with a mean age of 34.32 (±13.22) years and the mean age of onset of attacks of 18.24 (±9.316). Mean attack frequency was 2.73/month (±3.76). All were systematically screened for PFO by transcranial Doppler sonography (cTCD) and of MRI white matter lesions (WML) and infarcts and to search for possible correlations.

Results: cTCD detected a R-L shunt in 60 (47%) MA patients, in most of them (77%) even during normal breathing. Medium to large shunts occurred in 28% of MA patients. Prevalence of R-L shunt was equal in patients with strictly visual and those with visual and sensory aura (46%). There was no correlation between grade of R-L shunt and attack frequency/type, but the age at onset of attacks tended to be lower in patients with large R-L shunts (16.18 years old compared to 19 years old with no shunt, $P = 0.051$). White matter lesions on 5 mm MRI slices could be detected in 25 (22%) of MA patients. Prevalence of WML was not increased in the presence of a R-L shunt but the number of WMLs tended to be higher in patients with large shunts (Mean 2.32 vs. 0.72 in patients with no shunt, $P = 0.136$). There was no correlation between white matter lesion load and attack frequency. None of our patients had a detectable infarct on MRI, neither in the anterior nor in the posterior circulation territories.

Conclusions: We confirm the high prevalence of R-L shunts in a clinical sample of migraine with aura patients. In our sample R-L shunt was not correlated with disease severity nor with prevalence of white matter lesions on MRI but the number of WMLs tends to be higher in patients with large shunts. Neither WMLs nor shunt grades were correlated with disease severity. These data suggest that R-L shunts, and thus PFO, do not play a major role in migraine pathophysiology and pathogenesis.

PO281
Analysis of intracellular localization of the TRPV1 receptor in PC12 cells
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Objectives: We aimed to develop a fluorescence-based system capable of monitoring TRPV1 (transient receptor potential vanilloid-type 1) intracellular localization and to assess the influence of TRPV1 overexpression on cell viability.

Background: TRPV1 is a noxious heat, acid, and capsaicin-sensing receptor, which is primarily distributed on peripheral nociceptors in the trigeminal and spinal sensory systems. Targeted disruption of the TRPV1 receptor in mice resulted in suppression of inflammation-induced hyperalgesia. As neurogenic inflammation in the perivascular area of dural arteries is considered to be an important element in migraine pathophysiology, and allodynia, a hyperalgesic state that likely reflects nociceptor sensitization, not infrequently accompanies migraine attacks, TRPV1 blockade is a promising therapeutic strategy against migraine. Facilitated expression and trafficking to plasma membrane is known to contribute to TRPV1 sensitization. Hence, regulating TRPV1 trafficking to plasma membrane appears to be an effective therapeutic strategy. To this end, it is imperative to develop a system for observing intracellular dynamics of the TRPV1 receptor.

Methods: We prepared total RNA from rat trigeminal ganglia. TRPV1 cDNA was amplified by RT-PCR, and the resultant PCR product was subcloned into the EcoRI/KpnI sites of pEGFP-C3 vector (Clontech) with the full-length TRPV1 cDNA being arranged in frame after enhanced GFP cDNA (pEGFP-TRPV1). pEGFP-TRPV1 was transfected into PC12 cells. We confirmed expression of the EGFP-TRPV1 fusion protein by fluorescence microscopy and western blot analysis. Moreover, we applied a high concentration of capsaicin (300 μM) to EGFP-TRPV1-overexpressing PC12 cells and assessed cell viability by the TUNEL method.

Results: At 48 hours after transfection, approximately 70% of cells exhibited GFP signal. Correspondingly, western blot analysis using a TRPV1 antibody detected a band in the predicted molecular weight range of the EGFP-TRPV1 fusion protein. Immunoreactivity suggestive of oligomer formation of TRPV1 was also identified on the blot, which was likely to reflect the tetramer formation of TRPV1 as functional receptor unit. Confocal laser microscopy revealed that GFP signal was mainly localized in the periphery of cells, consistent with the expression in plasma membrane. In some cells, there was local clustering of GFP signal. Compared with control cells without EGFP-TRPV1 expression, EGFP-TRPV1-overexpressing cells exhibited enhanced DNA fragmentation detectable as early as at 2 hours after 300 μM capsaicin application.

Conclusions: The EGFP-TRPV1 fusion protein was useful in assessing intracellular localization of TRPV1 in the living state, which is expected to serve to the development of novel drugs capable of
PO283
The prostanoid IP receptor represents a possible target for the treatment of migraine

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Objectives: To explore possible role of IP receptor in migraine pathophysiology by examining the migraine eliciting effect of prostanoglin I₂.

Background: Prostaglandin I₂ (prostacyclin, PGI₂) acts via the prostanoids IP receptors expressed in trigeminal sensory afferents and cerebral arteries. When binding a prostanoylin-molecule, the receptor changes conformation and activates Gs protein with its activation of cAMP and increase in protein kinase A (PKA) activity. The cAMP-PKA pathway has been implicated in the generation of headache or migraine-like attacks and mechanical sensitization of dural sensory afferents.

Methods: Twelve patients with migraine without aura and 12 healthy volunteers were randomly allocated to receive intravenous infusion of PGI₂ (epoprostenol) 10 ng/kg/min or placebo over 25 min. We recorded headache intensity on a verbal rating scale (VRS) and associated symptoms during in-hospital (0–90 min) and post-hospital phases (1.5–12 h). Mean blood flow velocity in the middle cerebral artery (VMCA) and diameter of the superficial temporal artery (STA) were recorded by ultrasonography.

Results: Migraine patients: PGI₂ caused an immediate headache in 11 (92%) subjects compared with 2 (17%) subjects on placebo (P = 0.004). Seven (58%) patients reported delayed headaches compared with 3 (25%) on placebo (P = 0.125). Three (25%) patients on PGI₂ vs. 2 (17%) patients on placebo reported migraine like attacks (P = 1.000). On PGI₂ day 9 (75%) patients reported the immediate headache and 6 (50%) patients reported the delayed headache to mimic spontaneous migraine attacks. Healthy volunteers: 11 (92%) reported headache on PGI₂ during the in-hospital phase and 7 (58%) reported headache in the post-hospital phase. Vascular variables: both in patients and healthy volunteers median peak headache 1 (1–2.75) (quartiles) occurred 20 min after infusion start and were associated with a drop in VMCA indicating dilatation and dilatation of STA in both migraineurs (-10.5%; -14.9 to -6.0, 95% CI and 32.9%; 26.4 to 39.4, 95% CI) and healthy subjects (-4.6%; -1.6 to 7.6, 95% CI and 38.8%; 26.5 to 51.1, 95% CI).

Conclusions: PGI₂ elicit migraine like attacks in patients with migraine without aura and headache in healthy subjects. The immediate headache was associated with dilatation of cerebral arteries. Given that intracellular responses to PGI₂ are mediated via the IP-receptor we suggest that this receptor may be a potential target for the migraine treatment.
Results: During the in-hospital phase (0–120 min), 10 subjects reported headache on the PGD2 day and no subject reported headache on the placebo day (P = 0.002). The median peak headache, 1 (0–1) (quartiles), occurred 10 min after start of PGD2 infusion. In-hospital headache was associated with a drop in VmCA (-28.3%; 33.6–22.9%, 95% CI) indicating vasodilatation and dilatation of STA (55.7%; 46.7–64.6%, 95% CI). Ten subjects reported nausea and 10 subjects reported nasal congestion during the in-hospital phase. During the post-hospital phase (2–14 hour), 3 subjects reported delayed headache on the PGD2 day and 1 subject reported delayed headache on the placebo day (P = 0.625).

Conclusions: PGD2 is the strongest dilator of cerebral and extracerebral arteries studied so far in human models of headache. Nevertheless, it did not cause more headache than other prostaglandins. We suggest that vasodilatation is important, but a lack of sensitizing effect of PGD2 in sensory afferents is responsible for a mild headache inducing effect. PGD2 causes considerable amounts of nausea and nasal congestion and may be the cause of these symptoms in spontaneous migraine attacks.

PO285

Blink reflex and trigeminal system in chronic migraine

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Objectives: The functional state of central nociceptive system plays a significant role in pathophysiological mechanisms of migraine chronication and chronic migraine (CM). Most investigations are focused on inhibitory activity of different neuronal circuits, abnormal excitability of cortical and brainstem neurons. The aim of the study was to assess the excitability of trigeminal system (TS) and inhibitory mechanisms of brainstem in patients with CM.

Background: CM was diagnosed in 40 patients (2 male and 38 female, age 39.2 ± 8.9 years old) according to ICHD-II. The total number of days with headache was 21.7 ± 3.5/month, the total number of days with migraine headache was 8.3 ± 1.8/month (including severe attacks accompanied by vomiting, disadaptation and staying in bed). Pain intensity referred to CM was 7.8 ± 0.8 points according to visual analog scale.

Methods: The electrical stimuli perception threshold and registration thresholds of blink reflex R1, R2 and R3 components were analyzed in patients with CM and compared with the results of the same parameters from 20 healthy volunteers (3 male and 17 female, age 31.9 ± 8.3 years old). The level of stimuli subjectively sensed as an obvious influence was considered as a perception threshold. With standard protocol, the level of electrical stimuli intensity was considered as a threshold if every component was obvious and reproducible. The habituation of R3 was tested with frequency 0.066 Hz. The registration threshold of R3 component was lower in CM against control (P < 0.05) and in most patients the abnormal or absent R3 amplitude habituation was revealed. These data confirm that changes TS excitability on the brainstem level are related to decreased or disturbed inhibitory influence and took part in regulating mechanisms of nociceptive and pain control systems.

PO286

Abnormalities of motor cortical facilitation in migraine with aura (MWA): modulatory effects of repetitive transcranial magnetic stimulation (rTMS) and levetiracetam (LEV) treatment

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Objectives: To evaluate MEP and CSP to 5 Hz rTMS in MWA patients (before and after LEV treatment) as compared to healthy subjects.

Background: 5 Hz-rTMS trains progressively increase motor evoked potentials (MEPs) amplitude and cortical silent period (CSP) duration [1] to each pulse of the train, in normal subjects. This likely follows to activation of facilitatory circuits through LTP-like mechanisms. LEV is effective in MWA.

Methods: Eight 5 Hz-rTMS trains [10 stimuli each, 2 min intertrial interval, 120% of motor threshold (MT) intensity], were delivered over right hand motor area. Further 3 trains (10 stimuli) were delivered during a voluntary contraction (20% of maximum effort) to evaluate the CSP. MEPs size and CSP duration (to each magnetic stimulus), were recorded (over the right APB) in 12 patients (before and after three months levetiracetam treatment (500 mg b.i.d.) and in 12 healthy subjects.

Results: Differently from healthy subjects, where a progressive MEP and CSP increasing was found, in naive migraineurs MEP and CSP increased only after the fifth pulse of the train. However, the net potentiation with respect to first MEP and CSP was significantly greater in migraineurs. This facilitatory effect on MEP was completely lost in migraineurs after LEV treatment while the CSPlengthening remained unchanged.

Conclusions: These results, in agreement with other reports, show abnormalities of facilitatory circuits in migraine that could have a role in the pathophysiology of the disease.


PO287

Photophobia during acute migraine is associated with visual cortical excitability

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Objectives: To investigate the association between photophobia and visual cortical excitability in patients with migraine.

Background: Acute migraine is characterized by photophobia. The causative mechanism of this feature and its relationship to other headache profiles are not clear. In temporal proximity to migraine attacks, excitability of the visual cortex varies profoundly. The amplitudes of visual evoked potential or visual evoked magnetic field (VEF) increase when comparing perictical to interictical recordings.

Methods: Thirty-nine patients with migraine without aura were recruited from the headache clinic; their headache diary and control (mean severity, frequency, and length of migraine history) were collected. The migraine disability assessment (MIDAS) questionnaire
assessed migraine-related disability. On the day of evaluation, all patients sat comfortably and looked at an indicated area of a fluorescent light source for 5 seconds. The distance between the light source and the subject was kept at 1.5 meters and the luminance of the indicated area was 6000 cd/m². The discomfort induced or exacerbated by the light exposure was rated by the verbal numerical scale (0–10). Then the patient underwent VEF recordings with left-hemifield checkerboard reversals (check size 120', 3 Hz reversal) and 1500 responses were recorded. The P100m component of VEF was analyzed to obtain its peak latencies and amplitudes. The time interval between VEF recording and the most recent migraine attack prior to or after the recording was determined based on headache diaries. All measurements were compared between the patients evaluated during periictal period (presence of migraine attacks within a period of 2 days before and after the day of evaluation) and those during interictal period.

Results: Ten patients (all females, 35.6 ± 11.6 years) were evaluated during periictal period and the others (23F/6M, 32.3 ± 10.4 years), interictal period. The perical and interictal groups did not differ in age and headache severity, frequency and history length. However, the perical group had higher averaged rating of photophobia (4.0 ± 3.4 vs. 0.7 ± 1.3, P < 0.001, Mann–Whitney Test). There was no difference between the two patient groups in P100m latencies (103.4 ± 8.8 ms vs. 99.7 ± 8.9, P = 0.266) and amplitudes (44.6 ± 19.5 vs. 35.6 ± 15.9 nA, P = 0.154) (student t-test). Among the patients performed during periictal period, the rating of photophobia was correlated with P100m amplitudes (γ = 0.644, P = 0.044), headache days per month (γ = 0.650, P = 0.005) (Spearman’s correlation). In contrast, among the patients performed during interictal period, there was no correlation between photophobia ratings and P100m measurements or other headache profiles.

Conclusions: Photophobia associated with acute migraine might be derived from activation of the visual cortex.

PO288
Cervicogenic headache: a possible manifestation of peripheral vestibular dysfunction?
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Objectives: To discuss a possible mechanism whereby vestibular dysfunction may facilitate cervicogenic headache.

Background: Headache is a complex symptom with numerous possible etiologies. Though there are a number of well-defined disorders and patterns, not all types of headache have clear-cut explanations or mechanisms. Activation of cervical musculature via various mechanisms may contribute to cervically-mediated headache. The vestibulocolic reflex (VCR) participates in head stabilization and may be abnormal in patients with peripheral vestibular dysfunction. It is plausible that peripheral vestibular disorders may influence cervical spine biomechanics. The vestibular disturbance itself may otherwise be asymptomatic with no symptoms of dizziness or imbalance.

Methods: Single-center, randomized, double-blind, active placebo-controlled trial comparing therapy with botulinum neurotoxin type A plus local anesthetic trigger point injections followed by neck physiotherapy versus the same without botulinum toxin. 15 patients were enrolled in each group (Total 30). Results of this study were presented at AAN 2006 (Neurology 2006; 66 (Suppl 2): p. A376).

No significant difference was appreciated between the two groups. Within this study, all patients underwent infrared videonystagmography to evaluate for pathologic nystagmus. Eye movements were recorded to DVD for subsequent analysis. Testing included vibra-
PO290
Responses to achromatic and chromatic visual patterns in migraine patients
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Objectives: To study the responses to visual patterns of striped lines of different spatial frequency, luminance contrast and chromatic contrast in migraine with and without aura.

Background: Certain visual patterns can induce discomfort and illusions in normal subjects. Migraine patients seem to be particularly sensitive to achromatic visual patterns of certain spatial frequencies, but their sensitivity to chromatic visual patterns of different chromatic contrast has not been specifically investigated.

Methods: Twenty patients with migraine with aura (MA), 20 with migraine without aura (MWA) and 20 controls were studied. Headache-free patients and controls had to look at series of patterns of striped lines of different spatial frequency (0.5–20 cycles per degree), luminance contrast (C 90% and C 50%) and chromatic contrast (isoluminant red-green and blue-yellow patterns). The following parameters were investigated: 1) latency of the first spontaneous blink (s); 2) occurrence of unpleasant perceptions (0–3); 3) presence of illusions of motion, shape and colour; 4) presence of blurring vision; 5) presence of photophobia; 6) occurrence of nausea; 7) occurrence of headache.

Results: Unexpectedly, the first blink latencies were significantly (P < 0.01) longer in MA and MWA patients than in controls for both achromatic and chromatic patterns, regardless of spatial frequencies and subjective perceptions. Unpleasant perceptions, illusions, blurring vision and photophobia were significantly more prevalent in patients than controls. MWA patients had higher levels of unpleasant perceptions, illusions of motion, shape and colour, blurring vision, photophobia than MA patients in response to achromatic patterns. In contrast, MA patients were significantly more sensitive to isoluminant red-green chromatic patterns than MWA patients.

Conclusions: Migraine patients seem to be particularly troubled by visual patterns that act on different visual pathways. The parvocellular system, that acts on chromatic perceptions, was found to function differently in migraine with and without aura.

PO292
Top-down attentional control of sensory responses in visual cortex in migraineurs: an ERP study
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Objectives: The specific goal of this project is to examine aspects of the top-down attentional control of sensory responses in visual cortex in migraineurs.

Background: Previous research has shown that migraineurs have consistent abnormalities in basic sensory-level visual processing, specifically, that migraineurs do not habituate to repetitive innocuous stimuli. Given that one of the central roles of attention is to modulate early perceptual and discriminative aspects of visual processing, we examined aspects of the top-down attentional control of sensory responses in visual cortex in migraineurs.

Methods: We tested three participant cohorts in a canonical spatial cuing task: migraineurs with aura, migraineurs without aura, and age-matched non-headache controls. We looked at the P1 and N1 components of cued and uncued Event Related Potentials (ERPs).

Results: For parafoveal targets, controls showed a significant difference of P1 amplitudes to cued and uncued targets, while neither of the migraine groups showed this effect. For the N1 component, none of the groups showed significant differences of cued to uncued amplitudes to the targets.

Conclusions: Not only have we found that migraineurs show abnormal top-down control of sensory responses in visual cortex as measured via event related potentials (ERPs), but also that the way attention influences the P1 and N1 components is correlated in controls but independent in migraineurs. We find that migraineurs do not show the normal ability to modulate early perceptual and discriminative visual brain responses using spatial attention.

PO291
Time course of cerebral blood flow during migraine attack and after rizatriptan therapy, using arterial spin-labeled MR imaging
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Objectives: The purpose of this study is to investigate the changes of cerebral blood flow during migraine attack and after rizatriptan therapy using arterial spin-labeled (ASL) MR imaging.

Background: The pathophysiological mechanism of the migraine is still unclear. Recently, the trigeminovascular system has a main role in the pathophysiological mechanism of the migraine. From the animal studies, cortical spreading depression may induce the activation of the trigeminovascular system and may be a trigger of the migraine pathological mechanism. Also the activation or the functional change of brainstem nuclei, involving periaqueductal grey matter, raphe nuclei, locus ceruleus and hypothalamus may be a trigger of the migraine attack.

Methods: We performed an analysis of high field MR imaging examinations including ASL perfusion during migraine attack and 30 minutes and 60 minutes after oral administration of rizatriptan 10 mg. We generated quantitative imaging of perfusion and a single subtraction thin-section inversion time (TI) 1 periodic saturation with flow-sensitive alternating inversion recovery sequence. The advantages of ASL compared with conventional perfusion techniques include repeatability, absolute quantification, and the avoidance of intravenous contrast admission.

Results: A 32-year-old man with a history of migraine without aura presented with new-onset bilateral frontal pulsating headache. ASL images showed relative hypoperfusion in the hypothalamus and relative hyperperfusion in the frontal cortex as compared to the state without migraine attack. The patient treated with rizatriptan 10 mg, his headache improved soon. Repeat ASL images 30 minutes after the therapy demonstrated recovered relative perfusion in the hypothalamus and decreased relative perfusion in the frontal cortex as compared to the state during migraine attack.

Conclusions: These data suggested that hypoperfusion in the hypothalamus is closely related to migraine attack and rizatriptan recovers the hypoperfusion.
PO293
The role of neuroimaging in children and adolescents with headaches – multicenter study
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Objectives: The aim of this study is to evaluate the role of neuroimaging and to estimate the frequency of intracranial lesions in children and adolescents with headaches.

Background: Headache in children and adolescents is among the most common problems causing medical attention to their parents. Although they are generally benign, neuroimaging studies are frequently performed in clinical practice for the fear of missing serious underlying diseases. But, neuroimaging is rarely necessary unless the history or neurologic examination suggests structural etiologies. A few reports in literature assess the utility of neuroimaging in children and adolescents with headaches.

Methods: We retrospectively reviewed the medical records of all 1562 (male 724, female 838) new patients with headaches in 9 centers of the Pediatric Neurology Clinic of tertiary Hospitals. The mean age was 10.13 years (range 2–18). These patients were evaluated in a comprehensive neurologic examination and data recording age of onset, headache period, frequency, duration, intensity, location and quality of headache and neurologic or headache associated symptoms were obtained. Each headache was classified according to the International Classification of Headache Disorders, 2nd edition.

Results: Neuroimaging procedures were performed in 72.8% of the patients. The overall percentage of abnormal findings detected on neuroimaging was 9.3% (112/1204). The abnormal findings on neuroimaging were 50.0% (9/18) in patients with abnormal neurologic examinations, 12.9% (26/201) in changes in the type of headache and 10.1% (21/208) in neurologic dysfunction and 10.8% (9/83) in recent onset of severe headaches. Ten of the patients had undergone surgery because of neuroimaging results. There was no significant relation between abnormality on neuroimaging and gender, age, headache type, onset age of headache, headache period, duration, frequency, location and intensity of headache (P > 0.05).

Conclusions: Neuroimaging procedures in children and adolescents with headaches were very commonly performed. There was a significantly higher abnormality on neuroimaging among the patients with an abnormal neurologic examination (P < 0.001). Among patients who underwent neuroimaging because of the recent onset of severe headaches, a change in the type of headache, and/or a neurologic dysfunction, the rate of significant abnormality was very low. We suggest that more strict guidelines for pediatric headache patients are needed.

PO294
Surround suppression as a measure of cortical inhibition in migraine
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Objectives: The objective of the present study was to assess the strength of intracortical inhibition in migraineurs, specifically within the visual motion pathway.

Background: Reduced intracortical inhibition has been posited as a source of the hypersensitivity to visual stimulation seen in many migraineurs. Furthermore, a number of abnormalities in motion processing have been described in migraine (e.g., Shepherd, 2006; Antal et al., 2005; McKendrick & Badcock, 2004), focusing attention on the cortical projections of the magnocellular pathway. In the present study, we use surround suppression (Tadin et al., 2003), a task in which motion of large high contrast patterns is paradoxically harder to detect than small patterns. Weakened surround inhibition leads to superior motion direction discrimination for large stimuli at high contrast, an effect which has previously been reported in healthy elderly individuals (Betts et al., 2005).

Methods: Duration thresholds for discriminating direction of motion in gratings were measured in migraine with aura (MA; n = 19), migraine without aura (MoA; n = 20) and headache-free age-matched controls (C; n = 21) under three contrast levels (3%, 46%, 92%) and two stimulus size conditions (0.7° and 5°). Testing was binocular, viewing distance was 57 cm, and all subjects had corrected visual acuity of at least 20/25 in each eye.

Results: Four outliers (2 C; 2 MA; each >3 SD above group mean) were omitted from the analysis. Motion discrimination duration thresholds improved as contrast increased for small stimulus patches, but deteriorated with increasing contrast for large stimuli, as previously reported in normal subjects by Tadin et al. (2003). The main effects of stimulus size and contrast were statistically significant (P < 0.001), as was the interaction between size and contrast (P < 0.001), but neither the main effect of headache group, nor any interaction involving group reached statistical significance (all P-values > 0.19). Suppression indices [log (large stimulus threshold/small stimulus threshold)] were calculated for each subject and contrast. Again, ANOVA revealed a significance effect of contrast (P < 0.001), but no group effect (P = 0.34) or group by contrast interaction (P = 0.31). MA and controls showed nearly identical performance, whereas MoA showed a weak trend in the predicted direction of less surround suppression.

Conclusions: We found no evidence for impaired inhibition in MA and only a weak trend in MoA using this unique task in which weakened inhibition would actually improve performance, thus excluding the influence of generalized impairment. This finding is in contrast to results reported in normal aging where GABA-ergic inhibition is known to be weak (Leventhal et al, 2003) and surround suppression is also reduced.

PO295
TCD bubble test and migraine with aura
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Objectives: Objectives of this study were to determine differences of demographic features, characteristics of headache and aura in patients with migraine with aura according to results of TCD bubble test.

Background: According to results of several studies in which transcranial doppler (TCD) ultrasound was used for detection of right-to-left shunt, its prevalence is higher in patients with migraine with
aura, comparing with migraine without aura patients and healthy subjects.

Methods: The characteristics of aura and headache were analyzed in the group of 50 patients with migraine with aura and compared with the results of contrast-enhanced TCD ultrasound examination.

Results: In the group of 50 patients (82% female, 17 to 67 years old), 38 (76%) of them had positive TCD bubble test. Patients with positive TCD bubble test comparing to those with negative result were younger at the time of headache onset (17.1 ± 7.4 vs. 23.8 ± 11.1, \( P = 0.021 \)), had higher prevalence of sensory aura (76.3% vs. 41.6%, \( P = 0.036 \)) and positive family history of headache (68.4% vs. 27.3%, \( P = 0.033 \)). Differences between other demographic features (age at the time of examination, gender), characteristics of headache (frequency, localisation, intensity, quality of pain, duration, accompanying symptoms) and aura (duration, aura symptoms), in these two groups were not significant.

Conclusions: Patients with migraine with aura and positive TCD bubble test are younger at the time of headache onset, have higher prevalence of sensory aura and positive family history for headache, than patients without it.

PO297

Intercital stripe-pattern induced discomfort is related to ictal photophobia in migraine attacks

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Objectives: To investigate the relationship between responses to interctal stripe-pattern visual stress and photophobia during migraine attacks.

Background: Photophobia is a well-known symptom during migraine attacks. It is reported that migraine patients complained more discomfort than non-migraine patients by viewing stripe pattern. The association of two visual symptoms of migraine, ictal photophobia and interictal responses to stripe pattern, has not been elucidated.

Methods: Seventy-four migraine patients who visited outpatient clinics of two university hospitals were recruited. After completing questionnaire for their headache and photophobia, patients were evaluated for characteristics and associated symptoms of headache. Responses to interictal stripe pattern visual stress (visual stress test, VST) was administered by viewing 3 different types of black and white stripe patterns and was scored in 10-point visual analog scale (no discomfort as 0 and maximal discomfort as 10). Stripe patterns were printed in a 10 cm circular patch, a grating with square-wave luminance profile. Each stripe patterns were only different in the widths of stripes, 0.5 cm, 0.25 cm and 0.125 cm.

Results: Forty-two (56.8%) patients complained photophobia during migraine attacks. In all three stripe patterns VST, migraine patients with photophobia reported significantly more discomfort than migraine patients without photophobia (3.0 ± 2.4 vs. 0.9 ± 1.4 in 0.5 cm VST, 4.4 ± 2.1 vs. 1.9 ± 2.3 in 0.25 cm VST and 5.6 ± 2.5 vs. 3.5 ± 2.7 in 0.125 cm VST). There was no significant difference in headache intensity and migraine frequency between migraine with photophobia and migraine without photophobia.

Conclusions: Patients with photophobia reported more discomfort in 0.5 cm, 0.25 cm and 0.125 cm VST than migraine without photophobia.
PO299
Sun exposure and peripheral origin of migraine
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Objectives: To document sunexposure triggering frequent migraine attacks in thousands of patients in a coastal district of Southern India and thus to support a peripheral model for origin of migraine headaches.

Background: Migraine has a complex pathophysiology in which both central and peripheral components of trigeminal pain pathway probably play a significant role. Obscure are the mechanisms through which localized brain stem generator could be activated by diversity of triggers involved in migraine. There is increasing evidence that activation and degranulation of meningeal and other peripheral mast cells results in meningeal irritation, vascular dilatation and stimulation of nearby nociceptor nerve endings of trigeminal nerve, thus potentially contributing to the pathogenesis of migraine. In addition to the acute and chronic effects of sunlight, a variety of unusual reactions may occur soon after a brief sun exposure. Exposure to sunlight causes various skin disorders within a few minutes to protein degranulated manifestations. Etiology is uncertain, but may involve endogenous skin constituents functioning as photoallergens and leading to mast cell degranulation.

Methods: A total of 10 000 migraineurs were studied over a period of 5 years in two coastal hospitals (local temperature ranging from 26°C to 38°C). Age group 15 to 60 years. ICHD2 migraine diagnostic criteria and a special headache questionnaire suitting to this region of India were applied. All migraine triggers documented and the time between the sunexposure and the onset of pain recorded.

Results: 89% (8902) reported sunexposure as the predominant trigger. Pain started immediately after exposure in 41% (3650), within 2 hours in 32% (2849), 4 to 6 hours in 23% (2047), after 6 hours in 2% (179) and after 12 hours in 1.5% (133). 26 patients reported variable duration for each migraine attack. 13 patients reported more than 24 hours and 5, more than 48 hours. In the majority, pain started like tth (but throbbing- unilateral, bilateral or unilateral extending bilateral) to reach the maximum intensity within 10 minutes to 4 hours.

Conclusions: A subtle UV light induced peripheral mast cell activation and degranulation (akin to a very mild photodermatitis or phototoallergy) and formation of inflammatory mediators like histamine, prostaglandins and serotonin which stimulate surrounding nociceptors resulting in release of vasodilatory neuropeptides like CGRP and Substance P causing local increase in vascular permeability and plasma extravasation and thus leading on to neurogenic inflammation, could be a definite possibility in these large group of patients. Patients, parents and relatives were extremely satisfied with this peripheral model of origin to their migraine whenever external triggers were involved. They understood the central brain stem generator hypothesis and antidiromic activation much better after listening to the peripheral mechanism. This data requires confirmation by other studies.

PO300
Magnetic resonance investigation 3.0T detects white matter lesions of brain in case of chronic migraine
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Objectives: The purpose of the study was to investigate morphologic changes of white matter in patients with episodic and chronic migraine using 3T MRI.

Background: The population-based data indicate the presence of brain lesions in the posterior circulation in the case of migraine, notably those with aura.

Methods: We studied 21 patients with migraine (all women, 28–56 years old) according to the criteria of the Headache Classification II (2004) of the International headache Society. The study protocol included the neurological examination, answering questionnaires, quantifying the strength of headache and disability, MRI of brain using 3.0 Tesla (GE HDx). The MRI protocol included T1 WI, T2 WI, Diffusion-tensor imaging (DTI), Diffusion-weighted imaging, T2*–weighted GRE and MR-angiography. The investigation patient group included 16 patients with migraine without aura (MO), 5 patients with migraine with aura (MA); 13 patients had chronic frequent migraine (the number of migraine attacks >6 in a month) and 8 patients had episodic migraine (1–2 attacks/month).

Results: Frequent white matter lesions were identified in 16 patients. The white matter lesions were founded mostly in frontal and temporal lobes. The lesions were multiple (in all 7 cases), mono in 5 cases and the size ranged from 3–7 mm. Dilated of perivascular spaces were also found in 8 number of cases. The largest number of focal white matter lesions were found in patients with chronic migraine, with equal frequency in MO and MA and the highest number of lesions were found ipsilateral to the headache side.

Conclusions: The chronic migraine is a disabling disorder with organic structural damage. In our patients, focal white matter lesions could have been the result of avascular process, but the findings are non-specific in migraine. We have not find lesions in the posterior circulation, as has been previously reported.

Discussion: High field (3T) MRI verifies that mariners harbor focal white matter lesions. The nature and pathophysiology of these lesions remains to be elucidated.
PO302  
Pericranial tenderness during attacks in migraine patients

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Objectives: To demonstrate that muscle contraction abnormalities play an important role in the migraine mechanism, we investigated how many patients feel pericranial tenderness during migraine attacks.

Background: According to the international classification of headache disorders (ICHD), originally migraine and tension type headache are described as kinds of opposite concepts. Migraine is positioned as a vascular headache; on the other hand, tension-type headache is positioned as a non-vascular headache. The exact mechanisms of tension-type headache are not known. Peripheral pain mechanisms are most likely to play a role in infrequent and frequent episodic tension-type headache. Increased pericranial tenderness therefore recorded by manual palpitation is the most significant abnormal finding in patients with tension-type headache. We usually pay attention to pericranial tenderness for tension type headache patients, but not for migraine patients. In recent years, some investigators, however, have been reported muscle contraction abnormalities play a role of migraine mechanism. We thought this required further study about pericranial tenderness in migraine patients.

Methods: We studied pericranial tenderness during headache attacks using questionnaires given to 366 outpatients suffering from headaches (156 males, 210 females, with an average age of 47.3 years) in our hospital from May 2007 to December 2007. All of these patients completed the questionnaires. In addition, if they visited our hospital during their migraine attack, we checked pericranial tenderness.

Results: We analyzed 366 patient cases. Of these cases 128 patients had migraine (34 males and 94 females). Of these migraine patients, 68 patients felt pericranial tenderness during attacks. Furthermore, 43 of these 68 patients had a tension-type headache as comorbidity, while over a third of cases, 25 patients did not have a tension-type headache.

Conclusions: We revealed that significant numbers of migraine patients without tension type headaches feel pericranial tenderness during attacks. We believe this further demonstrates that muscle contraction abnormalities play a significant role in the migraine mechanism, as well as in the tension type headaches mechanism. Additionally, this may be a new clue to resolve the pathogenesis of migraine.

PO303  
Presence of right-to-left shunt in chronic migraine has little effect on the clinical presentation

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Objectives: To compare chronic migraine (CM) features in persons with and without right-to-left shunt (RtLS).

Background: RtLS is present in about 50% of those with episodic migraine with aura. The mechanism of this association is uncertain. We discovered that patients with CM have an unexpectedly higher rate of RtLS (66%). If RtLS has a pathogenic role in CM, clinical differences may exist between CM patients with and without RtLS.

Methods: Patients with current or past CM were eligible. A structured diagnostic interview was conducted. RtLS presence was detected by bubble transcranial Doppler, using agitated saline with autologous blood. Size was graded by the number of embolic tracks present.

Results: One hundred thirty-one patients completed the study. The rate of RtLS did not differ significantly between those who did and did not have aura (64% with aura, 67% without aura, P = 0.76). RtLS presence and size did not correlate with age of onset of episodic or chronic headaches, duration of episodic or chronic illness, or time to transformation from episodic to chronic migraine (P > 0.05 for all). RtLS presence and size did not correlate with age; headache location, quality, severity, or unilaterality; associated nausea, photophobia, phonophobia, or osmophobia; autonomic features; sensorimotor symptoms; vertigo/dizziness; confusion; alldynia; presence of prodrome; International Classification of Headache Disorders, 2nd edition, defined aura; or any aura-like symptom (P > 0.05 for all). RtLS presence weakly correlated (Φ = 0.18, P = 0.04) with current migraine frequency. Of the 86 CM patients diagnosed with RtLS, 28 (32.6%) had <15 days/month of headache at the time of study while 7 (15.6%) patients without RtLS had headache <15 days/month. RtLS presence weakly correlated with vomiting (Φ = 0.18, P = 0.04) and language dysfunction (Φ = 0.19, P = 0.03) during baseline headache. Of the 86 patients with RtLS, 18 (20.9%) reported vomiting and 53 (64%) reported language dysfunction, while among those without RtLS, only three (6.6%) reported vomiting and 20 (44.4%) reported language dysfunction with baseline headache. Blur vision was reported more often by patients with RtLS [by 59 of 86 (68.6%)] vs. 24 of 45 (53.3%) without], but this difference was not statistically significant (Φ = 0.15, P = 0.08).

Conclusions: The only characteristics associated with RtLS in patients with CM were headache frequency of <15 days/month at the time of study and having symptoms of vomiting and language dysfunction with baseline headache. In contrast to the episodic migraine population, aura does not correlate with RtLS in CM, suggesting differing mechanisms for these associations. Although RtLS may be present quite frequently in those with CM, these data do not support a hypothesis that it plays a pathogenic role.
PO304

The prognosis of persistent migrainous aura
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Objectives: We sought to assess the prognosis of continuous migrainous aura.

Background: The symptoms of a migrainous aura, in contrast to those of transient or permanent cerebral ischaemia are usually positive, examples including flashing zigzag patterns of light and parasthesiae. They usually last 20–40 minutes, though a total of 29 cases of such positive phenomena lasting for weeks or months have been reported in the last 25 years. We present a series of 15 patients with symptoms lasting a minimum of 2 months, without permanent physical signs or scan abnormalities.

Methods: We reviewed records and telephoned the patients.

Results: The symptoms in four of the patients had resolved after a mean of 7 months. Four were lost to follow-up, and the symptoms in the remaining six were continuing, for between 2 months and 10½ years. These included blurring and shimmering of vision, with wiggly, twig-like or zigzag lines, persistent after-images, and weakness of one leg with speech arrest. Headache was never a significant problem. A wide variety of treatments have been tried, including acetazolamide, topiramate, valproate, phenytoin, flunarizine and chlorpromazine; it was difficult to assess whether any of these proved of unequivocal value. None of the patients came to any long-term harm.

Conclusions: The pathogenesis of these phenomena remains poorly understood, but we presume it is in some way related to an inability to terminate the wave of cortical excitation that is believed to be the human equivalent of the spreading depression described in the rat.

PO305

Abstract withdrawn

PO306

Reading-induced migraine
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Objectives: We present five cases of migraine attacks triggered by reading and discuss the putative pathophysiology.

Background: Very many factors may aggravate or precipitate an attack of migraine. Visual stimuli have often been implicated. Reading as a migraine trigger has not been reported as a factor that interacts with patient's lives.

Methods: Case reports.

Results: In three patients, migraine was precipitated by reading any material for a short period of time. In two other cases, mother and daughter, migraine attacks occurred invariably when reading highly descriptive material specifically about migraine. Depending on the patient, attacks occurred within 10 minutes to 1 hour of reading. Prophylactic medications either had no effect on the reading-induced migraine (n = 1) or markedly decreased this triggering factor as well as decreasing overall migraine frequency (n = 4).

Conclusions: Discussion: Virtually any stimulus may aggravate or precipitate an attack of migraine in a susceptible individual. Reading involves several descriptive material specifically about migraine. Depending on the patient, attacks occurred within 10 minutes to 1 hour of reading. Prophylactic medications either had no effect on the reading-induced migraine (n = 1) or markedly decreased this triggering factor as well as decreasing overall migraine frequency (n = 4).

Conclusions: Discussion: Virtually any stimulus may aggravate or precipitate an attack of migraine in a susceptible individual. During an attack, a migraineur will instinctively avoid reading or any other potential irritant, preferring isolation in a quiet, dark environment. In the cases described above, reading was the main or sole triggering factor. The cases of the mother and daughter were unusual in that reading material had to be specifically about migraine for a migraine attack to be precipitated. Similar features have been noted in reflex epilepsy wherein cognitive activity induced seizures. Cortical neuronal hyperactivity lowers the threshold to stimuli, which may evoke migraine or epilepsy. The same factors that have been implicated in reading epilepsy may be invoked to explain reading-induced migraine. These include visual patterns, attention and cognitive functions, as well as the complexity and duration of reading material. For migraine, visual stimuli are more likely than proprioceptive impulses from eye muscles. The stimuli may include light intensity, color, symbols and a relationship to cognitive factors, such as comprehension and the complexity of reading material. More than one of these factors may be operative. These stimuli appear to enhance an already hyperexcitable cortex. In migraineurs the occipital cortex is the most hyperexcitable area. However, reading involves several areas in addition to the occipital lobe. Reading is a complex cognitive phenomenon involving visual analysis, memory and processing. During reading, PET scans reveal activation of the mid-temporal, frontal and medial extrastriatal cortices on the right as well as the left sides of the brain. Word processing involves the left posterior temporal and left inferior parietal cortex. There are, of course, connections with the associated visual cortex.

Conclusion: Reading-induced migraine may occur more often than is commonly recognized and is sometimes a major factor in disrupting patient’s lives.
PO308
Proposed visual screening measures for migraine research
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Objectives: This presentation proposes a series of screening measures, the inclusion of which would greatly enhance the reporting of studies of vision and migraine.

Background: The visual system has attracted considerable attention as one site of possible abnormality in migraine; migraineurs are unusually sensitive to a variety of visual stimuli including bright light, flicker, and spatially periodic patterns. However, many reports in the literature examining visual function either as their principle focus or in conjunction with other measures, fail to provide sufficient information about the basic visual abilities of their participants to allow other investigators to evaluate the experimental findings.

Methods: The following recommendations are based on the authors’ collective experience carrying out basic vision research and/or clinical visual assessment.

Results: We proposed the following minimum screening measures. (1) Visual acuity in each eye alone and binocularly, using ETDRS or other standard chart. Ideally both best corrected and uncorrected acuity in each eye should be recorded, along with the refractive correction used in the study. Existing refractive error and interocular differences in refraction may be important in understanding visual function; even if the actual study tests are carried out with correction and/or monocularly. (2) Contrast sensitivity, using the Pelli-Robson chart or similar clinical measure, provides additional valuable information about visual sensitivity at lower spatial frequencies not tapped by acuity measures. (3) The presence and quality of stereopsis can be assessed rapidly using the Titmus® or similar clinical test. If binocular interaction forms a crucial part of the study, a more sensitive test such as the TNO is recommended and an assessment of binocular alignment is warranted. (4) Colour vision tests are essential if the visual system is to understand their potential role in the trigeminocervical complex. (5) Visual discomfort measures of flicker and pattern glare should be included and considered as a covariate in any analyses. To obtain meaningful results all tests must be conducted under appropriate lighting conditions. In addition to these minimal screening measures, exclusionary criteria to consider include the presence of amblyopia or a history of “lazy eye”, and diseases that may affect the visual or oculomotor pathways such as optic neuritis, Parkinson’s disease, diabetes, glaucoma, and thyroid disease. Many drugs affect visual function and these too should be considered in subject exclusion and/or their use noted. Finally, frequently omitted but critical methodological information includes room lighting conditions, stimulus luminance and viewing distance, whether the test was carried out binocularly or monocularly and, if the latter, whether the other eye was occluded with an opaque patch or with a patch that allows light transmission.

Conclusions: An understanding of visual deficits revealed in migraine studies would be enhanced by the inclusion of standardized visual screening of the sort proposed here.

PO309
Is cervicogenic headache caused by local factors in the neck? an MRI analysis of the craniovertebral ligaments and membranes
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Objectives: Aim of present study is to investigate structural changes in the neck in people with cervicogenic headache.

Background: Injuries of alare and transverse ligaments have been shown in previous MRI studies. It is known that significant number of cervicogenic headache patients had neck trauma with whiplash mechanism in anamnesis.

Methods: Forty patients with cervicogenic headache, 19 with whiplash related headache and 17 patients with migraine (control group) were included in the study. The International Classification of Headache Disorders (ICHD II) and the classification by Sjaastad et al (Cervicogenic Headache Study group) were applied. All three groups were examined with MRI (a proton weighted MR imaging of the craniovertebral junction in three orthogonal planes) and diagnostic blockades (great occipital nerve blockades). Structural changes in the alar and transverse ligaments were graded by radiologist according to previous studies (grade 0–3), degenerative changes have also been graded.

Results: The results are currently being analyzed and will be presented at the congress.

Conclusions: Will be presented at the congress.

PO310
VPAC1 and PAC1 receptor antagonists inhibit activation of the parasympathetic outflow to the cranial vasculature to prevent autonomic responses and neuronal firing in the trigeminocervical complex
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Objectives: To study the effects of VPAC1, VPAC2 and PAC1 receptor antagonists in models of trigeminovascular nociception and activation of the parasympathetic outflow to the cranial vasculature, to understand their potential role in the trigeminovascular system and therefore the pathophysiology of primary headaches.

Background: Vasoactive intestinal peptide (VIP) and pituitary adenylate-cyclase activating peptide (PACAP) have been implicated in primary headaches. They have been shown to cause cephalic vasodilation in patients and animals, and VIP is released during cluster headache while PACAP-38 causes headache and migraine in patients. VIP and PACAP act on VPAC/PAC receptors.

Methods: Rats were anesthetized with pentobarbital (60 mg/kg) and cannulated for measurement of blood pressure and intravascular administration of supplementary anesthesia with propofol (15–20 mg/kg/hour-i.v. infusion). We used models of trigeminovascular nociception using stimulation of the dural vasculature and a novel approach that activates the trigeminal-autonomic reflex, using superior salivatory nucleus (SuS)/facial nerve stimulation, with intravital microscopy and electrophysiology, to explore the effect of VPAC/PAC receptor antagonists on trigeminal nerve activation. We also looked at autonomic responses through blood flow observations of the lacrimal duct/sac.

Results: Neurogenic dural vasodilation was inhibited by PACAP6-38 (130 mg/kg), a predominantly PAC1 antagonist, but not by PG97-267 (50 mg/kg, VPAC2) or VIP6-38 (300 mg/kg, VPAC2). There were no effects on neuronal responses in the trigeminocervical complex (TCC) in response to dural activation of trigeminal afferents. Neuronal firing in the TCC in response to stimulation of the SuS via the facial nerve was inhibited by PACAP6-38 (F1,56 = 2.89, P < 0.05) and PG97-267 (F1,49 = 3.81, P < 0.005), but not with VIP6-28. Similarly, both PACAP6-38 (F1,42 = 3.45, P < 0.01) and PG97-267 (F1,56 = 2.61, P < 0.05) inhibited evoked blood flow changes in the lacrimal sac/duct caused by SuS stimulation, while VIP6-28 had no effect.

Conclusions: The data indicate that only PAC1 receptor antagonists are able to inhibit activation of the trigeminal nerve via stimulation of dural efferents, but only at the neuromuscular junction. Whereas both PAC1 and VPAC1 receptor antagonists appear to be acting on the parasympathetic outflow to the cranial vasculature, to inhibit both neural responses in the TCC and autonomic facial responses.
The VPAC2 receptor does not seem to play a role in this pathway. PAC1 and VPAC1 receptor activation may be involved in the pathophysiology of primary headaches.

PO311
Characterization of the CGRP receptor antagonist telcagepant in human isolated cerebral and meningeal arteries
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Objectives: To compare relaxations to calcitonin gene-related peptide (CGRP) and antagonistic effects of telcagepant, as well as expression of the receptor elements calcitonin like receptor (CLR) and receptor amplifying membrane protein 1 (RAMP1) of the CGRP receptor in human isolated cerebral and meningeal arteries.

Background: CGRP is a potent vasodilator involved in migraine. The CGRP receptor antagonist olcegepant (BIBN4096BS) is effective in migraine, but can only be used systemically. Recently, an orally bio available CGRP receptor antagonist, telcagepant (MK-0974), was shown to be effective in migraine.

Methods: Human cerebral (cortex) (5M, 4F, 45–76 years, Ø 300–500 μm) and meningeal arteries (2M, 2F, 42–62 years, Ø 500–750 μm) were mounted in organ baths. Concentration response curves to CGRP were constructed in the absence or presence of telcagepant. For immunohistochemistry, slices of cerebral and meningeal artery were stained for RAMP1, CLR and actin in a double immunofluorescence staining.

Results: Telcagepant was devoid of any contractile or relaxant effects per se (tested up to 100 μM). CGRP induced concentration-dependent relaxations; Emax was 58 ± 6% (% of precontraction) in cerebral and 50 ± 11% in meningeal arteries, pEC50 values were 8.8 and 8.7 ± 0.2, respectively. Pre-treatment with telcagepant (10 nM) antagonized the CGRP-induced relaxation in a competitive manner with a pA2 value of 8.83 in cerebral arteries. In the meningeal arteries, telcagepant (1 μM) antagonized the CGRP-induced relaxations with a pK9 of 8.03 ± 0.16. Immunohistochemistry revealed a strong expression of CLR and RAMP1 in the smooth muscle cells in the media layer of both cerebral and meningeal arteries.

Conclusions: Telcagepant antagonizes relaxations to CGRP with a potency that is consistent between different human cranial arteries. In the absence of CGRP, telcagepant does not affect vascular tone. Our findings provide morphological and functional data on the presence of CGRP receptors in both cerebral and meningeal arteries which illustrates a possible site of action of the novel CGRP receptor antagonist telcagepant in the therapy of migraine attacks.

PO312
DHE repression of ATP-mediated sensitization of trigeminal ganglion nociceptive neurons involves activation of alpha2 adrenergic receptors
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Objectives: The goal of this study was to determine the cellular mechanisms by which DHE represses ATP-mediated sensitization of trigeminal nociceptive neurons.

Background: The ergot alkaloid, dihydroergotamine (DHE), which exhibits affinity for several types of receptors including serotonin, adrenergic, and dopamine receptors, is an effective treatment of moderate to severe migraine. Interestingly, DHE is reported to be superior to sumatriptan in preventing headache recurrence. This beneficial effect of DHE is likely due to its long duration of pharmacological activity as compared to triptans. The exact mechanism of action of DHE in treating migraine is not known but likely involves modulation of trigeminal nociceptive neurons.

Methods: Trigeminal ganglia isolated from 3 to 4 day-old Sprague Dawley rats were used to study the effect of DHE on co-stimulation of cultured neuronal cells. Intracellular calcium levels were measured in neurons via calcium imaging with Fura2-AM. The amount of CGRP secreted into culture media was determined using a CGRP-specific radioimmunoassay. Changes in MAP kinase phosphatases (MKP) 1,2, PKA, and P2X3 were measured via immunohistochemistry.

Results: While treatment of trigeminal neurons with ATP alone did not cause changes in intracellular calcium levels, pretreatment with ATP caused sensitization of neurons such that subthreshold doses of KCl significantly increased intracellular calcium levels. This sensitizing effect was reflected in CGRP secretion as ATP pretreatment caused significant elevations in the amount of CGRP released from trigeminal neurons in response to the same subthreshold doses of KCl. This sensitizing effect was shown to involve P2X3 receptor. Changes in the excitability state of neurons by ATP were accompanied by an increase in active PKA. Pretreatment with DHE greatly repressed increases in intracellular calcium and CGRP secretion in response to cotreatment with ATP and KCl. DHE also increased expression of the MKP 1 and 2 while correspondingly decreasing the amount of active PKA. Importantly, these cellular effects of DHE were blocked with an alpha2a and 2c adrenergic antagonist.

Conclusions: We propose that increased levels of ATP, as reported during cortical spreading depression, cause sensitization as well as stimulation of key inflammatory proteins in trigeminal nociceptive neurons. These stimulatory effects were repressed by DHE via a mechanism that likely involves increased expression of MKPs. In addition, we found that DHE repression of ATP-mediated sensitization involves activation of adrenergic receptors, and thus, functions differently than triptans. Taken together, our findings provide evidence for a novel mechanism of action for DHE that may help to explain, at least in part, its efficacy in aborting migraine attacks, reported low headache recurrence rate for DHE, as well as its clinical use to break the chronic migraine cycle.

PO313
Molecular investigations of BKCa channels and the modulatory β-subunits in porcine trigeminal ganglion: colocalization with CGRP
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Objectives: Ion channel function has been implicated in migraine pathology. We hypothesize that the large conductance calcium-activated potassium (BKCa) channel α- and β-subunits are present in the porcine trigeminal ganglion and co-localize with calcitonin gene-related peptide (CGRP).

Background: Migraine is associated with activation and sensitization of trigeminal neurons. The BKCa channels are essential for ion fluxes across the cell membrane contributing to electrical impulses regulating cell excitability and neurotransmitter release. The native BKCa
channel is composed of α- and β-subunits (β1–β4). Co-expression with the β-subunit modulates the channel activity changing Ca²⁺ sensitivity, kinetic behaviour and pharmacology. Studies from the dorsal root ganglion have shown that BKCa blockers increase neuronal firing in the dorsal root ganglion whereas the BKCa openers suppress neuronal firing activity.

Methods: We investigated the mRNA expression of BKCa channel and the modulatory β-subunits in the porcine trigeminal ganglion by reverse transcription polymerase chain reaction (RT-PCR). The distribution patterns of BKCa channel α-subunit mRNA and protein were investigated using in situ hybridization and histochemistry, respectively. Immunofluorescence imaging was used to investigate the co-expression of BKCa channels and CGRP. Western blotting was used to investigate the protein expression of the modulatory β1–β4 subunits.

Results: BKCa channel mRNA expression was detected in porcine trigeminal ganglion. In situ hybridization also verified BKCa channel mRNA transcripts in the trigeminal ganglion. Histochemistry showed immunoreactivity for the BKCa channel protein. Immunofluorescence imaging revealed co-expression of BKCa channels with CGRP immunoreactive trigeminal ganglion cells. The modulatory β2- and β4-subunit mRNA was detected in the trigeminal ganglion using RT-PCR. Western blotting detected β2- and β4-subunit protein in the trigeminal ganglion.

Conclusions: The present study showed expression of BKCa channel mRNA and protein in the porcine trigeminal ganglion. BKCa channel protein was co-localized with the neuropeptide CGRP in the trigeminal ganglion cell bodies. The modulatory β2- and β4-subunits were expressed in the porcine trigeminal ganglia. We suggest that BKCa channels may be involved in pain transmission through the trigeminal ganglion pathway. Furthermore, BKCa blockers may be potential drugs for the suppression of hyperexcitable neurons and β-subunits may be important modulators of the BKCa channel conductance. Future experiments should clarify the importance of BKCa channels in the trigeminal ganglion pathway in relation to migraine and pain signalling.

PO314
LY466195, a clinically active compound in the acute treatment of migraine, inhibits activation in the trigeminocervical complex and the ventroposteromedial thalamus after nociceptive trigeminovascular activation
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Objectives: To investigate whether kainate receptors in the trigeminocervical complex (TCC) and the ventroposteromedial thalamic nucleus (VPM) participate in the modulation of nociceptive transmission as suggested by clinical trials with compounds active at the kainate receptor.

Background: Migraine pathophysiology involves activation of neurons in the trigeminocervical complex (TCC) and third order neurons in the ventroposteromedial thalamic nucleus (VPM). The iGluR5 antagonist LY466195 was effective in relieving migraine in a randomized controlled trial, and mild reversible visual distortions were reported as a side effect. The extent of kainate and non-kainate activity of LY466195 might facilitate a better understanding of the place of kainate receptor antagonism as a potential anti-migraine strategy.

Methods: Rats were anesthetized with pentobarbitone (60 mg/kg) and cannulated for measurement of blood pressure and supplementary anesthesia. Cells responding to electrical stimulation of dura vessels and microiontophoresed ionotropic glutamate receptors agonists, were identified in the TCC (n = 37), and on separate sets of experiments in the VPM (n = 30). The effect of local application by microiontophoresis and of systemic administration of LY466195 was studied on trigeminocervical and thalamocortical activity in response to dural vessels stimulation and on glutamate agonists-evoked neuronal firing.

Results: Systemic administration of LY466195 significantly inhibited responses to dural electrical stimulation in the TCC at 100 µg/kg (n = 7; P < 0.05) by a maximum of 33%, but had no effect at the dose of 50 µg/kg (n = 5; P = 0.13). Administration of 200 µg/kg inhibited trigeminovascular nociceptive responses in the TCC (n = 5; P < 0.05) to the same extent as the 100 µg/kg dose, demonstrating a ceiling effect. LY466195 significantly inhibited responses to dural stimulation in the VPM by a maximum of 52% at 100 µg/kg (n = 6; P < 0.005), and by a maximum of 22% at 50 µg/kg (n = 6; P < 0.05). Local application of LY466195 by microiontophoresis strongly attenuated cell firing in response to meningeal stimulation both at the levels of VPM and TCC (n = 17; P < 0.005). However, further to the potent inhibition of post-synaptic kainate receptor evoked-firing (n = 17; P < 0.05) seen in both areas, microiontophoresis of LY466195 further revealed a glycine/serine site-independent action on the NMDA receptor complex (n = 23; P < 0.05).

Conclusions: The data highlight the possible anti-migraine therapeutic benefits of manipulating glutamate receptors, and especially kainate receptors and indicates further to the TCC, the thalamus as an important site of action of kainate-targeting anti-migraine treatments. The NMDA site actions of this compound, seen using microiontophoretic techniques, could suggest while the clinical efficacy of LY466195 involves iGluR5 kainate receptors, that the visual disturbance reported by patients may be NMDA receptor-mediated.

PO315
Pharmacological characterization and mRNA expression studies of VIP and PACAP receptors in human coronary arteries
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Objectives: To study the expression and function of VPAC1, VPAC2 and PAC1-receptors in human coronary arteries (CAs).

Background: VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase activating peptide) are endogenous peptides which partially share receptors. It has been shown that infusion of PACAP-38 causes migraine-like attacks, in both healthy and migrainous populations, while VIP causes only mild, transient headaches. VIP and PACAP both activate VPAC1 and VPAC2 receptors with almost equal affinity, while PACAP has ~1000 fold higher affinity for the PAC1 receptor. This may point to PAC1-receptor antagonism as a putative mechanism for acute or prophylactic migraine treatment, depending on the peripheral side effects. The role of the PAC1 receptor in human CA was characterized through myograph- and expression studies.

Methods: Human CAs were obtained from heart-beating donors. The fresh arteries were used in wire myograph experiments, and separate segments saved for mRNA expression studies. In the myograph setup, the arteries were pre-treated with the VPAC1 antagonist PG-97269 or the PAC1 antagonist PACAP (6-38), precontracted, and concentration-response curves to VIP and PACAP-38 were recorded. mRNA expression of VPAC1, VPAC2 and PAC1 in the arteries was studied by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

Results: In the myographs, PACAP-38, PACAP-27 and VIP caused concentration-dependent relaxations of human CA, with the order of potency being VIP>PACAP-27>PACAP-38. The respective pEC50 values were 8.42 ± 0.15, 7.66 ± 0.24 and 7.01 ± 0.15. Treatment with...
the PAC1-receptor antagonist PACAP(6-38) did not induce contraction per se. PACAP(6-38) caused no significant shift in response to neither VIP or the PACAPs. The VPAC1-agonist caused a reduction of the potency of VIP. Expression studies showed that mRNA for the PAC1 receptor was present in low abundance compared to neuronal tissue and heart muscle. mRNA for VPAC1 and VPAC2 receptors was present in relatively high amounts.

Conclusions: The predominant vasodilatory component of PACAP seems to be mediated by VPAC-receptors. The PAC1 receptor is present in low abundance in the coronary arteries, and antagonism causes no apparent contraction. Thus, this study suggests that if a PAC1-receptor antagonist is employed in migraine therapy, the risk of coronary constriction as a side effect will be minor.

PO316
Expression studies and pharmacological characterization of VIP and PACAP receptors in the cerebral circulation of the rat
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Objectives: To study the expression and function of VIP- and PACAP-receptors in the intracranial circulation of the rat in relation to migraine.

Background: Endogenous peptides VIP (vasoactive intestinal polypeptide) and PACAP (pituitary adenyl cyclase activating peptide) partially share receptors, and display potent vasodilatory properties in different vascular beds. PACAP exists in two isoforms, PACAP-27 and PACAP-38. Both VIP and the PACAPs activate the VPAC1 and VPAC2 receptors with nearly equal affinity, whereas the PAC1 receptor is almost exclusively dedicated to the PACAPs. Studies in migraineurs reported that infusion of PACAP-38 induces a stronger immediate headache than VIP, and contrary to VIP causes a delayed-phase migraine-like attack. This difference calls for further investigation of the distribution and effect of the receptors for these peptides.

Methods: The vascular effect of VIP, PACAP-27 and PACAP-38 was examined by wire myograph experiments on the isolated, precontracted middle cerebral artery (MCA) and basilar artery (BA) of the rat. The vasodilatory effect was challenged with peptide antagonists for the VPAC1 and/or VPAC2 receptors. Preliminary experiments were done with the pure PAC1 peptide agonist Maxadilan. mRNA expression of the receptors VPAC1, VPAC2 and PAC1 in the MCA, BA and middle meningeal artery (MMA) of the rat was examined by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR).

Results: VIP, PACAP-27 and PACAP-38 elicited comparable vasorelaxant action in isolated rat MCA and BA. Respective pEC50 MCA: 7.87 ± 0.17, 7.88 ± 0.12, 7.52 ± 0.10, respective pEC50 BA: 8.31 ± 0.27, 7.19 ± 1.14, 7.81 ± 0.17. PACAP-27 and PACAP-38 were equipotent in the two arteries, while VIP proved more potent in BA than in the MCA. The VPAC1 antagonist PG97-269 demonstrated more efficient blocking of the relaxant effects than the VPAC2 antagonist PG99-465 for all peptides in both vascular beds. The combination of the two antagonists blocked more efficiently than either alone. No marked dilatory effect was observed with the PAC1-agonist Maxadilan. qRT-PCR studies demonstrated that all 3 receptors were present in the tested vascular beds, but with the PAC1 receptor in relatively small amounts. Preliminary experiments in human cerebral arteries support this pattern.

Conclusions: The difference in headache-inducing potency of PACAP and VIP can not be attributed to higher dilatory potency of PACAP over VIP. The PAC1 receptor was found in relatively low abundance in the vascular tissue tested. These results correspond with preliminary results in human vessels. Combined results indicate that the higher tendency of PACAP over VIP to cause headache is due to non-vascular effects.

PO317
Pharmacological characterization of PACAPs, VIP and their receptors in the human meningeal artery
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Objectives: To pharmacologically characterize responses of putative adenyl cyclase activating polypeptides (PACAPs), vasoactive intestinal peptide (VIP) as well as their VPAC/PAC receptors in human meningeal arteries to obtain more knowledge about their role in migraine.

Background: Migraine pathophysiology most likely involves cranial vasodilatation caused by neuropeptides. The PACAPs (PACAP38 and PACAP27) and VIP are involved in various physiological processes, including dilation of cerebral arteries. Infusion of PACAP38, but not VIP, may induce migraine-like headache in migraine patients (Schytz et al. Brain 2009). Interestingly, PACAPs do not only stimulate the VPAC receptors like VIP but they also activate the PAC receptors.

Methods: Segments of human meningeal artery (Ø 0.50–0.75 mm) obtained perioperatively (5 M, 5 F, 42–75 years) were precontracted with 30 mM K+ and concentration response curves to the PAC/PAC receptor agonist PACAP38 and PACAP27 as well as the VPAC receptor agonist VIP were constructed in the absence or presence of the PAC receptor antagonist PACAP6-38 or the VPAC receptor antagonist [Ac-H1,D-F2,K15,R16,L27]-VIP(3-7)-GRF(8-27). mRNA expression (2 M, 5 F, 35–57 years) was measured using RT-PCR.

Results: PACAP38, PACAP27 and VIP induced relaxations of 34 ± 12% (n = 7), 50 ± 11% (n = 2) and 40 ± 10% (n = 6), respectively at a concentration of 1 μM. PACAP38 was less potent (pEC50 < 6.9 ± 0.1) than PACAP27 (pEC50 7.2 ± 0.4) and VIP (pEC50 7.4 ± 0.2). The VPAC/PAC receptor antagonists did not affect these relaxations. The mRNA expression of VPAC receptors was higher than that of PAC receptors, with a more pronounced expression of the VPAC1 receptor than the VPAC2 receptor.

Conclusions: PACAP38 is less potent vasodilator than PACAP27 and VIP in human meningeal arteries. Our antagonist experiments do not confirm involvement of either VPAC or PAC receptors, although mRNA of these receptors is present in human meningeal arteries. The low potency of PACAP38 seems to be in contrast with the observation that PACAP38, but not VIP, may induce migraine-like headaches in migraine patients. In view of the fact that the potency of the PACAPs and VIP in human meningeal arteries is considerably less than that of CGRP, the vasodilator properties of the PACAPs and VIP, as well as their vascular receptors, may be less relevant in migraine. Thus, PACAP38 may induce migraine-like headaches via a mechanism not involving meningeal vasodilatation.

PO318
Abstract withdrawn

PO319
Rizatriptan represses stimulatory effects of capsaicin in trigeminal ganglion and trigeminal nucleus caudalis
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Objectives: To better understand the cellular mechanisms by which rizatriptan functions as an anti-migraine drug by investigating its effect on capsaicin-stimulated trigeminal ganglia neurons in both in vitro and in vivo studies as well as in vivo in the trigeminal nucleus caudalis (TNC).
Background: Although we know that triptans are effective in aborting migraine attacks, the exact mechanism is still not known. It is thought that the triptans could block release of CGRP fromafferent terminals in the dura and thus, repress neurogenic inflammation and peripheral sensitization. Alternatively, triptans are thought to inhibit the release of CGRP and glutamate from trigeminal effenter terminals and thus, block activation of second order neurons and the development of central sensitization. Recent studies have clearly shown that triptans are most effective when administered before central sensitization occurs (mediated by activation of second order neurons and glia).

Methods: Intracellular calcium levels and CGRP secretion from cultured rat trigeminal ganglion neurons in response to capsaicin and rizatriptan was investigated. In addition, in vivo studies were conducted that involved activation of trigeminal neurons by injection of capsaicin alone or in combination with rizatriptan injection (i.m.) and changes in MAP kinase phosphatase (MKP) 1, active ERK, c-Fos, and GFAP determined by immunohistochemistry in neurons and glia in trigeminal ganglia and TNC.

Results: Capsaicin caused a significant rise in intracellular calcium that was coupled with increased CGRP release from cultured trigeminal neurons. The stimulatory effects of capsaicin on calcium levels and CGRP secretion were repressed by pretreatment with rizatriptan. Interestingly, rizatriptan caused a sustained low level increase in intracellular calcium and did not inhibit unstimulated CGRP release. In our in vivo studies, rizatriptan was found to inhibit expression of active ERK, a signaling protein involved in peripheral sensitization, in trigeminal ganglion neurons in response to capsaicin injection. The decrease in active ERK levels is likely due to the activity of MKP-1, whose expression in trigeminal ganglia neurons was induced by rizatriptan. Importantly, rizatriptan repressed the stimulatory effects of capsaicin at the level of the TNC. Rizatriptan reduced the increased expression of c-Fos, a marker of neuronal activation, and GFAP, a marker of glial activation, while increasing total MKP-1 levels in the TNC in response to capsaicin.

Conclusions: We found that rizatriptan mediates a low amplitude sustained increase in intracellular calcium and represses stimulated CGRP secretion from trigeminal neurons in response to chemical depolarization. Furthermore, results from our in vivo studies provide evidence that rizatriptan regulates expression of key signaling proteins in the trigeminal ganglion and TNC that are implicated in peripheral and central sensitization.

PO320
In vivo and in vitro studies of PGE$_2$ receptors in rat trigeminal vascular system – relevance for migraine
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Objectives: The objective of this study was to investigate the expression and function of prostaglandin E$_2$ (PGE$_2$) dilatory receptors, EP$_2$ and EP$_4$, in tissues relevant to migraine.

Background: PGE$_2$ is synthesized in substantial amounts at sites of inflammation where it acts as a potent vasodilator and mediator of pain. PGE$_2$ exerts its dilatory response by two G-protein coupled receptors (EP$_2$ and EP$_4$) through cyclic adenosine monophosphate (cAMP) mediated in peripheral vascular beds. Clinical studies reported increased ictal levels of PGE$_2$ in both blood and saliva of migraineurs. Furthermore, PGE$_2$ can induce migraine-like headaches with the concomitant vasodilatation of cerebral vessels.

Methods: In vivo: SD rats were used for intravital microscopy on a closed cranial window. We studied PGE$_2$ (1–3000 ng/kg), butaprost (EP$_2$ receptor agonist) (1–100 µg/kg) and ONO-AE1-329 (EP$_4$ receptor agonist) (1–3000 ng/kg) induced dilatation of the middle meningeal artery (MMA) (n = 4–6/group). PGE$_2$ (300 ng/kg i.c.) induced dilatation was studied in the absence and presence of: BGC20-1531 (EP$_2$ receptor antagonist) (100–3000 µg/kg i.c.), AH6809 (EP$_2$ receptor antagonist) (30–120 µg/kg i.c.) and SQ22536 (adenylyl cyclase inhibitor) (30–100 µg/kg i.c.) (n = 4–5/group).

In vitro: Isolated rat MMA and middle cerebral artery (MCA) were investigated in organ baths. PGE$_2$ (10 nM-10 µM) induced vasodilatation was studied in the absence and presence of BGC20-1531 (1 µM), L-161,982 (1 µM), AH6809 (10 µM) and SQ22536 (30 µM) (n = 4–7/group). PGE$_2$ receptor mRNA expression was investigated in MMA, MCA, basilar artery, trigeminal ganglion and trigeminal nucleus caudalis by use of PCR. EP$_2$ and EP$_4$ receptors mRNA expression levels was performed with quantitative real-time PCR in the same tissues.

Results: In vivo experiments showed that dilatation to butaprost (Emax 110 ± 18%, pED$_{50}$ 5.0 ± 0.17) was less pronounced compared to PGE$_2$ (Emax 207 ± 43%, pED$_{50}$ 7.0 ± 0.31) and ONO-AE1-329 (127 ± 15%, pED$_{50}$ 7.4 ± 0.09) in the MMA in vivo. BGC20-1531, AH6809 and SQ22536 significantly inhibited the PGE$_2$ induced vasodilatory response in rats. Likewise, the used antagonists significantly inhibited the PGE$_2$ relaxation in rat MMA and MCA in vitro. Conventional RT-PCR showed that all PGE$_2$ receptors (EP$_1$-EP$_4$) mRNA were expressed in the tested neuronal tissues and arteries. However, quantification of the mRNA expression profile of the dilatory receptors (EP$_2$ and EP$_4$) showed dominance of these receptors in MMA and MCA as compared with the investigated neuronal tissues.

Conclusions: In conclusion, PGE$_2$ induced vasodilatory responses both in vivo and in vitro. The response could be inhibited by EP$_2$ and EP$_4$ receptor antagonists, possibly via cAMP mechanisms. mRNA expression of the EP$_2$ and EP$_4$ receptors show that they are predominant in the arteries. Thus, these receptors are potential and more specific targets in the development of anti-migraine drugs.

PO321
K$_{ATP}$ channels of the subtype Kir6.1/SUR2B are potential targets for new migraine headache medicines
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Objectives: Our aims were to identify and characterize the K$_{ATP}$ channel subtype mediating the headache inducing effects of synthetic K$_{ATP}$ channel openers in tissues relevant for migraine pathology.

Background: Several clinical trials have shown that synthetic K$_{ATP}$ channel openers cause significant headache in normal subjects. Furthermore, calcitonin gene-related peptide (CGRP) induces vasodilation by a mechanism that involves opening of K$_{ATP}$ channels. Blockage of K$_{ATP}$ channels may therefore be effective in the treatment of migraine headache and/or other primary headaches. However, K$_{ATP}$ channels are ubiquitous and blocking them indiscriminately may cause unwanted side effects such as lowering of blood glucose. A K$_{ATP}$ channel subtype of potential relevance to migraine pathology must therefore be sought.

Methods: Molecular composition and pharmacological features of K$_{ATP}$ channels were studied in large rat and pig cerebral arteries (basilar arteries and/or middle cerebral arteries) as well as in large rat, pig and human meningeal arteries (middle meningeal arteries). Arterial mRNA expression of K$_{ATP}$ channel subunits was studied by conventional RT-PCR and quantitative real-time PCR. Protein expression of K$_{ATP}$ channel subunits was studied by Western blotting. In vitro effects of a panel of synthetic K$_{ATP}$ channel openers and the potential channel blockage by the Kir6.1 subunit-specific K$_{ATP}$ channel blocker PNU-37883A were assessed in isolated arteries (n = 6–13) mounted on wire myographs. Pressure myography was used to evaluate if smooth muscle or endothelial K$_{ATP}$ channels mediate the effects of synthetic K$_{ATP}$ channel openers in isolated rat
cerebral arteries (n = 3). Intravital microscopy on a closed cranial window was used to assess the effects of synthetic K_ATP channel openers and their potential inhibition by PNU-37883A in meningeal arteries of anaesthetized rats (n = 6–10).

**Results:** Our molecular studies demonstrate the presence of Kir6.1 and SUR2B K_ATP channel subunits in the large cerebral and/or meningeal arteries of rat, pig and man. In vitro, the K_ATP channel openers caused a concentration-dependent vasorelaxation with an order of potency which supports the presence of functional SUR2B K_ATP channel subunits: P 1075>L-levromakalim-pinicacidil-diazoxide. The pEC50 values were between 7.17 and 3.90 in rat, 7.40 and 5.56 in pig, 7.92 and 5.61 in human. PNU-37883A (10^{-7} M) potently blocked the K_ATP opener induced relaxations. Pressure myography experiments demonstrated that K_ATP channel opener induced relaxation of rat cerebral arteries directly through opening of smooth muscle K_ATP channels and not via endothelial K_ATP channels. In vivo, infusion of the K_ATP channel opener P-1075, L-levromakalim and pinacacidil caused dilatation of rat meningeal arteries which could be blocked by a low dose (0.5 mg/kg) of PNU-37883A.

**Conclusion:** Our data suggest that Kir6.1 and SUR2B K_ATP channel subunits are promising targets for new migraine headache medicines. Blockage of the Kir6.1/SUR2B K_ATP channel subtype will not have the unwanted clinical effects of the traditional K_ATP channel blockers.

PO322

**N-Methyl-d-Aspartate receptor channel complex blockers including memantine and magnesium inhibit nociceptive traffic in the trigeminocervical complex of the rat**

Storer RJ and Goadsby PJ

**Objectives:** To understand better the action of N-methyl-d-aspartate (NMDA) receptor channel complex (NMDA-R) antagonists in the inhibition of trigeminovascular nociception.

**Background:** There is clinical and experimental evidence to suggest that NMDA-Rs are involved in migraine pathophysiology. Uncompetitive NMDA-R antagonists, such as dizocilpine (MK-801) and ketamine, have been found to inhibit nociceptive trigeminovascular transmission in vivo electrophysiological studies, anatomical studies of c-Fos expression, and behavioral studies. Experimental cortical spreading depression, postulated as an experimental analog of aura, is mediated, at least in part, by excitatory amino acids such as L-glutamate and can be blocked by NMDA-R antagonists. The suggested clinical efficacy of memantine and magnesium in the treatment of migraine has prompted us to explore the action of these NMDA-R antagonists in the in vivo rat model of trigeminovascular nociception.

**Methods:** Extracellular electrical activity of wide-dynamic-range neurons (n = 11 in five male Sprague Dawley rats) in the trigeminocervical complex (TCC), responding to noxious and innocuous mechanical stimulation of their V1 (ophthalmic) receptive fields, and to electrical stimulation of afferent nerves from the middle meningeal artery or its branches and periarterial dura mater (MMA), was recorded. We examined the effect of NMDA-R blockade by local microiontophoretic application of specific antagonists onto neurons in the TCC activated by glutamate and NMDA.

**Results:** Application of aracine, agmatine, ifenprodil, and Ro 25–6981 (5–40 nA) inhibited neuronal responses to L-glutamate (n = 5, 10, 4, and 5, respectively) and NMDA (n = 5, 6, 5, and 5, respectively) in a reversible, dose-dependent manner, reaching significance even at low currents after NMDA stimulation (5 nA, P < 0.01) compared with current-matched sodium controls. The inhibition after L-glutamate stimulation was significant, but usually partial, even at higher currents (40 nA). Memantine and magnesium reversibly inhibited the neuronal response to receptive field stimulation and stimulation of the MMA (P < 0.05), whereas no such inhibition was observed with current-matched sodium controls.

**Conclusions:** These data provide further evidence to suggest that the pathophysiology of primary head pain conditions may involve pathological activation of NMDA-Rs, in particular NR2B-containing NMDA-Rs, and that their selective modulation may be a useful therapeutic strategy for migraine treatment.

PO323

**Specific modulators of NR2B-subunit-containing N-Methyl-d-Aspartate receptor channel complexes, including agmatine and Ro 25–6981, inhibit nociceptive traffic in the trigeminocervical complex of the rat**

Storer RJ and Goadsby PJ

**Objectives:** To understand better the action of subtype-specific N-methyl-d-aspartate (NMDA) receptor channel complex (NMDA-R) antagonists in the blockade of trigeminovascular nociception.

**Background:** Non-selective NMDA-R antagonists, such as dizocilpine (MK-801), ketamine, and (R)-2-amino-5-phosphonopentanoate (d-AP5) have been found to inhibit nociceptive trigeminovascular transmission in vivo. This experimental data and the suggested clinical efficacy of ketamine, memantine, and magnesium in migraine treatment indicate that NMDA-Rs may be involved in the nociception that is probably crucial in migraine. Non-selective NMDA-R antagonists with low affinity have restricted clinical efficacy, while higher affinity non-selective antagonists produce greater antinociception, but unacceptable side effects. One promising therapeutic approach is to use subtype-selective antagonists because the localization of NMDA-R subtypes is more restricted. Subtypes containing NR2B subunits are found in the superficial dorsal horn and have been implicated in nociception. Ifenprodil is a prototypical antagonist for NR2B-subunit-containing NMDA-Rs, aracine and agmatine are competitive inhibitors at the polyamine site, and Ro 25–6981 has greater potency and selectivity for these NMDA-Rs than its ifenprodil congener.

**Methods:** Extracellular electrical activity of wide-dynamic-range neurons (n = 20 in 12 anesthetized rats) in the trigeminocervical complex (TCC), responding to mechanical stimulation of their V1 receptive fields, and to electrical stimulation of the middle meningeal artery or its branches and periarterial dura mater (MMA), was recorded. We examined the effect of NR2B-subunit-containing NMDA-R modulation by direct microiontophoretic application of specific antagonists onto neurons in the TCC activated by glutamate and NMDA.

**Results:** Application of aracine, agmatine, ifenprodil, and Ro 25–6981 (5–40 nA) inhibited neuronal responses to L-glutamate (n = 5, 10, 4, and 5, respectively) and NMDA (n = 5, 6, 5, and 5, respectively) in a reversible, dose-dependent manner, reaching significance even at low currents after NMDA stimulation (5 nA, P < 0.01) compared with current-matched sodium controls. The inhibition after glutamate stimulation was significant, but usually partial, even at higher currents (40 nA). The NR2B-containing NMDA-R specific antagonists reversibly inhibited the neuronal response to receptive field stimulation and stimulation of the MMA (P < 0.05), whereas no such inhibition was observed with current-matched sodium controls. The polyamine spermidine (n = 10) could reverse inhibition by aracine, but did not in itself appear to have a positive modulatory effect.

**Conclusions:** These data provide further evidence to suggest that the pathophysiology of primary head pain conditions may involve pathological activation of NMDA-Rs, in particular NR2B-containing NMDA-Rs, and that their selective modulation may be a useful therapeutic strategy for migraine treatment.
PO324
Iontophoretic and intravenous effects of indomethacin and naproxen on trigeminal firing recorded in the trigeminocervical complex
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Objectives: To study the effects of indomethacin and naproxen on dural nociceptive inputs to the trigeminocervical complex (TCC).

Background: Little is known about specific mechanisms of NSAIDs that lead to the differences in clinical efficacy in the treatment of paroxysmal hemicrania/hemicrania continua. We used a model of trigeminovascular nociceptive activation to test for indomethacin and naproxen specific effects in the rat.

Methods: Male Sprague Dawley rats (n = 24) were anesthetized with pentobarbitone (60 mg/kg) and cannulated for further anesthesia, physiological monitoring and drug administration. After appropriate surgical preparation trigeminocervical wide-dynamic-range neurons, identified by noxious pinch and innocuous brush, responding to electrical stimulation of the dura mater adjacent to the middle meningeal artery (MMA) (stimulation parameters: 0.5 Hz, 0.1–0.2 ms, 11–18 V) and microiontophoresed L-glutamate, were identified and recorded using electrophysiological techniques. The effect of indomethacin and naproxen administered by microiontophoresis and intravenously was studied.

Results: Intravenous administration of indomethacin (5 mg/kg) showed a significant inhibition (∆F, t8 = 7.56 = 4.07, P < 0.001) on MMA-stimulation evoked firing in the TCC with a maximum of 17% 10 minutes post administration (∆t8 = 5.44; P < 0.001). Intravenous administration of naproxen (1 mg/kg) inhibited electrical evoked firing (∆F, t8 = 3.37, P < 0.05) with a maximum of 15% at 45 minutes post administration (∆t8 = 2.57; P < 0.05). Local application of indomethacin and naproxen by iontophoresis in the TCC had no significant effect on glutamate evoked firing compared with control and had no effect on MMA-stimulation evoked post stimulus histograms.

Conclusions: The results of this study suggest that NSAIDs are able to modulate trigeminovascular nociception via peripheral and/or central modulating mechanisms but not directly at the level of the TCC.

The TRPV1 receptor antagonist, A-993610, shows no effect on neurogenic dural dilation but is able to block capsaicin induced dilation
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Objectives: To study the effects of the potent and selective brain penetrant TRPV1 receptor antagonist, A-993610, on neurogenic dural dilation and capsaicin induced dilation.

Background: It has been proposed that TRPV1 receptors may play a role in modulating trigeminal sensory processing and as a consequence may serve as a therapeutic target in migraine. We utilized the model of intravital microscopy of the middle meningeal artery to study the involvement of TRPV1 receptors in trigeminocervical wide-dynamic-range neurons, it is likely that TRPV1 receptors have no potent role in acute migraine treatment.

PO326
CSF levels and binding pattern of novel CGRP receptor antagonists in rhesus monkey and human central nervous system: toward the development of a PET tracer
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Objectives: Migraine is a prevalent neurovascular disorder and recent clinical studies with the orally bioavailable CGRP receptor antagonist MK-0974 (telcepagante) have demonstrated the potential usefulness of this new class of anti-migraine therapeutics. Importantly, the anti-migraine activity of CGRP receptor antagonists may be partly dependent on their ability to cross the blood–brain barrier and to interact with their target. With the objective of establishing a target engagement assay for CGRP receptors, the feasibility to develop a PET tracer for this target was investigated.

Background: MK-0974, MK-3207 and CGRP receptor antagonist 1 (CGRPAP1) are all P-gp substrates.

Methods: To better understand the relationship of in vitro measures of CNS-penetration to in vivo cerebrospinal fluid (CSF) levels all 3 compounds were evaluated in cisterna magna-ported rhesus monkeys. Pharmacokinetic parameters were determined in CSF and plasma following oral dosing. A CSF/plasma ratio (%) was computed as an index of CNS penetration.

Results: The CSF/plasma ratio is ~1% for MK-0974, ~3% for MK-3207, and ~11% for CGRPAP1 based on AUC values, suggesting that all compounds can penetrate the brain. However, the CSF/plasma ratio for each compound is only ~30% of the unbound fraction in plasma indicating that the central and peripheral compartments are not freely equilibrating.

To map the distribution of CGRP receptors in rhesus and human brains, autoradiographic studies were performed with [3H]MK-3207 and [3H]CGRPA2, two molecules with high affinity for CGRP receptor (K i: 0.02 nM). Autoradiograms revealed a discrete expression of MK-3207 and CGRPAP2 binding sites in both species with high density in the cerebellum, brainstem and meninges. [3H]MK-3207.
PO327

The effect of the orexin-receptor blocker on cortical spreading depression


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Objectives: In the present study, we investigated the effect of the orexin-receptor blocker, SB334867, a selective orexin-1 receptor antagonist, on the CSD.

Background: Cortical spreading depression (CSD) is a short-lasting depolarization wave which moves across the cortex accompanied by changes in cellular activity and in cerebral blood flow (CBF). CSD has been discussed as a possible mechanism for the aura phase of migraine. We have recently observed that orexin-A induces an increase of cerebral blood flow in rats and suppresses the CSD (in vivo) in a concentration-related manner.

Methods: Six male Sprague-Dawley rats (350–450 g) were anaesthetized with α-chloralose and urethane, intubated, and ventilated mechanically. The right femoral artery was cannulated for measurement of blood pressure and the other physiological parameters. CBF was continuously monitored by laser-Doppler flowmetry. The cortical DC-potential was measured by extracellular platinum electrode. The stainless tube with polyethylene resin was placed in the right lateral ventricle to administer SB-334867 and orexin-A. At first, CSD was induced by dropping 1 M KCl on rat brain surface and DC-potential and CBF were observed in the steady state. After that, 10 nmol SB-334867, orexin-receptor blocker, was injected in right lateral ventricle, and CSD was evaluated for 1 hour. Then, the administration of SB334867, 0.3 nmol orexin-A was injected in right lateral ventricle, and CSD was estimated again. The average amplitude change of DC-potential and the frequency of CSD was also evaluated. For statistical analysis, we used paired t-test.

Results: After the intracerebroventricular (i.c.v.) administration of SB334867, there was no significant change in both the mean value of CBF (65.8 ± 5.42%, mean ± SEM) and amplitude of DC-potential (11.6 ± 0.5 mV). After the i.c.v. administration of orexin-A, the mean value of CBF was significantly decreased to 70.6 ± 5.3% of the value of the steady state (P = 0.01). There was no difference in the frequency of CSD between steady state and after the i.c.v. administration of SB 334867.

Conclusions: Our study showed that there was no significant decrease of the mean value of CBF compared with the steady state after i.c.v. administration of SB224867, and the mean value of CBF was significantly decreased of the value of the steady state after the i.c.v. administration of orexin-A. It is possible that the orexin-A induced inhibition of CSD may be mediated by the orexin-2 receptor. These results suggest that the orexin-2 receptor may have influence on the mechanism of CSD.

PO328

Glyceroltrinitrate infusion causes upregulation of CGRP- and nNOS-immunoreactive neurons in rat trigeminal ganglion

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Objectives: To examine if infusion of nitrovasodilators, a stimulus known to induce headache in migraineurs, increases calcitonin gene-related peptide (CGRP) and nitric oxide (NO) producing neurons in rat trigeminal ganglion.

Background: Nitrovasodilators such as glyceroltrinitrate (GTN) that produce NO in the organism are known to cause delayed headaches in migraineurs that may be accompanied by increased plasma levels of CGRP in the cranial venous outflow. Increased plasma levels of CGRP and NO metabolites have also been found in spontaneous migraine attacks. A similar treatment with NO donors induced elevated neuronal activity in the spinal trigeminal nucleus in a rat model of meningeal nociception. The present study was made to examine if these changes can be explained by an increase in CGRP and NO producing trigeminal afferents.

Methods: The NO donor glyceroltrinitrate (GTN, 250 µg/kg) or vehicle was i.v. infused for 2 hours into isoflurane anaesthetised rats. After further 4 hours of anaesthesia the animals were fixed by perfusion. Trigeminal ganglia were dissected from the skull base and cryosections were immunostained for detection of CGRP and neuronal NO synthase (nNOS). The ganglion neurons showing immunofluorescence for either these proteins were counted and compared with the total number of trigeminal ganglion cells. The NO synthase (nNOS) concentration in ganglia was also measured by the Griess reaction.

Results: Both CGRP- and nNOS-immunoreactive neurons as well as neurons showing both these markers were numerically increased after GTN infusion compared to vehicle treatment throughout the trigeminal ganglia. Moreover, NO synthase (nNOS) concentration in ganglia was also numerically increased after GTN infusion compared to vehicle treatment.

Conclusions: We conclude that high levels of NO induce the expression of CGRP and NO-producing enzymes in a feed-forward manner. Similar changes may be involved in nitrovasodilator-induced and possibly also in spontaneous headache attacks in migraineurs.

PO329

Pharmacology and expression of proteinase activated receptor-2 (PAR2) in rat trigeminal vascular system in relevance to migraine

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Objectives: Aim of the study was to evaluate the vascular effects of Proteinase-activated receptor-2 (PAR2) and its distribution in rat trigeminal vascular system.
Background: PAR2 belongs to novel class of G-protein coupled receptors which are activated by various serine proteases, like trypsin and mast cell tryptase. A study in children suffering from migraine reported that with the reduction in the number of miginaines, there was a parallel decrease in the urine tryptase levels (Olness et al., 1999). Mast cell degranulation which leads to release of its constituents like tryptase, per se can activate meningeal nociceptors, central to migraine pathogenesis. Migraine is also believed to be associated with trigeminal activation and with vasodilatation of cranial arteries. Therefore, we investigated the role of PAR2 in a preclinical in vivo model addressing the trigeminal vascular aspect of migraine. In addition we also investigated expression of PAR2 mRNA in the trigeminal vascular axis, using RT-PCR.

Methods: Male Sprague-Dawley rats were used for intravital microscopy on a closed cranial window and dural artery diameter as well as blood pressure changes were measured. For activating PAR2 we used SLIGRL-NH₂ (a synthetic PAR2 activating peptide), trypsin and compound 48/80 (a mast cell degranulator). These compounds were administered in half-log increments through intracarotid infusion. Quantitative-PCR was done on the samples obtained from basilar, cerebral and dural arteries as well as from trigeminal ganglion and trigeminal nucleus caudalis.

Results: SLIGRL-NH₂, trypsin and compound 48/80 induced dose-dependent dilatations in the dural arteries, with highest dose producing 120% increase in dural artery diameter. SLIGRL-NH₂ was the most potent vasodilator and all the three compounds were equi-effective. PAR2 mRNA was expressed in all the tissues investigated with significantly higher mRNA expression in basilar artery and also in trigeminal ganglion.

Conclusions: PAR2 agonists/activators are capable of dilating rat meningeal arteries. PAR2 receptors are present throughout trigeminal-vascular circuit, pivotal in migraine pathogenesis. Thus PAR2 research offers exciting prospect for furthering our understanding of migraine pathogenesis.

Reference:

PO330
High prevalence of aspirin resistance in migraineurs
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Objectives: To assess the prevalence of aspirin resistance in migraineurs following 14–21 consecutive days of aspirin (ASA) 325 mg.

Background: Migraineurs have increased platelet activation and aggregation during interictal periods and have an increased risk of cardiovascular disease (CVD) and stroke. Aspirin resistance is associated with adverse events in patients with coronary artery disease. The prevalence of aspirin resistance has not been reported in migraineurs.

Methods: This was a prospective, non-randomized, single-center study. Subjects who met International Headache Society (IHS) criteria for migraine and experienced ≥6 migraine headache days in the year prior to enrollment received ASA 325 mg for 14–21 consecutive days following a 14-day ASA/non-steroidal anti-inflammatory drug washout. Platelet reactivity in response to arachidonic acid pre- and post-intervention was measured using the VerifyNow® aspirin assay (Accumetrics, San Diego, CA). Aspirin Reaction Units (ARU) >460 following the 14–21 day ASA intervention was indicative of aspirin resistance (primary endpoint). Based on published data, >60% platelet inhibition was selected as a secondary endpoint of aspirin resistance. Migraine Disability Assessment (MIDAS), Headache Impact Test (HT-6), and monthly migraine frequency were measured prior to aspirin treatment.

Results: Fifty subjects completed the study. Mean age of patients (±SD) was 42 ± 12 years; 44 (88%) were female and 26 (52%) had migraine with aura by IHS criteria. According to MIDAS and HT-6 scores, subjects had significant migraine disability and burden (35 ± 29 and 63 ± 5, respectively), and experienced 8 ± 6 migraine days/month. Baseline ARU was 648 ± 24. Following 17 ± 2 days of ASA 325 mg, mean ARU was 442 ± 51. Twelve (24%; 95% confidence interval 12–36%) had ARU >460 indicative of aspirin resistance. Using the manufacturer’s more conservative threshold of 550 ARU, 4 (8%) subjects had aspirin resistance. Aspirin resistant subjects had lower hemoglobin than did aspirin responsive subjects (12.8 ± 1.4 vs. 13.7 ± 1.2, respectively; P = 0.03). Mean % platelet inhibition was 69 ± 17%; 12 subjects (24%) had >60% platelet inhibition.

Conclusions: The results of this pilot study indicate that migraineurs may have a higher prevalence of resistance to ASA 325 mg compared with the general population (<1%) or persons with cardiovascular disease (3.3%). These findings may have significant treatment implications in the use of antplatelet agents in migraineurs for migraine treatment/prevention and CVD and stroke risk reduction.
model. Our results suggest that, if AMPA receptor antagonists were shown to be effective in the treatment of migraine, this effect would not be related to a vascular mode of action.

PO332
Anti-inflammatory activities of gum mastic, the resin of Pistacia lentiscus
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Objectives: It has been showed Pistacia lentiscus L. has many effects such as antimicrobial, antifungal, hypotensive, antihyperlipidemia, gastric and duodenal anti-ulcer and traditionally been used in the treatment of hypertension, so this study was conducted to determine anti-inflammatory effect of Pistacia lentiscus resin in rats.

Background: The other Pistacia spp. possess multiple pharmacological effects such as anti-inflammatory, estrogen-like and anti-anticetemic.

Methods: Anti-inflammatory activity by Carrageenan-induced paw edema in rats is done. Experiment groups received resin (200, 400, 600 and 800 mg/kg) and control groups received diclofenac sodium (100 mg/kg) or equal volume of vehicle intraperitoneally one hour before and the volume of edema was measured with a plethysmometer prior and 3 hours after carrageenan injection. LD50 was assumed using 50% deaths within 72 hours after intraperitoneally administration of the resin at different doses in mice.

Results: Resin produced statistically significant inhibition of edema induced by carrageenan at all doses when compared with the control groups. Anti-inflammatory effect was dose-dependent. A 100% inhibition was observed at 800 mg/kg i.p. Equipotent activity was observed at 600 mg/kg i.p. with diclofenac (100 mg/kg i.p.). Resin exhibit no toxicity up to 3 g/kg body weights intraperitoneally in mice.

Conclusions: The results of present study support the folkloric utilization of P. lentiscus resin. Further investigation of individual compounds is needed to determine the mechanism of anti-inflammatory and antioxidant activities.

PO333
Pharmacological characterization of MK-3207, a potent and orally bioavailable CGRP receptor antagonist
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Objectives: To characterize the preclinical pharmacological profile of the CGRP receptor antagonist MK-3207.

Background: Calcitonin gene-related peptide (CGRP) is a neuropeptide with potent vasodilator activity and studies show that it plays a key role in the pathophysiology of migraine. In recent years, clinical studies have shown that CGRP receptor antagonists are effective in treating pain from migraine attacks. Both intravenous olcegepant (BIBN4096 BS) and oral telcapepant (MK-0974) have been effective, safe and well tolerated with efficacy similar to triptans without “triptan-like” cardiovascular side effects. The objective of this study was to develop potent and stable peptide antagonists against the CGRP receptor as potential migraine treatments.

Methods: CGRP receptor antagonists are effective in treating pain from migraine attacks. Both intravenous olcegepant (BIBN4096 BS) and oral telcapepant (MK-0974) have been effective, safe and well tolerated with efficacy similar to triptans without “triptan-like” cardiovascular side effects. The objective of this study was to develop potent and stable peptide antagonists against the CGRP receptor as potential migraine treatments. CGRP receptors are of three types: CGRP1, CGRP2 and CGRP3. The CGRP1 receptor is predominantly expressed in the central nervous system, whereas the CGRP2 receptor is expressed in the peripheral nervous system. The CGRP3 receptor is expressed in the skin and mucous membranes.

Conclusions: MK-3207 is a highly potent, selective, and orally bioavailable CGRP receptor antagonist.
Role of calcium channels in the acute canine basilar artery vasorelaxation produced by testosterone

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Objectives: The objective of this study was to determine the mechanisms involved in the vasorelaxation induced by testosterone in the canine basilar artery.

Background: Testosterone produces acute vasorelaxant effects on several blood vessels including the canine coronary artery. However, there are very few studies analyzing the effects of this steroid on canine intracranial arteries, such as the basilar artery, an important blood vessel in certain pathologies including migraine.

Methods: For this purpose, changes in isometric tension induced by testosterone in rings pre contracted with 60 mM KCl were determined in the presence of vehicle or of several antagonists/inhibitors.

Results: Our results show that testosterone, but not vehicle (ethanol 0.1%), produced concentration-dependent vasorelaxant responses. This vasorelaxation was unaffected by the inhibitors cycloheximide (synthesis of proteins), actinomycin D (transcription), aminoglutetimide (aromatase inhibitor), the antagonists flutamide (testosterone receptor) or by the potassium channel blockers tetraetylamonium (non selective), glibenclamide (KATP), but was partially blocked by iodoacetamide (aromatase inhibitor), the antagonists flutamide (testosterone receptor) or by the potassium channel blockers tetraetylamonium (non selective), glibenclamide (KATP), but was partially blocked by iodoacetamide (aromatase inhibitor)

Conclusions: This vasorelaxation induced by testosterone: (i) does not involve genomic mechanisms; and (ii) is mainly mediated by blockade of calcium channels and to a lesser extent by activation of potassium channels (BKCa, KB, and KV).

Sodium valproate but not gabapentin modulates trigeminovascular nociceptive transmission in the thalamus via GABA_A receptor mechanisms: implications for migraine

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Objectives: To study the potential mechanism of action of valproate and gabapentin, on thalamocortical relay neurons in the ventroposteromedial (VPM) nucleus of the rat activated by a trigeminovascular nociceptive stimulus.

Background: Thalamic activation is on functional imaging to occur in spontaneous attacks of migraine and trigeminovascular stimulation in animals excites neurons in the VPM. Previous studies have shown that the VPM nucleus can be a site of action of triptans and adrenergic compounds. A potential role for compounds acting at the GABA receptor would provide a further target for therapeutic consideration.

Methods: Rats were anesthetized with pentobarbital (60 mg/kg) and cannulated for measurement of blood pressure and supplementary anesthesia. Trigeminovascular nociceptive afferents were identified in the VPM by electrical stimulation of the superior sagittal sinus (SSS), and cell bodies identified by activation with L-glutamate. The local effects of valproate and gabapentin, ejected by microiontophoresis during SSS stimulation and microiontophoresis of L-glutamate, were studied. The GABA acting prophylactic compounds were further characterized with the selective GABA_A and GABA_B receptor antagonists bicuculline and hydroxysaclofen, respectively.

Results: Valproate inhibited the responses to SSS stimulation (n = 7; P = 0.001) and L-glutamate ejection (n = 14; P < 0.001). Co-ejection of the appropriate GABA_A receptor antagonist reversed this inhibition on both responses to L-glutamate (n = 10; P < 0.001) and SSS stimulation (n = 10; P < 0.005). The GABA_B antagonist exhibited no significant effects on valproate’s inhibitory actions (n = 8; P ≥ 0.09). Micriontophoric application of gabapentin on third order neurons in the VPM did not alter the responses to L-glutamate (n = 9; P = 0.78) and SSS stimulation (n = 9; P = 0.34).

Conclusions: The thalamus is a potential site of action of sodium valproate. Sodium valproate inhibits trigeminovascular nociception, through GABA_A receptor mechanisms whereas gabapentin has no effect on trigeminovascular nociception when ejected locally in the VPM nucleus. The results indicate that GABA_A receptors on thalamocortical neurons can modulate trigeminovascular nociceptive transmission in the VPM nucleus in vivo. Thalamic physiology and pharmacology of trigeminovascular neurons needs to be explored and considered when formulating a general understanding of primary headaches, such as migraine.

Migraine prophylaxis with herbal extracts from petasites and tanacetum versus propranolol and topiramate – a comparative review of double-blind randomised controlled trials

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Objectives: This descriptive review compared the effectiveness of two established “chemical” migraine preventive drugs, propranolol and topiramate, with two herbal extracts prepared from Petasites hybridus and Tanacetum parthenium.

Background: Guidelines from various migraine and headache organizations recommend beta-blockers as the first-line therapy for migraine prevention. However, herbal remedies appeal to patients with a desire for a natural treatment. In addition, herbal preparations are considered as a “mild” form of treatment with very few serious adverse events. If effective, phytoceuticals are a valid treatment option for migraine prevention. The special petasites CO2-extract PETADOLEX® and the feverfew-extract MIG-99 are the only herbal extracts that have been shown in two randomised and controlled trials with 293 and 365 patients, respectively, to be effective for migraine prevention.

Methods: Sixteen randomised double-blind and controlled trials were considered using reduction of migraine frequency and the percentage of therapy responders as endpoints, as recommended by the IHS.

Results: Propranolol (n = 2,075) and topiramate (n = 1,792) reduce migraine frequency approximately by 2 attacks per month. In each of the two herbal trials absolute attack reduction by petasites was 1.6 (n = 60) and 1.7 (n = 233), absolute attack reduction by feverfew was 1.8 (n = 147) and 1.9 (n = 218). However, feverfew was only effective in patients with at least 4 attacks per month at baseline. The percentage of therapy responders (at least 50% migraine reduction) for petasites was 45% and 68% and was in the same range as the numbers for propranolol (18.5%–48%) and topiramate (35%–63%) and higher than the numbers in the two feverfew trials (37%, 30%).

Conclusions: Even though more trial data exists for propranolol and topiramate than for Petasites and Tanacetum, the available information based on the mean percentage of therapy responders suggests that Petasites is as effective as the first-line migraine preventive drugs propranolol and topiramate, with two herbal extracts prepared from Petasites hybridus and Tanacetum parthenium.
PO338
Frovatriptan as preemptive treatment for fasting-induced migraine
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Objectives: To examine frovatriptan’s efficacy as preemptive treatment for fasting-induced migraine.

Background: Fasting is a common trigger of migraine. Since it cannot always be avoided, the development of a short-term preemptive approach would benefit migraineurs. Frovatriptan, because of its longer half-life, has been effectively used for short-term daily use to prevent menstrually related migraines, and might prove useful in the prevention of fasting-induced migraine.

Methods: This was a double-blind, placebo controlled, randomized, parallel group trial. Subjects with a history of fasting-induced episodic migraine were randomly assigned to receive either frovatriptan (5.0 mg) or placebo (ratio 1:1). Subjects took a single dose of study medication at the start of their 20-hour fast. Information about headache, intensity, associated symptoms, and rescue use was captured at defined time points from the start of the fast through 20 hours post-fast.

Results: Of the 75 subjects screened, 74 subjects were randomized, and 71 subjects completed the study. 4/71 subjects developed a headache ≤4 hours after the onset of the fast and therefore were excluded from the efficacy analyses, since their headaches were not considered to be associated with the fast. All subjects who took study drug were included in the safety analyses. Demographic characteristics for placebo and frovatriptan treatment groups included the following, respectively: Gender: 76.5% (26/34) female, 78.8% (26/33) female (Pearson Chi-square, $P = 0.82$); Mean age: 38.7 ± 12.7, 40.15 ± 11.8 ($t$-test, $P = 0.625$). The 2 treatment groups were also comparable with respect to number of migraine attacks/month, type of migraine (MWA, MwoA) and preventive use. 12/33 (36.4%) subjects who received active drug developed a headache between 6 and 20 hours after the start of the fast (1/33 mild, 11/33 moderate or severe, or progressed to moderate or severe within the 20-hour follow-up period). In the placebo group, 18/34 (52.9%) developed a headache (4/34 mild, 14/34 moderate or severe, or progressed to moderate or severe). However, the difference between the 2 treatment groups did not reach statistical significance; Pearson Chi-square, $P = 0.172$. KM survival analysis showed no difference between the 2 treatment groups with respect to the time of onset of headache of any intensity (Log rank, $P = 0.264$) and for the time of onset of a moderate or severe intensity (Log rank, $P = 0.634$).

Conclusions: More subjects on placebo developed a headache than those on frovatriptan; our pilot study did not achieve statistical significance, perhaps because of the small number of subjects. Because of frovatriptan’s effectiveness as short-term preventive for menstrual migraine, a larger study may be warranted in addressing the effectiveness of frovatriptan for the prevention of fasting-induced migraine.

PO339
Gliarial function inhibitors and headache
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Objectives: To evaluate the effectiveness of minocycline as an adjunctive preventive medication in patients with chronic migraine (CM) or new daily persistent headache (NDPH).

Background: Chronic daily headache (CDH) affects 4–5% of the United States population. NDPH and CM are clinically distinct subsets of chronic daily headache. Approximately 30% of patients who develop NDPH have had a preceding viral illness or infection. Tumor necrosis factor alpha (TNF alpha) is one factor that mediates chronic pain states. TNF alpha is released by activated glial cells, specifically microglia and astroglia. It is elevated in CDH. Minocycline, a tetracycline antibiotic, down-regulates pro-inflammatory cytokine output from glial cells and may help in the treatment of CDH.

Methods: Retrospective chart review of all patients over the age of 18, seen at the Jefferson Headache Center, with the diagnosis of NDPH or CM based on ICHD-2. All patients had been placed on minocycline 100 mg twice daily as an adjunctive preventive headache medication. Headache frequency (days per week with headache) and severity (based on a numeric 0–10 scale) were routinely assessed at every patient visit. We evaluated the reported headache frequency and severity at the initial visit when minocycline was started and compared this to the reported headache severity and frequency at a two-month follow-up visit. Two months was selected as the length of time for follow-up based on the approximate time it takes for preventive medications to become effective.

Results: Forty patients, aged 18 to 80 years were included (28 women and 12 men). 30 patients were diagnosed with CM and 10 with NDPH. The mean headache frequency for all patients prior to treatment with minocycline was 6.2 days per week. Post-treatment, mean headache frequency, irrespective of headache type, significantly decreased to 5.4 days per week. After treatment, 14 of the 30 patients with CM showed a decrease in headache frequency; 9 of these patients were re-classified as episodic migraine. The CM group showed a significant post-treatment headache frequency reduction, to a mean of 5.0 days per week. The NDPH group had a slight increase in headache severity and frequency that was not significant.

Conclusions: Minocycline 100 mg twice daily is effective at reducing headache frequency in CM, but not in NDPH, when used as an adjunct to preventive medication. It is an option that should be considered for patients with CM.

PO340
Morning headaches are related to sleep problems and poor daytime functioning – a population-based controlled study
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Objectives: To assess the prevalence of morning headaches in the Austrian population and factors associated with this symptom.

Background: Morning headaches show a prevalence between 5 and 8% in the general population and are associated with sleep disorders such as bruxism, periodic limb movements and obstructive sleep apnea syndrome. The aim of this paper was to assess the prevalence of morning headaches in the Austrian general population and to analyse the relation to quality of sleep and daytime functioning.

Methods: In a nationwide survey, we recruited 1000 adults (478 women, 522 men, aged >14 years). For this study, we selected all subjects with self-reported morning headaches as well as controls matched for age, gender, size of hometown, level of education and marital status.

Results: Forty-eight subjects reported morning headaches making a prevalence of 5% in the Austrian general population. Compared to controls subjects with morning headaches reported a longer sleep onset latency (13.5 ± 13.5 min vs. 26.5 ± 27.5 min, $P = 0.005$), and more often problems with sleep maintenance (22.9% vs. 64.6%, $P < 0.001$), restless legs (2.1% vs. 20.8%, $P = 0.01$), and regular use of sleep medication (29.2% vs. 64.6%, $P = 0.001$). Moreover, daytime sleepiness (18.8% vs. 50%, $P = 0.003$), difficulties in staying awake (18.8% vs. 47.9%, $P = 0.005$) and falling asleep unwillingly (8.3% vs. 29.2%, $P = 0.019$) were more in morning headache sufferers.

Conclusions: This population-based controlled study revealed that the occurrence of morning headaches is related to several self-reported sleep problems and impaired daytime function.
PO341
The prophylaxis of the frequency of migraine attacks with sertraline and cinarizin
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Objectives: This study is aimed to establish the sertraline and cinarizin efficacy in the prevention of Migraine Attacks (MA).

Background: The use of medications for the MA prophylaxis needs to have its medical justification, based on an objective frequency of MA or on the characteristics of the migraine itself, where the most important is the patient’s subjective experience of the intensity, length and accompanying phenomena during the MA itself.

Methods: The introduction criteria for six-month medicamentous prophylaxis was the number of MA in the previous six months. The minimum of frequency was three, and the maximum was six MA in a month. A single blind study was the method used in this research.

A total of 300 patients took part in the study (M:F = 96:204). Three groups of patients were formed. Each group consisted of 100 examinees, who, on the basis of IHS standards, suffered from a Migraine without (M1) and a Migraine with Aura (M2), (M1:M2 = 254:46).

The patients were obliged to, in the month preceding the study, keep a calendar of the frequency of MA. The patients in the first group were administered 50 mg of Sertraline, in a single daily dose for four months, and in the last two months the dose was reduced to 25 mg. The second group was administered 75 mg of Cinarizin during four months and 37.5 mg in the last two. The third group received placebo throughout the six-month period. The patients were controlled on a monthly basis and had an obligation to keep on the MA calendar. A percentage-based reduction of the number of MA in each group compared with the previous period was statistically processed after the first, third and sixth month of medicamentous prophylaxis and a month after the end of the administration of medications.

Results: In the first group, five patients withdrew from the research at various stages. After the first month of sertraline administration, the number of MA was reduced by 32.7%, after three 43.5%, and after six months 37.3%. A month after the termination of sertraline administration, the number of MA in the first group was reduced by 35.4%. In the second group, eight patients withdrew from the research at various stages. After the first month of cinarizin administration, the summed up number of MA in the second group was reduced by 45.2%, after three 56.1%, after six 52.4%. A month after the termination of cinarizin administration, the number of MA attacks was reduced by 41.3%. In the third group of patients, who, on the basis of IHS standards, suffered from a Migraine with Aura, 15 patients withdrew from the research.

After the first month, the frequency of MA dropped by 17.8%, after three 15.5% and after six 14.2%. A month after the termination of placebo administration, the number of MA in the third group was reduced by 7.4%. The percentage of frequency reduction in the placebo group does not exceed the values explained with the “placebo” effect.

Conclusions: In this study, a higher efficacy of cinarizin compared with sertraline has been established in the prophylaxis of the frequency of migraine attacks.

PO342
Impact of pharmacologic prophylaxis for migraine on use of abortive therapies
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Objectives: To examine the impact of prophylaxis on the use of abortive therapies for migraine.

Background: Persons with frequent and/or severe migraines often receive selected antidepressants, antiepileptics, or beta blockers as prophylaxis against migraine. Information is limited on the impact of prophylaxis on the use of abortive therapies for migraine in real-world clinical practice.

Methods: Using a US health insurance claims database spanning the period 1/1/2003 to 12/31/2005, we identified all migraine patients who initiated treatment with selected antidepressants (tricyclics [TCAs]), selective-serotonin reuptake inhibitors [SSRIs], bupropion, mirtazapine, trazodone, venlafaxine), antiepileptics (carbamazepine, divalproex sodium/sodium valproate, gabapentin, topiramate), or beta blockers (atenolol, metoprolol, nadolol, propranolol, timolol). Date of initial receipt of these agents was designated the “index date”. Patients with <6 months of complete data preceding and following this date (“pretreatment” and “follow-up”, respectively) were dropped from the study sample, as were those without evidence of migraine during pretreatment. Patients with evidence of depression were excluded from analyses of antidepressants; those with epilepsy, from analyses of antiepileptics; and those with hypertension or heart failure, from analyses of beta blockers. Changes (pretreatment to follow-up) in the percentages of patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, ergot alkaloids, isometheptene compounds, and triptans (ie, abortive therapies) were examined.

Results: We identified 1166 migraine patients who began treatment with TCAs; 696 with SSRIs; 493 with other antidepressants; 1896 with antiepileptics; and 936 with beta blockers. The most commonly used abortive therapies during both pretreatment and follow-up were triptans and opioids. The number of patients receiving abortive therapies was largely unchanged from pretreatment to follow-up, irrespective of prophylaxis received (Table).

Table. Use of abortive therapies before and after initiation of migraine prophylaxis

<table>
<thead>
<tr>
<th>Pretreatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients (95% confidence interval)</td>
<td></td>
</tr>
<tr>
<td>TCAs (N = 1166)</td>
<td>77% (75%, 79%)</td>
</tr>
<tr>
<td>SSRIs (N = 696)</td>
<td>83% (80%, 86%)</td>
</tr>
<tr>
<td>Other antidepressants (N = 493)</td>
<td>81% (77%, 84%)</td>
</tr>
<tr>
<td>Antiepileptics (N = 1896)</td>
<td>81% (79%, 82%)</td>
</tr>
<tr>
<td>Beta blockers (N = 936)</td>
<td>75% (72%, 78%)</td>
</tr>
</tbody>
</table>

Conclusions: In real-world clinical practice, use of abortive therapies for migraine does not change appreciably in patients who initiate prophylaxis.

PO343
Tonabersat repression of proteins involved in peripheral and central sensitization in response to acute or chronic inflammation
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Objectives: The focus of this study was to investigate the effect of the novel drug tonabersat on neuronal-glial cell communication via cellular channels formed by connexin 26 proteins as well as proteins implicated in peripheral and central sensitization using both acute and chronic inflammatory models.

Background: Activation of trigeminal nerves in response to a peripheral inflammatory stimulus causes increased communication between neurons and satellite glial cells via gap junctions. Gap junctions facilitate direct communication between two cells by connecting two hemichannels, which are comprised of 6 connexin (Cx) proteins. We have previously shown that tonabersat could block gap junction

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communication between trigeminal ganglion neurons and satellite glial cells and decrease the level of connexin 26 (Cx26) in response to potentiation with TNF and capsaicin. In this study, we wanted to investigate whether tonabersat treatment would repress Cx26 expression in neurons and glia in the ganglion and activation of second order neurons and glial cells within the trigeminal nucleus caudalis in response to acute or chronic inflammation.

Methods: The effect of tonabersat (i.p., injection, 10 mg/ml) on the temporal and spatial expression of Cx26 in trigeminal ganglion, and glial fibrillary associated protein (GFAP) and c-Fos in the trigeminal nucleus caudalis in response to injection of capsaicin or complete Freund’s adjuvant (CFA) in adult Sprague-Dawley rats was determined by immunohistochemistry.

Results: While basal levels of Cx26 were barely detectable in trigeminal neurons and satellite glial cells, the level of Cx26 was transiently increased in both cell types in response to capsaicin injections but was stably expressed following CFA injection. Treatment with tonabersat blocked both the transient and stable expression of Cx26 in neurons and glia cells and hence, intracellular communication. Importantly, tonabersat treatment also repressed both capsaicin (1 hour) and CFA (3-day) mediated increases in the expression of c-Fos in second order neurons and GFAP in glial cells within the trigeminal nucleus caudalis. The degree of inhibitory effects of tonabersat was found to be time-dependent.

Conclusions: We found that tonabersat inhibits expression of Cx26, facilitates signaling between trigeminal ganglion neurons and satellite glial cells, in response to either acute or chronic inflammation. Furthermore, our results provide evidence that tonabersat could block changes within second order neurons and glial cells within the trigeminal nucleus caudalis that are involved in promoting and sustaining nociceptive responses.

PO344
Oral Mg/B6 prophylaxis: augmentation of red blood cell magnesium levels alleviate chronic headache pain in menstrual migraine and migraine with aura patients

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Objectives: Magnesium deficiency effects on the severity and frequency of acute migraine attacks before and after oral supplementation in migraine with aura and menstrual migraine patients under sumatriptan therapy.

Background: Magnesium is now recognized as an N-methyl-D-aspartate (NMDA) receptor channel blocker can selectively inhibit glutamate induced spreading depression in the parietal and occipital cortices. Magnesium supplementation support possibility that a lower magnesium threshold could be related to a magnesium deficiency.

Methods: Thirty patients with migraine with aura (23 females and 8 males, mean age: 35 years) and twenty patients with menstrual migraine (mean age: 30 years) were diagnosed according to the classification of International Headache Society at a headache center in Warsaw Medical University Hospital. Patients were presented typical aura with chronic migraine headache (ICHD-II c; 1.2.1, mean disease duration: 9.7 years), menstrual migraine (ICHD-II c; 1.1.2, mean disease duration: 7.8 years) and no control group. 8 ml of venous blood sample was collected before and after 2 months of (300 mg Mg-B6/daily) oral supplementation during attack periods. Magnesium level was measured by atomic absorption spectrophotometry (850 nm, Perkin-Elmer 3030). Mg/B6 oral started on the 15th day of the cycle and continued till the next menses for 2 months in menstrual migraine patients and 2 months of Mg/B6 for migraine with aura. We assessed headache pain using the visual analog scale (VAS) and total pain index (TPI) in both groups.

Results: Red blood cell magnesium levels were low in 48% women experiencing menstrual migraine and 43% in migraine with aura. After 2 months of Mg/B6 therapy, red blood cell magnesium levels were significantly elevated in both migraines groups.

Conclusions: Low red blood cell magnesium levels could be a peripheral expression of the reduced brain magnesium concentration observed in migraine patients. Chronic migraine headaches were significantly associated with a low concentration of red blood cell magnesium. Mg/B6 supplement with sumatriptan therapy, could significantly reduce severity and frequency of migraine headaches.

Table 1. Magnesium-RBC level pre and post Mg/B6 therapy in migraine with aura patients

<table>
<thead>
<tr>
<th>Migraine with aura</th>
<th>Mean (mmol/l)</th>
<th>SD</th>
<th>Median (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>2.01</td>
<td>0.29</td>
<td>2.09</td>
</tr>
<tr>
<td>After</td>
<td>2.35</td>
<td>0.37</td>
<td>2.31</td>
</tr>
</tbody>
</table>

Table 2. Magnesium-RBC level pre and post Mg/B6 therapy in menstrual migraine patients

<table>
<thead>
<tr>
<th>Menstrual migraine (Mg-RBC)</th>
<th>Mean (mmol/l)</th>
<th>SD</th>
<th>Median (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>1.96</td>
<td>0.27</td>
<td>2.01</td>
</tr>
<tr>
<td>After</td>
<td>2.45</td>
<td>0.37</td>
<td>2.41</td>
</tr>
</tbody>
</table>

PO345
To report the use of flunarizine in children with headache in a tertiary neurology centre

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Objectives: To analyse the effectiveness and side effect profile of Flunarizine.

Background: Flunarizine is a calcium channel and dopamine antagonist. It has been used widely in Europe and Japan in Migraine prophylaxis. It is however, not licensed in the UK. The Children’s Headache Clinic at Great Ormond Street is a tertiary and quaternary referral service. Flunarizine has been used on a named patient basis since the inception of the clinic in 1999. This review was intended to inform current practice.

Methods: Retrospective case note review of flunarizine use at Great Ormond Street Hospital for children between July 1999 and March 2009.

Results: Forty-three children were identified: 26 male and 17 female. The mean age of the cohort was 11.5 years. The diagnostic categories were: migraine without aura (19), migraine with aura (10), sporadic hemiplegic migraine (7), familial hemiplegic migraine (5) and other migraine subtypes (2). The mean duration of headache prior to starting flunarizine was 66.8 months (range: 6 to 168 months). Eight patients (with hemiplegic migraine) were drug naïve for prophylaxis with the rest having been on a mean of 2.7 medications. The mean frequency of attack was 12 per month. Flunarizine was used for a mean duration of 14 months. Starting dose was 5 mg/day in all but three. Dose escalation was needed in 22 patients with a second escalation in 3 cases. Maximum dose was 15 mg/day. Response was measured by comparing the frequency and intensity of attacks pre and post Flunarizine and this data was available in 36 children (8 hemiplegic migraines). Improvement in symptoms was seen in 21, no improvement in 13 and worsening in two - response rate of 58%: 100% in the hemiplegic migraine and 46% in the remainder. Adverse effects were seen in nine children (21%) leading to discontinuation in eight. It was restarted in two, both with mild tiredness and a good response. A further nine discontinued due to lack of response. The adverse effects

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in a high oral bioavailability and a long half-life (63 hours), permitting a once or twice daily dosing regimen. Recent clinical experience indicates a place for zonisamide in the management of headache disorders.

Methods: 13 patients (pz), (4 F,7 M) mean age 42.8 years (SD 5.8), range 36–56 years, suffering from ECH (8pz) and CCH (5 pz) (ICDH '04 criteria) were studied. In all patients with ECH prophylaxis therapy with verapamil and carbolynthium. Besides several patients are not responders at this drugs. In these cases the use of antiepileptic drug has been proposed. Zonisamide, a new antiepileptic drug, has been reported efficacy in the migraines patients. The drug has mechanisms of action that suggest it may reduce the neuronal hyperexcitability. These mechanisms include facilitation of dopaminergic and serotonergic neurotransmission, reduction of glutamate-mediated synaptic excitation and increased gamma-aminobutyric acid (GABA) release. Zonisamide has a favourable pharmacokinetic profile which includes high oral bioavailability and a long half-life (63 hours), permitting a once or twice daily dosing regimen. Recent clinical experience indicates a place for zonisamide in the management of headache disorders.

Results: In patients with ECH the basal frequency of attack/days and 1, 2, 3 months respectively was 4.2 (SD 1.9); 2.4 (SD 0.9), 1.6 (SD 0.9), 0.8 (SD 1.1) (P < 0.0001). In patients with chronic CH the basal frequency of attack/days and 1, 2, 3 months respectively was 2.8 (SD 1.3); 0.4 (SD 0.3), 0.2 (SD 0.2), 0.1 (SD 0.1) (P < 0.05) (t-test analysis). In all patients zonisamide was well tolerated (5 patients complained somnolence, lack of concentration, vertigo and nausea but not withdrew the study).

Conclusions: These data showed a good efficacy in reduction of frequency of attacks. Still, the drug is tolerable, in fact none patients withdrew the study. Our study suggests that zonisamide could be an alternative or complementary prophylaxis therapy for ECH and CCH. Controlled studies are warranted to determine the efficacy of zonisamide in prophylaxis therapy for ECH and CCH.

Repression of acute and chronic inflammatory changes in trigeminal ganglion neurons and glia in response to cocoa enriched diets

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Center for Biomedical & Life Sciences, Missouri State University, Springfield, MO, USA

Objectives: To determine the cellular effects of a cocoa-enriched diet on neurons and glia in the trigeminal ganglion under basal conditions, and in response to acute or chronic inflammation.

Background: Recent studies involving Theobroma cacao have shown promise in the treatment of a variety of disorders. However, most research involving the beneficial effects of cocoa has been limited to in vitro studies. The balance between inflammatory protein kinases such as the MAP kinases (MAPK), and anti-inflammatory proteins such as the MAP kinase phosphatases (MKP) play a critical role maintaining homeostasis in the trigeminal nociceptive system. It is thought that an imbalance between MAPK and MKP proteins may play a role in the pathophysiology of migraine.

Methods: Sprague Dawley rats were fed a control diet or isocaloric diets enriched in cocoa [1% (g/g) or 10% (g/g)] for 14 days prior to an injection of capsaicin or complete Freund’s adjuvant (CFA). While capsaicin injection mediates an acute inflammatory response, CFA was used to cause a chronic inflammatory response. Levels of active ERK, active p38, iNOS, CGRP, MKP-1, MKP-3, and IL-10 were examined in trigeminal ganglion neurons and glia by immunohistochemistry. In addition, total RNA was isolated and then used in qPCR to determine the effect of cocoa enriched diets on CGRP mRNA levels.

Results: Rats that received injections of capsaicin or CFA were found to have increased levels of staining of the active forms of the MAPK’s ERK and p38 in trigeminal ganglion neurons, while CFA injections also caused increased expression of the signaling protein iNOS, which plays an important role in mediating inflammatory responses. However, the stimulatory effects of capsaicin or CFA on these signaling proteins were repressed at basal levels in rats fed cocoa enriched diets. Expression of MKP-1 was increased in both neurons and glia while MKP-3 and the anti-inflammatory molecule IL-10 were increased only in neurons in rats on a cocoa enriched diet. Furthermore, rats on cocoa enriched diets exhibited decreased CGRP mRNA and protein expression in trigeminal ganglion neurons.

Conclusions: Cocoa enriched diets are able to repress the stimulated expression of proteins associated with the promotion and maintenance of inflammatory and nociceptive responses. The inhibitory effects of cocoa are likely to be mediated via increased basal expression of the anti-inflammatory proteins MKP-1, MKP-3, and IL-10. To our knowledge, this is first evidence for the use of cocoa as a dietary supplement to cause an upregulation of MKPs and IL-10 as well as repress expression of acute and chronic inflammatory responses within trigeminal ganglia. Importantly, our data also provide evidence that cocoa contains biologically active compounds that could be beneficial in the treatment of trigeminal-mediated diseases of the head and face.

PO348 Pilot study to assess the efficacy of combining valproic acid with a clenching reduction dental splint (NTI) as prophylactic treatment for primary headache disorders

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Objectives: To demonstrate that the combination of medical and dental prophylactic treatments for primary headache disorders will produce a greater benefit than either treatment alone.

Background: Preventive treatments for migraine and tension type headache are often limited by patient compliance and poor tolerability, as escalating adverse side effects are anticipated as dosages of preventive medications increase. Primary headache disorders have multiple mechanisms that lead to ongoing headaches and it is likely that more than one treatment might be needed in an individual patient to control the disorder. To date, there are few studies that assess combination treatments in primary headache disorders. In this pilot study we describe a comparative study of the efficacy of nociceptive trigeminal inhibition (NTI) and Valproic acid (VA) in the treatment of migraine and tension-type headaches.

PO347 Repression of acute and chronic inflammatory changes in trigeminal ganglion neurons and glia in response to cocoa enriched diets
PO349
Sustained efficacy of botulinum toxin type-A (BTXA) on migraine-related disability over 3 treatment cycles in a community-based setting
Turner IM, Harding TM, DeVito DA and Lio R
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Objectives: To retrospectively assess the effect of botulinum toxin type-A (BTXA) on migraine disability over 3 consecutive treatment cycles scheduled at 3-month intervals in a community-based headache subspecialty practice.

Background: Prior studies using BTXA have shown a decrease in migraine-related disability, headache days and acute medication usage. These findings have the potential to result in a substantial reduction in disease burden for patients, employers, insurers and society if this is maintained over serial treatment cycles.

Methods: Forty consecutive patients treated for either chronic migraine (15 or more headache days per month) or high frequency migraine (8–14 days per month) who underwent 3 consecutive courses of BTXA treatment at 3-month intervals were retrospectively reviewed. The primary endpoint was a reduction in Migraine Disability Assessment Scores (MIDAS). Secondary endpoints included a decrease in headache days and as well as a decrease in acute medication use.

Results: Average MIDAS scores decreased from a baseline of 62.8 to 29.2 (treatment 1), 31.1 (treatment 2) and 24.8 (treatment 3) over 3 consecutive cycles. Headache days decreased from a baseline of average of 20.7 days per month to 11.6 (treatment 1), 9.8 (treatment 2) and 9.5 (treatment 3) days per month respectively. Monthly acute medication doses decreased from a baseline average of 51.5 to 27.85 (treatment 1), 24.25 (treatment 2) and 21.4 (treatment 3) for the 3 cycles of treatment.

Conclusions: In our retrospective analysis of 40 consecutive patients there was a sustained reduction in migraine-related disability, headache days and acute medication use.

PO350
Levetiracetam as migraine prophylaxis in topiramate-failures
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Headache Clinic, University of California, San Diego, Department of Neurology, San Diego, CA, USA

Objectives: To report a series of topiramate-failures (TFs) who demonstrate success with levetiracetam (LVT) for migraine prophylaxis, and to illustrate key characteristics that may be associated with success in this subgroup.

Background: Failure of standard prophylactic treatments for migraine poses an important dilemma for headache specialists. Previous studies suggest that LVT might be equal to topiramate (TPM) but with better tolerability. LVT has a unique mechanism of action.

Methods: We present a case series of TFs whose headaches improved dramatically with LVT. Patients were included with a diagnosis of migraine meeting the new IHS classification criteria, ≥4 days per month of migraine for ≥3 months, and previous treatment with TPM for ≥3 months. Patients were excluded if they had ≥20 days per month of migraine for ≥3 months, chronic use of opiate medication, or an uncontrolled medical condition, including concurrent severe depression.

Results: Seven patients with migraine are presented; 2 cases with aura, and 5 without aura. The mean age was 54, with 6 females and 1 male. The mean number of years with migraine was 20 (range of 5–40). Each patient had failed various standard prophylactic treatments including propranolol, amitriptyline, verapamil, valproic acid, and in all patients, TPM, with doses up to 400 mg per day. With respect to TPM, 2 patients discontinued treatment due to intolerable side effects including hair loss, excessive drowsiness, and cognitive slowing, 3 continued treatment and 1 discontinued treatment due to lack of therapeu-
tic response. The case series had a mean of 8 ± 4 migraine episodes per month prior to LVT. Each patient had dramatic improvement in headache control with LVT as an adjunctive therapy. All of the cases are currently on LVT with a mean treatment duration of 3 months and have responded with more than 50% reduction in attack frequency during the follow-up period. The mean dose of LVT that provided effective relief was 500 mg per day. All patients reported using less of their abortive medications. All patients tolerated LVT without adverse effects except for mild sedation (n = 1). Key characteristics among this case series included long-standing migraine history, migraine associated with menopause (n = 1), comorbid partial epilepsy (n = 1), and concurrent use of TPM (n = 3), verapamil (n = 2), propranolol (n = 1), venlafaxine (n = 1) and botulinum toxin injections (n = 1).

Conclusions: This case series suggests that some TFS with a long-standing migraine history may respond even to modest doses of LVT as an option for migraine prophylaxis, provides a rationale for performing further studies on the role of LVT in migraine.

PO351
The frequency and impact of restless legs syndrome in patients with migraine
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Objectives: To investigate the frequency of restless legs syndrome (RLS) among different primary headache disorders and clarify its impact on sleep disturbance in patients with migraine.

Background: An association between migraine and RLS was reported in clinic-based studies but a similar association in other headache disorders is uncertain. Both migraine and RLS are related to sleep disturbance. However, the impact of comorbidity of RLS on sleep is unknown in patients with migraine.

Methods: Consecutive patients with primary headache disorders were recruited in a headache clinic and were divided into 3 groups; migraine, tension-type headache (TTH) and cluster headache (CH) based on the ICHD-2 criteria. All patients filled out a comprehensive headache intake form, Migraine Disability Assessment (MIDAS) questionnaire, Hospital Anxiety and Depression scale (HADS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Score (ESS), a screening questionnaire for RLS and the International RLS Study Group (IRLSG) Rating Scale. RLS was diagnosed by a physician through telephone interview based on the criteria proposed by IRLSSG.

Results: A total of 894 patients (682F/ 212M, mean age 43.6 ± 14.2 years, range 18–93, migraine 654, TTH 193, CH 47) completed the study. The frequencies of RLS in different headache subgroups were 10.7% in migraine patients, 4.1% in TTH patients and 2.1% in CH patients (P = 0.005). In the migraine group, patients with RLS had higher frequencies of poor sleep (PSQI=5) (91.4% vs. 77.6%, P = 0.007), poor sleep efficiency (<85%) (67.3% vs. 49.2%, P = 0.007) and excessive daytime sleepiness (ESS') (48.6% vs. 30.5%, P = 0.002) than those without RLS. In addition, migraine patients with RLS reported a higher mean score in the HADS (16.8 ± 7.9 vs. 14.3 ± 7.8, P = 0.012) than those without RLS. After adjustment for sex, age, HADS scores, body mass index and headache disability, comorbid RLS was still an independent risk factor for poor sleep (odds ratio (OR) = 2.54, 95% CI: 1.03–6.25), poor sleep efficiency (OR = 1.82, 95% CI: 1.04–3.17), and excessive daytime sleepiness (OR = 1.90, 95% CI: 1.12–3.21) in patients with migraine.

Conclusions: This study demonstrated a higher frequency of RLS in patients with migraine, although the frequency was much lower than those reported in Western societies. Comorbidity with RLS worsened the sleep quality in patients with migraine. A history of RLS should be elicited in migraine patients who report sleep disturbances.

PO352
Changes on BDI-II with migraine chronicity: is it depression or sleep?
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1Research Division, Carolina Headache Institute, Chapel Hill, NC, USA; 2Physical Medicine and Rehabilitation, University of North Carolina, Chapel Hill, NC, USA

Objectives: To examine a population of migraineurs and their responses to items on the Beck Depression Inventory-II (BDI-II).

Background: Depression, a condition co-morbid with migraine, is a constellation of affective, somatic, and cognitive symptoms. A number of diagnostic criteria for relate to changes in sleep. We have previously reported that (1) chronic migraineurs almost uniformly endorse nonrestorative sleep, and (2) the prevalence of neck pain present on first awakening parallels that of headache present on awakening, and both increase with migraine chronicity. We hypothesize that in migraineurs, sleep complaints may be independent of depression and associated instead with migraine chronication.

Methods: In this prospective cross-sectional cohort study of 127 migraineurs, subjects were divided into three groups based on diary entries: those with episodic patterns for both headache and neck pain frequency (E/E), those with chronic patterns for both headache and neck pain (C/C), and those with a mixed pattern of either episodic headache/chronic neck pain or chronic headache/episodic neck pain (EC/CE). Subjects were examined by Headache Medicine specialists to exclude cervicogenic headache and fibromyalgia. All subjects completed the BDI-II, a widely used self-report depression inventory, prior to completing the daily diaries.

Figure 1

Figure 2
Results: Three items – tiredness, change in sleep, and loss of energy – were the only items endorsed by the majority of all migraineurs in the cohort; these items accounted for 27% or 38% of the total score on the BDI-II using multiple regression analysis. Migraine chronification was associated with increasing endorsement of sleep-related complaints on the BDI-II, whereas diagnosis of clinical depression on the BDI-II (total score) was not associated with migraine chronicity.

Conclusions: Migraine chronification is associated with an increase in sleep-related complaints on the BDI independent of clinical depression. This is consistent with our prior research showing that chronic migraineurs almost uniformly endorse nonrestorative sleep.

PO353 Refractory depression and anxiety in migraine
Tietjen GE1, Brandes J2, Peterlin BL3, Elfow A4, Dafer R5, Stein M5, Drexeler E6, Martin V6, Hutchinson S9, Aurora S10, Recober A11, Herkal NA1, Utley C4, White L1 and Khuder S3
1Neurology, University of Toledo College of Medicine, Toledo, OH, USA; 2Neurology, Nashville Neuroscience Group, Nashville, TN, USA; 3Neurology, Drexel University College of Medicine, Philadelphia, PA, USA; 4Neurology, University of Calgary, Calgary, AB, Canada; 5Neurology, Loyola University Medical Center, Maywood, IL, USA; 6Neurology, John Muir Medical Center, Walnut Creek, CA, USA; 7Neurology, Maimonides Medical Center, Brooklyn, NY, USA; 8Internal Medicine, University of Cincinnati, Cincinnati, OH, USA; 9Family Medicine, Orange County Migraine & Headache Center, Irvine, CA, USA; 10Neurology, Swedish Headache Center, Seattle, WA, USA; 11Neurology, University of Iowa, Iowa City, IA, USA

Objectives: To examine in a migraine clinic population frequencies of prior diagnoses and treatment of anxiety and depression in those with current anxiety and depression.

Background: Depression and anxiety are highly comorbid with migraine and influence headache frequency and disability. Methods: Electronic surveys were completed by patients seeking treatment in headache clinics at 11 centers across the USA and Canada. Physician-determined data for all participants included the primary headache diagnoses based on the ICHD-2 criteria, average monthly headache frequency, whether headaches transformed from episodic to chronic, and if headaches were continuous. Analysis included persons with migraine with aura, and migraine without aura. We collected information on sociodemographics, headache-related disability (HT-6), and comorbid conditions (self-reported physician-diagnosed), such as depression and anxiety, with age of symptom onset, medication treatment (past and current) and hospitalizations. In addition participants completed screening instruments for current depression (PHQ 9) and anxiety (BAI).

Results: A total of 1348 migraineurs (88% women) were included (mean age 41 years) in the study. Diagnosis of migraine with aura was reported by 40% and chronic headache (≥15 days/month) by 34%. Transformation from episodic to chronic frequency was reported by 26%. Forty-one percent had a history of depression with mean age of symptom onset at 28 years, 31% of this cohort had been on antidepressants, and 57% were taking them currently. On the PHQ 9 current screen 12% had scores consistent with major depression, and 15% had less severe depression. Of the 370 persons with current depression, the majority had previously received this diagnosis (66% vs. 34%, P = 0.0001). The average time between the onset of depression symptoms and current depression was 16 years. Thirty-one percent had a history of anxiety, with mean age of onset at 29 years. Nearly 80% of this cohort had taken medications for anxiety in the past and 45% reported current treatment for anxiety. On the BAI current screen 16% had scores consistent with severe, 30% with moderate, and 34% with mild anxiety. Of the 761 persons with current anxiety, a sizable minority had previously received this diagnosis (43% vs. 16%, P = 0.0001). The average time between anxiety symptom onset and current anxiety was 12 years. Frequency of chronic daily headache, transformed migraine, and severe headache-related disability were higher in migraineurs with current depression for 3 anxiety (P < 0.0001 for all).

Conclusions: Current depression and anxiety are associated with chronic disabling migraine. A substantial proportion of migraineurs with current depression and anxiety has longstanding diagnosis and treatment for these conditions. Identifying factors for refractory depression and anxiety may provide opportunity for risk modification and more aggressive treatment.

PO354 Assessment context alters observed relationships between migraine beliefs and migraine-related disability
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Objectives: To compare relationships among self-efficacy and locus of control beliefs, and relationships between these beliefs and migraine-related disability in three assessment contexts.

Background: The belief or expectancy that one’s migraines are inherent uncontrollable (perceived external versus internal locus of control), and the belief that one lacks the ability (self-efficacy) to take actions to influence, even potentially controllable migraines, are postulated by Social Learning Theory to increase migraine-related disability at any given level of migraine severity. We use data from the TSM (Treatment of Severe Migraine) trial to examine if assessment context might explain conflicting findings observed in studies that have examined these hypotheses.

Methods: After receiving Optimal Acute Therapy (OAT), 232 migraine sufferers were randomized into a 2 (placebo vs. propranolol) × 2 [Drug Therapy Only vs. Behavioral Migraine Management (BMM)] treatment design. The Headache Management Self-Efficacy Scale (HMSE; French, et al., 2000), Headache-Specific Locus of Control Scale (Martin, et al., 1990), and the Migraine-Specific Quality of Life Questionnaire subscales (MSQL; Jhingran, et al., 1998) were administered at the OAT run-in and after a five month dose adjustment/BMM treatment period. We examine relationships among expectancy measures and relationships between expectancies and MSQL scores in three assessment contexts: when patients were seeking treatment (headache severity and dissatisfaction with current therapy high and after receiving either drug therapy alone or combined with BMM.

Results: Generally, relationships among expectancies and between expectancies and disability differed by assessment context. For example, higher health care professional HSLC was associated with higher levels of disability prior to treatment (Role Restrictive and Emotion Function rs = 0.25 and 0.29, Ps < 0.01), but not after treatment (BMM rs = 0.01, 0.05, Ps > 0.05; Drug Therapy rs = 0.05, 0.10, Ps > 0.05), although these changes were only significant in the BMM groups [Pearson-Filon statistic (ZPF) = 2.06, 2.16, Ps < 0.05)]. Additionally, before treatment, higher chance (e.g., MSQL-Role Preventive Preventive r = 0.37, P < 0.01) and lower self-efficacy (MSQL Role Preventive r = -0.19, P = 0.001) were only marginally related to higher disability, but these variables accounted for a clinically significant portion of observed disability after treatment (MSQL-Role Preventive and Chance BMM r = 0.50; Chance medication r = 0.31; HMSE BMM r = 0.40; HMSE Medication r = 0.38, Ps < 0.001), though the increase in disability accounted for by chance LOC was only statistically significant in the BMM groups (e.g., MSQL-Role Preventative, ZPF = 2.04, P < 0.05).

Conclusions: Assessment context influenced observed relationships among expectancies as well as relationships between expectancies and headache-related disability. This effect may account for the conflicting findings in this literature. Future research should evaluate more sophisticated hypotheses that take into consideration the context of assessment.
PO355
Personality traits and psychological distress in persons with chronic tension-type headache. the Akershus study of chronic headache
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Objectives: To investigate personality traits and level of psychological distress in persons with chronic tension-type headache (CTTH) from the general population.

Background: Personality traits and psychological distress in persons with chronic tension-type headache has not been investigated in any large-scale population based study until now.

Methods: An age and gender stratified random sample of 30,000 persons aged 30–44 years from the general population received a mailed questionnaire. Those with a self-reported chronic headache were interviewed by neurological residents. The questionnaire response rate was 71% and the participation rate of the interview was 74%. The International Classification of Headache Disorders was used. To assess personality traits and level of psychological distress, the Eysenck’s Personality Questionnaire (EPQ) and the Hopkins Symptom Checklist-25 (HSCl-25) was used.

Results: Persons with CTTH had a significantly higher neuroticism score and had a significantly higher level of psychological distress than healthy controls from the general population. Headache- or medication days per month had no significant influence on the neuroticism- and lie scores or the HSCl-25 score.

Conclusions: Persons with CTTH revealed higher level of neuroticism and psychological distress than healthy persons. Whether this is due to premorbid psyche and/or secondary to the chronic pain is a question that future studies should address.

PO356
Abstract withdrawn

PO357
Negative impact of episodic migraine on a college population: psychiatric comorbidity, functional impairment, and school interference
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Objectives: To compare college episodic migraineurs with non-migraineurs on measures of depression/anxiety, functional impairment, and school attendance.

Background: Migraine has been consistently linked to increased rates of psychiatric comorbidities, impaired functioning, and reduced quality-of-life among clinical samples. However, very few studies have evaluated the impact of episodic migraine on university students and their school performance. This is a needed area of research because a significant minority of headache research is conducted with college students. The present study was designed to evaluate the extent to which episodic migraine negatively impacts psychological variables among this population.

Methods: Data were collected from 204 undergraduate students who participated for course credit. All participants completed an extensive battery assessing migraine symptomatology (ID Migraine and Brief Headache Screen (BHS)), current symptoms of depression (PHQ-9) and anxiety (GAD-7), health-related functional impairment (Medical Outcomes SF-20), and questions about how migraine has limited their daily activities in the past 3 months. Episodic migraineurs were conservatively defined as those who screened positive for episodic migraine on both the ID Migraine as well as the BHS (n = 52). Non-headache controls were those who had negative screens for both measures (n = 94). The remaining 58 had discrepant results on both measures and were excluded. Independent samples t-tests were used to compare the episodic migraineurs with the controls on the psychological variables.

Results: The retained 146 participants had a mean age of 19.05 years (SD = 1.55); 78% were female and 17.8% were of minority status. Episodic migraineurs showed impairment on the majority of psychological variables as compared to the non-migraineurs. Specifically, migraineurs reported significantly more symptoms of depression [t (144) = 5.46, P < 0.001; PHQ-9 total of 8.15 vs. 4.39] and anxiety [t (144) = 4.00; P < 0.001; GAD-7 total of 7.56 vs. 4.45], as well as higher levels of functional impairment related to Social Functioning, Mental Health, Health Perceptions, and Pain (all Ps < 0.04) on the SF20. Notably, migraine participants also reported missing significantly more days of school in the past 3 months than did controls [t (143) = 5.66; P < 0.001; 3.53 days vs. 1.26 days]. Mann-Whitney U tests confirmed the differences reported above.

Conclusions: College episodic migraineurs show higher rates of comorbid psychiatric symptoms, increased functional impairment, and reduced school attendance compared to non-migraineurs. Despite the fact that their migrainous headaches were infrequent and levels of psychiatric symptoms within the “mild” clinical range, non-treatment-seeking college migraineurs still evidence increased functional impairment and interference with school obligations. Academicians studying migraine should attend to the negative impact of migraine in college samples.

PO358
There is no harm in trying, or is there? A questionnaire study in patients with medication-overuse headache
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Objectives: In the present study, we assessed the interplay between analgesic use and psychological factors to try to identify predictors for MOH.

Background: Overuse of medication has consistently been linked with the existence of Medication-Overuse Headache (MOH). However, the mechanisms underlying this are still largely unknown.

Methods: A total of 149 headache patients, including both patients with episodic migraine (n = 113) and patients with a diagnosis of MOH (n = 36), were recruited from a headache centre and were asked to complete a battery of questionnaires.

Results: MOH patients, in comparison with those with episodic migraine, were more depressed, more disabled, had a higher frequency of pain and presented with more concerns about their medication use. In addition, there also seemed to be a difference in the type of medication that was used, with MOH patients having a higher triptan, analgesic and ergotamine use. Interestingly, MOH patients scored higher on attempting to solve their pain and lower on acceptance of pain. Furthermore, we found that persistent
PO359
Psychological treatment in military men: different headaches – different coping
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Objectives: The aim of our research was to create the differential approach to shot-time psychotherapy of headaches into inpatient department.

Background: The investigations performed in healthy military officers’ shows some specific features of this group. S. Spilier (2004) said that when younger officers are compared to junior managers, the officers tend to score lower on variables such as “recognizing and managing their emotions” as well as “playing attention to emotions of others”. But senior officers tend to score higher on these variables, as was the case of senior management.

Methods: Study covered 162 men from 18 to 60, 113 of which (69.8%) suffer from different types of headache. 78 men was the participants of local war in Chechnya in 90-th (mean age 32.7, SD = 1.54) and 84 men in Afghanistan in 80-th (mean age 46.3, SD = 1.38). It’s known that the differences between the mean score for the male and female groups are very significant, that’s why we took in our research only men. After clinical, neurological and psychological examination we divided all patients into three groups using randomization. First group (54 men) received shot-time hypnotherapy, second one – NLP, and in the third was no psychotherapy.

Results: Deep analysis of it’s structure reveals that more often patients suffer from posttraumatic headache (54.0%), TTH (29.2%), and migraine (7.1%). In comparison with posttraumatic group TTH had been characterized by less intensively of pain, shorter anamnesis of headache suffering and tendency to evening manifestation. Post-traumatic headache more often had comorbid autonomic nerve system dysfunction look like increased heat rate add changeable blood pressure. Psychological portrait of local war participant with headache include such features as: mild reactive and moderate personal anxiety, subdepressive condition, high level of personal disharmony and high level of stress (according to Holms score of social readaptation). We reliable more often revealed personality changes in men with headache than in patient without it.During the comparison between two more typical headaches – tension-type headache and post-traumatic one we reveal reliable differences in some metaproggrams between these patients for both age groups, especially in point “outcome preferences”: Patients with posttraumatic headache more often had toward preferences (69.9% in younger and 72.5% in older subgroup). For TTH group it was only 41.1% and 58.7% (P < 0.05). Older patients with TTH also had tendency to grow in “external reference” score (41.0% in compare with 26.3% in younger group). Persons with high measures in this score will want feedback and want to have other people’s opinion before deciding. Analyzing the effects of psychotherapy, we saw that post-traumatic headaches in more resistant to psychotherapy then TTH. In young patients with TTH the best effects of hypnotherapy both pain and comorbid depressive-anxiety symptomatic had been demonstrated. In posttraumatic group NLP methods was more effective.

Conclusions: So different headache have been associated with different coping style, that may explain the differences in the reactions to psychotherapy.
the scope of the searches was expanded to child migraine and child and adolescent headache. Supplementary reports that matched with search criteria were identified from the reference list of the retrieved studies.

Results: 19 studies were identified. 13 studies distinguished migraine headache from other headache types. 4 studies reported data specifically for adolescents, rather than combing data form adolescents and younger children. Methodological characteristics of studies and study findings will be presented in a Table. Mean levels of anxiety and depression symptoms as reported by the adolescent or their parent/caregiver were most often modestly elevated relative to established norms or healthy controls, but below established cutoffs for diagnosis of a DSM-IV mood or anxiety disorder. These modest elevations tended to be observed in both clinical samples and random samples from the school populations. Such elevations in symptom reports are consistent with either (or both): (a) affective distress in healthy adolescents that results from living with migraine, and (b) an elevated prevalence of DSM-IV mood and/or anxiety disorders in adolescents with migraine. In clinical samples, some evidence suggests that (b) is an important factor, with up to 30% of adolescents with migraine receiving a mood or anxiety disorder diagnosis based on clinical interview or established cut off scores on standardized tests. Inadequate diagnostic information is available from random school samples to know if this finding generalized beyond the clinic. Any conclusions are limited by small samples, the practice of reporting data only for combined samples of adolescents and young children, and for migraine and other headache types, use of diagnostic procedures of uncertain validity for identifying both migraine and mood/anxiety disorders and the lack of true population data.

Conclusions: The existing literature allows only tentative conclusions about the association of anxiety or mood disorders with adolescent migraine.

PO362
TREATMENT OF MEDICALLY INTRACTABLE SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS WITH CONJUNCTIVAL INJECTION AND TEARING (SUNCT) AND SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS WITH AUTONOMOUS SYMPTOMS (SUNA) WITH OCCIPITAL NERVE STIMULATION (ONS) IN 6 PATIENTS
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Objectives: To report on the outcome and follow up of 6 patients treated with ONS for medically intractable SUNCT and SUNA.

Background: SUNCT and SUNA are primary headaches characterised by repeated attacks of very severe, short-lasting, neuralgiform headaches in association with cranial autonomic features that usually occur several times daily. They can be medically intractable, in which case neurally destructive or cranially invasive treatments can be offered. ONS offers a non-destructive and relatively low risk surgical alternative.

Methods: Six medically intractable patients (5 SUNCT, 1 SUNA) were implanted with electrodes for bilateral occipital nerve stimulation. Data was collected retrospectively for demographics, diagnosis, previous treatments, ONS settings, pre-implantation and post-implantation headache characteristics (frequency, severity and duration), patients’ estimates of change in headaches and complications.

Results: At a median follow-up of 14 months (range 4–19), four patients reported a substantial improvement (95–100%), one reported moderate benefit (50%) and one patient reported a temporarily marked benefit (50%) for 6 months followed by recurrence of headache at the pre-ONS baseline for the subsequent 11 months. The onset of the benefit was generally rapid (within 2 weeks) with attacks recurring rapidly when the stimulator was switched off or malfunctioned. One patient developed hemicrania continua one month after implantation and was successfully treated with indomethacin.

Conclusions: ONS appears to offer a safe treatment option, without significant morbidity, for medically intractable SUNCT and SUNA.

PO363
IV LIDOCAINE TREATMENT FOR CDH AND NEW DAILY PERSISTENT HEADACHE
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Objectives: On the theory that migraines or other headache types may be neuropathically mediated or maintained as is the case of many neuropathic pain syndromes, we treated CDH and NDPH with this agent IV in the outpatient clinic.

Background: Lidocaine has been used to treat neuropathic pain from many sources by its ability to block sodium channels specifically and thus block neuropathic pain signaling in chronic pain disorders. We studied the safety and efficacy of this agent in the outpatient headache clinic, with monitoring, to treat these difficult-to-treat headache disorders.

Methods: Forty-two patients were treated (29 female/13 male) [average age 41.8 years] for refractory headaches (CDH and NDPH) in the clinic. 37 patients had a 5+ year history of CDH and 5 had NDPH for 3.3 years. An antecubital IV line was started with pulse oximetry monitoring. Patients had failed with usual home treatment for their usual headaches. A 3 hour infusion was utilized for each treatment session, with pulse oximetry monitoring. VAS headache scores were monitored every 20 minutes.

Results: The beginning severity for migraines was 7.65/10 in severity (VAS) before treatment and this was reduced to 2.1/10 in severity after treatment. 17 of 42 [40%] of patients had complete abolition of their migraines after treatment, lasting an average of 3.5 days. Average time of lidocaine infusion was 180 minutes per session and average dose was 364 mg of lidocaine. This resulted in a significant decrease in headache severity (P-value <0.001) for treatment of refractory CDH and NDPH. 24 patients had multiple IV treatment sessions with IV lidocaine, up to 4 such treatments on different days, or sometimes twice in one day. Other than transient drowsiness, lightheadedness or numbness of face and mouth, no other side effects were noted during treatment, including any neuropsychiatric symptoms.

Conclusions: We conclude that IV lidocaine can be used successfully in the outpatient clinic for treatment of refractory CDH and NDPH and that sodium channel over-activity may be playing a role in the maintenance or perpetuation of these headache patterns. Often, a favorable outcome, as seen in this study, allows choice of a sodium channel active agent IV in the outpatient clinic.

PO364
OCCIPITAL NERVE STIMULATION IN DRUG-RESISTANT CHRONIC CLUSTER HEADACHE
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Objectives: To evaluate the efficacy of ONS in drug-resistant CCH severely disabled from headache attacks and chronic steroids treatments.
Background: Chronic Cluster Headache sometimes results refractory to conventional pharmacological treatment and it is a challenge to alleviate this highly disabling condition. Neuromodulation has become an option for treatment, with the peripheral approach safer than the Deep Brain Stimulation.

Methods: Since 2004, 19 drug-resistant Chronic Cluster Headache patients from our Headache Centre have had implanted a suboccipital stimulator (ONS) initially only on pain side, then bilaterally due to the evidence of a side-shift even in those considered side-locked.

Results: 13 out of 19 continued in the follow-up. Actually, after a period variable from 1 to 12 months from the ONS-implant, insufficiently experienced and confident in the method, 5 underwent neurosurgery for Deep Brain Stimulation (DBS) because of a ‘failure’ of the ONS. In one the ONS device have been removed two months later because infected. Among 13 patients with ONS (11M, 2F; mean age 42.7 ± 9), mean follow-up is 21 ± 14 (range 3–52 months); the duration of illness is 13.8 ± 8.7 with chronic phase 7 ± 4.7. Mean number of CH attacks before ONS were at least 3 up to 8 per day in the last 6 months; in 7 patients pain-side was Right, 4 was Left and in 2 bilateral (in one case they were 50% on L or R side; in the other pain side was mostly on L with some shift on R). Eight performed well after ONS, resuming the episodic pattern or with <1 attack per day, moreover 5 of them without any treatment. Five have had partial advantage, with a drop in daily attack but still the need of lower doses of steroids, with one now waiting for surgery for battery failure, and last four subjects with only limited benefit with still daily attacks, anyway lower than before surgery.

Conclusions: In our case series of 13 drug resistant-CCH, 60% responded well to bilateral ONS with only 1/3 of them still having daily attacks. A deep analysis of the clinical features and personality trait could suggest which predictive factors may influence the outcome.

PO365
Problems in refractory chronic migraine with abuse: highlights from algorithmic analysis
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Objectives: To obtain an algorithm for the correct classification of states giving rise to lack of success in prophylaxis of chronic migraine with abuse.

Background: Generally, prophylactic treatments of migraine give results near to 50% since the response of the patient can vary from marked improvement to worsening.

Methods: So far, we have been unable to realise methods for evidencing patients’ features linked to the responder and non-responder prototype. Experience was carried out on 470 patients affected by chronic migraine with abuse. Here we used 114 variables: demographic including marital status, severe stalking, social and cultural level, opioidergic/ non opioidergic drugs assumption to control pain severity- acute therapy, abuse- abuse duration, treatment- treatment type and duration, pain features as hyperalgesia and allodynia, pain score during the last 10 migraine attacks, heredity of primary pain and migraine, comorbidities, results of routine examination, neuroimaging abnormalities of white matter, nocebo effect -which is here intended as the negative induced thinking about the possibility to resolve the problem reinforced by media communication-, insight of the disease resulting from 1) capacity of identifying the event as a pathology, 2) capacity of admitting the pathology, 3) capacity of admitting the need for a therapy, 4) capacity of admitting possible relapse, type/token index standardized at 1000 on a near 1000 words text written by the patient and regarding headache, psycho-neurological tests (Wang Test, Zung Test, MPPI, Randt Memory Battery), concurrency of CAM therapies and approaches. We used both traditional analyses and algorithm. In the first trial treatment outcome was binarily scored: 42 patients considered improved: “responders” and 22 patients considered “non responders”. The patients were randomly subdivided in the Traing and Testing phases. In the meanwhile a discriminant analysis was performed on database to compare predictional performance. Second trial gives rise to the following results.

Results: Algorithm correctly classified all conditions of unsuccessful preventive treatment. Prediction accuracy varied between 77.0% and 92.5%, discriminant analysis accuracy ranged from 55.5% and 80.2%. As confirmed by the following sample (428 patients) we can distinguish between discriminant variables: switch on for responders or non responders, indifferent variables: switch off for both responders and non responders, metastable variables, switched on for both categories. The switch off for non-responders were nocebo effect, MRI abnormalities - over 5 lesions in white matter attributed to ischemia-, psycho-neurological testing abnormalities, severe stalking, being single for a period of over 5 years when over 45 years old, type/token ratio lower than 20, lack of insight, 15 days/month or over opioidergic drugs assumption for a period of 4 months or over. Other variables are metastable.

Conclusions: This testing can aid to resolve other problems prior to start a preventive anti-migraine treatment. Some switch off variables are not possible to cure with a drug. It is not possible to define a classification of impact of the switch off variables.

PO366
Ketamine for treating multiple types of headaches
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Objectives: We studied the efficacy and safety of IV ketamine in the outpatient headache clinic to treat refractory migraines, cluster headaches, paroxysmal hemicrania, chronic daily headaches, tension-type headaches (CDH) and mixed headache disorders.

Background: We wanted to query whether NMDA-type glutamate receptor overactivity may play a role in the cause or maintenance of multiple types of refractory headaches. Ketamine is an antagonist of NMDA-subtype glutamate receptors at sub-anesthetic doses and thought to play a role in pain transmission and central sensitization. Very little information exists on this receptor subtype and any potential role in migraine pathophysiology, although central sensitization and allodynia play a part in the migraine and headache process and in chronic neuropathic pain disorders.

Methods: We studied ketamine intravenously (IV) in the headache clinic to treat refractory migraines and other headache subtypes in our attempt to offer patients effective treatment in the headache clinic. This is an open-label study. 247 patients were treated with IV ketamine: 162 patients with refractory migraines, 11 with cluster headaches, 4 with paroxysmal hemicrania (PH), 39 with chronic daily headaches (CDH) and 31 with headaches and face pain TN or TMD.

Results: Our average VAS scores for migraines and headaches was 6.9/10, although cluster headache scores were rated as 9.2/10 VAS. A total of 490 infusions of IV ketamine were utilized in the clinic with monitoring. 93% of patients with refractory migraines had a better than 50% of their VAS scores after acute treatment (to 2.2/10 VAS. 11 of 11 cluster had complete abolishing of their ongoing cluster episodes (average of 6.4 days) to 0/10 VAS and all 4 PH patients had complete abolishing of their PH headaches (average of 7 days). 68% of CDH patients had a better than 50% of their headache pattern for at least a week and 80% of headache/face pain patients had a better than 50% of their pattern. No patient fell asleep during treatment and there was no dysphoria or hallucinations or other side effects with treatment, other than short-lived “calmness” and light-headed feelings in 41% of patients, which was transient and removed with IV rate infusion reduction.
Conclusions: We conclude that IV ketamine for treating refractory migraines and many other headache/migraine sub-types is a very effective new form of treatment with an excellent safety margin. This can be done in the outpatient clinic setting with appropriate monitoring. It speaks to the involvement of NMDA glutamate receptors in the pathophysiology of refractory migraine and many other primary headache and pain disorders. This agent should be studied in a double-blind, placebo-controlled manner.

PO367

Abstract withdrawn

PO368

Evidence that migraine may be a risk factor for the development of complex regional pain syndrome
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Objectives: To assess the relative frequency of migraine and the headache characteristics of complex regional pain syndrome (CRPS) sufferers.

Background: CRPS and migraine are chronic, often disabling pain syndromes. Recent studies suggest that headache is associated with the development of CRPS.

Methods: Consecutive adults fulfilling IASP criteria for CRPS were included. Demographics, medical history, and pain characteristics were obtained. Headache diagnoses were made using ICHD-II criteria. ANOVA with posthoc tests were used for continuous variables and Fisher exact or Chi-square tests for categorical variables. The sample consisted of 124 CRPS participants.

Results: The sample consisted of 124 CRPS participants. The mean age was 45.5 years ± 12.0. Age and gender adjusted SMRs showed that those with CRPS were 3.6 times more likely to have migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a more severe form of CRPS. Specifically: migraine occurs in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS sufferers with migraine than without; and CRPS symptoms are present in a greater percentage of CRPS sufferers than expected in the general population; the onset of CRPS is reported earlier in CRPS suffers
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PO371
Hemorrhagic complications in reversible cerebral vasoconstriction syndrome are more frequent in women and in migrainers
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Objectives: To study the frequency, the different types, and the risk factors of hemorrhagic complications in reversible cerebral vasoconstriction syndrome (RCVS).

Background: RCVS is an acute vascular disorder characterized by severe headaches (often thunderclap headaches) with or without associated neurological deficits and reversible vasoconstriction of the cerebral arteries. Recent reports indicate the possibility of hemorrhagic complications (i.e., intracerebral, subarachnoid, and/or subdural hemorrhage) in the context of RCVS.

Methods: We analysed prospective data on 89 consecutive patients diagnosed with RCVS between 2004 and 2008 in our institution. Standard univariate and multivariate statistical tests have been applied to compare patient characteristics (age, sex, vascular risk factors, medication, drugs) between RCVS cases with and without hemorrhagic complications.

Results: Overall, 30 of the 89 patients with RCVS (34%) developed hemorrhagic complications, including cortical subarachnoid hemorrhage (n = 27), intracerebral hemorrhage (n = 11) and subdural hemorrhage (n = 2). Nine patients had overlapping bleeding locations. Univariate analysis showed that hemorrhages were more frequent in older patients (mean age 46.6 versus 41.6 years, P = 0.049), women (90% vs. 51%, P = 0.0017), patients taking sympathetic serotonin reuptake inhibitors (30% vs. 12%, P = 0.045) and those with a positive migraine history (43% vs. 19%, P = 0.022). Multivariate testing showed two independent factors significantly associated with a higher risk of bleeding in RCVS: 1) female gender (OR 4.05, 95% CI 1.46–11.2) and 2) having a history of migraine (OR 2.34, 95% CI 1.06–5.18).

Conclusions: Among cases with RCVS, women and patients with a positive migraine history seem to be at higher risk for hemorrhagic complications. Given the high proportion of hemorrhagic forms in our series (34%), a RCVS should always be considered in patients with intracranial hemorrhage in the setting of sudden severe headache, after the exclusion of an aneurismal rupture.

PO372
Sleep apnea headache in the general population. The Akershus sleep apnea project
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Objectives: To investigate the prevalence and clinical characteristics of sleep apnea headache in the general population.

Background: Sleep apnea headache is a secondary headache sub classified, according to the International Classification of Headache Disorders (ICHD-II), under headaches attributed to hypoxia and hypercapnia. The prevalence has been reported in variable levels from 15–60% in patients with obstructive sleep apnea. However, there is still controversy regarding the association of morning headache and obstructive sleep apnea.

Methods: A cross-sectional population based study. A random age and gender stratified sample of 40 000 persons aged 20–80 years residing in Norway were drawn by the National Population Register. A postal questionnaire containing the Berlin Questionnaire was used to classify respondents to be of either high or low risk of obstructive sleep apnea (OSA). 384 persons with high risk and 157 persons with low risk of sleep apnea aged 30–65 years were included for further investigations. They underwent an extensive clinical interview and a physical and a neurological examination by physicians, as well as a polysomnography (PSG). Those with apnea hypopnoea index (AHI) ≥5 were classified with obstructive sleep apnea. The diagnosis of sleep apnea headache was based on the International Classification of Headache Disorders (ICHD-II).

Results: In our population 23.3% of the respondents (19.9% of the women and 27.1% of the men) were classified as high risk of obstructive sleep apnea according to the Berlin Questionnaire. The estimated prevalence of obstructive sleep apnea in 30–65 years old in the Norwegian population was 17% (13% among women and 21% among men). Sleep apnea headache was diagnosed in 7.7% of the participants with obstructive sleep apnea. The median AHI in these participants was 18.3 with an interquartile range of 26.3. In comparison morning headache also was reported by 4.7% of the participants without obstructive sleep apnea, a non-significant difference (P = 0.16). When using cutoff of moderate (AHI ≥ 15) and severe (AHI ≥ 30) obstructive sleep apnea, the prevalence of sleep apnea headache increased to 8.6% and 10.1% respectively. However, the prevalence was still not statistically different from the prevalence of morning headache in participants with lower AHI (5.3%, P = 0.14 and 5.6%, P = 0.13, respectively).

Conclusions: Morning headaches were slightly more prominent among participants with obstructive sleep apnea compared to those without, but the difference did not reach statistical significance. Sleep apnea headache appears to be not as common in a population-based sample of obstructive sleep apnea as it has previously been reported in clinician driven studies.
PO373
The reversible cerebral vasoconstriction syndromes: a systematic review
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Objectives: To systematically review reported cases of the reversible cerebral vasoconstriction syndromes (RCVS) in order to better define their triggers, clinical symptoms, and diagnostic findings.

Background: The RCVS are a group of disorders characterized by their presentation with a thunderclap headache, absence of aneurysmal subarachnoid hemorrhage, normal or “near-normal” cerebrospinal fluid (CSF), and multifocal intracranial artery vasoconstriction which reverses within 12 weeks of symptom onset. Investigations are needed to better define risk factors for RCVS, its triggers, clinical presentation, diagnostic findings, treatment and outcome.

Methods: Two investigators independently performed the systematic search and applied inclusion criteria. Selected cases met the following criteria: 1) new onset headache; 2) no aneurysmal subarachnoid hemorrhage (i.e. not in basal cisterns); 3) multifocal intracranial artery vasoconstriction; 4) reversal of arterial vasoconstriction within 12 weeks of onset.

Results: Eighty publications contained 250 RCVS cases meeting our inclusion criteria. The female to male ratio was 6:1 (213:37) and mean age was 43 years (range 13–70 years). Predisposing conditions/triggers included: postpartum in 45/250 (18%) cases, migraine history in 54/200 (27%), bathing, physical exertion/Valsalva, and vascular trauma. Preceding exposure to a potentially triggering medication or illicit drug was reported in 111 cases (44%). Thunderclap headache was a presenting symptom in 214/233 (92%). Many without thunderclap headache had acute onset headaches reaching peak intensity in >1 minute. Transient neurologic deficits were present in 73/250 (29%) and persistent neurologic deficits were present in 26/250 (10%). CSF white blood cell count was >5/mm³ in 34/127 (27%) vs. 0/67 (0%), P = 0.009, had a higher mean maximum VMCA (124.2 ± 40.7 cm/s vs. 93.5 ± 29.6, P = 0.002) and a higher LI (2.6 ± 1.2 vs. 1.9 ± 0.5, P = 0.035). Patients with sulcal hyperintensity were more likely to have reversible posterior leukoencephalopathy (9/17 (53%) vs. 0/67 (0%), P < 0.001) or ischemic stroke (5/17 (29%) vs. 0/67 (0%), P < 0.001) than those without. Traits which did not differ significantly between patients with or without sulcal hyperintensity included gender distribution, headache characteristics, presence of blood pressure surge, and number of triggers and thunderclap headache attacks.

Conclusions: RCVS preferentially affects women, presents with acute onset headache, is associated with normal or near-normal CSF, and is commonly reported in the post-partum and after exposure to specific drugs. Migraine may be a risk factor for development of RCVS. Transient neurologic deficits occur in about 1/3 of cases and persistent deficits in 10%. Cortical subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke, and cerebral edema are not rare complications. Vasoconstriction is most commonly identified in the anterior circulation, specifically the middle cerebral artery.

PO374
Sulcal hyperintensity on FLAIR imaging in reversible cerebral vasoconstriction syndromes
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Objectives: To study the frequency and clinical significance of sulcal hyperintensity (also called Ivy sign) on fluid-attenuated inversion recovery (FLAIR) images in patients with reversible cerebral vasoconstriction syndromes (RCVS).

Background: Sulcal hyperintensity on FLAIR images is observed in patients with moyamoya disease. Slow flow or engorged sulcal anastomotic collateral vessels are possible etiologies. Recently, we noticed the same finding in patients with RCVS during ictal stage, a finding not previously reported.

Methods: Patients with RCVS were recruited from August 2000 to March 2009. Their FLAIR images of brain MRI during the acute stage were retrospectively reviewed. Sulcal hyperintensity sign was defined as continuous or discontinuous linear high signal intensities along the cortical sulci and subarachnoid space. We also collected clinical profiles and the mean flow velocities of the middle cerebral artery (MCA) (VMCA) and Lindegaard index (LI) of transcranial color-coded sonography studies.

Results: After excluding 6 patients without FLAIR images, the brain MR imaging of 84 patients with RCVS (8 males and 76 females, mean age 48.6 ± 10.9 years, range: 10–76 years) were reviewed. Seventeen of them (20.2%) had sulcal hyperintensity on their FLAIR images. Compared with patients without sulcal hyperintensity, patients with this finding were younger (42.5 ± 12.4 years vs. 50.1 ± 10.1, P = 0.009), had a higher mean maximum VMCA (124.2 ± 40.7 cm/s vs. 93.5 ± 29.6, P = 0.002) and a higher LI (2.6 ± 1.2 vs. 1.9 ± 0.5, P = 0.035). Patients with sulcal hyperintensity were more likely to have reversible posterior leukoencephalopathy (9/17 (53%) vs. 0/67 (0%), P < 0.001) or ischemic stroke (5/17 (29%) vs. 0/67 (0%), P < 0.001) than those without. Traits which did not differ significantly between patients with or without sulcal hyperintensity included gender distribution, headache characteristics, presence of blood pressure surge, and number of triggers and thunderclap headache attacks.

Conclusions: The sulcal hyperintensity sign on FLAIR images in patients with RCVS is related to severe cerebral vascular disturbance and indicates an increased risk of ischemic complications.
PO375
Medication overuse in secondary chronic headache – raised severity of dependence scores. The Akershus study of chronic headache
Lundqvist C1,2,3, Aaseth K1,4, Grande RB1,5, Benth JS3,4 and Russell MB1,4
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Objectives: To evaluate pattern of medication overuse and dependency-like behaviour in subjects with secondary chronic headache (=15 days/month for at least 3 months) in a cross-sectional epidemiological survey.

Background: Chronic secondary headaches are often associated with medication overuse, though the pattern and characteristics of such overuse in the general population have not been sufficiently described.

Methods: A posted questionnaire screened a sample of 30,000 30–44 year old from the general population for chronic headache. Those with self-reported chronic headache were interviewed by neurologists and people with secondary chronic headaches were identified. The International Classification of Headache Disorders was used. Data was analyzed with split file methodology. Interviews and examinations were conducted at the Akershus University Hospital, Oslo, Norway. Dependency-like behaviour was assessed by the Severity of Dependence Scale (SDS) score.

Results: 55 (49%) of the 113 persons with secondary chronic headaches were found to have medication overuse. 58% overused simple analgesics and 31% overused combination analgesics. The SDS score was significantly higher among those with than without medication overuse (5.5 vs. 1.9) and could be used for identifying those with medication overuse. The sensitivity, specificity, positive and negative predictive values for detection of medication over users were 0.82, 0.82, 0.82 and 0.83, respectively. Neither medication overuse pattern, nor the SDS scores differed significantly in the subgroups head and/or neck trauma, headache attributed to chronic rhinosinusitis or cervicogenic headache.

Conclusions: Thus, similarly to primary chronic headache, the SDS score correlates with medication overuse also in persons with secondary chronic headache. The high SDS scores suggest dependency-like behaviour. The use of the SDS score on patients with frequent headache episodes may contribute to detection of medication overuse and better management of this group of patients.

PO377
Chronic rhinosinusitis gives a 9-fold increased risk of chronic headache. The Akershus study of chronic headache
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Objectives: To study the association of chronic headache and chronic rhinosinusitis in a population based sample.

Background: Headache attributed to chronic rhinosinusitis (HACRS) is a not validated diagnosis in the International Classification of Headache Disorders and epidemiological data on chronic rhinosinusitis among those with chronic headache are lacking.

Methods: This is a cross-sectional epidemiological survey. A population based sample of 30,000 persons, stratified by age and gender, received a mailed questionnaire. Those with a possible chronic headache were interviewed by neurological residents. The criteria of the American Academy of Otolaryngology – Head and Neck Surgery was applied to diagnose HACRS, otherwise the International Classification of Headache Disorders was used.

Results: The questionnaire response rate was 71%, and the participation rate of the interview was 74%. Of 517 persons with chronic headache, 46 (9%) had HACRS. Compared with the general population, persons with chronic rhinosinusitis have an at least 9-fold increased risk of having chronic headache. A 3-year follow-up showed that HACRS symptoms were significantly improved after treatment with nasal surgery, nasal corticosteroids, discontinuation of overused headache medications and discontinuation of nasal decongestants or unspecified reasons.

Conclusions: Chronic rhinosinusitis is significantly associated with chronic headache and HACRS is likely to be a distinct type of headache.
PO378
Prevalence and clinical characteristics of post-traumatic headaches following complicated mild to severe traumatic brain injury
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Objectives: To assess the prevalence of post-traumatic headache (PTH) soon after, and 3 months after injury, as well as ascertain clinical characteristics of these headaches.

Background: PTH is classified as a secondary headache disorder, but little is known about the prevalence and clinical characteristics of these headaches. Systematic study of these headaches may optimize assessment and treatment approaches in individuals following traumatic brain injury (TBI).

Methods: Seven rehabilitation centers in the US (TBI Model Systems participants) administered questionnaires to patients over the age of 16 following acute complicated mild to severe TBI. These patients were participating in inpatient rehabilitation. Assessment included prior headache history, clinical characteristics of current headaches using IHC classification systems immediately following injury and 3 months post injury.

Results: To date, individuals enrolled were 70% male, 75% white, with an average age of 42.8 years. 55% were involved in vehicle accidents and 28% were injured in a fall. Of 326 who were neurologically intact to provide information, 15.5% reported headaches prior to injury, and 43.9% endorsed headache post injury. Data collected at 3 months on 263 subjects showed 32% reporting ongoing headaches. In 3 months post injury.

Conclusions: A significant number of individuals endorse headache immediately after a complicated mild to severe TBI. Some individuals describe prior history of headache and further evaluation is ongoing to compare clinical features of pre and post-injury headaches. While prevalence of PTH decreases 3 months post-injury, it persists in approximately one-third of TBI patients. Further evaluation of characteristics of PTH is important in developing appropriate assessment tools and treatment modalities.

PO379
Medication overuse headache in Argentinian center
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Objectives: Estimate the impact of medication overuse headache (MOH) in specialised headache center in Buenos Aires.

Background: MOH is a complex entity with different clinical expression where the patients who previously suffered an episodic migraine or tension type headache, have 15 days/moth of pain and use analgesics more than two times a week. It is essential identify the analgesics overuse. Argentina is one of the Latin American (LA) countries where people have free access to combinations of ergotamine with other drugs (caffeine, ibuprofen, analgesics and antiemetics), NSAID but no to triptans or opioids. There is no data about MOH frequency, with medication they overuse and other characteristics of these groups of patients in our country.

Methods: During two months 100 first visit patients at FLENI were interview by a headache specialist. All of them completed a clinical report form for diagnosis of MOH. Age, sex, pain feature, time of evolutions, use of medication, use of medication, use of xanitines and other co-morbidities were include in a questionnaire for each patient. The diagnosis of primary headache and MOH was established according to the IHS classification.

Results: 74 patients were classified as MOH, 86% women, range age 20–72 years and 62% have University degree. Primary headache at the beginning were migraine without aura:46.88%, tension type headache :14.6% and both 39.06%. Most commonly overuse was combination of different tablets:NSAID, caffeine, ergotamine (40.54%), fixed combination of ergot:36.49%, simple analgesic:20.27% and triptan only 2.7%. Preventive treatment was report in 23% of patients. Concurrent use of multiples xanitines was significant: 71.62% (mate, coffee, tea). In MOH patients were indentified 47.3% with insomnia, 85.71% of smokers met criteria of MOH.

Conclusions: The present is the first study to examine the incidence of MOH in an Argentinian headache center, as most of LA countries there is no data about this problem. The analysis of this group of patients indicate that in our country the main overuse correspond to the combination of ergotamine with other drugs making a difference with European and North-American countries. Preventive treatment is considered to play an important role in reduction of headache frequency. We found a group of other disorders in our MOH patients such as insomnia, associated pain syndrome, other addictions, and psychological factors. Identified each of them may help in the management of this headache. The education in LA countries of this topic may contribute to a better approach to the diagnosis and treatment.

PO380
Abstract withdrawn

PO381
Expectations for treatment in patients with medication overuse headache
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Objectives: The present study aimed to evaluate medication overuse headache (MOH) patients’ expectations on headache treatment to better meet the future patients’ expectations and improve the doctor-patient relationship.

Background: Medication overuse headache (MOH) is the most common secondary headache, affecting 2–3% of the general population. The condition is not generally recognized but when recognized, the prognosis is fairly positive if specific treatment programmes are employed.

Methods: A questionnaire, including items on patients’ expectations of headache treatment, was created. After testing a pilot version on 10 patients in one tertiary, Italian headache centre, the final version was tested in a group of 65 consecutive MOH patients from three tertiary headache centres in Italy, Germany and Denmark in April 2008.

Results: All included patients completed the questionnaire. 51% expected their headache to be cured, 71% expected an effective prevention of headache episodes and 57% expected fast relief of the headache episodes. 80% and 75% respectively expected a reduction in frequency and intensity.

Conclusions: Patients had high expectations to the efficiency of their headache treatment. Surprisingly more than half the patients expected their headache to be cured. This stress the need for detailed and realistic initial information emphasizing that headache cannot yet be cured. The vast majority will experience a significant improvement in frequency and/or intensity after detoxification as most
patients expected. Interestingly more than half the patient population considered it important to receive information and education about self-management and understanding of headache. To meet the patients’ expectations of in this way becoming an active partner in their own treatment it is of major importance to include continuous education of the patient.

**PO382**

‘Alarm bell headache’: a secondary stabbing headache

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**Objectives:** To describe a form of stabbing headache associated with intracranial, potentially dangerous abnormalities, such as unruptured aneurysms, vascular malformations and tumours.

**Background:** A primary stabbing headache is characterized by a sharp pain of short duration felt on the surface of the head that may occur once in a lifetime or several times in a single day. It is a relatively common cephalalgia reported by 2–8% of the population.

**Methods:** Since 2003 we have observed 41 patients with intracranial abnormalities (18 pituitary adenomas, seven meningeomas, eight acoustic schwannomas, two glomus jugularis, four unruptured saccular aneurysms, one frontal oligodendroglioma, and one occipital arterio-venous malformation) associated with stabbing headache.

**Results:** The characteristics of the secondary stabbing headache attacks observed in those patients were the following: (a) a gradual enhancement in pain severity with an increase in frequency over the last few months or years (crescent pattern); (b) a dura mater contact with the lesion; (c) repeatedly confined to one or a few points on the head; (d) unilateral on the same side as the lesion; (e) precipitated by head movements; (f) association with abnormal signs (e.g. loss of vision, proptosis, amenorrhoea, galactorrhoea, hearing loss, epileptic seizure, etc.); (g) associated with larger intracranial lesions; (h) usually appearing at a later stage; (i) predominantly affecting women; and (j) resolution after surgery or dexametasone treatment.

**Figure 1** shows the RMI of a woman with right temporal stabbing headache associated with a right pituitary adenoma (left side of the viewer), and the arteriography of a man with a right carotid-ophtalmic aneurysm and stabbing headache on the right eye (right side of the viewer).

**Figure 2** shows the RMI of a woman with left frontal stabbing headache and a left frontal oligodendroglioma contacting the dura mater (right side of the viewer) and the cerebral falx where the tumor was in contact (operatory view, left side).

**Conclusions:** When an individual presents one or more of the characteristics described above we should consider it as a warning sign, indicating that something abnormal is occurring inside the head, such as a vascular or neoplastic expanding mass with dural contact, in which case an evaluation with neuroimaging is imperative.

**PO383**

Study of chronic headache of acromegaly

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**Objectives:** Authors studied the process how the growth hormone (GH) secreting pituitary adenoma causes a chronic headache.

**Background:** A patient with GH secreting pituitary adenoma (acromegaly) sometimes complains a chronic headache. Successful treatment of reducing GH often provides pain relief. Though GH exerts its most effects through insulin-like growth factor 1 (IGF-1), it is not clear that the pathway through IGF-1 is implicated in the acromegalic headache.

**Methods:** Six acromegalic patients with macroadenoma (more than 10 mm diameter of the adenoma) that authors treated from February 1, 2008 to April 30, 2009 complained the chronic headache. Headache phenotype, blood hormonal test, and radiological picture were examined.

**Results:** Headache mimicked migraine without aura in five patients and tension-type headache in one patient. Triptans prescribed in two patients showed a transient effect. Bromocriptine, a dopamine receptor agonist, reduced serum GH level and provided headache relief. Octreotide, an inhibitor of GH and IGF-1 secretion, reduced headache in four patients and exacerbated headache in two patients. Pegvisomant, an inhibitor of GH receptor and normalizing substance of IGF-1, were used in 1 patient and exacerbated a headache. MR image showed suprasellar or intracavernous tumor extension in these six cases.

**Table. Headache phenotype and blood hormonal test**

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Headache mimicked</th>
<th>Headache reduced by</th>
<th>GH (ng/ml)</th>
<th>IGF-1 (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 year-old woman</td>
<td>Migraine without aura</td>
<td>bromocriptine, octreotide</td>
<td>11.6</td>
<td>980</td>
<td></td>
</tr>
<tr>
<td>35 year-old woman</td>
<td>Tension-type headache</td>
<td>bromocriptine, octreotide</td>
<td>35.2</td>
<td>1340</td>
<td></td>
</tr>
<tr>
<td>40 year-old woman</td>
<td>Migraine without aura</td>
<td>bromocriptine, octreotide</td>
<td>23.0</td>
<td>466</td>
<td></td>
</tr>
<tr>
<td>40 year-old woman</td>
<td>Migraine without aura</td>
<td>bromocriptine, octreotide</td>
<td>7.5</td>
<td>853</td>
<td></td>
</tr>
<tr>
<td>40 year-old man</td>
<td>Migraine without aura</td>
<td>bromocriptine, octreotide</td>
<td>12.0</td>
<td>1180</td>
<td></td>
</tr>
<tr>
<td>41 year-old man</td>
<td>Migraine without aura</td>
<td>bromocriptine, octreotide</td>
<td>35.4</td>
<td>1350</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1**
Conclusions: Pituitary macroadenoma can cause a headache through the meningeal stimulation by the tumor itself. However, it is widely known the suprasellar and/or intracranial extended pituitary tumor do not always induce a chronic headache. The patient of the left picture did not complain a headache. The patient of the right picture suffered from a chronic pulsating headache. The results of blood hormonal tests indicate that the acromegalic headache is exerted through endocrinological pathways. The acromegalic chronic headache was reduced by bromocriptine and worsened by pegvisomant. Octreotide sometimes worsened the acromegalic headache. In addition to the IGF-1 mediated pathway, another process of GH may be implicated in the acromegalic patient’s headache.

PO384
Persistent facial pain after corneal surgery: two cases illustrating a novel cause of traumatic trigeminal neuropathy
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Objectives: To report a novel cause of traumatic trigeminal neuropathy.

Background: Trigeminal neuropathy is a condition characterised by sensory disturbance in the distribution of the trigeminal nerve. It can be caused by a wide variety of conditions including trauma, tumours, connective tissue disorders, infections, or neurovascular conflict. There are however no reported cases of this condition arising following iatrogenic injury to the cornea.

Methods: Two case reports are presented of patients experiencing persistent facial pain following ophthalmic surgery.

Results: PN, a 42 year old man, underwent surgical correction of refractive error of the left eye using UltraLASIKplus with Intrafarse in February 2007. He experienced localised eye pain following the procedure. Over the following weeks this pain spread to involve the left face, hemicranium, and shoulder. When first seen in our service in April 2008 he continued to complain of pain and sensory disturbance in a trigeminal distribution. Examination was normal, apart from ipsilateral greater occipital and posterior auricular tenderness. MRI imaging was normal. Blink reflexes were normal. A diagnosis of trigeminal neuropathy was made. His symptoms have not responded to amitriptiline, gabapentin, pregabalin, indometacin, sodium valproate, or blockade of the greater occipital, posterior auricular, or supraorbital nerves. In January 2007 JU, a 42 year woman, underwent right-sided phacoemulsion and removal of cataract, followed by infraocular lens implantation. She experienced localised eye pain following the procedure. Over the following weeks this pain did not subside, but spread to involve the left cheek, jaw, and neck, despite treatment with simple analgesics, non-steroidal inflammatories, and nortriptiline. She experienced sensory disturbance in the painful areas. When seen in our service in March 2008, neurological examination was normal, apart from ipsilateral carotid tenderness. There was no greater occipital nerve tenderness. MRI imaging of the brain and neck was normal, as was MR angiography. A diagnosis of trigeminal neuropathy was made. Her symptoms have not responded to indometacin, topiramate, or pregabalin.

Conclusions: Traumatic trigeminal neuropathy is an extremely uncommon but recognised consequence of dental treatment and destructive surgical procedures of the trigeminal nerve. It is not clear why this often devastating adverse event should occur so rarely. In these cases, the nature of the pain experienced, the temporal relationship to ophthalmic surgery involving necessary damage to the cornea, and the absence of any other structural lesion of the ipsilateral trigeminal nerve on detailed imaging, make traumatic trigeminal neuropathy the only tenable diagnosis. It is hoped that publication of these cases will stimulate further investigation of this condition, allowing a proper appreciation of its incidence. This will allow patients undergoing ophthalmic surgery to be fully informed, as part of the consent process, of the possibility of developing persistent post-operative pain.

PO385
Prevalence rates of hypertrophic pachymeningitis in patients with prolonged headache
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Objectives: Hypertrophic pachymeningitis is condition characterized by significant chronic inflammatory thickening of the cranial dural mater frequently which is presenting with symptoms such as headache and cranial neuropathy. In this study, we report a prevalence rates of hypertrophic pachymeningitis in prolonged headache patients.

Background: Hypertrophic pachymeningitis is an usual inflammatory disease involving hypertrophic changes in the cranial duramater, and results invarious cranial neuropathies, including hearing loss and facial paralysis. Known causes of the disease are syphilis, tuberculosis, fungal infections, bacterial meningitis, sarcoidosis, Wegener’s granulomatosis, polyarteritis nodosa, trauma and hemodialysis. We report a prevalence rates of hypertrophic pachymeningitis in prolonged headache patients and we present an interesting case of hypertrophic pachymeningitis, which was considered to be attributable to Epstein-Barr virus in a patient complaining of ongoing severe headaches with unknown cause.

Methods: This study involved 22 patients, six males and 16 females who visited our hospital with prolonged headache between January 2009 and February 2010. Assessment of the presence of MRI was carried out in our patients with chronic headache, prevalence rates of hypertrophic pachymeningitis were computed with that of the prolonged headache patients.

Informed written consent to undergo measurements of each antibody was obtained from each patient who understood the purposes and procedure of the study.

Results: There were 22 patients with prolonged headache whose age ranged between 24–64 (mean 43) years old. The mean duration of illness was six (range 2.5–34) months. Among the 22 patients, 9.9% were intracranial hypotension, and 4.5% were hypertrophic pachymeningitis, and 9.9% were cluster headache, and 21.2% were migraine, and 54.5% were tension type headache.

Table 1. Baseline characteristics and features of prolonged headache in our patients

<table>
<thead>
<tr>
<th>Type of prolonged headache</th>
<th>Hypertrophic pachymeningitis</th>
<th>Hypotension</th>
<th>Headache</th>
<th>Migraine</th>
<th>Tension type headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n = 22)</td>
<td>1 (4.5%)</td>
<td>2 (9.9%)</td>
<td>2 (9.9%)</td>
<td>5 (21.2%)</td>
<td>12 (54.5%)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Figure 1
The figures in the left shows a normal head (left) MRI images, with no abnormal findings. The figure in the middle and the right show inhomogeneously enhanced head MRI images of the corona section and the ophtalmic section, respectively. As indicated by the arrow, the figure above partially enhanced left temporal cortex and midbrain may present enhanced central and thickening of the temporal cortex.
PO386
The severity of dependence scale detects people with medication overuse. The Akershus study of chronic headache
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Objectives: To evaluate the Severity of Dependence Scale (SDS) in people with the primary chronic headache diagnoses of chronic migraine (CM) and chronic tension-type headache (CTTH) and analyze pattern of medication overuse.
Background: Tools for quick and easy identification of medication overuse is needed and more knowledge about medication-overuse and dependency is needed.
Methods: This is a cross-sectional epidemiological survey. An age and gender stratified random sample of 30,000 people, 30–44 years, from the general population of Akershus County, Norway were sent a questionnaire that screened for chronic headache (≥15 days of headache per month the last month or year). Neurological residents interviewed those with self-reported chronic headache. The International Classification of Headache Disorders (ICHD-II) was used. Split file methodology was employed for data analysis.
Results: The screening questionnaire response rate was 71%, the participation rate of the interview 74%. Among 405 people with primary chronic headache, 95% had chronic tension-type headache, 4% had chronic migraine, and < 1% had other primary chronic headaches. Of 386 persons with chronic tension-type headache, 44% had medication overuse and 47% had co-occurrence of migraine. Simple analgesics, combination analgesics, triptans, ergotamine, opioids and combination of acute medications were overused by 65%, 27%, 4%, <1%, 1% and 2%, respectively. The mean SDS score was significantly higher in those with than without medication overuse (5.6 vs. 2.7; P < 0.001).
Conclusions: The SDS questionnaire detects medication overuse and dependency-like behaviour in persons with chronic migraine and chronic tension-type headache.

PO387
A population-based study of tension-type headache in obstructive sleep apnea. The Akershus sleep apnea project
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Objectives: To investigate the effect of obstructive sleep apnea on the prevalence of tension-type headache.
Background: While sleep disturbances previously have been related to tension-type headache, much less evidence of such a relationship exists than in migraine.
Methods: A cross-sectional population based study. A random age and gender stratified sample of 40,000 persons aged 20–80 years residing in Akershus, Hedmark or Oppland County, Norway were drawn by the National Population Register. A postal questionnaire containing the Berlin Questionnaire was used to classify respondents to be of either high or low risk of obstructive sleep apnea (OSA). 384 persons with high risk and 157 persons with low risk of sleep apnea aged 30–65 years were included for further investigations. They underwent an extensive clinical interview and a physical and a neurological examination by physicians, as well as a polysomnography (PSG). Those with apnea hypopnoea index (AHI) ≥ 5 were classified with obstructive sleep apnea. Tension-type headache was diagnosed according to the International Classification of Headache Disorders (ICHD-II).
Results: The estimated prevalence of obstructive sleep apnea in 30–65 year olds in the Norwegian population was 17% (13% among women and 21% among men). Infrequent, frequent and chronic tension-type headache were diagnosed in 4.0%, 19.5% and 3.0% of participants with obstructive sleep apnea and in 3.3%, 33.6% and 1.7% of those without obstructive sleep apnea. Frequent tension-type headache was significantly more prevalent among participants with obstructive sleep apnea (P < 0.001), while the prevalence of infrequent and chronic tension-type headache was not significantly different in the two groups. Similar patterns were found when using cutoff of moderate (AHI ≥ 15) and severe (AHI ≥ 30) obstructive sleep apnea.
Conclusions: Frequent tension-type headache was significantly more prevalent among participants without obstructive sleep apnea. There seem to be no clear relationship between obstructive sleep apnea and tension-type headache in the general population.

PO388
Disturbances of hormonal status in women of reproductive age with chronic tension headache
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Objectives: Tension-type headache is the most prevalent of the primary headache disorders. Both the chronic and episodic forms of the disorder are more common in women than in men.
Background: 100 women with chronic tension headache and 30 women with episodic tension headache have been examined. Women who took oral contraception, with pregnancy and chronic diseases were excluded from the study.
Methods: The study techniques include: neurological examination and radioimmunometrical methods.
Results: The investigation results of possible pathogenic correlation of tension headache and functional status of hypophysial-ovarian
Involvement of NOS isoenzymes in sustained facilitation of neck muscle nociception in mice:implications for tension-type headache

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Objectives: Investigating the putative involvement of Nitric Oxide Synthase (NOS) in ATP-mediated facilitation of neck muscle nociception.

Background: Increased neck muscle tenderness is a characteristic for tension-type headache (TTH). The unspecific NOS inhibitor L-NMMA decreases pain and tenderness in chronic TTH (Brain 122:1629–35, 1999). In a translational mouse model of neck muscle nociception, administration of α,β-meATP (ATP) into neck muscles induces sustained increase of neuronal excitability in the brainstem (Cephalalgia 26:697–706, 2006). L-NMMA prevents and reverses this facilitation. The present study addresses the hypothesized involvement of NOS isoenzymes in ATP-evoked neck muscle facilitation.

Methods: Bilateral infusion of ATP (1 μM, 25 μl) into semispinal neck muscles was performed in 40 anesthetized C57BL/6J mice. Impact of neck muscle nociception on brainstem processing was electrophysiologically assessed via the jaw-opening reflex (JOR). The JOR was elicited by electrical tongue stimulation and monitored 45 minute before and 150 minute after ATP infusion. Isotonic saline (control), the selective neuronal NOS inhibitor NPLA (0.5, 1, 2 μg/kg), or the inducible NOS inhibitor 1400W (2 mg/kg) were intraperitoneally injected 30 minute before or 90 minute after ATP infusion.

Results: Baseline JOR was neither affected by NPLA nor by saline. Consecutive application of saline and ATP induced significant reflex facilitation (329 ± 28%, mean ± sem, P < 0.001). Preceding NPLA decreased (1 mg/kg: 21 ± 31%) or even abolished reflex facilitation (2 mg/kg: -3 ± 26%) in a dose-dependent manner for at least 90 minute. Neither subsequent 2 mg/kg NPLA nor saline affected established reflex facilitation. In contrast, subsequent administration of 1400W significantly attenuated reflex facilitation (-37 ± 10%).

Conclusions: ATP reliably induced sustained facilitation of neck muscle nociception. Preceding NPLA application prevented this facilitation in a dose-dependent manner. Subsequent NPLA was not effective on established reflex facilitation. Subsequent inducible NOS inhibition partially reversed facilitated neck muscle nociception whereas L-NMMA induced complete reversal. Thus, neuronal NOS probably play an important role in induction of facilitation whereas inducible NOS are involved in the maintenance of nociceptive facilitation in the brainstem. These results point to a major role of NOS isoenzymes in neck muscle nociception and may provide for future treatment options in TTH patients.
Background: Topiramate is approved for migraine prophylaxis in adults for migraine. Recently, topiramate treatment resulted in significant benefit compared with placebo in chronic migraine. Acupuncture has been largely used for migraine sufferers in western countries; however, the convincing evidence of the efficacy and safety of acupuncture in treatment of CM was yet demonstrated. Therefore, we conducted a pilot study: prospective, randomized clinical study comparing the efficacy of acupuncture and topiramate in the treatment of CM.

Methods: Patients were required to have a diagnosis of chronic migraine with or without medication overuse that satisfied the ICHD-II (2006) criteria during the last 3 months prior to trial entry, with an established migraine history for at least 1 year. Twenty-four patients with CM were randomly divided into two treatment groups: (1) Topiramate group, 4-week titration (initiated at 25 mg/day has and increased by 25 mg/day weekly to a maximum of 100 mg/day) followed by 8-week maintenance period (n = 12), (2) administered acupuncture in Guanzhu (BL-2), Fengchi (GB-20), Taiyang (EX-HN-5) bilaterally in their 24 sessions over 12 weeks (n = 12). Patients had to keep a headache diary from the baseline period (diary 1) and treatment period (diary 2–4). Each diary covered 4 weeks. The primary efficacy parameter was the change in the number of monthly migraine attacks. The secondary efficacy measures included reduction in migraine days, headache index and MIDAS. Efficacy was measured by comparing the first diary, which was made in the baseline period, with the diaries of the treatment period (diaries 2–4). Statistical analysis was on intention to treat basis.

Results: Twenty-four patients comprised the intent-to-treat population. Monthly migrainous days reduced from 22.2 to 12.8 (40.1%) in the acupuncture group compared to a reduction from 22.7 to 13.8 (37.8%) in the topiramate group. Monthly migraine attacks declined in the acupuncture group from 13.5 during baseline to 8.0 (39%) in the final month and from 13.6 attacks during baseline for topiramate group to 8.9 (33.5%) at the final visit. The headache index declined from 17.9 to 10.1 (45.3%) in the acupuncture group compared to a decline from 17.3 to 10.8 (37.9%) in the topiramate group (P = 0.03). The mean MIDAS score declined from 67.2 to 12 (81.9%) in the acupuncture group compared to a decline from 67.3 to 18 (71.6%) (P = 0.02) in the topiramate group. No serious adverse effects were noted in both groups. In the acupuncture group, side effects were reported by 8% of the patients. In the topiramate group, side effects were reported by 41% of the patients.

Conclusions: Acupuncture treatment was more effective and well tolerated compared to topiramate in the treatment of CM. For those who are not tolerant to topiramate, acupuncture treatment can be an alternative choice. However, further investigation with a larger sample size is recommended.

PO394
Histological demonstration of a leptomeningeal hemangioma as a cause of a nevoid vertigo syndrome
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Objectives: To present eight new cases of olfactory hallucinations, or phantosmias, in primary headache disorders and review previously reported cases.

Background: Olfactory hallucinations occur frequently with psychiatric disease and temporal lobe epilepsy but have rarely been associated with primary headache disorders. Studies to date quote a low prevalence of phantosmias in migraine, though details regarding these hallucinations and their relationship to headache attacks are lacking.

Methods: Case series and literature review.

Results: Phantosmias were identified in 20 patients from the literature (19 with migraine, one with cluster) and eight new patients (six with migraine, one with cluster, one with new daily-persistent headache (4%). Phantosmias occurred either prior to attacks (68%), during attacks (29%), or both (4%). Seven percent of patients also experienced hallucinations without headache. Hallucination duration ranged from seconds to 24 hours (median: 5 to 10 minutes). Patients experienced conventionally unpleasant smells (75%), pleasant smells (11%), or both (14%); one patient experienced a smell that evolved from sweet to malodorous. Coexistent gustatory (n = 2) and auditory (n = 1) hallucinations were seen in some patients with migraine. Comorbid depression or anxiety was documented in 24%. No patient had a personal or family history of psychosis.

Conclusions: These patients had olfactory hallucinations, or phantosmias, in the absence of epileptic phenomena, cerebral lesions or psychosis. Their exclusive association with headaches, the time course of the symptoms and the prompt remission with treatment support the hypothesis that the olfactory hallucinations were part of the headaches. Phantosmias usually occur in women with migraine, and are typically unpleasant. While visual hallucinations are a common migraine aura, olfactory hallucinations are rare. Perhaps spreading depression of the olfactory cortical areas accounts for this phenomenon.

PO393
Olfactory hallucinations in primary headache disorders: 8 new cases and a review of the literature
Grosberg BM, Tarshish S and Robbins MS
Department of Neurology, Montefiore Headache Center, Albert Einstein College of Medicine, Bronx, NY, USA

Objectives: To present eight new cases of olfactory hallucinations, or phantosmias, in primary headache disorders and review previously reported cases.

Background: Olfactory hallucinations occur frequently with psychiatric disease and temporal lobe epilepsy but have rarely been associated with primary headache disorders. Studies to date quote a low prevalence of phantosmias in migraine, though details regarding these hallucinations and their relationship to headache attacks are lacking.

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Conclusions: These patients had olfactory hallucinations, or phantosmias, in the absence of epileptic phenomena, cerebral lesions or psychosis. Their exclusive association with headaches, the time course of the symptoms and the prompt remission with treatment support the hypothesis that the olfactory hallucinations were part of the headaches. Phantosmias usually occur in women with migraine, and are typically unpleasant. While visual hallucinations are a common migraine aura, olfactory hallucinations are rare. Perhaps spreading depression of the olfactory cortical areas accounts for this phenomenon.
Conclusions: Some NH can be triggered by coughing or sexual activity. The presence of these alarm symptoms makes this focal headache even more suspicious, clearly reinforcing the need to carefully rule out the existence of underlying structural lesions. In case 3, the pain disappeared after surgical removal of a torental meningioma, similarly to a previously reported case, opening up the issue of whether some NH might in fact be secondary to intracranial processes, most likely of meningeal nature. These observations lead us to believe that primary and secondary forms of NH should be considered and its diagnostic criteria reviewed.

PO395
Co-existence of hemiplegic migraine (HM) with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA): a case series
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Objectives: To describe the association between HM and SUNCT or SUNA.

Background: HM is defined as migraine with aura consisting of motor weakness, and may be sporadic or familial. SUNCT and SUNA are primary headaches characterised by attacks of very severe headaches in association with cranial autonomic features. Hitherto, HM has not been reported to be associated with SUNCT or SUNA.

Methods: The case notes of patients with HM and SUNCT or SUNA were reviewed to identify patients who had co-existence of these disorders. Data were collected for demographics, diagnosis and treatments.

Results: Five patients (four female, one male) were identified (mean age 45 years). three have a strong family history of primary headaches, but none reported HM, SUNCT or SUNA. With HM, all experienced significant aura (three visual, three aphasia and three brainstem symptoms) with both sensory and motor hemiplegic symptoms lasting longer than an hour in three individuals, and as long as 3 days in two patients. Aura was always followed by headache, three patients experienced nausea and vomiting, sensory phobias and motion sensitivity. Headache frequency ranged from twice weekly to once monthly, with duration of several hours to 3 days. Two patients had SUNCT and three had SUNA occurring independently of, and sometime after the onset of HM. The duration of the attacks ranged from seconds to 10 minutes with a frequency of between 15 and 50 attacks per day. Attacks were accompanied by cranial autonomic features, differentiating them from Primary Stabbing Headache. All described restlessness and two experienced migrainous features (nausea and sensory phobias). One patient reported a cutaneous trigger. Both patients with SUNCT experienced aura: one with visual, sensory and motor components and one with pure sensory symptoms. There was no clear relationship between the timing of SUNCT/SUNA and hemiplegic aura or migraine. Interestingly one patient also had chronic cluster headache. All had unremarkable clinical examinations and imaging. Non-steroidal anti-inflammatory drugs and triptans were helpful for migraine in three and two patients, respectively. With regard to preventives, one patient found partial benefit from a combination of Flunarazine and Gabapentin, and one from Topiramate. One patient had considerable improvement in both HM and SUNCT with Lamotrigine. Two patients had temporary improvement following a course of intravenous Dihydroergotamine. Two patients had short lived improvement from greater occipital nerve injection and one experienced a worsening of headache symptoms.

Conclusions: The prevalence of sporadic HM is estimated to be approximately 0.05% and although the exact prevalence of SUNCT/SUNA is unknown it is felt to be rare. Both differ in terms of pathophysiology and pathways involved, but also share common neurological mechanisms. The finding of these rare syndromes coexisting suggests there may be a common denominator, of which channel dysfunction is an attractive hypothesis.

PO396
Classifying vestibular migraine: demographics, associated features, and triggers
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Objectives: To review the clinical features of vestibular migraine (VM).

Background: Migraine and vestibular symptoms (VS) often co-exist within an individual. In diziness clinics, up to 38% of patients (pts) have migraine. In headache clinics, up to 50% of migraineurs have any vestibular symptom. Although the association of migraine and VS is well documented, this relationship remains unknown to many physicians due to a lack of standardized diagnostic criteria. Neuhauer and Lempert recommended diagnostic criteria for VM, but they were tested in only 33 pts and require a very strict adherence of symptomatology. [i] Pts without prior migraines or those with a continuous feeling of imbalance are excluded from the diagnosis. Furthermore, the current International Classification of Headache Disorders does not include VM.

Methods: This is a two phase study. In phase one, we retrospectively reviewed charts of pts diagnosed with VM in order to identify common symptoms, features, and triggers that may define the disorder. In phase two, we will use these findings to develop and validate a questionnaire for screening VM. Herein, we present the results of phase one.

Results: We identified 147 pts (100 female, 47 male) ranging in age from 15 to 92 (mean age 45). The mean age of migraine headache onset preceded VS by 8 years (30.7 vs. 38.7). 39% of pts had aura. 62 pts reported a gradual onset of VS; in 48 symptoms began suddenly. The most common vestibular symptoms reported were: unsteadiness 134 (91%), balance disturbance 120 (82%), lightheaded 113 (77%), and vertigo 84 (57%). 48% of pts noted an association of VS with headache, 27% did not, and 25% were unsure. Of the 147 pts, 68 (46%) were chronic sufferers from onset, 32 (22%) had episodic symptoms, and 47 (32%) had transformed from episodic to chronic with an average time of 7.23 years from onset until transformation. Common triggers of VM are listed in table 1.

Table 1.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Don't Know or Blank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescent lights</td>
<td>80</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Bright lights</td>
<td>75</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Crowds</td>
<td>82</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Malls</td>
<td>76</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>Shelves</td>
<td>61</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Target department store</td>
<td>30</td>
<td>40</td>
<td>77</td>
</tr>
<tr>
<td>Busy patterns (rugs)</td>
<td>78</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Riding trains</td>
<td>54</td>
<td>41</td>
<td>52</td>
</tr>
<tr>
<td>Watching trains</td>
<td>63</td>
<td>32</td>
<td>52</td>
</tr>
<tr>
<td>Escalators</td>
<td>53</td>
<td>54</td>
<td>40</td>
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<tr>
<td>Weather</td>
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<td>59</td>
<td>29</td>
</tr>
<tr>
<td>Hallways</td>
<td>37</td>
<td>53</td>
<td>57</td>
</tr>
<tr>
<td>Supermarkets</td>
<td>56</td>
<td>40</td>
<td>31</td>
</tr>
</tbody>
</table>

Conclusions: VM is a heterogeneous condition with varying symptomatology. Patients may exist along a spectrum from episodic to chronic as in typical migraine. As many patients herein described
would not meet criteria previously proposed, new criteria which account for the heterogeneity and natural history of the disease are necessary to adequately diagnose VM in those who suffer from it.

PO397
Confusional migraine – not only a children’s disease
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Objectives: To describe the concept of confusional migraine in adults.

Background: Acute confusional migraine (ACM) was first described in 1970 in paediatric patients and remained a diagnosis used for this age group thereafter. In the previous literature mild head trauma has been discussed as a precipitating factor.

Methods: We present a series of nine cases of adolescents and adults (mean age 36years; 16–62years, see table) suffering from attacks of typical migraine with aura, which were associated with transient confusional states.

Results: The confusional state lasted on average 2–3 hours. Half of the patients reported two or more such attacks. Only one of them reported mild head trauma in the past. Further investigations were unremarkable in all patients and did not suggest underlying structural abnormalities, epilepsy or cerebrovascular disease. In none of these patients we found another cause to explain the observed phenomenon.

Conclusions: The temporal course of the confusion as well as the association with visual and other aura symptoms suggest cortical spreading depression as the underlying pathophysiology. Based on this series of patients we suggest expanding the concept of confusional migraine from the paediatric population to adults.

PO398
Botulinus toxin, type a, for treating co-morbid migraines/headaches and TMD symptoms
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Objectives: We studied botulinus toxin, type A, intradermally, to treat headaches of facial origin that fulfilled IHS criteria for migraine. We queried an effect on sensory afferent or non-cholinergic fibers to reduce pain and migraine in these patients with intradermal application of the toxin, a novel injection technique.

Background: Botulinus toxins can play a role in reducing pain and headache disorders, although there is no formal approval for these toxins in treating these disorders.

Methods: 48 patients were entered. All received intraderal botulinum toxin, type A, 100 units. Intraderal botulinum toxin, type A, was given on the side of predominant side of TMD/migraine involvement. 100 Units of Botulinum toxin, type a, [BoNTA] showed statistically significant reductions of TMD pain and migraine frequency. Headache reductions in frequency were P < .001, with an average of 14 headaches a month to 2.5 headaches per month. TMD pain reduced 73% VAS after BoNTA treatment to an average of 12.6 weeks. Reductions in migraine severity continued at P < .002 compared to placebo over 12.5 weeks. No side effects were noted with botulinum toxin. All patients were followed monthly. Migraine frequency and severity was assessed monthly. 48 patients were entered in this open-label study. All patients received 100 units BoNTA. Intraderal botulinum toxin, type A, was given on the side of predominant migraine headaches. All patients were followed monthly. Migraine frequency and severity was assessed on a monthly basis by each study patient.

Results: BoNTA showed statistically significant reductions of migraine frequency, as well as severity both at 1 month and at 3 months. Headache frequency was 17.2 headaches per month, as compared with 3.6 headaches per month after treatment. Headache reductions in frequency were P < .001 for BoNTA. Reductions in migraine severity continued at P < .002 compared to baseline data after 3 months. No side effects were noted with botulinum toxin, type A.

Intraderal botulinum toxin, type A, reduced significantly the frequency and severity of migraines associated with TMD symptoms. Safety/tolerability of intraderal botulinum were excellent.

Conclusions: Intraderal dosing may involve mechanisms of action that do not utilize cholinergic motor nerve elements and may involve alterations in pain transmission pathways, and a novel approach to use of botulinum toxin, type A for TMD and co-exists mignaines.

PO399
Gastroparesis in migraineurs: is there a clinical syndrome?
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Objectives: To identify a clinic population of patients with migraine and gastroparesis. To determine if the relationship is a clinical syndrome, identify features and associated factors.

Background: Delayed gastric emptying is associated with acute migraine attacks evidenced by the gastric emptying scan, the gastric impedance method, and indirect pharmacological studies. Historically, gastric stasis has been theorized as the underlying mechanism; however, recent physiological studies suggest that gastroparesis may be insidious, occurring outside of a migraine attack. The association between migraine and idiopathic gastroparesis is unknown. The association may be secondary to autonomic nervous system dysfunction, migraine complications, or abnormalities in higher cortical processing of pain perception. Clinical descriptions of migraine patients with gastroparesis has not been previously reported.

Methods: The electronic medical records were used to identify migraine patients with a history of gastroparesis. A chart review was completed to identify demographics, medical history, and migraine type including abdominal migraine, attack frequency, depression indices, and disability measures. Patients were recruited for clinical assessments: the temporal relationship between migraine and gastroparesis exacerbation, correlations between disability measures.

Results: 53 patients identified in EMR with gastroparesis and migraine. 87% female, 13% male, average age of 40.0 (range 16–77, SD 16.0). 7.5% with abdominal migraine and 62.3% with typical migraine with aura, which were associated with transient confusional states.
chronic migraine. Average age of migraine onset was 20 years (range 2–61, SD 12.9). Average duration of migraine was 18 years (range 2–47, SD 13.9). Average BDI score 14.3 (SD 13.8) and average MIDAS score 73.2 (SD 81.1). 10 patients with thyroid disease (18.9%), fibromyalgia 7 (13.7%), psychiatric disease 21 (37.7%), gastric reflux 9 (17.0%), previous abdominal surgery 7 (13.2%), orthostatic hypotension 6 (11.3%), interstitial cystitis 4 (7.5%). A few patients described a temporal relationship between migraine attacks and abdominal pain.

Conclusions: Although uncommon, a subset of patients with migraine and gastroparesis appear to have a temporal relationship between peripheral and central pain exacerbations. Patients with gastroparesis and migraine are more likely to carry the diagnosis of cystitis, orthostatic hypotension and fibromyalgia than other clinic patients. Patients with migraine and gastroparesis are commonly on medications that may negatively impact gastric emptying. More studies are needed to determine the prevalence, clinical relationship, and impact of gastroparesis in migraine.

PO400
Repetitive migraine aura triggered by acute cerebral disease
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Objectives: To discuss the role of acute cerebral disease as a possible migraine trigger.

Background: Migraine aura that usually precedes headache attacks in migraine with aura is thought to be caused by cortical spreading depression. Attacks with aura can be triggered by trauma in susceptible individuals (1). In animal models cortical spreading depression (CSD) can be triggered by trauma (2) and in head trauma, but also severely affected stroke patients repetitive episodes of CSD have been recorded (3, 4).

Methods: We present 3 patients (table 1) in whom acute cerebral disease (two with viral meningitis, one with minor stroke due to carotid stenosis) probably triggered recurrent migraine auras with repetitive reversible focal neurologic symptoms.

Results: In two patients, lumbar puncture showed mononuclear pleocytosis, in one patient MRI of the brain revealed multiple ischemic lesions in the border zone between vascular territories.

Conclusions: The temporal course with slowly progressive development of reversible symptoms and a normal EEG made ischemic or epileptic etiology unlikely. Clinical presentations similar to two of our patients had been referred to as 'syndrome of transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL)' and 'Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis'. We hypothesize that besides CSF lymphocytosis also small acute vascular lesions, and possibly any other brain lesion can trigger repetitive migraine auras in susceptible individuals.

References:

PO401
Abstract withdrawn
PO403
Facial neuralgia and vitamin B 12 deficiency
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Objectives: This study relates to a series of patients presented with isolated unilateral facial neuralgic pain independent of trigeminal neuralgia and peripheral neuropathy. These patients showed presence of serum B 12 deficiency and responded to the treatment with parental therapy with B 12.

Methods: Seventeen patients (10 women and seven men) presented with frequent episodes of facial neuralgic pain not typical of trigeminal neuralgia. The neuralgic pain is unilateral in distribution and usually not triggered by any external stimulus. The neurological examination is normal including the corneal/facial sensation and the strength of both facial and trigeminal nerve innervated muscles. Subjective decrease in touch and pain sensation is noted on the affected side. All patients complain of numbness on the affected side. The blink reflex, trigeminal nerve evoked response, serum B 12 and methyl malonic acid levels were abnormal. The treatment with parental B 12 improves the clinical and electrophysiologic parameters. The neuroimaging studies of the brain were unremarkable. None had any symptoms of peripheral neuropathy.

Results: The B 12 deficiency facial neuralgia is primarily noted unilaterally, though electrophysiologic studies manifest subclinical abnormalities on either side. The blink reflex and the trigeminal nerve evoked response studies were more frequently abnormal on the clinically effected side. The improvement of the electrophysiologic parameters noted with treatment with parental B 12 treatment. All patients had abnormal methyl malonic acid level, indicating defective gastrointestinal absorption of B 12. The neuralgia is more frequent on the site showing frequent development of cold sores (herpes simplex labialis). The facial neuralgia is independent of development of peripheral neuropathy.

Conclusions: Vitamin B 12 deficiency can cause isolated facial neuralgia independent of peripheral neuropathy. The distribution of neuralgia in the territory of trigeminal nerve. The unilateral involvement is more frequent than bilateral. The blink reflex and trigeminal nerve evoked response studies are frequently abnormal on the neuralgic site and show improvement with parental treatment with B 12. The B 12 deficiency facial neuralgia in more common on the site showing frequent development of cold sores.

PO404
Laser treatment of burning mouth syndrome – a case report
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Objectives: To present a case report of a 59 year old female with a recalcitrant Burning Mouth Syndrome who showed significant improvement to three cycles of low energy level laser therapy.

Methods: The patient complained of burning pain in entire tongue, palate and gums, bilaterally. It was 7/10 in intensity and unresponsive to recurrent courses of antibiotics, antifungal agents, antidepressants (Amitriptyline, duloxetine, fluoxetine, escitalopram), anticonvulsants like (clonazepam, phenytoin, gabapentin, pregabalin, carbamazepine), and antioxidant agents. The patient underwent three cycles of BIOLASE, WATERLASER LASER at 0.5 watts with air (10%) and water (10%). The tip was defocused 3 mm above the tissue surface. The tissue was blanched, carbonized and became speckled white. The cycles were conducted one week apart.

Results: After three cycles of laser therapy, the patient reported significant recovery of the burning pain with intensity decreasing to 0/10 and has persisted ever since.

Conclusions: Use of laser therapy on painful aphthous ulcers has already been described. It is possible that the laser therapy may have acted to stimulate small nerve fiber repair, or through the gate controlled theory of pain through stimulation of large neurons.

PO405
The use of triptans and dihydroergotamine in patients with migraine with prominent neurological symptoms: a case series
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Objectives: To describe the experience of patients with hemiplegic or basilar migraine who have used the triptans or dihydroergotamine (DHE).

Background: The triptans and DHE are the most effective acute migraine treatments available. The United States Federal Drug Administration has placed contraindications on the use of these agents in hemiplegic and basilar migraine. However, these types of migraine are often refractory to treatment with other analgesic medications. The prescribing contraindications make clinical trials of these agents in variant migraine unlikely. Thus, case series are useful in providing information about the safety and efficacy of triptan and DHE use in basilar and hemiplegic migraine.

Methods: Retrospective medical record review of cases of hemiplegic or basilar migraine seen by the author at a tertiary headache center over the past 5 and half years. Diagnosis was based on the International Classification of Headache Disorders. Efficacy and treatment applications. The prescribing contraindications make clinical trials of these agents in variant migraine unlikely. Thus, case series are useful in providing information about the safety and efficacy of triptan and DHE use in basilar and hemiplegic migraine.

Results: six patients with hemiplegic migraine and 10 patients basilar migraine who have used the triptans or dihydroergotamine (DHE).

Conclusions: In this tertiary referral center population, the triptans and DHE were effective and safe in the treatment of patients with basilar and hemiplegic migraine.

PO406
Occipital neuralgia with and without migraine: difference in pain characteristics and risk factors
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Objectives: To determine whether there are differences in pain characteristics and risk factors between patients with isolated occipital neuralgia (ON) compared to patients with ON who also had migraine headache (ON+M).
Background: Occipital Neuralgia is an uncommon cause of headaches, but can be associated with symptoms that occur in common headache disorders like migraine.

Methods: Cross-sectional study involving 35 consecutive patients with occipital neuralgia each of whom answered a 14 item-questionnaire. All patients met International Headache Society criteria for diagnosis of ON. Chi-square tests were performed to compare ON+M (n = 20) and ON (n = 15) groups. When small cells (< 5) occurred, Fisher exact tests were used.

Results: There is no difference in age, gender or ethnicity between the two groups. All patients had pain and tenderness in the back of their head. However, 16 patients with ON + M reported that pain traveled to their scalp, whereas only seven patients in the ON group reported this finding (P = 0.008). 25% patients described pain as being dull in (ON + M) group whereas none of the ON group reported dull pain. The majority of patients in both groups reported pain in the neck and shoulders 70% in ON + M group versus 67% in ON group. 55% patients in ON + M group and 60% in ON group reported extremely tender points in their upper back next to the shoulder blades patients and the difference was not significant (P = 0.9). When asked whether they had trouble finding a comfortable position on the pillow at night, 55% ON + M and 60% ON patients responded affirmatively, but difference between the two groups was not clinically significant. There was no difference between the two groups in history of whiplash/head injury, whether patients exercised, used weight lifting, or carried heavy bags. However, there was a significant difference between ON + M and isolated ON group (10/20, 3/12) (P = .05) in the use of chiropractors or massage therapy in the recent few months. 10 of ON+M group and only three patients from ON alone had seen a chiropractor recently (P = 0.04)

Conclusions: Patients with ON + M had significantly more complaints of pain traveling to the scalp and presence of scalp tenderness and tingling compared to isolated ON. 25% patients in the ON+ M group described pain as ‘dull’ whereas none of the isolated ON group reported this characteristic. There was higher use of chiropractors and massage therapy in ON + M group than isolated ON. There may be significant differences in patients with ON + M compared to isolated ON with regards to pain characteristics. Migraine patients should also be screened for symptoms of occipital neuralgia, since there may be many similarities in presentation. Larger studies are needed to address this issue.

PO407
Abstract withdrawn

PO408
Hypnic headache: the first Egyptian case
Saqr MM and Kamal H
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Objectives: Case report of a case of hypnic headache.

Background: Hypnic headache is an headache disorder, Little is known about the clinical characteristics and treatment options of this headache disorder. A 63-year-old woman from Alexandria, Egypt; came complaining of one month history of recurrent attacks of short lived headache. The attacks would typically come at 4–5 am on almost daily basis, the headache occurred exclusively during night. The headache pain was dull, bilateral, severe in intensity, and usually awaken the patient from sleep. The pain was not associated with nausea or autonomic symptoms. Patient tried paracetamol, hypnotics, however with no clear benefit. Physical examination, routine chemistry, erythrocyte sedimentation rate (ESR) were normal. A brain computed tomography was normal for age. The patient was prescribed indomethacin 100 mg at bed time, the headache improved and patient had uninterrupted sleep. Patient continued to be headache free for 6 months after starting therapy. The drug was tapered gradually, 3 months after stoppage and patient is still headache free.

PO408
Hypnic headache: the first Egyptian case
Saqr MM and Kamal H
Medicine, Qassim College of Medicine, Buraydah, Qassim, Saudi Arabia

Objectives: Case report of a case of hypnic headache.

Methods: A 63-year-old woman from Alexandria, Egypt; came complaining of one month history of recurrent attacks of short lived headache. Usually lasting around 20–30 minutes; the attacks would typically come at 4–5 am on almost daily basis, the headache occurred exclusively during night. The headache pain was dull, bilateral, severe in intensity, and usually awaken the patient from sleep. The pain was not associated with nausea or autonomic symptoms. Patient tried paracetamol, hypnotics, however with no clear benefit. Physical examination, routine chemistry, erythrocyte sedimentation rate (ESR) were normal. A brain computed tomography was normal for age. The patient was prescribed indomethacin 100 mg at bed time, the headache improved and patient had uninterrupted sleep. Patient continued to be headache free for 6 months after starting therapy. The drug was tapered gradually, 3 months after stoppage and patient is still headache free.