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OR1

Optical and Selective Activation of Astrocytes Can Trigger Cortical Spreading Depression

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Objectives: We tested the hypotheses that direct optical activation of astrocytes is sufficient to initiate cortical spreading depression (CSD) and that CSD can be evoked by methods that do not involve deformation or damage of tissue, supra-physiological levels of potassium, or the application of exogenous drugs.

Background: CSD is a slowly propagated wave of electrical and vascular activity that is believed to underlie the migraine aura, and CSD is also triggered by local injury to the brain. The cellular mechanisms by which CSD could be spontaneously triggered remain poorly understood. In experimental models, CSD is commonly elicited by pinprick to the cortical surface, by application of high concentrations of KCl, or by tetanic electrical stimulation. Here, we investigated a less invasive, cell-specific method of triggering CSD.

Methods: The channelrhodopsin-2 (ChR2) receptor was selectively expressed in GFAP+ cells in mice. For *in vitro* investigations, hippocampal slices were prepared from these GFAP-ChR2 mice. For *in vivo* studies, mice were anesthetized, a thinned-skull cortical window was made, and a tungsten electrode and fiber optic were inserted through separate burr holes. For both preparations, a 473nm laser coupled to a fiber optic activated ChR2, and CSD was visualized with optical intrinsic signal imaging (OIS) and recorded as changes in local field potential.

Results: In GFAP-ChR2 mice, activation of ChR2 with blue light elicited CSD, whereas the same intensity and duration of light exposure produced no CSD in wild-type littermate controls. Similarly, blue light activated spreading depression in hippocampal slices from GFAP-ChR2 mice but not from controls. The OIS characteristics of optically triggered CSD were different from those associated with KCl-evoked CSD, suggesting distinct cellular responses.

Conclusions: These studies indicate that astrocytes can play a primary role in the initiation of CSD, and that CSD can be generated by a relatively non-invasive optical approach.

OR2

Magnetic Resonance Angiography Reveals Intracranial but No Extracranial Arterial Dilatation during Migraine Attacks

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Objectives: The aim of the present study was to measure extracranial and intracranial arteries during attacks of migraine without aura.

Background: Extracranial arterial dilatation has clinically been considered the cause of pain in patients suffering from migraine without aura.

Methods: We performed high-resolution magnetic resonance angiography (MRA) in 24 female patients with migraine without aura during spontaneous unilateral migraine attacks. Fifteen patients were also scanned

30 min after treatment with 6 mg subcutaneous sumatriptan. Primary endpoints were difference in circumference of extra- and intracranial arterial segments comparing the pain and the non-pain side and the attack and attack-free day. The extracranial arterial segments included: the external carotid (ECA), the superficial temporal (STA), the middle meningeal (MMA) and the cervical part of the internal carotid ($ICA_{cervical}$) artery. The intracranial arterial segments were: the cavernous ($ICA_{cavernous}$) and cerebral ($ICA_{cerebral}$) parts of the internal carotid, the middle cerebral (MCA) and the basilar artery (BA).

Results: We found no dilatation of the ECA, MMA, STA, $ICA_{cervical}$ or BA ($p > 0.05$). The $ICA_{cavernous}$ and $ICA_{cerebral}$ were dilated (10.5%, 10.2%) on the pain side compared to the non-pain side ($p \leq 0.02$). The MCA was dilated on both sides during attack ($p < 0.05$). Administration of sumatriptan caused constriction of the extracranial arteries ($p \leq 0.034$) but the $ICA_{cerebral}$ and the MCA remained unchanged ($p \geq 0.124$).

Conclusions: Migraine pain was not accompanied by extracranial arterial dilatation and only by slight intracranial dilatation. Sumatriptan relieved the headache and constricted extracerebral, but did not constrict the dilated cerebral arteries.

OR3

Light of Intrinsically Photosensitive Retinal Ganglion Cell (ipRGC) Causing Migraine Headache Exacerbation

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Objectives: The peak wavelength of intrinsically photosensitive retinal ganglion cells (ipRGC) differs from those of rod and cone cells. This study was conducted with the objective of determining whether light stimulation by the peak wavelength of ipRGC might induce migraines.

Background: Recently, a study revealed that both the extrinsic photoactivation of ipRGC and the intrinsic photoactivation of melanopsin may be involved in the exacerbation of migraines by light stimulation. However, light-induced migraine attacks triggered by the peak wavelength (480nm) of ipRGC have not yet been reported.

Methods: We investigated the threshold for uncomfortable glare created by light stimulation. The first study population consisted of 46 consecutive migraine patients. Headaches were diagnosed based on the ICHD-II criteria. Light stimulation was achieved using light-emitting diodes through the interference filter which permeabilized three different specific wavelengths (480nm, 550nm, 610nm). The subjects were allowed to adapt in a darkroom for 5 min. They were then asked to evaluate the discomfort glare caused by a wavelength chosen at random from the three kinds used. Each wavelength had seven luminance levels in the range of 110 to 3900cd/m^2.

Results: Migraine patients complained of uncomfortable glare more frequently than the control patients for all of the wavelengths employed. The discomfort glare of wavelength (480nm) for migraine patients was significantly greater than for the control subjects at all luminance levels (110-1860cd/m^2). The discomfort glare of wavelength (550nm) for migraine patients was significantly greater than for the control subjects at luminance levels (1330 and 2650cd/m^2). The discomfort glare of wavelength (610nm) for migraine patients was significantly greater than for the control subjects at luminance levels (1980cd/m^2). Light stimulation with the peak wavelength (480nm) of ipRGC induced migraine attacks more frequently than extensive-wavelength (550 and 610nm). The light source most frequently perceived as causing discomfort in the migraine group was the 480nm (39 cases), followed by the 550nm (4 cases) and the 610nm (3 cases).

Conclusions: It is reported that migraine pain was worsened by light, even in blind patients in whom rod and cone damage had caused the loss of image formation. Light stimulation with the peak wavelength of ipRGC induced migraine attacks more frequently than extensive-wavelength (550 and 610nm). We determined that migraines were easily induced by the peak wavelength (480nm) of ipRGC, though not in the case of blind migraine patients. These results confirm that ipRGC are involved in the triggering of migraine attacks by light.

OR4

The Selective Cannabinoid Type-2 Receptor Agonist, JWH-133, Abolishes Mechanical Allodynia in a Model of Post-Traumatic Headache

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Objectives: The potential therapeutic mechanisms of a selective cannabinoid type-2 receptor agonist compared to a CGRP antagonist and triptan agent in a model of post-traumatic headache will be discussed. The use of rat and mouse models of post-traumatic headache to study sensitization of the trigeminovascular system will also be examined.

Background: Post-traumatic headache (PTH) is a prominent symptom of a concussion and prevalent among patients with mild and moderate traumatic brain injury. The cannabinoid type-2 receptor (CB_2R) has an anti-nociceptive role in neuropathic and inflammatory pain models; but, until now, modulation of the CB_2R has not been evaluated as a potential therapy for PTH. CB_2R activation (unlike CB type-1 receptor activation), is not associated with psychoactive effects, making it an ideal therapeutic target. The mechanism of the CB_2R-mediated anti-nociceptive response is unclear.

Methods: A CB_2R agonist (JWH-133 at 1 mg/kg) was compared to a triptan (Sumatriptan), a CGRP antagonist (MK8825), and saline in a model of controlled cortical impact (CCI) injury. CCI was induced in wild-type and CB_2R knockout mice with and without treatment with the CB_2R agonists (JWH-133 or 0-1966), or a CB_2R antagonist (SR144528). Craniotomy and incision-only mice were included as controls. Baseline and weekly periorbital and paw von Frey (mechanical) allodynia testing were performed for up to four weeks post-injury. CGRP immunoreactive trigeminal ganglia cells and growth-associated protein (GAP-43) in the trigeminal nucleus caudalis (TNC) were determined using immunohistochemistry and western blot. Blood-brain-barrier (BBB) permeability was evaluated using sodium fluorescein (NaF) (BBB disruption is a possible mechanism contributing to sensitization). Intracellular adhesion molecule (ICAM) mRNA, and tumor necrosis factor-alpha (TNF-α) mRNA in vehicle and CB_2-treated groups were measured using qRT-PCR.

Results: Cortical injury causes a significant reduction in periorbital and forepaw von Frey mechanical thresholds ($p<0.001$), but not hindpaw thresholds. CB_2R agonist treatment prevented the reduction of periorbital thresholds (allodynia) after CCI ($p<0.001$); allodynia was only partially attenuated in the Sumatriptan-treated (10 mg/kg) ($p<0.05$) and CGRP antagonist-treated (100 mg/kg) ($p<0.01$) groups. CGRP and GAP-43 co-localize in the TNC post-injury. CB_2R agonist treatment reduced the CCI–induced increase in GAP-43 levels in the TNC and the number of CGRP positive cells in the trigeminal ganglia compared to controls ($p<0.001$). CB_2R agonist treatment significantly attenuated post-CCI increases in BBB permeability, ICAM and TNF-α mRNA ($p<0.05$).

Conclusions: CB_2R agonist treatment in an in vivo model of head trauma modulates nociception and peptidergic synaptogenesis. CB_2R stimulation probably works through immune mechanisms; direct neuronal mechanisms may also be involved.

OR5

Preference of Cortical Spreading Depression for Sensory Cortex

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Objectives: Determine the susceptibility of different cortices to cortical spreading depression.

Background: It is not known why aura is primarily a sensory phenomenon. It is possible that sensory cortex is intrinsically more susceptible. On the other hand it may be that aura events in non-sensory cortex are less clearly perceived (the 'silent spreading depression' hypothesis). We tested the susceptibility of cortex to cortical spreading depression (CSD) and anoxic depolarization (AD) in mice, in an attempt to understand this question.

Methods: Optical intrinsic signal imaging and field potential recording in mice.

Results: We first used a large 4*4 mm craniotomy to expose a wide area (including motor, somatosensory, cingulate, retrosplenial, association, and visual cortex) to increasing concentrations (8-120 mM) of potassium until CSD was elicited. Wide field optical intrinsic signal imaging (OIS) allowed identification of the initial CSD focus. 80% of CSD events began in either barrel cortex or visual cortex ($n=21$). Additional experiments with craniotomy extended 2 mm more laterally and exposing barrel cortex, S2, auditory cortex, primary and lateral secondary visual cortex showed an identical pattern ($n=5$). The identity of barrel and visual cortex was confirmed by generating whisker and visual OIS maps. Because any craniotomy preparation could bias the onset location of CSD, we performed a separate series of experiments in which a completely uniform stimulus (systemic anoxia) elicited AD. Skull was left intact and no head fixation was used, in order to eliminate the possibility of injury-induced events. All AD events began from barrel cortex ($n=7$).

Conclusions: We conclude that CSD is preferentially inducible in primary sensory cortex in mice. The predilection of aura for primary sensory cortex in humans may have a similar mechanism.

OR6

Extracranial Projections of Meningeal Afferents and Their Impact on Meningeal Nociception and Headache

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Objectives: Neuronal tracing and functional measurements in rat models were combined to decipher the extracranial impact on meningeal nociception relevant to headache generation.

Background: Headaches are caused by activation of intracranial afferents innervating the dura mater and cerebral blood vessels. An involvement of the pericranial tissue in headache generation is debated. Anatomical data suggest innervation of pericranial tissues possibly contributing to an extracranial origin of headaches.

Methods: For in vivo neuronal tracing, lower molecular weight dextrane amines were applied to the periost underlying rat temporal muscle. Labelling was observed two days later in the parietal dura mater, trigeminal ganglion and spinal trigeminal nucleus and evaluated with confocal and electron microscopy. In the hemisected rat head extracellular recordings were made from meningeal nerve fibers activated by extra- and intracranial electrical and mechanical stimulation. In a similar preparation, release of calcitonin gene-related peptide (CGRP) from the cranial dura mater during injection of capsaicin into the pericranial muscles like the temporal and the upper neck muscles was quantified. In vivo the same chemical stimulation was used while meningeal blood flow was recorded with laser Doppler flowmetry.

Results: In the parietal dura mater, retrogradely labelled C- and Adelta fibers were found ramifying extensely. Their branches followed mainly arterial vessels. More proximally the nerve fibers accompanied the middle meningeal artery and projected through the spinosus nerve into the trigeminal ganglion. In the maxillary and mandibular but not ophthalmic division of the trigeminal ganglion small- and middle-sized neuronal cell bodies were labelled; some fibers could be traced into the spinal trigeminal nucleus. Electrophysiological recordings showed that same afferent fibers can have mechanosensitive receptive fields both in the dura mater of the middle cranial fossa and in the parietal periost. Noxious stimulation of the deep temporal muscle by capsaicin caused an increase in CGRP release from the dura mater and elevated the meningeal blood flow.

Conclusions: Retrograde tracing and functional measurements suggest that collaterals of meningeal nerve fibers innervating the middle cranial fossa project through the skull into extracranial structures like periost and deep muscles and form functional connections between extra- and intracranial tissues. This finding offers a new explanation how noxious stimulation of pericranial tissues can directly influence meningeal nociception possibly associated with headache generation.

OR7

The Thalamic Reticular Nucleus Is Activated by Cortical Spreading Depression in Freely Moving Rats: Prevention by Acute Valproate

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Objectives: The present study is designed to investigate the behavioral alterations induced by cortical spreading depression (CSD) in freely moving rats and accompanying activation of certain subcortical brain structures along with TNC.

Background: Pain is a sensation that requires a conscious state of mind for its full perception, though majority of experimental animal studies addressing the mechanisms underlying painful conditions, mainly in migraine models, are conducted under anesthesia. Therefore, behavioral studies in consciously behaving animals are valuable in translational research in pain disorders such as migraine. CSD is linked with migraine headache and the available data is scarce regarding its effects on subcortical brain structures in behaving rats.

Methods: CSD induced behavioral parameters were recorded by using a combination of an automated behavioral analysis system and a video camera in freely moving rats. Neuronal activity was also acquired during CSD.

Immunohistochemistry for c-fos was employed to detect activation pattern as well as confirmation of CSD. The effects of acute valproate administration on behavioral parameters and c-fos activation were evaluated.

Results: CSD significantly decreased locomotor activity, induced freezing behavior and immobility in freely behaving rats. Other behavioral parameters such as grooming, wet dog shake, eating, drinking and rearing were not significantly altered. Valproate pretreatment decreased CSD-induced freezing episodes and reversed the CSD-induced reduction in locomotor activity. ECoG indicated no epileptiform discharges during freezing episodes. In addition to robust c-fos activation in the cerebral cortex, CSD significantly increased c-fos expression in trigeminal nucleus caudalis (TNC), amygdala, and thalamic reticular nucleus (TRN) ipsilaterally. The c-fos activation was prominent in the visual sector of TRN and not detected in somatosensorial and auditory TRN sectors. Electrophysiological recordings revealed that CSD could propagate into the TRN. Whereas acute valproate administration did not alter the electrophysiological properties of SD in the cortex, it significantly blocked CSD induced c-fos expression in TNC and TRN, but not in amygdala.

Conclusions: Multiple CSDs activate trigeminal pain nucleus in the brainstem and reticular nucleus in the thalamus in freely moving rats. Anti-migraine action of valproate may also include TRN among other sites in the brain. TRN involvement during CSD in conscious and behaving rats is a novel finding that may have mechanistic and therapeutic implications as a new target in migraine.

OR8

Stimulation of the Sphenopalatine Ganglion (SPG) for Cluster Headache (CH) Treatment: Pathway CH-1 Study – Therapeutic Benefit and Patient Satisfaction after One Year

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Objectives: We aimed to evaluate the sustained benefits of patient controlled, on-demand SPG stimulation in chronic CH patients implanted with the ATI Neurostimulator for one year in the Pathway CH-1 (CH-1) study.

Background: Chronic CH is a disabling neurological disorder often refractory to medical therapy. Novel, effective and well tolerated therapies are needed. Results of a randomized, controlled, study of on-demand SPG stimulation with the ATI Neurostimulation System demonstrated effective acute CH pain relief and in some patients, may be related to decreased attack frequency. Clinically and statistically significant improvement in quality of life (QoL) and reduction in headache disability were also reported.

Methods: 43 patients dissatisfied with CH treatment were enrolled in the CH-1 study; as of December 2012, 32 patients had completed the one-year study; of those, 23 were enrolled in a Long Term Follow Up (LTFU) study. Nine patients were not enrolled in LTFU due to early or investigator termination from CH-1. Mean time from implant to LTFU enrollment was 15 months (range: 12-18). Headache disability (HIT-6), QoL (SF-36v2) and a Patient Experience Survey (PES) were administered to all LTFU patients.

Results: At enrollment, 78% (N=18) of patients indicated their "overall evaluation of the ATI Neurostimulation System for treating their CH" as good or very good. 78% (N=18) found SPG stimulation a useful therapy in treating their CH. 83% (N=19) found surgical effects tolerable and the implanted neurostimulator comfortable or did not notice it and 100% (N=23) found the stimulation sensation tolerable. 65% (N=15) did not have significant side effects after stimulation. 91% (N=21) would make the same decision again to treat their CH with the ATI Neurostimulation System, and 96% (N=22) would recommend the ATI Neurostimulation System to someone else.

HIT-6 and SF-36v2 improvements were reported at LTFU enrollment. 57% (N=13) of patients experienced clinically significant improvement in headache disability compared to baseline (greater than the mean clinically significant difference, -2.3 units). SF-36v2 physical (PCS) and mental (MCS) scores each improved by greater than or within the clinically significant difference range of 3 to 5 units in 52% (N=12) and 61% (N=14) of patients, respectively. Overall, 70% (N=16) had clinically significant improvements in PCS, MCS or both.

Conclusions: Headache disability, QoL and PES results from more than one year of continued usage indicate that SPG stimulation with the ATI Neurostimulator is a robust therapy with sustained benefits and a high level of patient satisfaction.

OR9

Persistent Frequent Nausea as a Predictor of Progression to Chronic Migraine: Results from the American Migraine Prevalence and Prevention (AMPP) Study

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Objectives: Assess persistent frequent headache-related nausea (PFN) in persons with episodic migraine (EM) in 2007 and 2008 as a predictor of new onset chronic migraine (CM) in 2009.

Background: Though nausea is a cardinal feature of migraine, its influence on migraine progression has not been evaluated.

Methods: Using data from the 2007 and 2008 AMPP surveys, we identified subgroups with episodic ICHD-2 migraine and PFN or no or low frequency nausea associated with headache (NLFN). PFN was defined by the presence of headache-related nausea $\geq$ half the time in both 2007 and 2008. NLFN was defined by nausea $<$ half the time or absent with headache in both years. Participants with classified with CM in 2009 if they met symptom criteria for migraine with headaches averaging $\geq$15 days/month in the past three months. Univariate differences in demographics for PFN and NLFN were evaluated with Chi-square. Binary logistic regressions were performed hierarchically to assess progression to CM in 2009 as a function of nausea status in 2007 and 2008. Model 1 assessed demographics (age, sex, annual household income). Model 2 added headache-related disability (MIDAS Questionnaire). Model 3 added depression (Patient Health Questionnaire-9). All three models included a migraine symptom severity composite score (MSS score) to control for the impact of other headache symptoms (e.g., pain features, photophobia, phonophobia). Odds ratios (ORs) and 95% confidence intervals were used to (CI) contrast the PFN and NLFN groups on progression to CM in 2009.

Results: There were 3,182 respondents with headache symptom and frequency data available for all three years of the analysis. PFN was found in 43.7% (1,389) of EM respondents and 3.4% (47) progressed to CM. NLFN was seen in 27.6% (877) of respondents with EM and 1.5% progressed to CM. In comparison with NLFN, PFN was more common in females ($p<0.001$) and Caucasians ($p<0.05$). PFN was associated with a doubling of the risk of progression to CM after adjusting for demographics and MSS score (OR 2.14, 95%CI 1.11-4.12, $p=0.023$). The addition of headache-related disability minimally attenuated the association (OR 2.00,95%CI 1.03-3.87, $p=0.04$). With the addition of depression, the OR fell to 1.90 and just missed statistical significance (95%CI: 0.98-3.71, $p=0.059$) suggesting the effect was robust but underpowered in this analysis.

Conclusions: Persistent frequent nausea associated with headache is common (43.7%) in the migraine population. After controlling for demographics, migraine symptoms and headache-related disability, those with persistent frequent headache-related nausea remained about twice as likely to progress to CM compared to migraineurs with NLFN. Persistent frequent migraine-related nausea could be a marker for CM progression risk or in the causal pathway.

OR10

Co-Occurrence of Cluster Headache and Trigeminal Neuralgia: Cluster-Tic Syndrome in the LUCA Population

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Objectives: To determine the prevalence and nature of trigeminal neuralgia in a large group of cluster headache patients.

Background: Cluster-tic syndrome is a rare headache syndrome in which trigeminal neuralgia and cluster headache co-occur. The existence of cluster-tic syndrome as a separate entity is questioned, and figures on prevalence of simultaneous existence of cluster headache and trigeminal neuralgia are not available.

Methods: As part of a nationwide study on headache mechanisms in cluster headache (LUCA), we collected clinical data of 244 cluster headache patients using a semi-structured telephone interview.

Results: In 11 (4.5%) of cluster headache patients, attacks fulfilling International Headache Society (ICHD-2) criteria for trigeminal neuralgia were also present. In all cases trigeminal neuralgia occurred ipsilateral to cluster headache and in the majority (82%) in the ophthalmic branch. In eight of these eleven patients (73%) the frequency and

time-pattern of trigeminal neuralgia seemed to parallel cluster headache and was likely a part of the cluster headache spectrum. In the three remaining patients cluster headache and trigeminal neuralgia were unrelated in time and appeared to occur independently.

Conclusions: In conclusion, trigeminal neuralgia co-occurred in 11/244 (4.5%) of cluster headache patients. In only 3 (1.2%) patients trigeminal neuralgia seemed to occur independently from cluster headache episodes.

OR11

Experimental Activation of the Sphenopalatine Ganglion Provokes Cluster-Like Attacks in Humans

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Objectives: To investigate the effect of low frequency stimulation of the sphenopalatine ganglion in cluster headache patients.

Background: High frequency (HF) stimulationof the sphenopalatine ganglion (SPG) is an emerging abortive treatment for cluster headache (CH) attacks. HF SPG stimulation is thought to exert its effect by physiologically blocking parasympathetic outflow. We hypothesized that low frequency (LF) SPG stimulation may activate the SPG, causing increased parasympathetic outflow and thereby provoking cluster attacks in CH patients.

Methods: In a double-blind randomized cross-over study seven CH patients implanted with an SPG neurostimulator were randomly allocated to receive HF or LF stimulation for 3 min on two separate days. We recorded headache characteristics and autonomic symptoms during and after stimulation.

Results: Six patients completed the study. Three out of 6 patients **(**50 %) reported ipsilateral cluster-like attacks during or within 30 min of LF SPG stimulation. These cluster-like attacks were all successfully treated with the therapeutic HF SPG stimulation. One out of 6 reported a cluster-like attack with 3 min HF SPG stimulation, which was also successfully treated with continued HF therapeutic SPG stimulation.

Conclusions: LF SPG stimulation may induce cluster-like attacks with autonomic features, which can subsequently be treated by HF SPG stimulation. Efferent parasympathetic outflow from the SPG may initiate autonomic symptoms and activate trigeminovascular sensory afferents, which may initiate the onset of pain associated with CH.

OR12

Posterior Hypothalamic Region Deep Brain Stimulation in Short Lasting Unilateral Neuralgiform Headache with Conjunctival Injection and Tearing (SUNCT)

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Objectives: Previous case reports on posterior hypothalamic region deep brain stimulation (PH-DBS) for SUNCT are limited to a total of three patients [(1-3)]. We present clinical and outcome data on six new patients with intractable SUNCT treated with PH-DBS.

Background: SUNCT is a primary headache syndrome characterised by short lasting attacks of unilateral pain accompanied by prominent lacrimation and redness of the ipsilateral eye. SUNCT is refractory to standard medical treatments in a small minority of patients. Neuroimaging studies have suggested a role of the posterior hypothalamus in its pathogenesis.

Methods: Six SUNCT patients underwent PH-DBS with an MRI-guided and MRI-verified approach without microelectrode recording. The target on stereotactic T2-weighted imaging lay between the mammillothalamic tract and the anteromedial quadrant of the red nucleus. Details of headache characteristics and adverse events were recorded at regular reviews. Headache load (defined as the [severity (on the visual analogue score)] x [duration] x [frequency] of the headaches) of each patient was calculated at each review point.

Results: All leads were within 1.0mm of intended target point on postimplant imaging. Stimulation was monopolar with a range 0.4-3V throughout the follow up period. The median follow up period was 9.5 months (range 3-34). Three patients had pure SUNCT and three multiple

headache types (additional cluster and or migraine). Median improvement in SUNCT headache load at final follow up was 79% (range 22-100%). Five out of six patients had obtained a 50% or more objective improvement in headache load at last follow up. No significant difference appeared to exist between pure SUNCT and mixed headache patients, although clinically the suggestion was pure patients fared better; this may be due to the short follow up in some patients.

Conclusions: PH-DBS may be a useful treatment in intractable SUNCT. Further investigation is needed to discover if those with a single headache syndrome do better than those with mixed headaches.

OR13

Anxiety and Migraine: A Population-Based Cross-Sectional Study in Korea

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Objectives: To assess the association between anxiety and migraine in a population-based sample in Korea.

Background: The association between anxiety and migraine has been observed. However, most studies are reported in Western countries and population-based studies regarding anxiety and migraine have rarely been reported in Asian countries including Korea.

Methods: We selected a stratified random population sample of Koreans over aged 19-69 and evaluated them with a 60-item semi-structured interview designed to identify headache type using ICHD-2 criteria. We included Goldberg short screening scale for anxiety (GSSA) scores to assess individuals' anxiety. We defined as having anxiety if an individual's GSSA score was 5 or more.

Results: Of 2762 participants, the 1-year prevalence of all types of headache and migraine were 47.1% and 5.4% respectively. The 1-year prevalence of anxiety was 10.0%. Anxiety was more prevalent in women than in men (8.1% vs. 11.8%, $p = 0.001$). The highest prevalence of anxiety was found in aged 50-59 in men (9.8%) and aged 19-29 in women (14.3%). Anxiety was more prevalent in migraine group comparing to non-migraine headache group or non-headache controls (30.4% vs. 13.3% vs. 5.3%, $p<0.001$). Migraineurs with substantial-to-severe impact (HIT-6 score$\geq$56) more commonly had anxiety comparing to migraineurs with no-to-some impact (HIT score$<$56) (47.0% vs. 17.1%, $p<0.001$). Migraineurs with anxiety reported more frequent attacks per month (7.4$\pm$9.7 vs. 2.6$\pm$3.9, $p<0.001$), more severe pain intensity (VAS score 7.1$\pm$1.5 vs. 5.9$\pm$2.0, $p<0.001$), higher HIT-6 score (59.3$\pm$9.0 vs. 52.3$\pm$8.7, $p<0.001$), higher proportion of decreased activity (48.9% vs. 26.0%, $p=0.006$) and absence from work, school or house chores by headache (28.9% vs. 11.5%, $p=0.009$) comparing to migraineurs without anxiety.

Conclusions: Anxiety is prevalent among migraineurs in Korean population. Migraineurs with anxiety had more severe headache symptoms and more disabilities comparing to migraineurs without anxiety.

OR14

Nociceptive Trigeminal Neurotransmission Is Inhibited by the Dual Orexin Receptor Antagonist DORA-12

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Objectives: The aim of the study was to investigate the efficacy of the dual orexin receptor antagonist (DORA-12) on neuronal transmission of the trigeminovascular system in an *in vivo* model of trigeminal activation.

Background: The hypothalamus and its ascending and descending connections to pain processing structures within the brain have been shown to be involved in the pathophysiology of migraine. Besides its involvement in pain as such and in the sleep-wake cycle, premonitory symptoms of a migraine attack are mainly of hypothalamic origin. Preclinical evidence indicates that hypothalamic influence on migraine and sleep is significantly mediated by the orexinergic system. In animal models of dural nociceptive activation, the activation of Ox_1 and Ox_2 receptors has opposing effects. While administration of orexin A, which activates Ox_1 and Ox_2 receptors, inhibits nociceptive activation, orexin B, which mainly activates Ox_2 receptors has pronociceptive properties. The effect of simultaneous antagonism on both receptors has not been tested in animal models of migraine.

Methods: In male Sprague-Dawley rats under general propofol anesthesia (20-25 $mgkg^{-1}h^{-1}$) the middle meningeal artery (MMA) and its trigeminal afferents were stimulated using a bipolar stimulating electrode through a cranial window. Stimulus-evoked and background activity of second order neurons were recorded using a tungsten electrode placed in the trigeminocervical complex (TCC). Experimental groups received intravenously administered DORA-12 ($1mgkg^{-1}$) or its vehicle (25% hydroxypropyl-beta-cyclodextrin) and neuronal activity was recorded over 60 minutes.

Results: Stimulus-evoked neuronal activity was significantly inhibited by intravenously administered DORA-12 when compared against baseline ($p<0.05$) while vehicle control had no significant effect.

Conclusions: The results of the study indicate that the dual orexin receptor antagonist DORA-12 attenuates central effects of dural-evoked trigeminovascular nociception in an *in vivo* model of trigeminal activation that has been shown to be highly predictive for a potential clinical efficacy for migraine. The results suggest simultaneous antagonism of both orexin receptors might offer a novel mechanism for the treatment of migraine.

OR15

Structural Changes in Visual and Auditory Processing Brain Areas of Migraineurs from the General Population Using Voxel-Based Morphometry (VBM)

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Objectives: To investigate structural brain alterations in a large sample of migraine patients selected from the MRI Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA)-2 study, a 9-year follow-up MRI study on the progression of brain changes in a population-based sample of migraineurs.

Background: Previously, VBM studies demonstrated regional structural brain changes in migraineurs from specialized headache centers. It is unknown whether brain architecture is regionally altered in migraineurs from the general population.

Methods: 1.5 T 3D whole brain T1-weighted MRI scans were acquired in 84 migraineurs (52 with aura, 32 without aura) and 35 healthy controls selected from the Maastricht subpopulation of the CAMERA-2 study. Images were post-processed using state-of-the-art VBM, applying DARTEL in SPM8, and regional volumes were compared voxelwise, corrected for age, sex and total intracranial volume ($p<0.001$, uncorrected, minimum cluster size of 20 voxels). Subanalyses assessed the influence of attack frequency ($<$ vs. $\geq$ 1 attack/month) and disease activity (active vs. inactive).

Results: Grey matter volume in migraineurs was regionally increased in the left angular and the right middle temporal gyrus, and the left lateral geniculate nucleus and decreased in the right occipital gyrus (V3A and MT+ territories). White matter tracts in the occipital lobe showed volume reduction that was not explained by the presence of white matter hyperintensities in these areas. These changes were not essentially influenced by migraine subtype, attack frequency or disease activity.

Conclusions: Cortical visual and auditory processing areas and connecting white matter pathways are regionally altered in migraineurs from the general population. These changes may underlie stronger responses in migraineurs to sensory stimulation, suggesting that cortical hyperexcitability plays a pivotal role in migraine pathophysiology. The underlying histopathology for these changes still needs to be elucidated, though. Structural brain changes in inactive migraineurs question the reversibility of these changes.

OR16

Response Properties, Trajectories and Anatomical Characterization of Primary Afferent Neurons That Innervate the Calvarial Periosteum

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Objectives: To investigate the response properties and trajectories of primary afferents innervating the calvarial periosteum of the rat.

Background: Headaches are believed to result from the activation and sensitization of intracranial meningeal nociceptors. However, local anesthesia of extra-cranial tissues, in particular the scalp, can provide headache relief, suggesting that activation afferents innervating extra-cranial deep-tissues may also plays a role in headache genesis. One such potential sensory innervation is that of the calvarial periosteum. In this work we therefore investigated

the response properties of these afferent as well as their central trajectories.

Methods: The response properties of the calvarial perisoteal afferents were examine using single unit recording in the trigeminal ganglion of anesthetized rats. Application of local anesthetic and surgical ablation of peripheral nerve branches were employed to investigate the trigeminal sensory nerve branches through which these calvarial periosteal afferents project centrally. Retrograde tracing were used to characterize the trigeminal cell bodies of calvarial periosteal afferents.

Results: A total of 90 calvarial periosteal afferents were characterized using electrophysiology. Afferents had conduction velocities ranging between 0.7 and 40 m/s with most falling in the range of A-delta and C units. All but 2 afferents were mechanosensitive and most (95%) of the units displayed a slowly adapting pattern of mechanosensitivity. About 20% of the a-delta and 80% of the C-units exhibited various degrees of ongoing activity. C-units had higher levels of ongoing activity. Local application of a mixture of inflammatory mediators (inflammatory soup) activated 44% of the neurons and led to mechanical sensitization in about 60% of the units. About 10% of the afferents tested were activated by low pH (5.0), but none of the units responded to capsaicin. Anatomical studies revealed that the majority of the afferents innervating the dorsal periosteum, rostral to the lambdoid suture were branches of the supraorbital nerve, projected primarily to the V1 branch of the TG and had cell body size ranging from 200-2200 μm^2.

Conclusions: The data indicate that the calvarial periosteum is innervated by mechanosensitive primary afferent neurons with nociceptive features that project to the TG ganglion primarily through extracranial nerves. Activation and sensitization of calvarial periosteal afferents may play a role in the pathogenesis of headaches with extra-cranial origin and perhaps also contribute to the genesis of post-traumatic headaches.

OR17

Cognitive Dysfunction during a Migraine Attack – A Study on Migraine without Aura

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Objectives: To compare cognitive performance of episodic migraine patients' in-between and during attacks of migraine without aura, using an extensive battery of cognitive and behavioral tests and controlling for potential confounders.

Background: Cognitive symptoms are significant contributors to patients' disability during migraine attacks. Frequent complaints include executive symptoms (attention, planning, judgment, initiative, speed) language and memory. Studies on neuropsychological performance during migraine attacks have limitations and produced conflicting data.

Methods: Prospective observational randomized cross-over study with two neuropsychological evaluations of the same subject in two conditions – during an untreated spontaneous migraine without aura attack and in-between attacks.

Results: Thirty-nine patients (37 females), with an age average of 38.2 years were included and 24 completed the study. Migraine impact in our sample was mild there was no associated depression. In the majority of tests performed, subjects always performed worse during the attack, changes attaining statistical significance in: stroop word reading ($p=0.001$), stroop color naming ($p=0.003$), phonemic verbal fluency ($p=0.010$), CVLT total learning ($p<0.0001$), CVLT short term and delayed recall with ($p<0.0001$) and without ($p=0.001$) semantic help and logical memory delayed recall (p 0.006). Differences were unrelated to age, gender, literacy, order of and time lapse between evaluations, anxiety and pain intensity and duration (during the evaluated attack).

Conclusions: Our results suggest that cognitive performance globally diminishes during the migraine attack, supporting patients' subjective complaints. The pattern of cognitive impairment is consistent with a dysexecutive syndrome and learning defect, suggesting the existence of reversible cortical dysfunction in pre-frontal and temporal brain areas during the migraine without aura attack.

OR18

Follow-Up of the Secondary Findings from the International Headache Genetics Consortium Meta-Analysis

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Objectives: The objective of this study was to identify new genetic loci predisposing to migraine, based on the secondary findings from the recent International Headache Genetics Consortium meta-analysis, and to gain more information about the genetic susceptibility to migraine.

Background: Migraine is a common, episodic neurovascular disorder with significant heritability. Eight loci have been reported in genome-wide association studies (GWAS) thus far. Recently, our Consortium conducted a GWAS meta-analysis of 23,000 migraineurs and 95,000 controls, uncovering genome-wide *significant* association at 12 loci ($P < 5 \times 10^{-8}$), of which 8 are located in or immediately outside genes with known function in synaptic or neuronal regulation. In addition, we identified 134 independent secondary loci with genome-wide *suggestive* p-values $<1 \times 10^{-5}$.

Methods: We performed a replication analysis in a new study cohort from 23andme, with 11,000 migraine patients and 52,000 controls. SNP data at the 146 implicated loci were examined to confirm existing and identify novel variants predisposing to migraine. In addition, a meta-analysis of the previous study and the new cohorts was performed, for a total of 34,000 migraineurs and 147,000 controls, and new pathway- and network analyses of the new loci are presented. All participants were of European ancestry.

Results: Here, we present the results of the replication analysis from the new cohorts, as well as a combined meta-analysis of the discovery and replication studies, identifying four new loci with significant association to migraine. At one of these loci, significant association is observed to a missense variant for the first time in migraine. In addition, we report how the newly identified loci fit in the biological context of the migraine genes from previously reported GWAS studies.

Conclusions: We report the results of the largest genetic study in migraine thus far. The added statistical power of the new cohorts allowed us to demonstrate significant association to several new migraine loci, including the first common missense variant in common forms of migraine. The implication of the genes at these loci, and their respective biological pathways and mechanisms, sheds further light on the pathophysiology of migraine.

OR19

Endogenous Opioids Mediate the sTMS Effects in the Sensory Thalamus of Migraine Models

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Objectives: The current study aimed to investigate whether opioid mechanisms are potentially involved in the mechanism of action of sTMS.

Background: Recent clinical trials demonstrated that single pulse transcranial magnetic stimulation (sTMS) can be a promising novel treatment in migraine with aura. We have previously demonstrated that a potential mechanism of action of sTMS is blockade of cortical spreading depression and inhibition of third order thalamic neurons with trigeminovascular input, possibly through interactions with an ipsilateral cortico-thalamic relay.

Methods: Neurons responding to electrical stimulation of dural vessels were identified in the ventroposteromedial thalamic nucleus by means of electrophysiology, in anesthetized rats. The effects of sTMS (170 μs rise time), delivered over the corresponding hemisphere, were studied on spontaneous and trigeminovascular activity (Aδ- and C-fibers firing) of third order thalamic neurons. In a separate set of experiments, the efficacy of sTMS was tested on third order thalamic neurons in animals that have been pre-treated with intravenous administration of naloxone (5 $mgkg^{-1}$), a broad spectrum opioid receptor antagonist. The effects of naloxone on thalamic activity in the absence of sTMS were investigated in a different experimental group and compared to animals that received vehicle control.

Results: sTMS (0.8-1.3 Tesla) significantly decreased spontaneous neuronal firing of third order thalamic neurons ($P < 0.05$) and C-fiber activity in response to dural vessel stimulation ($n = 5$; $P < 0.05$), but had no effect on Aδ-fiber activity ($n = 8$; $P = 0.29$). Pre-treatment with naloxone blocked the inhibitory actions of sTMS on both the spontaneous neuronal firing and on C-fiber induced activity ($P \geq 0.29$). Naloxone alone had no significant effect on the firing rate of third order thalamic neurons ($P \geq 0.46$).

Conclusions: The mechanism of action of sTMS in the treatment of migraine potentially involves modulation of third order ipsilateral thalamic neurons, possibly through a cortico-thalamic relay. Endogenous opioid transmission is

one of the neurotransmitter pathways involved in this modulation.

OR-WA

Investigating the Premonitory Phase of Migraine with $H_2{}^{15}O$ PET

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Objectives: To identify brain areas, if any, activated in the premonitory phase of migraine using positron emission tomography (PET).

Background: Many migraine patients experience premonitory symptoms warning them of an impending headache (1). The advantages of investigating the premonitory phase are several - imaging may give us brain areas involved in the earliest part of the attack and possibly tell us of the origin of various symptoms since these occur in the absence of pain.

Methods: We used nitroglycerin (GTN) to trigger premonitory symptoms and migraine headache (2). Scans were conducted with positron emission tomography (PET) with $H_2{}^{15}O$ to measure regional cerebral blood flow as a surrogate marker for neuronal activation (3). The main outcome was comparing the first premonitory scans of all patients (without pain) > baseline scans (n=8) to identify areas involved in the premonitory phase. As a sub-group analysis, we then compared patients with and without photophobia i.e. increased sensitivity to light in the premonitory phase (n=10), and patients with and without nausea in the premonitory phase (n=10), to identify areas specifically involved in photophobia and nausea respectively.

Results: 1. Comparing the first premonitory scans of all patients > baseline scans of all patients showed significant activations in the right postero-lateral hypothalamus, right ventral midbrain area, right periaqueductal grey (PAG), right dorsal pons, and various cortical areas including occipital, temporal and frontal cortex. Premonitory symptoms included tiredness, neck stiffness, thirst, frequent urination, photophobia, nausea, yawning and mood changes. All patients developed either right-sided or bilateral but predominantly right-sided headache.

2. Comparing the premonitory scans of patients with photophobia > premonitory scans of patients without photophobia showed significant activations in the extrastriate visual cortex (Broadmann area 18).

3. Comparing the premonitory scans of patients with nausea > premonitory scans of patients without nausea showed significant activations in the upper dorsal medulla in the region of nucleus tractus solitarius, dorsal motor nucleus of vagus and nucleus ambiguus, and the PAG.

Conclusions: Activation of key brain areas in the premonitory phase before headache suggests that the brain is the prime mover in migraine. Hypothalamic activation can explain the majority of the premonitory symptoms. Photophobia and nausea in migraine may arise from primary activation of the occipital cortex and upper dorsal medullary nuclei respectively rather than resulting from trigeminal activation (and pain) since these symptoms occurred in the absence of pain and were associated with these activations.

OR20

Sleep Disturbance and Affective Comorbidity among Episodic Migraineurs

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Objectives: The present study sought to 1) assess the role of sleep quality, daytime sleepiness, and sleep hygiene among a large sample of episodic migraineurs; 2) assess relations between sleep disturbance and headache-related variables; and 3) determine if these relations remain after accounting for comorbid depression or anxiety.

Background: Previous research has shown that sleep disturbance and affective comorbidities are common among migraineurs. Despite the well-established role of insomnia in migraine, its central characteristics (sleep quality, daytime sleepiness, and sleep hygiene) have rarely been explored among episodic migraineurs. Further, although affective comorbidities and sleep disturbance commonly co-occur, few studies have investigated whether sleep disturbance is merely a complication of the affective disorder (Vgontzas et al., 2008).

Methods: 292 young adults (69.9% female, *M* age=19.19 years [3.21]) completed measures of headache and headache disability, sleep disturbance (PSQI, Buysse et al., 1988; SHI, Mastin et al., 2006; ESS, Johns, 1991), and psychiatric symptomatology (PHQ-9, Kroenke et al., 2001; GAD-7, Spitzer et al., 2006). Migraine diagnosis was verified with a structured diagnostic interview. Independent t-tests and chi-square analyses were used to compare migraineurs and controls on sleep disturbance and psychiatric symptoms. A MANOVA compared groups on multiple sleep hygiene behaviors. Linear regression analyses were used both to

assess the role of sleep disturbance in predicting headache-related variables (disability, frequency, and severity).

Results: 78 (26.7%) participants met ICHD-II criteria for episodic migraine ($M = 5.26$ headache days/month [3.90]; M severity = 6.70/10 [1.51]). Compared to controls, episodic migraineurs reported significantly poorer sleep quality on the PSQI ($M = 8.90$ vs 6.63, $p < .001$) and poorer sleep hygiene on the SHI ($M = 38.27$ v. 36.63, $p = .046$). A significantly higher proportion of migraineurs reported clinically-significant levels of poor sleep quality (85.90% v. 62.02%, $\chi^2 < .001$) and daytime sleepiness (54.5% v. 40.7%, $\chi^2 = .037$). Individual sleep hygiene behaviors did not differ significantly between groups, however. Poor sleep quality predicted greater migraine-related disability ($R^2 = 16.0\%$, $p < .0001$) and higher headache frequency ($R^2 = 6.5\%$, $p = .02$). Sleep quality remained a significant predictor of disability even after controlling for depression and anxiety ($\Delta R^2 = 4.5\%$, $p < .0001$).

Conclusions: Poor sleep quality is the component of insomnia that best characterizes migraine, and its effect on migraine disability is not entirely attributable to comorbid depression or anxiety. Sleep interventions should consider means of improving sleep quality rather than sleep hygiene per se. Further, the effects of these interventions on comorbid depression/anxiety merit continued evaluation.

OR21

Candesartan Versus Propranolol for Migraine Prophylaxis: A Randomized, Triple-Blind, Placebo-Controlled, Double Crossover Study

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Objectives: To see whether the superiority of candesartan over placebo, shown in one previous study[1], could be confirmed, and if so, whether the effect was comparable to that of propranolol (non-inferiority analysis), and whether adverse events (AEs) were different.

Background: Drug prevention of attacks is desirable and indicated in many migraine patients, but it is used in relatively few, possibly because of limited effect, side effects or contraindications. Candesartan has been shown to be effective as a migraine prophylaxis in one previous study, but corroboration is lacking, and no study has compared this drug with first-line preventative drugs.

Methods: This was a triple-blind, double crossover study, with 72 adult patients with episodic or chronic migraine, recruited in an outpatient clinic and through advertisements. Participants underwent three 12-weeks' treatment periods on either candesartan 16 mg, propranolol slow-release 160 mg, or placebo.

The primary outcome measure was days with migraine headache per 4 weeks. Secondary measures were days with headache, hours with headache, proportion of responders (≥50% reduction of migraine days from baseline), and AEs.

Results: In the intention-to-treat analysis, candesartan and propranolol were both superior to placebo (2.95 ± 2.28, and 2.91 ± 2.16, versus 3.53 ± 2.17 migraine days per month, p=0.02 for both comparisons, Wilcoxon's paired signed rank test, blinded statistical analysis). Candesartan was non-inferior to propranolol (and vice versa). Candesartan and propranolol were also similar on most secondary measures of efficacy, and superior to placebo. The active substances caused more AEs than placebo, but the AE profiles differed.

Conclusions: It is confirmed that candesartan 16 mg is effective for migraine prevention, with an effect size similar to propranolol 160mg, and with somewhat different AEs. Candesartan should be included in the arsenal of drugs recommended for migraine prevention.

OR22

Estrogens Modulate Susceptibility to Cortical Spreading Depression in Rat Independently of 5-HT Neurotransmission

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Objectives: To determine the influence of 17β-estradiol (E2) modulation on KCl-induced CSD and on the suppressive effect of 5-hydroxytryptophan (5-HTP) on CSD frequency in rat.

Background: The aura symptoms in migraine are most likely due to cortical spreading depression (CSD). High estrogen levels, like those associated with pregnancy, are supposed to increase cortical excitability and thus to favor CSD. Migraine is also considered a "low 5-HT" condition. Serotonin depletion causes both deficient pain control and changes in cortical excitability in humans *(Hamel, 2007)* as well as enhanced CSD susceptibility in rat *(Supornsilpchai*

et al., 2006). Gonadal hormones influence the 5-HT metabolism. We have previously shown that 5-HTP, the 5-HT precursor, can decrease CSD frequency in female rats and that this effect varies along the ovarian cycle (unpublished data).

Methods: Adult female Sprague-Dawley rats (n=8/group)were ovariectomized and subcutaneously implanted with silastic capsules filled with E2 mixed with cholesterol (E2) or with cholesterol only (chol).Two weeks later, CSDs were elicited in half of the animals in each group by applying a cotton ball soaked with 1M KCl over the occipital cortex and recorded by DC electrocorticogram for 1 hour. In the remaining animals, the capsules were removed to mimic an abrupt drop in E2 and CSDs were recorded 20 h later (E2w and cholw groups). One hour before the recording session all animals received an i.p. injection of 5-HTP (100 mg/kg) or NaCl.

Results: CSD frequency was significantly enhanced in animals treated for 2 weeks with E2 compared to "chol" controls (p=0.025). E2 withdrawal normalized CSD frequency.5-HTP injections significantly decreased CSD frequency in all animal groups (p=0.004) and this effect was independent of estrogen levels.

Conclusions: High E2 levels increase the susceptibility to CSD in ovariectomized females, which might be relevant for the aggravation/appearance of migraine with aura during pregnancy or intake of estrogen-containing contraceptive pills. Furthermore, the rapid decrease of CSD frequency after E2 withdrawal may explain whymigraine with aura attacks, contrary to attacks without aura, are rarely menstrually-related. Finally, changes in central 5-HT transmission influence CSD susceptibility in females independently of E2 levels.

OR23

Posterior Insula Does Not Age in Migrainous Women

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Objectives: Recent studies have shown alterations in a number of cortical regions in migraine patients [1, 2]. The aim of this study was to assess the effect of aging on migraine brain in order to determine if there are abnormal patterns of aging in migraine brain.

Background: The posterior insula is an integrative association cortical region for multisensory-motor processing. Prior findings in migraine patients have indicated a significant change in the posterior insula in female migraineurs where female migraineurs had shown to have thicker posterior insula compared with male migraineurs and healthy controls of both sexes[3]. It has also been shown that the trigeminovascular neurons of the posterior thalamus project to insula [4], which may explain some of the common disturbances in neurological functions during migraine.

Methods: Ninety-two female migraine patients (N=46 migraine patients and N=46 healthy control subjects) underwent a magnetic resonance imaging (MRI) session on a 3.0T Siemens scanner. All of the migraine patients were episodic migraineurs who were selected according to the International Classification for Headache (ICHD-2; http://www.i-h-s.org/upload/ct_clas/ihc_II) definition for episodic migraine. In order to be included in the study they had to havesuffered from migraines for more than three years. Images were processed offline using the automatic parcellation tools of the Freesurfer image analysis software (http://surfer.nmr.mgh.harvard.edu/) that enables reconstruction of cortical surfaces and detection of submillimeter differences in cortical thickness between patients and healthy control subjects.

Results: Vertex-wise comparisons between the two cohorts to determine the differences between the age and cortical thickness correlation revealed significant difference between the cohorts in the posterior insula bilaterally. While in the healthy group there is cortical thinning by age in the migraine group there was no decline in the cortical thickness in the posterior insula by age.

Conclusions: As part of the normal aging process, the majority of the cortex regions become progressively thinner. In this study we compared the differences between the aging of the brains of female migraine patients and age-gender matched healthy controls. Our findings suggest that the posterior insula region in migraineurs does not thin by age (which positively correlated with the duration of the disease (R^2=0.804, p-value=2.4e-10)) suggesting that this may either reflect adaptive or maladaptive responses to migraine.

OR24

Prevalence and Characteristics of Headache in Schoolchildren in Japan: A Population-Based Study

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Objectives: The aim of this study was to reveal the prevalence, characteristics and impact of headache in elementary and junior high schoolchildren in Japan.

Background: Migraine and tension-type headache (TTH) was reported to affect approximately 8% and 10%-25% of pupils, respectively. The incidence of migraine among Japanese junior high school children was reported to be 4.8% in one study, and only few population-based studies have been done about the prevalence and the type of headache despite of the disturbing symptoms for pupils. Here we applied a population-based study to reach the objective.

Methods: Subjects included 3,403 pupils at 13 elementary (6 to 12 years of age) and 7 junior high schools (12 to 15 years of age) in Hitachi-Omiya City (population 42,000). They were surveyed using a computer-scored questionnaire comprising 26 items based on International Classification of Headache Disorders; the 2nd Edition diagnostic criteria for migraine and TTH. These questions probed thefeatures of headache, effects on daily life, and treatments by physicians or medications. We obtained informed consent from all pupils and parents.

Results: Responses were obtained from 3,285 pupils (elementary school, 2,115; junior high school, 1,171; recovery rate, 96.5%). Migraine was estimated to be prevalent among 241 pupils from the result of this investigation (prevalence rate 7.3%; male, 41.9%; female, 57.7%). Among 241 pupils with migraine, thirty-eight (1.2%) had typical aura, twenty-five (0.8%) had basilar-type, and two (0.06%) had hemiplegic migraine. TTH was estimated among 222 pupils (prevalence rate 6.8%; male, 48.6%; female, 50.9%). Pupils who had headache more than 15 days in a month were 10 (0.3%) for migraine, and 7 (0.2%) for TTH. The majority of pupils, those with TTH (162/222, 72.9%), and with migraine (146/241, 60.6%) had not visited physician. The percentages of pupils who only used over-the-counter drugs were 28.8% (64/222) with TTH and 34.9% (84/241) with migraine. Absence from school for more than one day per 3 months was reported by 28 pupils with migraine (11.6%) and 17 with TTH (7.7%). Irritability was reported by 100 students with migraine (41.5%) and 61 with TTH (27.5%). The common causes of secondary headaches were infection (663/3285, 20.2%), rhinosinusitis (99 pupils, 3.0%), and ophthalmological problems (59 pupils, 1.8%).

Conclusions: The prevalence of migraine in our study was similar to those of previously reported studies in other pediatric populations, and the prevalence of TTH was lower than the previous studies. The facts that the majority of pupils with headache had not visited physicians suggest at least some of them were inappropriately treated. Our study also revealed that certain amounts of children were annoyed by headache-related absence from school and irritability. Therefore, it is important to educate parents and school officials about headache preventions strategies in health care programs for children.

OR25

Cardiovascular Profile in Childhood and the Risk of Migraine in Adulthood

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Objectives: To identify early life risk factors of migraine.

Background: Obesity and other cardiovascular risk factors have been associated with migraine. To our knowledge, there are no data from prospective longitudinal cohorts assessing cardiovascular risk factors in childhood and their association with migraine in adult life.

Methods: We used data from the Muscatine Study, an ongoing population-based longitudinal cohort study that began in 1970 and has followed school-age children into adulthood. Body mass index, triceps skinfold thickness, total cholesterol, total triglycerides, and diastolic and systolic blood pressure were measured between 1970 and 1981 in school age participants. Since then, serial measurements of these and other parameters were obtained from examinations in young- and middle-adulthood. A screening questionnaire that included the ID Migraine questions and other socio-demographic information was mailed to members of the Muscatine Study Longitudinal Adult Cohort (n=677; 296 males and 381 females, mean age 52). Those who screened positive for migraine underwent a semi-structured telephone interview by a senior neurology resident (JLK, AHT). Migraine was diagnosed using the ICHD-II criteria and further information such as age of onset, frequency of attacks, acute and preventive treatment, etc., was obtained during the telephone interview. Here, we present preliminary results obtained from the mailed questionnaires.

Results: We received 419 completed screening questionnaires. Participation rate was 65% and there were no differences in age, gender or previous diagnosis of migraine (self-reported diagnosis from a physician), between responders and non-responders. Analysis of risk factors

at the time of the last school survey examination, mean age 15.4 (SD=1.8), suggested higher total cholesterol ($p = 0.0843$) and significantly higher total triglycerides ($p = 0.0101$) in those with migraine in adult life. In young-adulthood, mean age 27.6 (SD=4.0), there was suggestion of higher total cholesterol to HDL ratio ($p = 0.0810$) and body mass index ($p = 0.1098$), and significantly higher diastolic blood pressure ($p = 0.0115$) in those with migraines in adult life. Analysis of risk factors from a later adult examination, mean age 34.9 (SD=3.3), showed higher body mass index ($p = 0.0547$), significantly higher total cholesterol to HDL ratio ($p = 0.0119$), higher total triglycerides ($p = 0.0424$), and significantly lower HDL cholesterol ($p = 0.0113$) in those with migraines in adult life.

Conclusions: These preliminary data analyses suggest that an adverse lipid profile in childhood is a risk factor for migraine in adulthood. Furthermore, adult migraineurs had significantly higher diastolic blood pressure as young adults. Finally, our results are consistent with population studies that have found an association between migraine and body mass index and unfavorable lipid profile. Future analysis will utilize telephone interview confirmation of migraine status (ICHD-II), and will further investigate risk factor associations by fitting multivariable models to compare cohort members with vs. without migraines.

OR26

Cognitive Behavioral Treatment Plus Amitriptyline Leads to Clinically Significant Reductions in Headache Frequency and Migraine-Related Disability: A Randomized Clinical Trial in Pediatric Chronic Migraine

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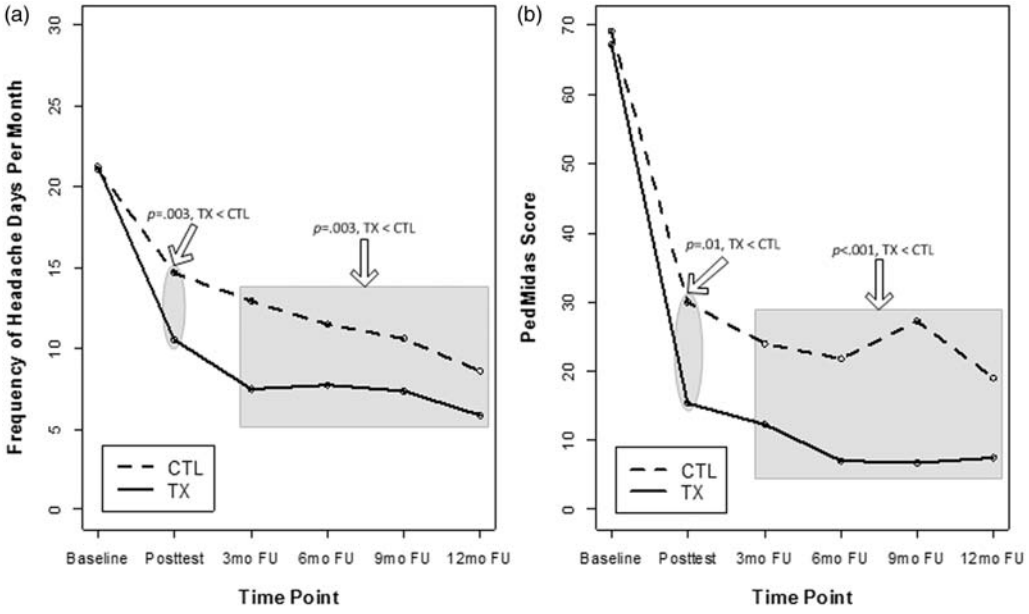
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Objectives: Test a combined psychological & pharmacological intervention (TX) versus a pharmacological intervention plus attention control (CTL) in youth ages 10-17 diagnosed with chronic migraine.

Background: Up to 50% of patients seen by pediatric headache specialists are diagnosed with chronic migraine, yet proven treatments do not exist. Randomized clinical trials are the only means to obtain the needed evidence base to inform practice. Combined psychological & pharmacological treatment holds promise for optimal clinical impact based on prior adult trials[1] and Cochrane reports on the efficacy of cognitive behavioral treatment of pediatric chronic pain[2].

Methods: The co-primary endpoints were headache frequency (days measured by 28-day diary) and migraine-related disability (PedMIDAS). Treatment effects were measured at baseline, 20 weeks (post treatment), and then at 3, 6, 9, and 12-month follow-up. Psychological intervention was cognitive behavioral therapy (including biofeedback); pharmacological intervention was amitriptyline (goal dose of 1 mg/kg/day). Attention control was equal to psychological intervention in terms of contact frequency & face-to-face time, and involved education and support.

Results: 135 subjects met intent to treat criteria (TX: 64; CTL: 71). Mean age 14.4 years; 15% minority; 79% female; Mean baseline headache frequency of 21 days; Mean baseline PedMIDAS of 68 (severe disability grade). No



differences between groups at baseline. TX and CTL were safe and well tolerated. Primary outcomes are presented in a figure. For TX group, a > 50% headache reduction was seen in 66% at post-treatment, 86% at 12-month f-up; proportion no longer chronic migraine was 71% at post-treatment, 88% at 12-month f-up; PedMIDAS score < 20 (mild to no disability) was 75% at post-treatment, 88% at 12-month f-up.

Conclusions: Within 20 weeks of combined psychological & medication treatment, youth with chronic migraine show clinically significant reductions in headache frequency and migraine-related disability. At 12-month f-up, almost 9 out of 10 subjects no longer had chronic migraines and were mild to no disability grade. The results of this combined psychological & medication intervention are at a level of clinical significance that should immediately impact practice in headache medicine. These findings demonstrate a greater frequency reduction (-11 per month) compared to those found in studies of pharmacological treatments approved for chronic migraine in adults (e.g., topiramate: Published trials[3-5]: Range of -3.5 to -5.8 days per month, and onabotulinumtoxinA: Meta Analysis[6] = -2.3 headaches per month).

OR27

Stigma towards Migraine

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Objectives: The objective of the study was to evaluate stigma towards individuals suffering from migraine.

Background: Migraine is a disabling episodic disorder. In addition to the clinical features of the syndrome, individuals with migraine are often subject to stigma by friends, family, and co-workers. However, few empirical data exist on this phenomenon (Young et al., 2013). We utilized the contrastive vignette technique to compare attitudes towards individuals with migraine with attitudes towards individuals with three other episodic disorders: epilepsy, panic disorder, and asthma.

Methods: We utilized the well-validated Attitudes towards Mental Illness Questionnaire (AMIQ) to assess stigma (Luty et al., 2006). Subjects were recruited via the crowdsourcing website Mechanical Turk, and were compensated $0.25 for completion of the short survey. Subjects were randomly assigned to assess a fictional vignette of one of four conditions; each condition described an individual with attacks of migraine, epilepsy, panic disorder, or asthma occurring nearly every week. Respondents were then presented with the AMIQ. The maximum potential score on the AMIQ is 500, with higher scores indicating greater stigmatizing attitudes. In addition to demographic data, subjects were also asked if they had ever had an episode of the relevant disorder, if they had ever been diagnosed with the relevant disorder, and if they had a family member or close friend diagnosed with the relevant disorder.

Results: The survey was completed by 765 individuals. All subjects resided in the USA and were at least 19 years of age, with a mean age of 28.3 (± 0.3 SEM) years. 60.3 percent of subjects were women. The lowest AMIQ score in this survey was obtained when the individual in the vignette was described with asthma (250.1 ± 3.3 SEM). The AMIQ scores for the other vignettes were significantly higher than that for asthma, but not significantly different from each other: migraine (266.5 ± 3.4 SEM), panic (267.7 ± 3.7 SEM), and epilepsy (262.3 ± 3.9 SEM).

Conclusions: The data demonstrate that stigma against individuals with migraine is of equal magnitude to stigma against individuals with epilepsy or panic, and significantly higher than that for asthma.

OR28

Cardiovascular Contraindications to Triptans in the Migraine Population: Results from the American Migraine Prevalence and Prevention (AMPP) Study

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Objectives: Estimate rates of cardiovascular (CV) contraindications to triptan use in persons with episodic migraine (EM) in the US population and estimate the population at high risk based on Framingham scores.

Background: Triptans are widely prescribed acute migraine treatments with well-known CV contraindications.

Methods: Respondents to the 2009 AMPP study reported prior CV contraindications (events: myocardial infarction, TIA, stroke, claudication and angina; procedures: coronary angioplasty, stenting or bypass surgery, carotid artery surgery or stenting, and peripheral artery bypass surgery). ICHD-2 criteria were used to identify EM cases (ICHD-2 migraine diagnosis with average <15 headache days/month). The sample was stratified by sex and

age (<40, 40-59 and ≥60). Frequency counts were generated for each CV event and procedure. Observed rates for CV contraindications were applied to US Census-derived estimates of EM for each age strata. Modified Framingham Risk scores (derived from self-reported data on age, sex, body mass index, diabetes, hypertension, smoking, cholesterol) identified persons free of events and procedures at high risk for silent myocardial ischemia.

Results: Of 11,799 respondents to the 2009 survey, 6,723 (1,496 males, 5,227 females) met criteria for EM. CV events or procedures were reported by 11.1% of those aged <40 (n=1,457), 18.7% of those 40-59 (n=3,716) and 33.6% of those ≥60 (n=1,550). Males had slightly higher rates for events and procedures across all age strata. Census-based projections of net CV events and procedures yielded 4.71 million persons with EM in the US (1.17 million males and 3.54 million females) where triptan use may be contraindicated. Based on Framingham scores, an additional 1.5 million (0.38 million males and 1.12 million females) are at high risk for silent myocardial ischemia.

Conclusions: Triptans are contraindicated in an estimated 4.71 million Americans with migraine based on CV events and procedures. An additional 1.5 million may be at high risk for silent myocardial ischemia. These individuals have been shown elsewhere to have substantial unmet treatment needs.

OR29

The Presence of Posterior Circulation Territory (PCT) Infarct-Like Lesions in Migraine Does Not Depend on Attack Frequency: An MRI Study in 87 Chronic Migraine (CM) Women

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Objectives: To determine whether CM patients are at increased risk of PCT infarct-like lesions on MRI.

Background: Two general population studies have found that migraine in general, and especially women with aura, has an increased risk of MRI PCT infarct-like lesions. In addition, there was a trend for a higher risk of PCT lesions in those migraine subjects with a higher migraine attack frequency, which would have obvious clinical and management implications (1,2).

Methods: After signed informed consent, brain MRIs were obtained in women from our headache clinic meeting CM criteria according to 2006 revised IHC-II. To keep radiologists blinded we also obtained brain MRIs in 10 episodic migraine patients. Brain MRIs were acquired on a 1.5T unit Signa LX 9.1 (General Electric Systems, USA). Protocol includes whole brain weighted images in saggital T1 (5 mm slices), axial FLAIR T2 (3 mm) and combined proton density and T2 fast spin echo (3 mm). Two independent neuroradiologists carefully analysed all the images.

Results: Brain MRIs were obtained in 87 CM women. Their ages ranged from 18 to 68 years (mean 43.3 years) and the length of CM ranged from 0.5 to 38 years (mean 9.7). Forty-eight patients (56.3%) had at least one vascular risk factor. Twenty-eight (32.2%) met overuse criteria. Forty-two women (48.3%) had a previous history of migraine with aura attacks, though the frequency of auras was below one per month in all patients except one. Only four were not on preventatives. The prevalence of right to left shunt with transcraneal echo was 57%. We found PCT infarct-like lesions in only 3 (3.49%) patients aged 42, 48 and 54 years and with a history of migraine with and without aura attacks. One of these patients was a smoker. They had no other vascular risk factor. Right-to-left shunt was seen in two (one massive and one non-massive) of these patients.

Conclusions: Following the same MRI methodology, the frequency of PCT lesions in our CM was below that found in the two general population studies. Therefore, at least for the PCT, frequency of migraine attacks itself does not seem to be a factor increasing the risk of vascular brain lesions.

OR30

Relative Contribution of Migraine with Aura on Stroke Subtypes in Women

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Objectives: To evaluate the relative contribution of migraine with aura on the incidence of major stroke subtypes in a large prospective cohort of initially apparently healthy women.

Background: Migraine with aura has been consistently linked with increased risk of ischemic stroke and there is also some evidence that it increases risk of hemorrhagic stroke. However, the contribution of migraine with aura to the occurrence of major stroke subtypes relative to other important vascular risk factors remains unclear.

Methods: Prospective cohort study of 27,860 women aged ≥45 who were participating in the Women's Health Study, were free of any cardiovascular disease at baseline, and for whom we had self-reported information on migraine and lipid measurements. Women were followed for medical record-confirmed stroke. A neurovascular neurologist classified stroke into major subtypes (ischemic, hemorrhagic, unknown). We used multivariable standardization models to evaluate the contribution of MA to stroke subtype risk relative to other major vascular risk factors.

Results: At baseline, 5130 women reported migraine of whom 1435 (40%) reported migraine with aura. During 15 years of follow-up, 528 total strokes were confirmed (430 ischemic, 96 hemorrhagic, 2 unknown). The overall incidence rates (95% confidence intervals) per 1000 women per year were 1.2 (1.1-1.4) for total stroke, 1.0 (0.9-1.1) for ischemic stroke, and 0.2 (0.2-0.3) for hemorrhagic stroke. For total, ischemic and hemorrhagic stroke, MA was strong contributor.

Conclusions: In this large, prospective cohort of women, migraine with aura is a strong relative contributor to increased risk of total, ischemic, and hemorrhagic stroke. A history of migraine with aura should be considered an important risk marker for strokes of any kind.

Table: Incidence rate* per 1000 women per year for total, ischemic, and hemorrhagic stroke, according to risk factors in the Women's Health Study (N=27,860).

	Total Stroke	Ischemic Stroke	Hemorrhagic Stroke
Risk factor	Incidence Rate (95% CI)	Incidence Rate (95% CI)	Incidence Rate (95% CI)
Migraine with aura	4.3 (3.0-6.0)	3.4 (2.3-5.0)	0.8 (0.3-1.8)
Systolic blood pressure ≥180 mmHg	3.7 (2.2-6.2)	3.1 (1.8-5.5)	0.5 (0.1-2.3)
Body mass index ≥35 kg/m^2	3.2 (2.1-4.9)	2.5 (1.5-3.9)	0.8 (0.3-2.6)
History of diabetes	3.9 (2.7-5.6)	3.3 (2.2-4.8)	0.7 (0.1-3.5)
Family history of myocardial infarction	2.9 (2.2-3.7)	2.2 (1.7-3.0)	0.6 (0.3-1.2)
Currently smoking	2.9 (2.3-3.7)	2.5 (1.9-3.3)	0.4 (0.2-0.8)

CV Events and Procedures	Aged <40	Aged 40-59	Aged ≥60
Myocardial Infarction	6 (0.4%)	112 (3.4%)	104 (8%)
TIA	17 (1.2%)	135 (3.9%)	101 (7.2%)
Stroke	11 (0.8%)	72 (2.1%)	76 (5.4%)
Claudication	85 (6.2%)	294 (8.6%)	182 (13.1%)
Angina	58 (4.2%)	271 (7.9%)	192 (13.7%)
Coronary Bypass Surgery	11 (0.8%)	41 (1.1%)	49 (3.2%)
Coronary Angioplasty/ Stenting	15 (1.0%)	114 (3.1%)	100 (6.5%)
Carotid Artery Surgery/Stenting	10 (0.7%)	28 (0.8%)	22 (1.4%)
Peripheral Artery Bypass Surgery	10 (0.7%)	32 (0.9%)	16 (1%)
Respondents with ≥1 Event/Procedure	151 (11.1%)	623 (18.7%)	460 (33.6%)

*Data are adjusted for all variables in the Table plus age, cholesterol, alcohol consumption, exercise, history of hormone replacement therapy, and postmenopausal status.

P1

Factors Underlying Triptan Discontinuation

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Objectives: To identify factors that correlate with triptan discontinuation among migraine patients.

Background: It is unclear why many patients who are prescribed triptans do not adhere to treatment. This study investigated correlates of triptan discontinuation.

Methods: Multi-center cross-sectional survey conducted by Headache Fellow members of the American Headache Society Headache Fellows Research Consortium at U.S. tertiary care headache clinics. Subjects were migraine patients who currently used triptans (use within 3 months and for ≥ 1 year) or previously used triptans (no use within 6 months; prior use within 2 years). Univariate analyses compared current triptan users to past users for: migraine characteristics, other treatments, triptan education, efficacy, side effects, type of prescribing provider, Migraine Disability Assessment (MIDAS) and Beck Depression Inventory (BDI) scores. Multivariable

logistic regression modeling was used to determine factors that best correlated with triptan discontinuation.

Results: Compared to current triptan users (n=207), those who had discontinued use (n=69) were more likely to overuse abortive medications (30 vs. 18%, p=.04), to have ever used opioids for migraine treatment (57 vs. 38%, p=.006), and have higher MIDAS (median 40 vs. 18, p=.001) and BDI scores (mean 10.3 vs. 7.4, p=.009). Current triptan users were more likely than discontinuers to have had their triptan prescribed by a specialist (neurologist, headache specialist, or pain doctor) (74 vs. 54%, p=.003) and to report headache resolution (53 vs. 14%, p<.001) or lessened pain (71 vs. 28%, p<.001) from their triptan. On a 1-5 scale (1=strongly disagree, 5= strongly agree), triptan users felt they had more: control over their migraines (2.9 vs. 2.1), triptan satisfaction (4.0 vs. 2.3), confidence in their prescribing provider (4.5 vs. 4.0), and were more educated about triptan use (4.2 vs. 3.7) (p<0.001 for all comparisons). Although both current and prior users reported similar side effect rates (48 vs. 43%, p=0.49), the main reasons for discontinuation were lack of effect (44%) and side effects (29%). The strongest correlate of triptan discontinuation was lack of efficacy (OR=17, 95% CI [9, 33]). Other factors associated with discontinuation included MIDAS>24 (OR 2.6, [1.5, 4.6]), BDI >4 (OR 2.5, [1.4, 4.5]), and a history of ever using opioids for migraine therapy (OR 2.2, [1.3, 3.8]).

Conclusions: Current triptan users reported receiving more education about their triptans, felt they had better control over their migraines, and were more likely to receive their triptan from a specialist compared to prior users. Discontinuation was most correlated with lack of efficacy. Discontinuation was also associated with more migraine related disability, depression, and the use of opioids for migraines. Although we cannot determine if these factors contributed to discontinuation or are results of discontinuation, targeting these factors may decrease the likelihood of triptan discontinuation and improve overall migraine control.

P2

Education and Decision Making at the Time of Triptan Prescribing: Patient Expectations vs. Actual Practice

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Objectives: To compare patient expectations to actual practice regarding triptan patient education and the patient's role in decision making when triptans are prescribed.

Background: Patient satisfaction and adherence with treatment recommendations are optimized when education about prescribed treatments and the level of patient involvement in treatment decisions match patient expectations.

Methods: Multi-center prospective observational study conducted by the American Headache Society Headache Fellows Research Consortium at tertiary care academic headache clinics. Subjects were episodic and chronic migraine patients (n=292) who recently used triptans. Data regarding triptan education that patients actually received and their involvement in decision making when the triptan was prescribed, as well as patients' expectations regarding education and their desired role in decision making were collected via questionnaires.

Results: The main source of triptan education was the prescriber for 66.1% of patients and self-education for 17.0%, while 6.9% reported receiving no triptan education. 92.3% felt the prescriber should be the main source of education while only 3.8% thought self-education should be the main source.

Patients most preferred to receive education about deciding if a triptan should be taken, when to take the triptan, and triptan side effects; 79.5%, 85.6% and 67.5% reported having actually received this education, respectively. Patients were less interested in education about cost and obtaining triptan refills. Patients preferred to be educated about taking other medications with triptans, the number of triptan doses they could take per migraine and what to do if the triptan does not work; 61.5%, 86.0%, 60.1% reported having received this education, respectively. Although patients were less interested in education about triptan mechanism of action, 48% reported having received such education. Subjects preferred education about the most common side effects as opposed to "all" possible side effects, and they preferred discussion rather than handouts.

92.0% of patients want to participate in making triptan treatment decisions with their prescriber. However, 55.1% reported that the prescriber was the sole decision maker.

Conclusions: Consistent with patient expectations, the main source of education about triptans is typically the

prescriber. Although patients did not think that self-learning should be the main source of education, 23.9% reported that self-learning was their main education source or that they received no triptan education. Although the majority of patients want to be involved in the triptan prescription decision making process, over half of patients reported that the entire decision was made by the prescriber. Triptan education and the decision making process when prescribing a triptan should be improved to better match patient expectations.

P3

Early Efficacy of Non-Oral, Acute Anti-Migraine Drugs Evaluated by Comparing Time-Effect Curves and Pharmacokinetics

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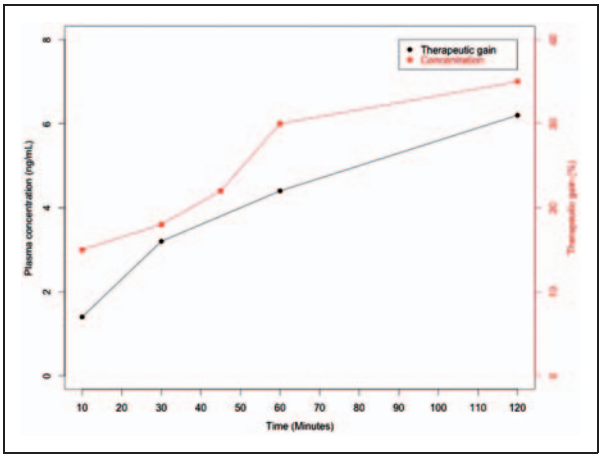
Objectives: Headache relief after oral triptans is usually evaluated in randomised, controlled trials (RCTs) after 2 h. Migraine patients, however, want rapid and complete relief. Onset of relief has in some RCTs with non-oral anti-migraine drugs been estimated as the first time point when the drug is significantly better than placebo. The difference can, however, at this time point in very large RCTs be only a few percent and is thus clinically irrelevant. Instead the time-effect curve for therapeutic gain (TG)(percentage responding to active drug minus percentage responding to placebo) up to e.g. 2 h should be drawn. This allows a clinically relevant evaluation of the speed of efficacy and the maximum effect.

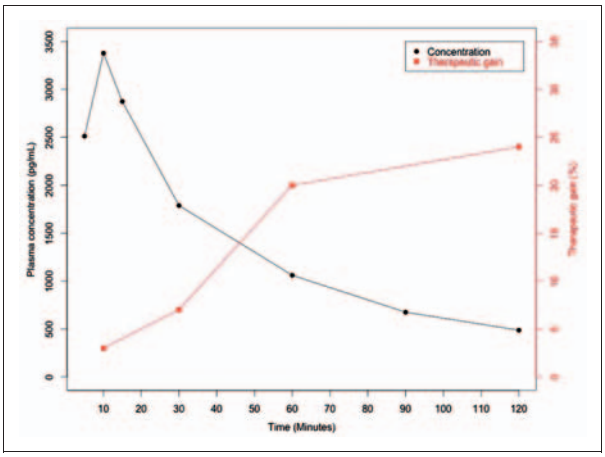
Background: In addition, when combining these time-effect curves with the known pharmacokinetics for this mode of administration on can get information on some possible basic pharmacodynamic attributes and mechanism of action of the drugs, the purpose of this paper.

Methods: The TG for headache relief after intranasal zolmitriptan 5 mg in a very large RCT (n = 1,868), aiming at evaluating the onset of effect, is shown in Figure 1 together with plasma concentration from a study in healthy volunteers. There is a parallel increase in time of TG and plasma concentrations of zolmitriptan indicating a quick equilibration between drug in blood and effector site.

Results: In contrast, the time-effect curve for TG for headache relief after orally inhaled DHE 0.5 mg versus plasma concentrations of DHE as shown in Figure 2 demonstrates a considerable time-lag between response and pharmacokinetics. This is most likely caused by a slow equilibration between drug in blood and its effector site. A slower dissociation of DHE than sumatriptan from the 5-HT1B/1D receptor and and this finding has been used to explain the low recurrence rate after DHE. In addition, it could explain the slow onset of effect.

Conclusions: These 2 examples illustrate that one cannot simply transfer early pharmacokinetics to early efficacy in acute migraine treatment and that quite different T_{max} (10 min after orally inhaled DHE and 1.5 h after intranasal zolmitriptan) may result in similar time-effect curves, Figg. 1 and 2. Theoretically, the pharmacodynamic delay of DHE could be due to both a vascular effect or a CNS effect.





P4

Efficacy and Safety of a Novel Breath-Powered™ Powder Sumatriptan Intranasal Treatment for Acute Migraine

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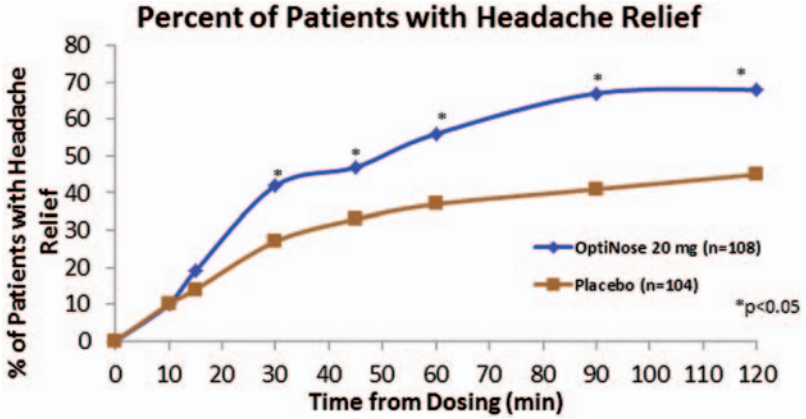
Objectives: To compare the efficacy and safety of OptiNose Breath-Powered sumatriptan powder to placebo in the treatment of patients with moderate to severe migraine headache.

Background: Patients taking oral triptans commonly cite slow onset of action, inadequate pain relief, and adverse effects as reasons for dissatisfaction[1]; nausea or vomiting can also be a barrier to use. Adverse effects known as "triptan effects" are most often associated with formulations and doses that produce higher plasma levels. In a small trial, low dose sumatriptan powder delivered with an OptiNose Breath Powered device produced a headache relief rate approaching that previously reported with injections without the attendant side effects[2]. These results supported conduct of a larger trial.

Methods: Single-dose, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients had history of migraine for ≥1 yr prior to entry and reported ≥1 headache, but <15 headache days, per month. Patients were randomized to an OptiNose Breath Powered device containing either 20 mg of sumatriptan powder (15 mg emitted dose) or placebo. Patients treated an attack reaching moderate or severe intensity and recorded symptoms at scheduled times.

Results: 223 patients received treatment (112 sumatriptan powder and 111 placebo). The mean age was 42 yrs.; 85% were women. For the primary outcome, 68% of patients in the OptiNose sumatriptan powder group reported pain relief at 120 min vs. 45% in the placebo group ($p<.01$). Pain relief curves diverged early, reaching statistical significance at 30 min (42% vs. 27%; $p<.05$). At 120 min, 37% of patients receiving OptiNose sumatriptan powder had reported complete relief compared with 17% for placebo ($p<.01$), while 70% vs. 45% reported meaningful relief ($p<.001$). Among patients with pain relief at 120 min, 65% sumatriptan powder and 53% placebo (ns) had continued pain relief at 24 hrs. Large reductions in nausea, phonophobia, and photophobia were reported in both groups; between-group differences were not statistically signficant. No systemic adverse events were reported in more than one patient. Only one patient reported mild and transient tingling in the hands and head. The most common (>5%) AEs reported were product taste (22%), nasal discomfort (13%), and rhinitis (6%); all transient and generally mild.

Conclusions: This study replicates the previous finding that the OptiNose Breath Powered device delivering low dose sumatriptan powder produces early headache relief in a high percentage of patients compared to placebo and to historical rates with oral treatment, and a high rate of headache relief. Treatment was well tolerated, with few systemic adverse effects.



P5

The Risk of Serotonin Syndrome with Concomitant Use of Triptan Antimigraine Drugs and SSRI/SNRI Antidepressants: A Population-Based Surveillance Study

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Objectives: To identify the true risk of serotonin syndrome with concomitant prescribing of triptan antimigraine medications with SSRI/SNRI type antidepressant drugs by review of an exposed population.

Background: In 2006 the US Food and Drug Administration (FDA) issued an Advisory about the risk

of serotonin syndrome with concomitant use of drugs from two widely prescribed medication classes: 1) selective serotonin reuptake inhibitor (SSRI) and selective norepinephrine reuptake inhibitor (SNRI) antidepressants and 2) triptan antimigraine drugs.

SSRI/SNRI antidepressants and triptan antimigraine drugs are widely prescribed. 20-25% of triptan users are also prescribed SSRI or SNRI antidepressants. Because there have been no population-based studies that link co-prescription with the outcome of serotonin syndrome, the true risk remains unknown.

Methods: We first identified the number of unique patients within the Partners system who were prescribed a triptan from 2001-2010, and then what proportion were concomitantly prescribed an SSRI or SNRI. We also examined this information for each year separately to identify whether the proportion of patients with co-prescriptions changed over the period of the study, especially following the 2006 FDA warning. Within these populations we searched for the yearly and aggregate outcome of serotonin syndrome.

Results: From 2001-2010, among 15,221± 3 patients with triptan monotherapy, there were 216± 3 cases of EPS. Among 5282± 3 patients with co-prescription there were 135 ±3 cases of EPS. Evaluation by year showed, as expected, lower case numbers and no decrease in triptan monotherapy or co-prescription following the Advisory. Nor was there a change in the proportion of patients diagnosed with EPS, even though one might expect that physicians would be more alert to possible cases of serotonin syndrome after the Advisory. It does not appear likely that cases were mistakenly diagnosed as neuroleptic malignant syndrome. The proportion of patients with EPS in both groups was very low overall but consistently higher in the triptan-only group than the co-prescription group.

Conclusions: Triptan monotherapy and co-prescription of triptans and SSRIs/SNRIs appear to be associated with a low risk of serotonin syndrome. These preliminary data suggest that the large population of patients with co-existent affective disorders and migraine may not need to forgo management of one condition in order to treat the other. They further imply that it may be unwarranted for decision support systems to issue automatic safety alerts for co-prescriptions. Finally, it seems likely that detailed analysis may suggest that the FDA Advisory should be reconsidered.

P6

SumaRT/Nap Verses Naproxen in Treatment and Disease Modification of Migraine: A Pilot Study

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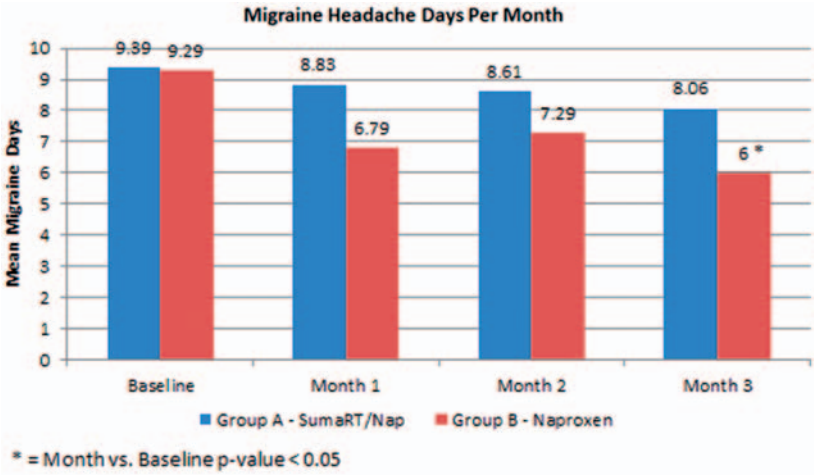
Objectives: This pilot study compared 2 acute migraine medications in treating attacks of migraine and reducing the number of future attacks, thereby modifying disease progression.

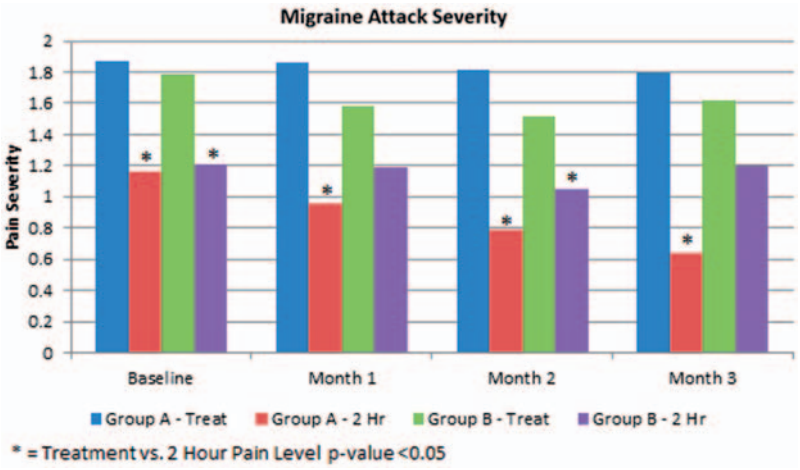
Background: Patients suffering with moderate to severe attacks of migraine desire acute treatment. As migraine frequency increases, so too can the risk of medication overuse. Frequent administration of acute medications may act both as an acute and prophylactic treatment.

Methods: A randomized comparator trial of 39 subjects, 18 to 65 years of age, with frequent episodic migraine with or without aura, as defined by ICHD-2, in Stage 2 (3 to 8 headache days per month) or Stage 3 migraine (9 to14 headache days per month) was conducted at 2 headache centers in the US. Subjects were randomized 1:1 to treat 14 or fewer migraines per month with SumaRT/Nap (Group A) or naproxen sodium (Group B) for 3 months.

Results: Subjects in Group B had a statistically significant reduction in migraine headache days at month 3 compared to baseline ($p=0.0002$): primary endpoint. Group A had a reduction of migraine headache days but this decrease did not reach statistical significance over baseline ($p=0.2$). In addition, subjects in Group B had a statistically significant reduction of migraine attacks at all three months of the study compared to baseline. A greater than 50% reduction in the number of migraine days at month 3 occurred in 43% (6/14) of subjects in Group B compared to 17% (3/18) of subjects in Group A. SumaRT/Nap was statistically superior to naproxen at 2 hours in reducing the migraine headache severity. The amount of acute medication used decreased from Baseline to Months 1-3 for both groups. Both treatments were well tolerated.

Conclusions: Naproxen sodium provides headache relief at 2 hours and reduces frequency of headache days and migraine attacks. Despite both groups using similar quantities of naproxen, this was not seen in SumaRT/Nap. SumaRT/Nap is more effective as acute treatment at 2 hours in reducing headache severity but does not significantly reduce attack frequency or the number of headache





days. If confirmed, these results may have implications for migraine progression and MOH.

P7

Sumatriptan Transdermal System Is Significantly Less Likely To Cause Treatment Emergent Nausea Than Placebo

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Objectives: The objective of this study was to compare the incidence of treatment-emergent nausea (TEN) in patients treated with the sumatriptan iontophoretic transdermal system (sumatriptan TDS, Zecuity™) or placebo.

Background: TEN develops in up to 20% of patients treated with oral triptans. It may arise as a treatment-related adverse event or as a consequence of oral therapy. Assessing non-oral therapies may clarify the mechanisms of TEN and contribute to improved management.

Methods: This study used a randomized, parallel-group, double-blind, placebo-controlled design to compare the efficacy and tolerability of the sumatriptan TDS with placebo. The eligible subset included migraineurs who were free of nausea at baseline, took study medication, and provided data on nausea at 2 hours. The primary endpoint of this post-hoc analysis was the proportion with TEN at 2 hours.

Results: Among 454 treated patients, 239 were free of nausea at baseline and eligible for analysis; 130 patients

treated with sumatriptan TDS and 109 with placebo. The incidence of TEN was significantly lower with sumatriptan TDS than with placebo from 1 hour through 24 hours post-baseline (Figure 1), indicating a protective effect of active treatment. At 2 hours post-treatment, patients treated with placebo were three times more likely to have TEN as those treated with sumatriptan TDS (13.8% vs 4.6%, p <0.001).

Conclusions: Sumatriptan TDS prevents treatment emergent nausea relative to placebo. This non-oral therapy has benefits not only in relieving nausea, but also in preventing its emergence.

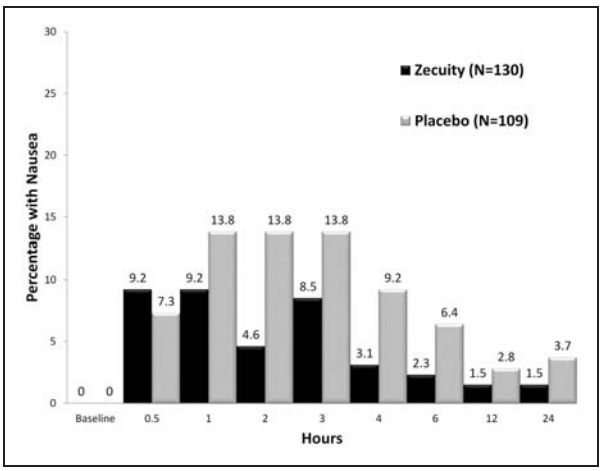


Fig 1. Proportion with TEN in patients treated with sumatriptan TDS or placebo (N=239)

P8

Early Response to Intravenous Fluid for Children with Acute Migraine in the Emergency Department

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Objectives: Assess the early response to intravenous fluid hydration in children with treatment-resistent migraine.

Background: Children with migraine frequently present to the Emergency Department (ED) for treatment despite little evidence to support decision-making. Many ED migraine treatment strategies are preceeded by a bolus of intravenous (IV) fluid yet there is no data on the efficacy of this intervention. The study will also support the planning of future trials.

Methods: Single-blind, 'placebo-challenge' study of 10 mL/kg IV 0.9% sodium chloride (NaCl) for children aged 6-17 years presenting to a tertiary pediatric hospital ED in Canada with treatment-resistant migraine. The primary outcome was complete headache relief (pain-free) at 30 minutes. Secondary outcomes included headache relief (change on visual analogue scale (VAS) > 20 mm), nausea, headache recurrence, and return to ED within 24 hours. Patients were randomized into two groups: (A) no medication given before 30 minutes and; (B) expectation that medication may have been given simultaneously. Participants in group B observed a 5 mL syringe with 0.9% NaCl injected into their IV line and were read a standard script that it 'may or may not' have included their medication. All participants were treated with standard of care following the 30 minute assessment and followed-up by phone at 24 hours. Analysis was performed blinded to group allocation using Stata 12.1.

Results: Two-hundred and twelve subjects were screened in a 19-month period and 46 randomized with a mean age of 13.3 years; 31 (67.4%) females. Five did not complete the 24-hour follow-up call. Demographics (age, sex) and baseline characteristics (headache severity, nausea, emesis, hydration, migraine history) were similar between groups. Complete headache relief (pain-free) was low at 30 minutes with 1/24 in Group A (no expectation) and 1/22 in Group B (expectation; p=0.7). Headache relief (VAS decrease > 20 mm) at 30 minutes was also similar (p=0.6) with 6/24 (25%) in group A and 7/22 (31.8%) in group B. Ten participants (21.7%) had relief in nausea (VAS change > 20 mm). The mean decrease in VAS from baseline to 30 minutes was similar (p=0.93) with 12.3 mm (95% CI 4.6-20) for group A and 12.7 mm (95% CI 6.8-18.5) for group B. Following standard care, twenty-one (n=21/42; 50%) were moderately or extremely satisfied with their treatment. One participant reported a minor intravenous related adverse event and 3 returned to the ED in 24 hours.

Conclusions: Only a small proportion of children with migraine in the ED experienced complete headache relief at 30 minutes after a bolus of IV normal saline. The 'expectation of treatment' did not influence the response rates. Future ED intervention trials for migraine in children can use IV fluid as a component of the regimen or a 'placebo-challenge' phase without requiring a significant sample size adjustment. Unlike adult migraine studies in the ED, few children return in 24 hours.

P9

Spinning out of Control: The Black Box of Basilar Migraine

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Objectives: To demonstrate that triptans are a safe and effective abortive treatment for migraines with basilar type features.

Background: Basilar migraine, also known as basilar-type migraine and basilar artery migraine, is a migraine sub-type that involves symptoms that are thought to originate from the brainstem and/or from bilateral simultaneous hemisphere activation. (1). The term basilar migraine can be traced back to a paper by Bickerstaff in 1961, which suggested that basilar artery vasoconstriction is part of the pathophysiology of this primary headache disorder (2). Since the coining of the term basilar migraine, and its inclusion in the ICHD-II, there has not been any significant evidence suggesting that posterior circulation oligemia or ischemia occur as part of the pathophysiology of basilar migraine. Despite the lack of evidence for basilar artery vasoconstriction, the US Food and Drug Administration (FDA) mandates that package labeling includes that triptans are contraindicated in patients with basilar migraine (3). Despite this package label contraindication, many physicians prescribe triptans to patients that either meet criteria for basilar migraine or have some features consistent with this diagnosis.

Methods: This retrospective IRB approved study was conducted at the John R. Graham Headache Center (JGHC). A search was conducted using the electronic medical record for patients with a diagnosis of migraine with basilar migraine features who used a triptan between 7/2010-7/2011. The terms utilized for the migraine with basilar features search were migraine AND basilar, dysarthria, vertigo, tinnitus, hyperacusia, diplopia, ataxia, altered/loss of consciousness, and spells. Visual and sensory criteria were not utilized due to the confounding with migraine with aura that can occur with a text search.

Results: The total number of patients identified was 29. Side effects to triptans were mild, and occurred in only a few patients. Triptans were effective in 58% of patients.

Conclusions: In this retrospective study, triptans were used safely and effectively for the abortive treatment of migraines with basilar type features. There has been no clear evidence that basilar type migraine symptoms occur due to basilar artery spasm or constriction, and these data suggest that further justification is warranted regarding the black box warning for the use of triptans in basilar type migraine. These data also suggest that beta blockers, tricyclic antidepressants, anti-convulsants, and Botox injections have some efficacy in the treatment of migraines with basilar type features.

29 Subjects (Age 18-69)

Aura	
Without Aura	19
Visual Aura	8
Visual/Sensory Aura	1
Language Aura	1

Basilar Features	
Vertigo	12
Tinnitus	4
Spells	4
Ataxia, Tinnitus	3
Vetigo, Tinnitus	3
Diplopia	2
Ataxia	1

Effective Prophylaxis	
Topamax	7
Amitirptyline	5
Botox	2
Atenolol	1
Zonisamide	1
Amitriptyline, Lisinopril	1
Depakote, Verapamil	1

Triptans Used	
Sumatriptan	22
Eletriptan	12
Zomitriptan	11
Rizatriptan	4
Almotriptan	3
Naratriptan	3
Frovatriptan	2

Number of Triptans Used	
One Triptan	16
Two Triptans	7
Three Triptans	3
Five Triptans	1
Six Triptans	1
Seven Triptans	1

Adverse Events	
Neck Dystonia	1
Rash	1
GI Upset	1

P10

Emergency Treatment of Migraine at Rio de Janeiro. Are the Patients Getting the Right Thing?

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Objectives: The aim of this study is to evaluate the approach and treatment provided to migraineurs in emergency departments (ED) of private hospitals at Rio de Janeiro, Brazil.

Background: Emergency treatment of migraine attacks may vary with geographical location and resources. In developing countries, the drugs used may not reflect or fulfill the best options, the evidence-based medicine and even the needs of the patients.

Methods: Every migraine patient according to the IHS – II, attending the Headache Center of Rio and previously treated for an attack in an ED belonging to Hospital Copa D'Or, Quinta D'Or, Barra D'Or or Clinica São Vicente was included if able to describe medications used and time of permanence at the scene. Written treatment reports were also used as proof of care delivered. The Hospitals are located in Rio de Janeiro Municipal area and were chosen arbitrarily and because they are considered as having high standards by most of the health plans.

Results: Forty one patients (31 women, 10 men, ages 20-76, mean 39,9 years) were included in the period of 2005-2012. The patients had an average headache frequency of 4,7 attacks/month (1 to 10) and 5 patients (3 women, 2 men) had migraine without aura and migraine with aura. The remaining patients had migraine without aura. The average time in the ED was 6,7 hours (2-13h) and only 16 patients (39%) left the hospital with a higher than 50% relief in headache intensity. Eighty percent of the patients received IV metamizole (dipyrone) whereas 36,6% had IM tramadol and 46,3% received IV nonsteroidal anti-inflammatory medications (mostly tenoxican). Only 3 (7,3%) patients received injectable sumatriptan and 6 (14,6%) chlorpromazine. More than one drug was administered to 36 (87,8%) patients.

Conclusions: Although with poor evidence, tramadol is one of the mostly used medications in EDs of Rio de Janeiro for the acute treatment of migraine. Metamizole is also commonly used because it is cheap and well tolerated, but not very effective. Contrarily, sumatriptan is expensive while chlorpromazine usually demands attention and time during and after administration for patient's monitorization. Considering the small percentage of patients leaving the hospital with higher than 50% headache relief despite the long average duration of care, we suggest that even the high standard hospitals in Rio change their paradigm of treatment for migraine attacks. Medical education may be an useful way of improving that.

P11

Randomized Comparison of the Pharmacokinetics of Sumatriptan Powder Delivered with the OptiNose Breath Powered™ Intranasal Device to Imitrex Nasal Spray, Tablet, and Injection

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[1]*OptiNose Inc., Yardley, PA, USA.*

Objectives: To compare the pharmacokinetics and safety of 20 mg sumatriptan powder administered with the novel OptiNose Breath Powered intranasal device with Imitrex 20 mg nasal spray, 100 mg tab, and 6 mg subcutaneous inj.

Background: Intranasal administration of sumatriptan has been proven to produce relief from migraine with substantially lower systemic exposure than injection or tablets. However, drug distribution within the nasal cavity from nasal sprays is inconsistent, with much of the dose dripping out the front of the nose or swallowed[1]. This reduces nasal absorption, contributes to bitter taste, and may reduce predictability of treatment response. OptiNose Breath Powered devices produce broader, more superior and posterior intranasal deposition than standard liquid sprays[2]. A unique OptiNose product is being developed with an intranasal sumatriptan powder to enhance the speed and extent of nasal absorption in pursuit of meaningfully improved clinical benefits.

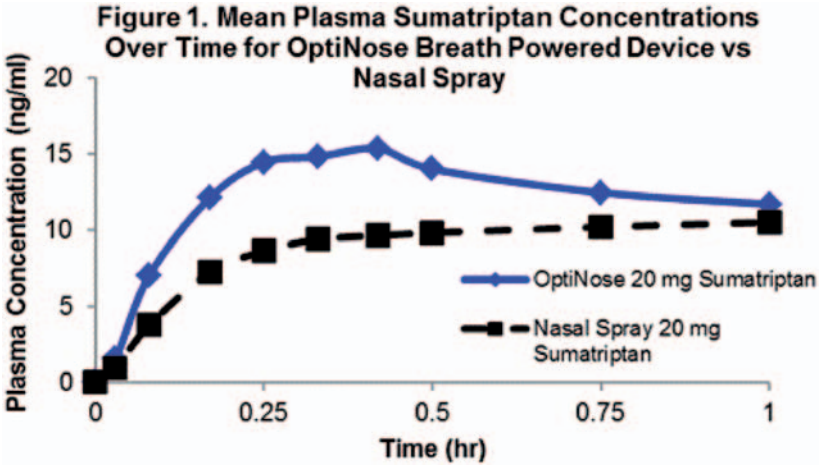
Methods: Single-dose, randomized, 4-period cross-over pharmacokinetic study in 20 healthy volunteers. After dosing, plasma samples were taken through 14 hours with a 7 day washout between periods.

Results: The nasal formulations produced a substantially lower peak (Cmax) and total exposure ($AUC_{0\text{-}t,0\text{-}\infty}$) than the tablet and inj. OptiNose Breath Powered sumatriptan produced an earlier peak exposure and yielded >60% higher early plasma exposure ($AUC_{0\text{-}15}$ min and $AUC_{0\text{-}30}$ min) than the nasal spray despite emitting 20% less drug. A significantly greater proportion of sumatriptan was absorbed from the nasal cavity, following administration with the OptiNose device in the first 30 min after dosing. All treatments were well tolerated.

Conclusions: Sumatriptan powder delivered with the OptiNose Breath Powered device is not bioequivalent to any tested sumatriptan product, produces earlier and

Pharmacokinetic Parameters	OptiNose 20 mg$^{\Omega}$ Mean ±SD (N=20)	Imitrex IN 20 mg$^{\Omega}$ Mean ± SD (N=20)	Imitrex Tab. 100 mg Mean ± SD (N=20)	Imitrex Inj. 6 mg Mean ± SD (N=20)
C_{max} (ng/mL)	20.8 ± 12.2	16.4 ± 5.7	70.2 ± 25.3	111.6 ± 21.6
$AUC_{0\text{-}15min}$ (ng*hr/mL)	2.1 ±1.6	1.2 ± 0.8	0.7±0.7	16.2±4.0
$AUC_{0\text{-}30min}$ (ng*hr/mL)	5.8* ± 4.1	3.6 ± 1.9	8.1 ± 5.0	39.7 ± 7.1
$AUC_{0\text{-}t}$ (ng*hr/mL)	63.0 ± 20.3	59.1 ± 17.7	292.6 ± 87.5272	127.3 ± 17.3
$AUC_{0\text{-}inf}$ (ng*hr/mL)	64.9 ± 20.6	61.0 ± 17.8	308.8 ± 92.4	128.2 ± 17.4

SD=standarddeviation*the 90% CI of the geometric mean ratios comparing OptiNose 20 mg to Imitrex IN was above 100% and was below 100% for the comparisons with Tablet and Inj; $^{\Omega}$OptiNose device emitted dose is 16mg split between the two nostrils. ImitrexIN emitted dose is 20mg.



faster absorption than any form but injection, and has more efficient nasal absorption than Imitrex nasal spray.

P12

Efficacy of the Sumatriptan Iontophoretic Transdermal System (Zecuity™) in Migraine Patients with and without Nausea at Baseline

J. Goldstein[1], C. O'Neill[2], J. Griesser[3], M. Pierce[2]

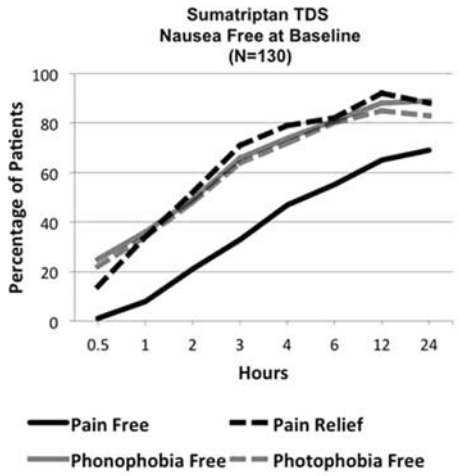
[1]*San Francisco Clinical Research Center, San Francisco, CA, USA;* [2]*NuPathe Inc., Conshohocken, PA, USA;* [3]*The Griesser Group, Conshohocken, PA, USA.*

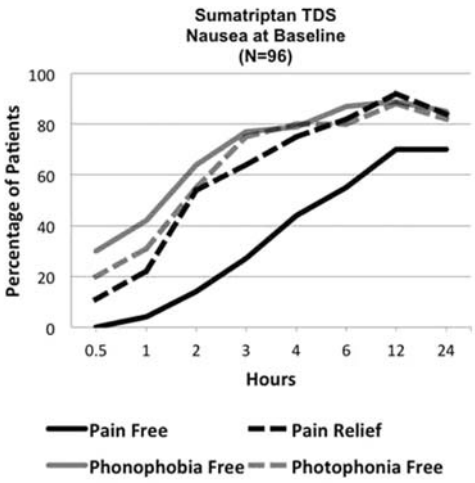
Objectives: This post-hoc analysis of Phase III clinical trial data evaluates the efficacy of the sumatriptan iontophoretic transdermal system (sumatriptan TDS) in patients with and without nausea at baseline.

Background: The sumatriptan TDS is a unique delivery system that uses a low-level electrical current to deliver sumatriptan through the skin. This product has recently been approved by the FDA for the acute treatment of migraine headaches in adults with and without aura. Nausea during migraine occurs often and can impact response to oral medications. Because migraine patients with nausea are less satisfied with current medications; there is need for an effective product that can address migraine-related nausea.

Methods: PREDICT (Study NP101- 007) was a randomized, double-blind, placebo controlled Phase III clinical trial conducted in 469 patients aged 18-65 years who treated one moderate to severe migraine attack with sumatriptan TDS or placebo. Freedom from pain two hours post patch activation was the primary endpoint. Secondary endpoints included pain relief and freedom from nausea, photophobia and phonophobia. This post-hoc analysis evaluated headache pain severity, photophobia, and phonophobia in patients with and without nausea at baseline.

Results: In the overall patient population, sumatriptan TDS was significantly more effective than placebo on the primary endpoint of freedom from pain at two hours post patch activation. This significant difference





was also demonstrated in the secondary endpoints of pain relief and freedom from nausea, photophobia and phonophobia. Significant pain relief and relief from nausea were seen as early as one hour post patch activation. At two hours, 84% of patients receiving sumatriptan TDS were nausea free (p=0.025). Of the patients who reported nausea at baseline, 69% were nausea free at two hours with sumatriptan TDS vs 44% on placebo. The occurrence of nausea was less at all time points post sumatriptan TDS activation vs placebo. Patients with nausea at baseline were more likely to have severe pain (31%) vs patients without nausea (16%); however the efficacy of sumatriptan TDS across both primary and secondary endpoints was similar regardless of the nausea status at baseline.

Conclusions: The sumatriptan iontophoretic transdermal system has demonstrated efficacy in the treatment of migraine headaches. This post-hoc analysis demonstrates that the efficacy is maintained regardless of the presence of nausea and that nausea symptoms and headache pain are rapidly relieved.

P13

Evidence-Based Guideline of the American Headache Society: A Report on the Pharmacologic Treatment of Acute Migraine in Adults

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Objectives: To provide an updated recommendation for acute migraine treatment based on evidence in medical literature.

Background: Migraine frequently requires acute pharmacological treatment for acute attacks. Previous acute guidelines published in 2000 provided guidance for acute migraine treatment based on published studies and we undertook an update. 1 Members of the guidelines sections of the American Headache Society participated in this project.

Methods: We performed a standardized literature search for articles related to acute migraine treatment based on American Academy of Neurology guidelines from 1998 to 2010. Based on these results, two authors selected abstracts for full text review. Two reviewers assessed each qualifying study for its quality of evidence. The authors recommended treatments based on levels of evidence, wtih a Level A recommendation requiring at least 2 Class I studies and Level B recommendation 1 Class I or Class II studies.

Results: The migraine specific medications almotriptan, eletriptan, frovatriptan naratriptan, rizatriptan, sumatriptan, zolmitriptan and dihydroergotamine nasal spray and inhaler are effective (Level A) and ergotamine and intravenous ergotamine are probably effective (Level B) for acute migraine.

Multiple non-specific medications are effective in acute migraine including aspirin, acetominophen, diclofenac, ibuprofen, naproxyn, rofecoxib, butorphenol nasal spray, codeine, and the combination of acetominophen/aspirin/caffiene (Level A). Ketoprofen, intravenous ketorolac, metamizole (dipyrone), intravenous magnesium, and the combination of both isometheptene compounds and

tramadol/acetominphen are probably effective (Level B) for migraine. The antiemetics prochlorpromazine, droperidol, chlorpromazine, and metoclopramide also are probably effective (Level B).

There is inadequate evidence for the use of corticosteroids including dexamethasone, intravenous valproic acid (Level C) and butalbital (Level C) for acute migraine. Octreotide is probably not effective for acute migraine (Level B).

Conclusions: Multiple options for the acute treatment of migraine exist, although there are important differences in their relative efficacy and adverse events.

P14

Total Migraine Freedom (TMF) for Single Pulse Transcranial Magnetic Stimulation (sTMS) Versus Triptans for the Early Acute Treatment of Migraine

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Objectives: To compare the magnitude of the treatment effect for sTMS versus triptans in randomized placebo-controlled trials using an early treatment design where treatment was administered while pain was mild.

Background: sTMS is effective and well tolerated for the acute treatment of migraine with aura. Triptans are the gold-standard for the acute treatment of migraine. No head-to-head studies have compared the efficacy of sTMS to triptans. Total Migraine Freedom (TMF) at two hours (2hTMF) is a composite endpoint that incorporates freedom from pain, photophobia, phonophobia, and nausea. It is a sensitive, patient-centric, clinically relevant summary measure which more powerfully measures treatment effects than the four co-primary endpoints it incorporates.

Methods: The clinical literature was systematically reviewed to identify placebo or sham-controlled mild pain trials of acute migraine treatment with sTMS or triptans. We identified one eligible sTMS study and 3 triptan trials. For each study we computed the absolute risk reductions (ARR) for 2hTMF (2hTMF for active – 2hTMF for sham/placebo). Data for the sTMS are summarized including all sites and excluding a single site which had a dramatically high placebo response.

Results: ARR for 2hTMF for the sTMS study were 12.2% for all sites and 26.3% excluding a single site. For triptan trials, ARR for 2h TMF were as follows: rizatriptan 10mg (27.5%), eletriptan 20mg (10.4%), eletriptan 40mg (41.0%), sumatriptan 50mg, (21.4%), and sumatriptan 100mg (28.1%).

Conclusions: TMF is a patient-centric, clinically relevant, composite endpoint. sTMS demonstrates efficacy in a range that overlaps with the triptans for this robust treatment outcome measure. Head-to-head comparative studies of triptans with sTMS are recommended.

P15

Blood Pressure Changes after Administration of Dihydroergotamine Via Intravenous or Orally Inhaled Routes

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Objectives: The objective of this analysis was to compare acute changes in blood pressure (BP) with intravenous (IV) dihydroergotamine (DHE) and orally inhaled DHE, and to examine a possible relationship to maximum DHE plasma concentrations (C_{max}).

Background: DHE has often been characterized as a vasoconstrictor with the potential to produce significant changes in BP. The use of DHE is contraindicated in patients with ischemic heart disease and uncontrolled hypertension. Much of the previous experience has been with parenteral administration and vascular effects may have been related to doses administered and high initial concentration achieved. A retrospective analysis of three head to head studies was performed to compare plasma levels and BP changes seen following IV and orally inhaled DHE.

Methods: Data from three crossover clinical studies compared BP changes at specific intervals between 10 and 120 minutes post- treatment and C_{max} with DHE administered via oral inhalation (1.0 mg nominal) and DHE administered IV (1.0 mg).

Results: Change from baseline BP data over 1 hour post-dosing from three cross-over studies were compared following IV DHE (n=93) or orally inhaled DHE (n=95). IV DHE produced a consistent pattern of 8-11 mmHg mean increase in systolic BP at 10 minutes after administration. Orally inhaled DHE resulted in an average increase in systolic BP of 1-5mmHg. Effects on diastolic blood pressure were of similar magnitude to the systolic BP changes for both routes of administration. Mean C_{max} values occurred on average before 10 minutes post- dosing, and were approximately 28,000-45,000 pg/mL with IV DHE and 2500 pg/mL with orally inhaled DHE. There appears to be a direct relationship between C_{max} and increases in BP. Increases in BP were transient and returned to baseline values by 60-90 minutes irrespective of the route of administration.

Conclusions: These results show that the effect of DHE on BP varies with the route of administration. IV DHE has a greater effect on BP than orally inhaled DHE and correlates with the higher C_{max} produced with IV DHE. At the intended therapeutic dose of orally inhaled DHE (1.0 mg nominal), there was no clinically significant effect on BP.

P16

Cambia Dual Mechanism of Action Involves Inhibition of Prostaglandin Production and Novel Activation of the Inhibitory Voltage-Dependent M-Type Potassium Current (i.e., KCNQ2/Q3 Channel Opener)

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Objectives: To raise awareness and call attention to the fact that Cambia may differ from other COX1/COX2 inhibitors by its ability to act as novel KCNQ2 and KCNQ3 potassium channel opener.

Background: Cambia is a non-steroidal anti-inflammatory drug (NSAID) indicated for the acute treatment of migraine attacks with or without aura in adults 18 years of age or older. Recent evidence that diclofenac, the active molecule of Cambia, acts as KCNQ2/Q3 potassium channel opener suggest that its therapeutic effectiveness in migraine may involve direct inhibition of neuronal excitability and firing.

Methods: Literature review.

Results: The M-type potassium channel generates subthreshold voltage-gated K^+ current (M-current) that regulates neuronal excitability by stabilizing membrane potential. As such, modulation of this non-inactivating K^+ channel, whose conductance is in the voltage range of action potential initiation, inhibits repetitive neuronal firing. In 1998, the KCNQ2/Q3 channel complex has been identified as the molecular correlates of the M-current. Since then, they have been found: (I) peripherally in the initial segments of C- and Ad- fibers, and centrally in the spinal cord, thalamus and cerebral cortex, (II) as potent inhibitors of nociceptive neurons, and (III) as effective anticonvulsants. In the context of migraine, KCNQ2/Q3 channel openers may reduce the firing of trigeminovascular neurons in the trigeminal ganglion, medullary dorsal horn and thalamus, and reverse cortical hyperexcitability – a hallmark of migraine pathophysiology.

Conclusions: Diclofenac ability to inhibit prostaglandin production, repetitive neuronal firing and cortical hyperexcitability may allow it to reverse certain aspects of migraine headache not previously shown to be reversed by other NSAIDs.

P17

Comparison of Frovatriptan Plus Dexketoprofen (25 mg or 37.5 mg) Versus Frovatriptan Alone in the Treatment of Migraine Attacks with or without Aura: A Pilot Study

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Objectives: To assess the efficacy and safety of frovatriptan 2.5 mg plus dexketoprofen (25 or 37.5 mg; FroDex 25 or FroDex 37.5) compared with frovatriptan 2.5 mg alone (Frova) in the acute treatment of migraines.

Background: Drugs for migraine attacks include triptans and non-steroidal anti-inflammatory drugs; their combination could provide greater symptom relief.

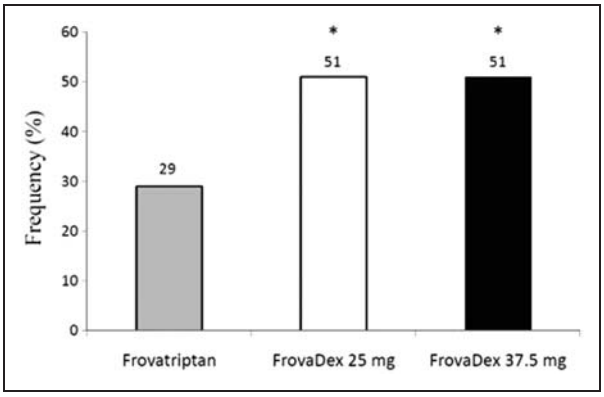
Methods: 314 subjects with a history of migraine, with or without aura, were randomized to Frova, FroDex 25 or FroDex 37.5 and treated one migraine attack. This was a multicenter, randomized, double-blind, parallel-group, pilot study. Primary end-point was the proportion pain-free (PF)

at 2 hours. Secondary end-points included sustained pain-free (SPF) and relapse within 48 h.

Results: Frequency (%) of pain-free at 2 h after administration of Frovatriptan alone, Frovatriptan+Dexketoprofen 25 mg and Frovatriptan+Dexketoprofen 37.5 mg in the 279 patients of the intention-to treat population. Asterisks indicate a statistically significant difference ($p<0.05$) between the group treated with Frovatriptan alone and the groups treated with combination therapy. The proportions of subjects PF at 2 hours were better with each combination therapies than with Frova.

Proportions of SPF at 24 hours were 24% for Frova, 43% for FroDex 25 ($p< 0.05$) and 42% for FroDex 37.5 ($p<0.05$). SPF at 48 hours was 23% with Frova, 36% with FroDex 25 and 33% with FroDex 37.5 (p=NS). Relapse was similar for Frova (22%), FroDex 25 (29%) and FroDex 37.5 (28%) (p=NS). Drug-related adverse events were equally low between the different treatments.

Conclusions: The combination of frova and dexketoprofen improved initial efficacy at 2 hours compared to frova alone whilst maintaining efficacy at 48 hours in this study. The safety profiles were comparable. The intrinsic pharmacokinetic properties of the two single drugs contribute to this improved efficacy profile.



P18

Efficacy of Frovatriptan vs. Other Triptans in Weekend Migraine: Pooled Analysis of Three Double-Blind, Randomized, Crossover, Multicenter, Italian Studies

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Objectives: To evaluate the efficacy of four different triptans in weekend vs. workday migraine attacks through a pooled analysis of individual data from three Italian, randomized, double-blind, cross-over, multinational studies.

Background: Migraine attacks may often occur during days off. Limited evidence is available on the efficacy of antimigraine drugs in these weekend migraines.

Methods: Subjects with a history of migraine with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3). Each patient had to treat 1 to 3 attacks with each drug in no more than 3 months. For this retrospective analysis patients with at least one migraine attack without aura on any Saturday or Sunday were selected. Within-treatment efficacy during weekends and workdays was compared.

Results: 188 (54%) of the 346 patients of the intention-to-treat analysis had weekend migraine and were included in the analysis. A total of 569 attacks occurred during the weekend and 1281 during workdays. The proportion of pain free at 2 hours did not significantly differ between weekend and workday attacks for frovatriptan (26% vs. 27%) or for the comparators (34% vs. 32%). Also, pain relief episodes were similarly distributed between weekend and non-weekend attacks (frovatriptan: 40% vs. 42%; comparators: 49% vs. 43%, p=NS). Conversely, rate of relapse at 48 hours was significantly ($p<0.05$) less during weekend attacks for frovatriptan (17% vs. 30% workdays), while this was not the case for comparators (weekends 34% vs. workdays 40%, p=NS).

Conclusions: Our study provides the first evidence that frovatriptan may represent a particularly favourable option for treating weekend migraine attacks.

P19

Frovatriptan vs. Other Triptans for the Acute Treatment of Oral Contraceptive-Induced Menstrual Migraine: Pooled Analysis of Three Double-Blind, Randomized, Crossover, Multicenter, Italian Studies

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Objectives: To review the efficacy of frovatriptan vs. other triptans, in the acute treatment of OCMM through a pooled analysis of three individual randomized Italian studies.

Background: Oral-contraceptive-induced menstrual migraine (OCMM) is a particularly severe form of migraine triggered by the cyclic hormone withdrawal.

Methods: Subjects with a history of migraine with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3). The studies had an identical multicenter, randomized, double-blind, crossover design. After treating 1 to 3 episodes of migraine in no more than 3 months with the first treatment, patients switched to the other treatment for the next 3 months. In this retrospective analysis, the subset of 73 of the 280 women of the intention-to-treat population taking combined oral contraceptives and experiencing a migraine attack during the withdrawal phase, were analyzed.

Results: The proportion of pain free and pain relief at 2 hours were 25% and 51% with frovatriptan and 28% and 48% with comparators (p=NS). At 24 hours, 71% and 83% of frovatriptan-treated patients and 60% and 76% of comparator-treated patients were pain free ($p<0.05$ between treatments) and had pain relief (p=NS), respectively. Relapse at 24 and 48 hours was significantly ($p<0.05$) lower with frovatriptan (17% and 21%) than with the comparators (27% and 31%).

Conclusions: Our results suggest that, due to its sustained antimigraine effect, frovatriptan may be particularly suited for the management of OCCM as compared to other triptans.

P20

Efficacy of Frovatriptan and Other Triptans in the Treatment of Acute Migraine of Hypertensive and Normotensive Subjects: A Review of Randomized Studies

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Objectives: To systematically evaluate the efficacy of frovatriptan and other triptans in the acute treatment of migraine, in patients classified according to a history of arterial hypertension, enrolled in three randomized, double-blind, crossover, Italian studies.

Background: Some studies suggest that the association between high blood pressure (BP) and migraine might not be uncommon and might induce more severe and more difficult to treat forms of migraine.

Methods: Subjects with a history of migraine with or without aura were randomized to frovatriptan 2.5 mg or rizatriptan 10 mg (study 1), frovatriptan 2.5 mg or zolmitriptan 2.5 mg (study 2), frovatriptan 2.5 mg or almotriptan 12.5 mg (study 3). After treating up to 3 episodes of migraine in no more than 3 months with the first treatment, patients switched to the alternate treatment for the next 3 months. The present subgroup analysis assessed triptan efficacy in 60 subjects with a history of treated or untreated essential arterial hypertension (HT) and in 286 normotensive (NT) subjects.

Results: HT patients were older (45 ± 8 years vs. 37 ± 10 years NT, $p<0.001$) and with a higher prevalence of males (27% vs. 15% NT, $p<0.05$). As expected, entry BP and heart rate values were higher in HT than NT patients. During the study, migraine attacks with aura were significantly more prevalent in HT subjects (21% vs. 13% NT, <0.001). The proportion of pain free at 2 hours did not significantly differ between HTs and NTs for either frovatriptan (25% vs. 26%) and the comparators (39% vs. 32%). Pain relief was achieved in significantly ($p<0.05$) fewer episodes in HT subjects

for either frovatriptan (41% vs. 52% NT) and comparators (48% vs. 58%). Rate of relapse at 48 hours with frovatriptan was similarly low in HTs and NTs (29% vs. 31%), while with the comparators it was significantly ($p<0.05$) larger in HTs (62%) than in NTs (44%). No difference in the occurrence of adverse events was reported between HT and NT. No increment in BP or heart rate values was observed during the study in HT subjects.

Conclusions: Our analysis suggests that HT individuals in general tend to be less responsive than NT migraineurs to triptan therapy. However, frovatriptan, in contrast to the other triptans studied, seems to have a sustained antimigraine effect in both HT and NT patients.

P21

Sumatriptan Transdermal System (TDS) Can Be Correctly Assembled, Applied, and Activated during Migraine Attacks

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Objectives: To validate the ease of assembly, application, and activation of the sumatriptan iontophoretic transdermal system (sumatriptan TDS, Zecuity™) during a migraine attack.

Background: Lontophoresis is a noninvasive drug delivery method that, using low electrical current, moves solubilized drugs across the skin to the underlying tissue. With sumatriptan TDS, pre-programmed doses of sumatriptan are automatically delivered via a transdermal patch, allowing therapeutic drug levels to be reached without mechanical penetration or disruption of the skin. A usability study evaluated the ease of assembly, application, and activation of the sumatriptan TDS.

Sumatriptan TDS Assembly

Methods: This study assessed a single use of sumatriptan TDS in adult migraineurs and healthcare professionals (HCPs). Subjects were divided into 3 groups: migraineurs trained to use sumatriptan TDS, migraineurs not trained to use sumatriptan TDS, and HCPs not trained to use sumatriptan TDS. Sixteen subjects participated in a pre-summative usability test, and 48 subjects participated in a formal summative test. Subjects were 20–64 years old and 83% female. They rated usability on a scale of 1–7, with 1 being difficult and 7 being easy.

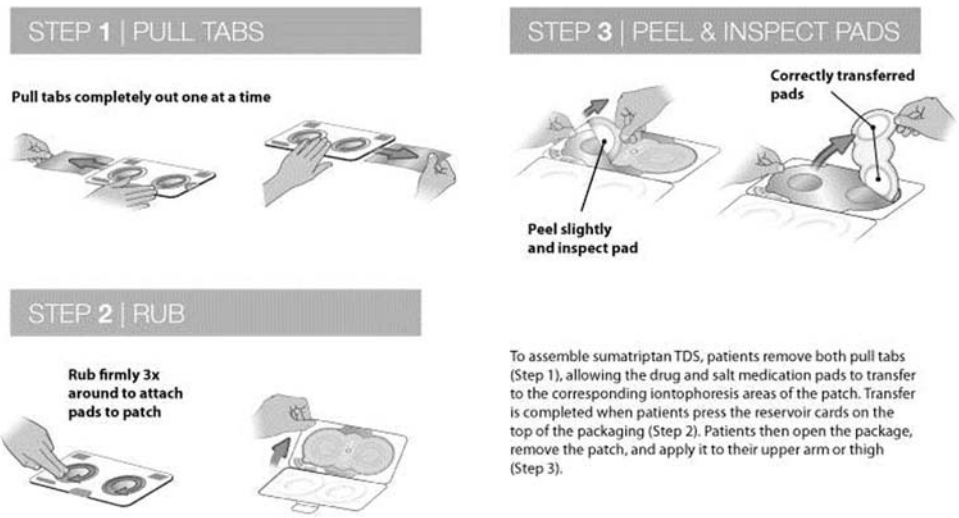
Results:

Pre-summative testing

Of the 16 sumatriptan TDS patches assembled and applied, 100% were assembled, applied, and activated successfully. The mean score for ease of assembly was 6.3, and the mean score for ease of application/activation was 6.8.

Summative testing

Of the 48 sumatriptan TDS patches assembled and applied during summative testing, 100% were assembled, applied, and activated successfully, with no user errors, one close call, and no operational difficulties observed. Among migraineurs, 3% had a mild attack, 69% had a moderate



To assemble sumatriptan TDS, patients remove both pull tabs (Step 1), allowing the drug and salt medication pads to transfer to the corresponding iontophoresis areas of the patch. Transfer is completed when patients press the reservoir cards on the top of the packaging (Step 2). Patients then open the package, remove the patch, and apply it to their upper arm or thigh (Step 3).

attack, and 28% had a severe attack. Across all three groups, the mean score for ease of assembly was 6.1, and the mean score for ease of application/activation was 6.8. For subjects who were trained and subsequently returned to the testing facility for evaluation of usability while in distress of a mild to severe migraine attack, the number of days between training and testing ranged from 0–20, with a mean of 3.6.

Conclusions: The results of this study indicate that sumatriptan TDS can be assembled,applied, and activated safely and successfully during a mild to severe migraine attack. Across all subject groups in both the pre-summative and summative testing, including trained and untrained migraineurs in distress of a migraine attack (97% moderate to severe) and untrained HCPs, patch assembly, application, and activation was 100% successful. In addition, subjects rated sumatriptan TDS very high (6.8 out of 7.0) for ease of use.

P22

Enrichment Clinical Trial Designs Do Not Decrease the Placebo Response Rate in Pediatric Studies: A Systematic Review of Triptan Trials

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Objectives: To assess the effect of enrichment design, study design, and route of delivery on the placebo response rate in randomized controlled trials of triptan medications in the pediatric age group.

Background: Numerous triptan medications approved for use in adults have failed to demonstrate efficacy in children or adolescents and the high placebo response rate is often implicated. More recently studies have used enrichment designs in which particpants who respond to placebo in the early, single-blind, run-in phase are not randomized to the double-blind phase. A systematic review of clinical trials for triptan medications was conducted to evaluate and compare the placebo response rate.

Methods: Seven bibliographic databases, four clinical trial registers, and the grey literature were searched. 6995 references were identified using a sensitive search strategy for prospective randomized controlled trials of children or adolsecents with acute migraine comparing a triptan medication to placebo. Pain-free and headache relief at 2 hours were the primary efficacy outcome measures. The proportion of placebo responders and standard error were calculated for each study and data entered into RevMan 5.2.3 (Cochrane Collaboration) for analysis. Meta-analysis, forrest plots, and tests for sub-group differences were calculated using generic inverse variance as the statistical method and the random effects analysis model.

Results: The placebo response rate overall for all 22 triptan studies was 21% (95% CI 18-25) for pain-free as the outcome and 48% (95% CI 44-53; 21 studies) for headache relief. The placebo response rate did not significantly decrease ($p=0.22$) with the enrichment design studies at 17% (95% CI 9-25; 3 studies; $I^2=85\%$) and normal design at 22% (95% CI 19-26; 19 studies; $I^2=65\%$) for pain-free as the outcome and 47% (95% CI 47-57; 2 studies, $I^2=0\%$) and 48% (95% CI 42-54; 19 studies; $I^2=84\%$) respectively for headache relief. No significant differences in the placebo response rate were observed between oral and intranasal triptan studies for pain-free ($p=0.35$) or headache relief ($p=0.7$). However placebo response rates were significantly lower ($p=0.001$) in studies with a cross-over design at 40% (95% CI; 8 studies; $I^2=58\%$) compared with 54% (95% CI 49-59; 13 studies; $I^2=78\%$) for headache relief as the outcome, but not statistically significant ($p=0.14$) for pain-free at 19% (95% CI 15-22) and 23% (95% CI 18-27) respectively.

Conclusions: Enrichment designs have not significantly changed the placebo response rate in randomized contolled trials of triptan medications in the pediatric age group. Oral versus intranasal delivery also did not alter the placebo response rate. The cross-over trial however was associated with a signifcantly decreased placebo response rate with headache relief as the outcome, but was not significant with pain-free as the outcome. High between study variation was observed suggesting other mechanisms other than those explored in this study may affect placebo response.

P23

Comparison of Methods for Delivering Drug to Regions of Deep Intranasal Nerve Structures: Review of Human Data

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Objectives: Review of publications reporting human *in vivo* regional quantification of nasal deposition by gamma scintigraphy to assess deep delivery of drug to target nerve regions.

Background: Delivery of drug to deep intranasal nerve structures may improve treatment of a number of

neurologic disorders. This includes migraine, where the trigeminal system is believed to play a key role in the pathophysiology. We review available data on *in vivo* human deposition patterns with devices intended to provide reliable and efficient drug delivery to upper/posterior nerve structures.

Methods: A MedLine search identified only 5 relevant human gamma-deposition studies. One study compared a traditional spray pump to nasal inhalation from a standard nebulizer delivering small particles intended to increase deposition beyond the nasal valve. Another study compared two spray pumps with different plume characteristics. In both studies the nasal cavity was divided in 9 segments and ratios between inner (I) and outer (O) segments and upper (U) and lower (L) segments were reported. Another study compared two novel nasal nebulizers, a sonic jet nebulizer and a vibrating mesh nebulizer with suction from the exit nostril. Finally, two studies compared the deposition patterns of traditional spray pumps to liquid and powder versions, respectively, of novel Breath Powered Bi-directional™ delivery devices.

Results: Mean U:L and I:O ratios were higher with the nebulizer vs. spray pump suggesting more deposition in the upper and posterior regions, but up to 56% of the dose was inhaled to the lungs. The spray pumps were not statistically different from one another. The comparison of novel nebulizers showed maximum deposition for both to be 2 cm from the nostril in the horizontal plane, corresponding to the location of the nasal valve. In the vertical plane the maximum distribution with the mesh nebulizer was closer to the nasal floor than the sonic jet nebulizer (0.75 cm vs 1.2 cm). Both Breath Powered delivery devices deposited significantly higher fractions in the upper posterior parts of the nose compared to traditional spray pumps (Sum of upper + middle posterior segments: Powder 53.5% $\pm$ 18.5 vs. Traditional spray 15.7% $\pm$ 13.8, $p < 0.02$).

Conclusions: Human *in vivo* testing shows that Breath Powered devices significantly improve deposition in the intranasal regions where nerve structures can be targeted for therapeutic benefit in migraine and other disorders. This delivery is not associated with the inefficient and potentially dangerous lung inhalation seen with nebulizers. The promise of therapeutic benefit from reliable, practical deep intranasal delivery may now be achievable.

P24

Patient Satisfaction with MAP0004: Results of an Optional Survey during a Long-Term Open-Label Safety Study

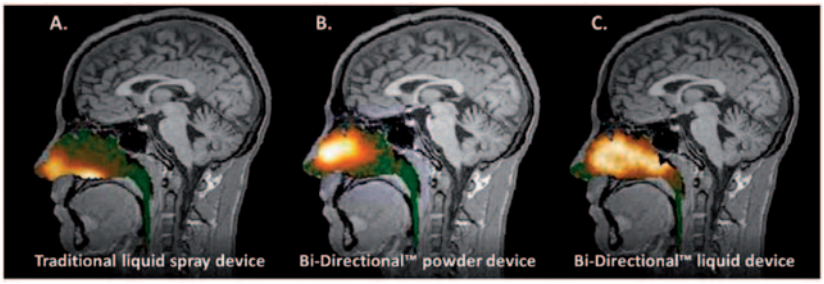
S. Aurora[2], D. Buse[3], B. Lu[1], D. Kellerman[1], W. Cooper[4], S. Kori[1]

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Objectives: To assess satisfaction with the TEMPO® inhaler as a delivery system, and satisfaction with MAP0004 compared to previous migraine medications.

Background: MAP0004 is an investigational orally inhaled dihydroergotamine which has been shown to be effective in treating migraine in a randomized, double blind controlled study. MAP0004 was administered through a TEMPO inhaler. As the administration involved the use of an inhaler with a potential for unfamiliarity and inconvenience of administration, subjects were invited to complete a voluntary survey questionnaire to assess satisfaction with the use of the inhaler and perceived efficacy of the investigational drug.

Methods: Subjects who participated in an open-label, long-term safety study and were participating at week 24 were given an option to complete a survey to assess the ease of use, perceived efficacy, and side effects of the drug. The survey consisted of 16 questions, categorized into comparison to previous medications (8), convenience of use (4), medication aftertaste (3) and overall satisfaction (1). The questionnaire was not a validated instrument. Participation was voluntary and was completed by subjects at different intervals (24 or 54 weeks) during the study. Response options to questions ranged from strongly agree to strongly disagree on a five point scale. Not all questions



were answered by every subject and items with missing and N/A answers were excluded. No formal statistical inferences were made and responses are presented as a normalized percentage of the responders agreeing or disagreeing with the statements.

Results: A total of 197 subjects completed at least one survey. As compared to their previous medications, subjects perceptions of MAP0004, as reflected in the survey results, included: works more consistently (68%); works faster (63%); better pain relief (53%); longer pain relief (54%); return to normal activity faster (63%); works even when taken late (57%); prevents recurrence (62%); and works better when taken early (83%). 58% preferred MAP0004 over their previous medications. 88% felt it was easy to use and 83% convenient to use. 64% reported it to be as convenient to use as their previous medications. 58% reported medication after taste, but 77% said that after taste was tolerable, and 84% said the taste would not prevent them from asking for a MAP0004 prescription. 69% indicated that they would ask for a MAP0004 prescription if the product was available.

Conclusions: In this non-validated survey, the majority of the respondents preferred MAP0004 over their previous prescription migraine medication. A majority reported that the inhaler was easy and convenient to use. Survey participants reported after taste associated with the drug, and indicated that it would not prevent them from requesting a prescription for the study drug if the product was available.

P25

Incidence of Adverse Events with MAP0004 Does Not Increase with Increased Frequency of Dosing: Results from a Long-Term Phase 3 Study

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Objectives: To evaluate the incidence of adverse events after administration of one, two and multiple doses per month of MAP0004 over a period of one year.

Background: The efficacy and safety of MAP0004, an investigational product candidate which delivers dihydroergotamine (DHE) through the lung via a breath-synchronized, metered dose inhaler (TEMPO®), has been demonstrated in treating an acute attack of migraine in placebo-controlled clinical trials. DHE has a long half-life and prolonged binding to receptors compared to sumatriptan. This post-hoc analysis was undertaken to evaluate if the properties of DHE would lead to a cumulative effect, and result in an increase in adverse events after repeated administration.

Methods: This is a post-hoc analysis of a long term study to evaluate the safety and tolerability of MAP0004. All adverse events reported by study subjects during their scheduled study visits during the study period were recorded and mapped to organ systems and preferred terms according to the MedDRA classification. The incidence of adverse events in those subjects who self-administered one dose per month were compared to those who received two doses per month and three or more doses per month using Fisher's exact test.

Results: A total of 288 subjects received at least one dose of the study drug per month for twelve consecutive months. 77 subjects received one dose per month, 121 received two doses per month, and 90 received three to six doses per month. The incidence of adverse events was similar in the three groups, and the incidence of adverse events was not significantly higher in those who averaged three or more doses per month compared to those who averaged one dose per month. The most common adverse events, as expected in any population followed over a year, were upper respiratory infections, but their incidence was similar in all three groups. Potential DHE related AEs such as nausea, GI symptoms, fatigue, chest symptoms were also similar in all three groups. Comparisons at the individual event level found only dizziness and asthma being significantly different when comparing to one dose per month, and in both cases the incidence was lower with increased doses.

Conclusions: In this post-hoc analysis of a long term safety study, repeated administration of MAP0004 of up to six doses per month resulted in no increased incidence of adverse events compared to administration of one or two doses per month.

P26

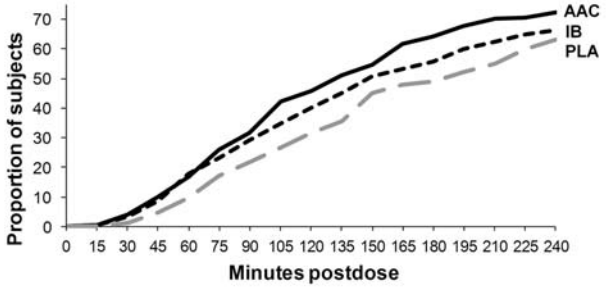
The Fixed Combination of Acetaminophen, Acetylsalicylic Acid, and Caffeine Is Faster and More Effective Than Ibuprofen for Acute Treatment of Patients with Severe Migraine

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Objectives: To compare a fixed combination containing acetaminophen, acetylsalicylic acid, and caffeine with ibuprofen for acute treatment of severe migraine.

Fig 1. Time to meaningful relief: AAC vs IB (N = 660).



	Median time (min)	*P* value		
		AAC v. IB	AAC v. PLA	IB v. PLA
AAC	131.6			
IB	147.7	0.026	0.010	0.250
PLA	180.3			

AAC, acetaminophen 250 mg, acetylsalicylic acid 250 mg, caffeine 65 mg per tablet; IB, ibuprofen 200 mg per tablet; PLA, placebo.

Background: Many migraineurs use only nonprescription medications, but their effectiveness is not well understood in patients whose attacks feature the most severe migraine pain. We compared two widely used nonprescription agents in a patient population representing the full spectrum of migraine, including patients who require bed rest and/or vomit frequently.

Methods: Subjects (n=1555) with ICHD-2 migraine were included in a multicenter, double-blind, randomized, parallel-group, placebo-controlled, single-dose study. No patients were excluded due to severity of symptoms or degree of disability. They were randomized to receive a single two-tablet dose of either (1) acetaminophen 250 mg, acetylsalicylic acid 250 mg, and caffeine 65 mg per tablet (AAC); (2) ibuprofen 200 mg per tablet (IB); or (3) placebo (PLA). The subset of 660 migraineurs whose treated attack had severe pain was extracted for post hoc analysis.

Results: At most time points, AAC and IB relieved the severe pain and associated symptoms of migraine significantly better than PLA. AAC was significantly better than PLA for mean pain relief (PAR) from 45 minutes through 4 hours ($p \leq 0.004$); mean pain intensity difference (PID) from 45 minutes through 4 hours ($p \leq 0.006$); % headache response (HR) from 90 minutes through 4 hours ($p \leq 0.013$); % pain-free at 3 and 4 hours ($p \leq 0.003$); functional disability (FD) % reduced to little or none from 1 through 4 hours ($p \leq 0.005$); % free from nausea at 2 hours ($p=0.049$), from phonophobia from 90 minutes through 4 hours ($p \leq 0.007$), and from photophobia at 2, 3, and 4 hours ($p \leq 0.036$); % used rescue medication over the 4 hours ($p=0.018$); and time to meaningful relief (132 minutes vs 180 minutes, $p=0.010$). AAC was significantly superior to IB for mean PAR at 45 minutes and at 1, 2, 3, and 4 hours ($p<0.04$); mean PID from 60 minutes through 3 hours ($p<0.05$); % HR at 2 hours ($p=0.04$); FD % reduced to little or none at 3 hours ($p=0.013$); % free from phonophobia at 3 hours ($p=0.04$) and from photophobia at 15 minutes ($p=0.03$); and % used rescue medication over the 4 hours ($p<0.001$). Compared with IB patients, AAC patients also reported significantly faster meaningful relief (132 minutes vs 148 minutes, $p=0.026$; Fig 1).

Conclusions: In patients with severe migraine pain, AAC and IB are significantly more effective than PLA, and AAC provides significantly faster and more effective relief than IB.

P27

Withdrawn by the author.

P28

A Breath-Synchronized Pressurized Metered Dose Inhaler as a Delivery System for Migraine Treatment

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Objectives: The TEMPO® inhaler differs from traditional press-and-breathe pressurized metered dose inhalers (pMDIs) and healthcare practitioners may not be aware of these differences and the potential use of oral inhalation in the treatment of migraine.

Background: Oral inhalation offers advantages as a route of administration for the treatment of migraine compared with IV and oral administration. Oral inhalation is non-invasive and inhalers are portable and don't require visits

to the ER or a physician's office for administration. Additionally, the lung provides a large absorptive surface area and a highly permeable membrane in the alveolar region to allow for rapid absorption of drug into the systemic circulation, avoiding hepatic first-pass metabolism. A breath-synchronized pMDI, the TEMPO inhaler, has been developed as an investigational drug product for the delivery of dihydroergotamine (DHE) to treat migraine in adults (MAP0004).

Methods: The TEMPO inhaler differs from traditional pMDIs in that it is breath-synchronized, using the patient's inhalation maneuver to trigger the release of drug. Once the patient's inspiratory pressure exceeds the triggering threshold (~18-20 mbar), a cradle assembly depresses a pressurized canister filled with DHE suspended in propellant, dispensing the drug in an aerosol. Breath-synchronization eliminates the coordination requirements of traditional pMDIs where the patient must manually depress the pMDI canister while simultaneously synchronizing the release of drug with a deep inhalation. Poor coordination between actuation and inhalation may result in a small percentage of drug reaching the lung, as the majority of the aerosol plume impacts in the oropharynx and is swallowed. The internal flow control chamber (FCC) in the TEMPO inhaler replaces add-on spacer devices used to reduce plume velocity and minimize oropharyngeal deposition often seen with traditional pMDIs. The FCC creates a vortex that suspends and slows down the discharged aerosol plume. This allows drug particles to be entrained within the patient's inhaled airflow and bypass the larynx and deposit in the lung periphery.

Results: The TEMPO inhaler generates a highly reproducible mass of aerosol within the fine particle range of 1-5 mm (mean = 2.8 mm), which is optimal for peripheral lung deposition. Data from 4 clinical lots of MAP0004 (DHE in the TEMPO inhaler) studied in adult migraineurs demonstrate a reproducible emitted mass of DHE. This, coupled with reduced oropharyngeal deposition and a highly respirable aerosol plume, results in a reproducible mass of DHE reaching the lung periphery where it can be rapidly absorbed into the systemic circulation.

Conclusions: The TEMPO inhaler is a novel delivery system for migraine therapies as it is able to generate and release an aerosol plume consisting of highly respirable particles that is coordinated with a patient's inhalation, reducing oropharyngeal deposition and promoting drug deposition in the lung periphery for a more homogenous distribution throughout the lungs.

P29

The Efficacy of Acupressure on the P6 Antiemetic Point: Relief of Migraine-Related Nausea

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Objectives: The aim of the trial was to evaluate the efficacy of acupressure on the P6 point for the amelioration of migraine related-nausea.

Background: After head pain, nausea is one of the most debilitating symptoms of migraine.

Methods: 41 Patients, 39 female and 2 male, participated in the trial. The participants' average age was 47 years. They had been suffering from migraines for on average 26 years and had experienced an average of 33,1 migraine days over the previous three months. The average migraine pain intensity was 7,1 on a score from 0 (no pain) to 10 (strongest pain); the average intensity of nausea was 6,2 on a score from 0 (no nausea) to 10 (severest nausea). Patients were instructed to use the SEA-Band acupressure bands instead of taking antiemetics during their next migraine attack and to complete and return a migraine attack diary.

Results: After using the acupressure band, 34 (83%) patients noticed a reduction of nausea. Reported nausea after therapy was 2,9 on the 10-point scale from 1 (significantly weaker) to 10 (significantly stronger). Eighteen patients (44%) reported that their nausea was significantly weaker. The relief of nausea was reported after an average of 28.7 minutes. The average duration of the migraine attacks was 21,5 hours. The Sea-Band was worn on average for 17.9 hours. Forty patients (98%) reported that they would use Sea-Band during migraine attacks again.

Conclusions: Results show, that the use of an acupressure band can reduce migraine-related nausea. The advantage of this therapy is that it is drug-free and has no risks or side-effects such as dizziness or tiredness. Its effect is rapid, and it is easy and inexpensive to use. A randomized trial comparing drug treatment and acupressure is warranted.

P30

Migraines Induced by Toothaches

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Objectives: Case report.

Background: Migraine- a neurovascular headache is mostly accompanied by phonophobia, photophobia, nausea, and scalp allodynia. Known triggers include food, hormonal changes, stress, abnormal sleep, and drugs. Migraine triggered by tooth pain is clinical observation with minimal literature support.This article describes two cases of migraines induced by toothaches, both which were completely relieved by a dose of triptans. The episodes failed to recur once the offending tooth was treated.

Methods: Case Report 1: A 40-year-old female patient presented with chief complaints of pain in right face with concomitant headaches and no prior history of migraine. History of composite restoration (two months ago) with subsequent tenderness and periapical pathology and progressed to headache over 3 days. Onset as "sensitivity" on the upper right front teeth (6, 7, 8) which progressed to headache over 2-3 days, throbbing right-sided headache with a pain level of 8/10 with scalp allodynia, photophobia, and nausea. Pain radiated from upper right tooth to eye, ear, and right side of the head. Diagnostic block of tooth #7 reduced "toothache" by 90% but not other pains.

Since she complained of chest pain with worst headache ever, patient was referred to Emergency Room.Intranasal Sumatriptan administered there reduced pain to 1/10 in approximately 6 minutes. Root canal treatment done, no more migraine attacks reported.

Case Report 2: A 26-year-old female patient had chief complaint of pain in upper left posterior tooth. Pain started two days ago as migraine with classic symptoms with "pulsating/throbbing" quality for both tooth and headache. Radiograph confirmed pathology on palatal root of tooth #14. Local anesthetic blockade reduced "toothache" by approximately 90% and intranasal sumatriptan 10 mg brought headache to 1/10 in 10 minutes. Endodontic treatment of tooth #14 completed & no further migraines headaches reported as of four month follow up.

Results: Discussion: As described earlier there are known triggers for migraine, it may mimic such other pains as toothaches.

Trigeminal vascular model proposed by Moskowitz suggests the involvement of trigeminal nerve in pain distribution of migraine. Increased excitability to stimuli within the trigeminal nerve distribution has been implicated in the pathophysiology of migraine. Role of trigeminal neuronal nociceptive activity is known.

Conclusions: Odontogenic pain has been reported to occur with migraines but causal/contributory effect of toothache as a trigger needs further study.

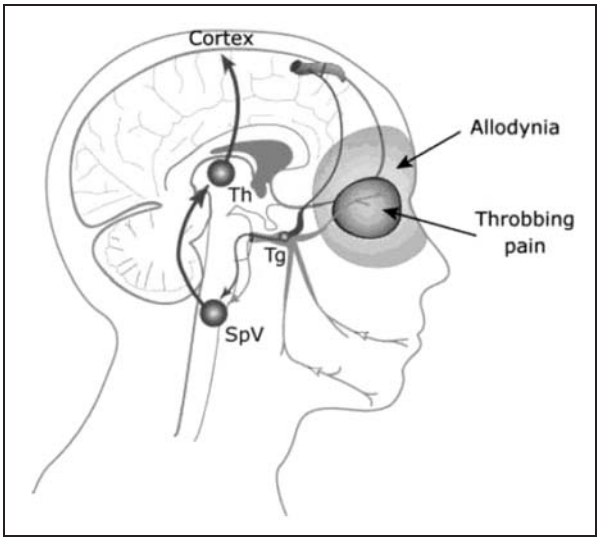


Figure 1. Trigeminovascular Pain Pathway of Migraine. Tg = Trigeminal Ganglion; SpV = Spinal Trigeminal Nucleus; Th = Thalamic Nuclei From Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of pain and strain of migraine. *J Comp Neurol.* 2005; 493:914, with permission.

P31

Sleep Duration and Sleep Disturbance in Chronic Daily Headache: Results from Korean Sleep-Headache Study

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Objectives: To assess the relationship between sleep duration and sleep disturbances in individuals with chronic daily headache (CDH).

Background: Sleep disturbance is a common complaint among individuals with CDH. Sleep disturbance and sleep duration are reported to be closely related. However, the sleep disturbances of CDH regarding sleep duration were not reported yet.

Methods: We selected a stratified random population sample of Koreans aged 19-69 and evaluated them with a 60-item semi-structured interview designed to identify headache type, sleep duration and sleep disturbances. We assessed weekday (WD) and weekend (WE) sleep durations. We also investigated sleep disturbances such as daytime sleepiness, insomnia, sleep apnea using Epworth sleepiness scale (ESS), insomnia severity index (ISI), Berlin questionnaire (BQ), respectively. We defined a CDH subjects if a subject reported experiencing headache more than 15 days per month for more than 3 months during the previous year.

Results: Of 2762 participants, the 1-year prevalence of episodic headache (EH) and CDH were 45.5% and 1.7%, respectively. WD sleep durations were not significantly different between EH and CDH groups (p=0.716). CDH group showed higher ESS score (7.8±5.7 vs. 6.1±4.0, p<0.001), higher ISI score (8.1±7.1 vs. 5.0±5.3, p<0.001) and higher sleep apnea risk (≥2 categories in BQ, 11.3%. vs. 5.2%, p<0.001) comparing to EH groups. WE sleep durations were not significantly different among 3 groups (p=0.54).

Conclusions: Although sleep durations were not significantly different between EH and CDH groups, individuals with CDH reported more daytime sleepiness, more insomnia and more sleep apnea comparing to individuals with EH.

P32

Clinical and Demographical Characteristics of Patients with Medication Overuse Headache in Argentina and Chile: Analysis of Latin American Section of COMOESTAS Project (Continuous Monitoring of Medication Overuse Headache in Europe and Latin America: Development and Standardization of an Alert and Decision Support System)

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Objectives: To describe the clinical and demographics characteristics of 240 patients enrolled in COMOESTAS study in Latin American section.

Background: European and U.S studies show that MOH preferentially affects women (3.5:1) in their 40s and the primary headache is migraine in 65% of cases. The average time is 20.4 years since headaches onset, 10.3 years of medication overuse and 5.9 years of chronic daily headache. In these countries the overused medications changed over the past two decades: MOH due to ergotamines decreased and abuse of triptans, simple analgesics and combination medications increased. High frequency of both pain episodes and use of medication, use of more than one type of drug, chronic backache, higher levels of emotional stress and low level of pain tolerance are all associated with MOH. Recently, an association with sleep disorders has been recognized.

Methods: The Latin American section of COMOESTAS project started working in 2008. The global project has the objective to evaluate the impact of a communicational platform in the management of these patients.

110 patients were recruited in Chile and 130 in Argentina. A neurologist who confirmed MOH diagnosis interviewed all of them. History of habits, family and personal medical history were taken. General and neurological exams were performed.

Results: Mean patient age was 38.6 years, 80% were women. Mean time since headaches onset was 21 years and 3.86 years for duration of medications overuse. Previous diagnoses were migraine without aura: 77.5% and migraine with aura: 18.8%. 57% of the patients reported emotional stress related to family, work or other causes; 56% reported insomnia. Most overused medications were acute drug combinations containing ergotamine (70%), NSAIDS (33.8%) and triptans (5.4%).

Conclusions: Our study with Latin American patients shows three differences with the reported European and US studies. Migraine had a higher prevalence as a primary headache. Ergotamine is more frequently abused. Medication overuse time is significantly shorter, even tough the time since headache onset is the same. Ergotamine containing medications are the cheapest and more available headache treatment in our countries. This could explain both the higher migraine incidence as primary previous headache as its high abuse frequency. The current overused drugs profile in Latin America is similar to what Europe and US use to have two decades ago. Changing this situation is one of our priorities.

P33

Obesity in Children with Chronic Daily Headaches: Association with Headache Type and Disability

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Objectives: To examine the association between obesity and chronic daily headaches in children, and the relation to headache type and disability.

Background: The association between obesity and headache has been well-established in adults, but only a few studies have examined this association in children.

Methods: The authors retrospectively evaluated 102 children with chronic daily headaches from their Pediatric Neurology Clinic. Data regarding age, gender, headache type, duration and disability, along with height and weight were collected. Body mass index (BMI) was calculated, and percentiles were determined for age and sex. Headache type and disability were compared between normal weight, at risk for overweight and overweight children.

Results: A higher prevalence (39.2%) of obesity was found in the whole study group compared to the general population. The diagnosis of transformed migraine, but not of chronic tension type headache, was significantly associated with being at risk for overweight (OR=2.41, 95% CI 1.21-4.67, P=0.01) or overweight (OR=2.32, 95% CI 1.1-5.56, P=0.04). Regardless of headache type, a high BMI percentile was associated with increased headache disability and overuse of medications, but not with duration of attacks.

Conclusions: Obesity and CDH in children are associated. Although obesity seems to be a risk factor for transformed migraine more than for chronic tension type headache, it is associated with increased headache disability and medication overuse regardless of headache type.

P34

Prognostic Factors in the Treatment of Chronic Daily Headache: 6-Month Prospective, Face-to-Face, Follow-Up Study

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Objectives: To investigate the prognostic factors that might effect the responsiveness to the preventive treatment of CDH in a 6-month, prospective, face-to-face, follow-up study.

Background: Prognostic factors might impact chronic daily headache treatment.

Methods: Patients were recruited from headache outpatient clinic and evaluated by headache experts according to the ICHD-II criteria. Of those who diagnosed as CDH, both chronic migraine (+medication overuse headache) (CM) and chronic tension-type headache (+medication overuse headache) (CTTH) included in the study. Subjects were given preventive treatment according to their CDH type and general health status. Follow-up visits were scheduled for the 1st, 3rd and 6th months. At the first visit a questionnaire including demographic characteristics, patient history, drugs they are still using, life style characteristics, headache characteristics and body mass index was answered by the subjects. A total of 130 parameters were evaluated. All subjects were given headache diaries and asked to record required data. Face-to-face evaluation was made at every follow-up visit. A decrease $\geq$50% in headache days was accepted as a succesfull treatment. $p \leq 0.05$ was accepted significant.

Results: 108 subjects were included in the study between September 2010 and February 2011. Of those 97 (89.8%) were women (mean age: 41.8$\pm$11) and 11 men (10.2%) (mean age: 40.0$\pm$10.8). 75 of the subjects diagnosed as CM and 33 as CTTH. 64 (59.2%) subjects ended up the study by coming the last follow-up visit at month 6.

An interim analysis at month 3 and final analysis at month 6 were made. In CM subjects' successful treatment rate was 70.4% and 81% at month 3 and 6 respectively. Treatment rate was 50% in CTTH sufferers both at month 3 and 6. In the total CDH group smokers ($p \leq 0.03$) and subjects suffering from headache between 15 and 20 days/month ($p \leq 0.01$) responded better to the treatment at month 3. Smoking ($p=0.04$), mediterrenean diet ($p \leq 0.01$) and less tea consuming (less than 4 cups/day) ($p=0.04$) suggested a better prognosis at month 6. At month 3 in the CM group employed subjects ($p=0.02$), subjects suffering headache between 15-20 days/month ($p=0.04$) and headache history less than 10 years ($p=0.04$) showed better response to the treatment. At month 6 there was not any significant difference between responders and non-responders in the CM group. In CTTH group there was not any significant difference between responders and non-responders both at month 3 and 6.

Conclusions: Smoking, mediterrenean diet and less tea consuming suggested a better prognosis in the treatment of CDH. In CM group employment, less headache days and history of headache less than 10 years were the prognostic

factors suggesting a better response to treatment at month 3. In CTTH group none of the parameters suggested a better response both at month 3 and 6. Also in this group treatment rates were lower compared to CM group.

P35

Idiopathic Hypertrophic Cranial Pachymeningitis: A Rare Cause of Chronic Headache and Progressive Cranial Neuropathies: A Case Report

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Objectives: We report a rare case of a 75-year-old male presented with chronic daily headache for more than one year and later on developed deafness, vocal cord paralysis, ophthalmoplegia, and loss of vision. On physical examination, there was ptosis and left gaze palsy, pale optic disc, only light perception on both eyes, weak gag reflex and gross hearing loss.

Background: Idiopathic hypertrophic pachymeningitis is a rare chronic fibrosing inflammatory disease characterized by marked diffuse thickening of the cranial dura that causes progressive neurological deficits by compression of anatomic structures by the meninx, thickened by inflammation. Headache is probably related to dural inflammation.

Methods: Work up included cranial MRI that revealed abnormal pachymeningeal enhancement or thickening of the dura in the posterior fossa, cavernous sinus and orbital apex and bilateral mastoiditis. CSF analysis showed elevated CSF protein, negative results for AFB, KOH, VDRL, TB PCR and bacterial culture, and no malignant cells. ANCA, ANA and RF were negative. Search for occult malignancies was negative. There was elevated ESR, consistent with an inflammatory process.Based on MRI, and having ruled out infectious, neoplastic, collagen/vascular disease as a cause of pachymeningeal enhancement, our diagnosis was Idiopathic hypertrophic pachymeningitis.

Results: After initiation of pulse corticosteroid therapy, methotrexate and maintenance prednisone, there was remarkable improvement on hearing, swallowing, and ocular muscle movement, less headaches and marked regression of pachymeningeal enhancement on repeat MRI. However, profound vision loss remained unchanged.

Conclusions: A high index of suspicion and recognition of this rare disease is important because early institution and long-term maintenance of steroid may result to complete or partial remission of the neurologic deficits and may help prevent irreversible neurologic sequelae, especially blindness.

P36

Polysomnographic Characteristics of Sleep in Patients with Sleep Disorders Who Also Have Headaches

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Objectives: The objective of this retrospective study was to see whether any differences in polysomnography exist between those patients who have sleep disorders without headache, and those who have sleep disorders and who also have headaches of various types.

Background: Recent research in the field of headache has focused on the relationship between headache and sleep disorders, mostly with sleep disordered breathing. We wanted to investigate whether any specific differences exist between PSG's of patients with and without headache.

Methods: A cohort of 621 patients (210 male and 411 female) who presented to a Midwestern neurology institute sleep disorders center over the course of one year for diagnostic polysomnography were studied retrospectively. One hundred fifty three (153) patients with unclassified headaches were excluded from the analysis.

Two hundred fifty seven (257) patients did not have a headache diagnosis and were used as the control group from which patients with the following diagnoses were compared; Chronic Daily Headache (CDH), Migraine with Aura, and Migraine without Aura. There were some patients with dual diagnoses, but each group was looked at individually.

Results: The group was made up of the following with regard to gender: Chronic Daily Headache: 17 male, 98 female; Migraine with aura: 19 male, 86 female; Migraine without aura: 8 male, 63 female; No headache diagnosis: 121 male, 136 female.

Conclusions:
1. Headache is common in patients with sleep disorders.

2. No striking differences among the polysomnograms of the headache subtypes of Chronic Daily Headache, Migraine without Aura, and Migraine with Aura were seen, though a large number of patients with uncharacterized headache remains a limitation of this study.

3. A follow-up study of the response of patients with headache to treatment of their sleep disorders will hopefully shed some further light on the relationship of sleep disorders and headache.

	No Headache Diagnosis	Chronic Daily Headache	Migraine without Aura	Migraine with Aura
WASO (minutes)	86.1	68.9	59.2	56.3
RERA Index (events/hour)	23.7	27.8	24.2	30.1
AHI (events/hour)	14.7	5.0	7.5	4.6
R-R Intervals >10 beats/minute	70.4	69.0	70.1	68.4
Stage Wake %	18.1	15.4	13.8	12.6

P37

Manual Therapies for Chronic Primary Headaches: A Systematic Review

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Objectives: This paper systematically reviewed randomized clinical trials (RCTs) assessing the efficacy of manual therapies for chronic primary headaches.

Background: About 3% of the general population suffers from chronic headache which has significant health, economic and social costs. We reviewed papers on manual therapies for chronic primary headache.

Methods: The literature search was done on CINHAL, Cochrane, Medline, Ovid and PubMed. All RCT written in English using either of the manual therapies for chronic migraine or chronic tension-type headache (CTTH) were evaluated. Headache diagnoses were preferentially classified according to the criteria of the International Headache Societies II and relevant revisions. The methodology of each study was evaluated, covering study population, intervention, measurement of effect, data presentation and analysis. The maximum score was 100 points, and $\geq$50 points was considered to be methodology of good quality.

Results: RCTs on manual therapies for chronic migraine or chronic TTH reveals favourable effect i.e. massage therapy (MT), physiotherapy (PT), osteopathic intervention (OI) and spinal manipulative therapy (SMT). A MT study showed statistical significant improvement in headache intensity post-treatment and follow-up as compared to control for CTTH ($p<0.05$), while a PT study also showed statistical significant improvement in headache intensity at follow-up for CTTH ($p<0.001$). Number of headache days was statistically significant improved in an OI study as compared to control at follow-up for CTTH (0=0.016), while mean headache intensity reduced the last 4 weeks of treatment and follow-up by 40% and 42% in a SMT study for chronic migraine. A precise review on manual therapies for chronic primary headache applying rigorous criteria will however, be presented at the congress.

Conclusions: Manuel therapy show efficacy in the management of CTTH and chronic migraine.

P38

Medication Overuse for Treatment of Acute Migraine Attacks as Predictable Cause of Development of Status Migrainosus

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Objectives: The aim of this paper is to determine what medication, used for the treatment of migraine attacks, is the most frequent cause of status migrainosus when being overused.

Background: Numerous studies have revealed that medication overuse to stop migraine headaches may provoke chronic headaches. It is also known that medication abuse may provoke prolonged migraine headaches – status migrainosus.

Methods: Unsponsored, prospective study lasted 18 months. It involved 127 patients (F:M= 89:38 of age 36 $\pm$ 16) who reported to the Emergency Room of the Headache Centre with status migrainosus and fulfilled

the criteria for chronic headaches caused by medication overuse in order to treat frequent migraine attacks. The IHS criteria for status migrenosus and chronic headaches caused by medication overuse (IHS 2004) were applied. 92 subjects who overused one medication were divided into 7 groups according to the medication type (Caffetin=[paracetamol+propyphenazone+coffein+codeine], Diclofenac, Acetylsalicylate, Sumatriptan, Nimesulide, Paracetamol and Ibuprofen). 35 patients who overused two or more medications were also divided according to the type of medications into 3 groups (Caffetin=[paracetamol+propyphenazone+ coffein+codeine]+ Diclofenac, Caffetin=[paracetamol +propyphenazone+ coffein+codeine]+Ketoprofen and Diclofenac+ Paracetamol).

Results: Out of the total of 92 patients who overused one medication 56 patients (60.87%) used Caffetin. Out of 35 patients who overused 2 medications 23 patients (65.71%) used the combination Caffetin=paracetamol +propyphenazone+coffein+codeine]+Diclofenac. Both in subjects who used one medication ($p<0.01$) and those who used 2 medications ($p<0.01$), statistically high differences between overused medications were detected, causing status migrainosus.

Conclusions: The study reveals that status migrainosus due to medication overuse is most frequently caused by the overuse of Caffetin=[paracetamol+propyphenazone+coffein+codeine] administered as mono treatment and in combination with another medication.

Keywords: migraine, status migrainosus, medication overuse, Caffetin.

P39

A Multidisciplinary Approach for the Management of a High-Risk, Opioid Dependent Chronic Orofacial Pain Patient Using High Dose Opioid Therapy. A Case Report

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Objectives: The objective of this abstract is to describe the case of a 21 year old female who visited our pain center witha chief complaint of daily facial pain and headaches.

Background: Despite all improvements in our knowledge and understanding of the pathophysiology of chronic facial pain, there are still many questions that have not been answered adequately regarding the optimal treatment that should be applied in chronic pain patients.

Methods: When the patient presented to our clinic she was treated for chronic daily headaches and migraines primarily with pharmacologic means. She also had a diagnosis of fibromylagia accompanied by psychiatric comorbidities.

The treatment regimen at the time of the initial evaluation included Oxycodone / Acetaminophen (10/325, q 6 hrs, 1 1/2 years), Cyclobenzaprine (10 mg, q 8 hrs, intermittently for 3 years), Celecoxib (200 mg bid, 6 months to one year), Diazepam (10 qd, 4 years), Escitalopram (10 mg qd, 4 years) and Acetaminophen/Aspirin/Caffeine (3-4 a day, 1 1/2 years). Sumatriptan, Sertraline hydrochloride and Bupropion had also been tried, but had all failed to provide any degree of relief. Non-pharmacologic interventions included chiropractic treatment and massage therapy, again without any therapeutical effect.

Results: After the patient's first visit, the initial diagnostic impression was myofascial pain disorder, and possible medication overuse headache. Secondarily, she had a psychiatric diagnosis of major depression and substance use disorder.

According to the classification of the American Academy of Orofacial Pain, the patient met criteria for centrally mediated myalgia, which is a possible result of a prolonged nociceptive input into the CNS. In addition, she met criteria for probable medication-overuse headache according to the classification of the International Headache Society (IHS), as well as DSM IV TR criteria for a major depression disorder and substance use disorder. Her affective symptoms had been continuously present for months and included depressed mood, anhedonia, restless sleep, fatigue, feelings of guilt, thoughts of suicide, and difficulty in functioning due to impaired concentration.

It was concluded that management of her possible substance uses issues and medication regimen were priorities. She was referred to an inpatient detoxification unit with an admission, and then followed with additional treatment recommendations.

Conclusions: This case report emphasizes the fact that long term treatment with high dose opioids could in many cases have an adverse effect on treatment and complicate the patient's clinical diagnosis. Prior to deciding on treatment modalities, the clinician should first appreciate the effect of the opioids on the overall symptomatology and make conclusions accordingly.

P40

*In*cidence of Chronic Headache Diagnoses and Etiologies at Altitude

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Objectives: Establish the incidence of chronic headache diagnoses and etiologies in patients at altitude.

Background: Introduction:

The prevalence of chronic headache is approximately 4%. Women are affected three times more often than men. The majority patients suffer from either chronic tension-type headache, chronic migraine, or medication overuse headache.

Methods: Descriptive study cohort, cross the adult population attended during February, March and April 2013, in outpatient internal medicine at Hospital de Clínicas, La Paz Bolivia.

Inclusion criteria:

Chronic headache is encompasses several different specific headache diagnoses characterized by frequent headaches.

Men and women from age 14.

Exclusion criteria

Under 14 years.

P41

Physical Therapy Management for Chronic Headaches

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Objectives: The challenges of managing patients with chronic headaches (CH) are well known. The faculty physical therapy (PT) practice at the University of Southern California (USC) works closely with USC's Division of Neurology in the treatment of patients with CH. The purpose of this presentation is to describe the role of PT in the management of patients with CH.

Background: Primary goals of PT are to improve the patients' self-management strategies, reduce the severity and frequency of headaches and identify postural dysfunction and other triggers that contribute to their headaches. Therapists develop an individualized treatment program that will improve posture and body mechanics thereby improving patients' tolerance for work, home and recreational activities.

Methods: Comprehensive PT treatment is centered around self-management to empower patients to utilize awareness of triggers, ideal movement strategies, and individualized exercises to manage headaches. Through patient education patients can recognize and manage musculoskeletal, stress and fatigue-related triggers and utilize proper ergonomics, posture and movement strategies.

Poor posture is often associated with over-activation of musculature which can trigger pain into the head. Postural endurance therefore focuses on improving the balance of muscle function in the neck and trunk.

Movement re-education improves muscular efficiency by using optimal movement strategies during daily activities. Compensatory movement patterns can contribute to prolonged pain and muscle imbalance leading to chronicity.

Spinal mobilization techniques help improve thoracic and cervical mobility as decreased mobility in these regions can hinder achievement of pain-free range of motion and refer pain into the head. Desensitizing myofascial trigger points can further decrease pain and improve tolerance to movement re-education and strengthening.

Results: PATIENT CASE A 27-year-old female came to PT with a 13-year history of headaches and a 2-year history of CH diagnosed as Occipital Neuralgia and Chronic Migraines. Medications include Depakote, Migrelief, Relpax and Botox.

After 30 sessions over 5 months her HIT-6 score improved by 9 points and average headache intensity decreased by 50% eliminating the need to take any days off work during her last two months of treatment (see table).

Conclusions: In conclusion we believe the addition of PT can improve the quality of life in patients with CH. Furthermore, emerging research has shown that spinal manipulation techniques play a role in changing cortical excitability (CE) within the brain. Since differences in CE have been demonstrated in patients with chronic migraines, this would be an interesting research direction. Future research is also needed to determine who would

benefit most from PT and describing the mechanisms by which PT helps.

	Cervical Right rotation (degrees)	Cervical Left rotation (degrees)	Number of missed Days per month	Average Headache Intensity	HIT -6	Deep Cervical Flexor Endurance (sec)	Deep Cervical Extensor Endurance (sec)
Initial	45 w/ head pain	70	2	8/10	70/76	0	7
Discharge	70	70	0	4/10	61/76	15	35

P42

Exploring the Border-Zone between Episodic Migraine (EM) and Chronic Migraine (CM): An Examination of Medical Comorbidities in the US Population

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Objectives: To compare rates of medical comorbidities among three headache-frequency-dependent migraine subgroups: low frequency episodic migraine (LFEM): 0-9 days/month, high frequency episodic migraine (HFEM): 10-14 days/month, and CM: ≥15 days/month.

Background: EM is defined by migraine with <15 headache days per month; however, this may be a heterogeneous group when medical comorbidities are examined.

Methods: The American Migraine Prevalence and Prevention Study (AMPP) is a longitudinal, US-population-based study. The proportion of respondents with self-reported diagnoses of various cardiovascular and pulmonary risk factors and diseases (CVPRD) was assessed. Odds ratios (ORs) and 95% Wald confidence intervals (CIs) adjusted for age, sex and income were calculated comparing groups.

Results: Of 18,500 study respondents to the 2005 AMPP survey, 10,609 had LFEM, 640 had HFEM and 655 had CM. For nearly all CVPRD contrasts disease rates were not different between CM and HFEM. For example, 24.4% of those with CM had asthma compared to 22.0% with HFEM (OR=1.2, NS). This absence of difference was true for bronchitis, chronic obstructive pulmonary disease (COPD), heart disease/angina, high blood pressure, and stroke. Individuals with CM had significantly higher rates of high cholesterol compared to HFEM (1.32 [1.03,1.69], p≤0.027). Both CM and HFEM had significantly higher rates of disease compared to LFEM, though CM significantly differed on more CVPRD contrasts than HFEM. Effects were adjusted for age, sex and income. Results of all contrasts for all groups will be presented and discussed.

Table 1. Pulmonary and Cardiac Comorbidity Profiles of Migraine Subsets.

Condition	HFEM N (%)	CM N (%)	CM vs. HFEM OR (95% CI), p value/significance
Asthma	141 (22.0)	160 (24.4)	1.2 (0.9,1.5)*
Bronchitis	102 (16.0)	126 (19.2)	1.2 (0.7,1.9)*
Emphysema/COPD	21 (3.3)	32 (4.9)	1.38 (0.78,2.44)*
Heart Disease/Angina	53 (8.3)	63 (9.6)	1.06 (0.72,1.58)*
High Blood Pressure	190 (29.7)	221 (33.7)	1.13 (0.88,1.45)*
High Cholesterol	174 (27.2)	224 (34.2)	1.32 (1.03,1.69), p≤0.027
Stroke	18 (2.8)	26 (4.0)	1.28 (0.69,2.38)*

*Indicates non-significance (NS).

Conclusions: The medical comorbidity profiles of HFEM have much in common with CM, suggesting that HFEM and CM may bear a close biological relationship. Detection bias may contribute to these findings.

P43

Exploring the Border-Zone between Episodic Migraine (EM) and Chronic Migraine (CM): An Examination of Psychiatric Comorbidities and Chronic Pain in the US Population

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Objectives: To compare rates of psychiatric comorbidities and chronic pain among three groups with migraine defined by headache day frequency: low frequency episodic migraine (LFEM): 0-9 days/month, high frequency episodic migraine (HFEM): 10-14 days/month, and CM: ≥15 days/month in a large, US population based sample.

Table. Psychiatric and Chronic Pain Comorbidity Profiles of Migraine Subsets.

Condition	LFEM N (%)	HFEM N (%)	CM N (%)	HFEM vs. LFEM OR(95% CI), p value	CM vs. LFEM OR (95% CI), p value	CM vs. HFEM OR (95% CI), p value/significance
Anxiety	1,993 (18.8)	177 (27.7)	198 (30.2)	1.59(1.33,1.91), p≤0.001	1.80 (1.51,2.15), p≤0.001	1.13 (0.88,1.44)*
Bipolar Disorder	298 (2.8)	26 (4.1)	30 (4.6)	1.23 (0.99,1.54), NS	1.56 (1.06,2.31), p=0.02	1.25 (0.93,1.67)*
Depression	1,767 (17.2)	162 (26.0)	192 (30.2)	1.62 (1.34,1.96), p≤0.001	2.00 (1.67,2.40), p≤0.001	1.23 (0.96,1.59)*
Chronic Pain	1,599 (15.1)	150 (23.4)	206 (31.5)	1.69 (1.39,2.05), p≤0.001	2.49 (2.08,2.97), p≤0.001	1.47 (1.14,1.89), p≤0.003

*Indicates non-significance (NS).

Background: EM is defined broadly by migraine with <15 headache days per month; however, this may be a heterogeneous group when parsed into low and high frequency EM. HFEM may have more in common with CM than with LFEM in terms of psychiatric comorbidities.

Methods: The American Migraine Prevalence and Prevention Study (AMPP) is a longitudinal, US-population-based study. Depression (Patient Health Questionnaire [PHQ-9]) and respondent self-report of having received a diagnosis of "nervousness or anxiety", "bipolar disorder/mania", and "chronic pain" were assessed. Odds ratios (ORs) and 95% Wald confidence intervals (CIs) adjusted for age, sex and income were calculated comparing headache frequency groups.

Results: Among 18,500 eligible study respondents age ≥18 to the 2005 AMPP survey, 10,609 had LFEM, 640 had HFEM and 655 had CM. The proportion of respondents with anxiety increased with headache frequency from (18.8% to 30.2%) and was significantly different between CM and LFEM but not between CM and HFEM. The same pattern was seen with depression and bipolar disorder in that rates increased with headache frequency and were significantly different between CM and LFEM, but not between CM and HFEM. Rates of chronic pain also increased across headache frequency groups (from 15.1% to 31.5%) and were significantly different among all three groups.

Conclusions: Those with CM have higher rates of psychiatric commodities and chronic pain than persons with EM; although in the case of psychiatric comorbidities, rates were not significantly different between CM and HFEM, suggesting that these two groups may have substantial biological overlap.

P44

Improving the Classification of Migraine Subtypes: An Empirical Approach Based on Latent Class Analysis

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Objectives: Utilize latent class analysis (LCA) to improve migraine classification, and validate classification accuracy by testing whether accuracy of prognosis improves after statistical classification.

Background: Current primary headache classification is symptom-based and uses somewhat arbitrary boundaries developed by expert consensus. Symptom profiles and headache frequency are used to distinguish chronic migraine (CM).

Methods: The AMPP study is a longitudinal, US population-based study. Surveys were mailed to a sample of 24,000 persons with severe headache identified in 2004 and followed annually until 2009. The analysis sample included those with ICHD-2 migraine, partitioned into episodic migraine (EM: <15 headache days/month) or CM (≥15 headache days/month), and probable migraine (PM). LCA identified 5 subgroups of migraine (taxa) using data on migraine symptom severity, average migraine pain intensity, headache-related disability, cutaneous allodynia, depression, and monthly headache and migraine days as 2005 taxa determinants. Validity of these taxa was examined by contrasting the rate of CM onset at follow-up.

Results: 2005 AMPP data were used for LCA and 2006-2009 data were used to assess taxa prognosis. 12,860 subjects were eligible for classification analysis (n=10,162

LFEM; n=601 HFEM, n=1,302 PM, n=795 CM). Of these, 3,152 (24.5%), 1,076 (8.4%), 3,896 (30.3%), 2,251 (17.5%) and 2485 (19.3%) were assigned to Taxon 1, 2, 3, 4 and 5, respectively. EM was the largest contributor to each taxa, constituting more than 80% of each taxon other than Taxon 2. Taxon 2 was enriched with the most severe spectrum of migraine including the highest concentrations of CM (28.4%) and HFEM (22.6%), while Taxon 5 represented the least severe end of the spectrum without CM and only 0.08% HFEM. Validity of taxon assignment was tested by the ability of taxon membership to predict prognosis. Membership in Taxon 2 predicted increased risk of progression to CM with only 78% of previously CM-free Taxon 2 remaining CM-free at follow-up, while 98% of Taxon 5 remained CM-free.

Conclusions: LCA extends traditional clinical syndrome-based diagnoses suggesting that the currently defined headache frequency boundary may be suboptimal. LCA can serve as a tool to parse phenotypic heterogeneity of natural subgroups possibly leading to migraine classification that more closely maps to homogeneous genotypes.

P45

Quadripulse Repetitive Transcranial Magnetic Stimulation on Visual Cortex for Chronic Migraine Prevention: A Pilot-Trial

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Objectives: To study in a pilot trial the effect of QP rTMS over the visual cortex in the preventive treatment of chronic migraine.

Background: Contrasting with episodic migraine, chronic migraine can be compared to a "never ending attack" (1) with normal habituation of visual-evoked cortical potentials (VEP) andan increaseof 1st block VEP amplitude suggesting heightened cortical preactivation levels(2).

Quadripulse repetitive transcranial magnetic stimulation (QP rTMS) is able to durably modify the excitability of the underlying cortex. QP rTMS with long interstimulus interval (ISI) has an inhibitory effect, thus reducing the amplitude of 1st block VEP (3).

Methods: We recruited 10 patients (mean age 45.5; 8F, 2M) suffering from chronic migraine (ICHD-2 1.5.1). Seven also fulfilled the diagnostic criteria for medication overuse headache (ICHD-2 8.2). All had stable preventive treatment for at least 2 months.

We applied QP rTMS with a 50ms ISI (4 pulses at 20 Hz every 5 s for 30 minutes) using a figure-of-eight coil over the visual cortex (Oz). The intensity of the stimulation was set at 80% of phospheneor 90% of motor thresholds. QP rTMS was applied twice a week for 4 weeks. Patients filled in a headache diary before, during and after treatment (T0=the month before QP rTMS; T1=during the 4 weeks of QP rTMS; T2=the month after QP rTMS).We evaluated depression and anxiety at T0 and T1 respectively with Beck's Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI-Y2).

Results: A majority of patients improved significantly after QP rTMS therapy. Migraine days decreased on average from 20/month at T0 to 11/month at T1 (-47%, $p<0.05$) and severe attacks were reduced by 54% ($p<0.05$). Forty % of patients were 50% responders while 70% reversed from the chronic to the episodic form of migraine. Acute medication intake was numerically decreased, but this just fall short of statistical significance. One month after QP rTMS (T2) the clinical improvement remained stable with an average 10.4 migraine days/month, i.e. 48% reduction compared to baseline ($p<0.05$). There were no adverse events. BDI and STAI scores were similar before and after treatment. Interestingly, medication overuse did not modify the response to QP rTMS therapy.

Conclusions: This pilot trial demonstrates for the first time that 2 weekly sessions of inhibitory QP rTMS can be effective in the preventive treatment of chronic migraine, with or without medication overuse. The therapy significantly reduced migraine days and 70% of patients reversed from chronic to episodic migraine. Moreover, inhibitory QP rTMS was devoid of any adverse effect. These results indicate that a large sham-controlled trial is worthwhile in chronic migraine.

P46

Exploring the Border-Zone between Episodic Migraine (EM) and Chronic Migraine (CM): An Examination of Sociodemographics and Headache-Related Disability in the US Population

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Objectives: To compare sociodemographics and headache-related disability among three groups with migraine defined by headache day frequency: low frequency episodic migraine (LFEM): 0-9 days/month, high frequency episodic migraine (HFEM): 10-14 days/month, and CM: ≥15 days/month in a large, US population based sample.

Background: EM is defined by migraine with <15 headache days per month; however, this may be a heterogeneous group if parsed into low and high frequency EM when examined by sociodemographics and headache-related disability. HFEM may have more in common with CM than with LFEM on several dimensions.

Methods: The American Migraine Prevalence and Prevention Study (AMPP) is a longitudinal, US-population-based study. Sociodemographic variables and headache-related disability (MIDAS questionnaire) were assessed. Odds ratios (ORs), rate ratios (RRs) and corresponding 95% Wald confidence intervals (CIs) were calculated comparing EM groups and CM. Analyses of current employment status were adjusted for age, sex and income. Ordered logistic regression was used to model annual household income. Negative binomial regression was used to model headache-related disability.

Results: Among 18,500 eligible study respondents age ≥18 to the 2005 AMPP survey, 10,609 had LFEM, 640 had HFEM and 655 had CM. In comparison with the LFEM group, those with HFEM and CM reported significantly lower household income levels ($p < 0.001$), were less likely to be employed full time ($p < 0.05$), and were more likely to be occupationally "disabled" ($p < 0.001$). When comparing the sociodemographic profile between HFEM and CM, there were no significant differences with regard to these characteristics. Headache-related disability was greatest for CM, lowest for LFEM and intermediate in HFEM. Respondents with CM were significantly more likely to miss days of work or school due to headache compared to LFEM (RR 4.67, 95%CI 3.52, 6.20; $p \leq 0.001$); but significant differences were not observed between HFEM and CM.

Conclusions: The impact and burden of migraine were similar in terms of sociodemographics and headache-related disability between individuals with CM and those with HFEM. Those with LFEM had significantly less headache-related disability and burden on several dimensions. The similarities between the HFEM and CM groups and their distinctions from the LFEM group, when coupled with the documented transitions between HFEM and CM suggest that these two groups may have substantial biological overlap.

P47

Withdrawn by the author.

P48

Improving Function by Targeting Function: Efficacy of an Interdisciplinary Outpatient Program

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Objectives: Determine efficacy of outpatient interdisciplinary program in improving function and quality of life after IV treatment for chronic migraine.

Background: We are unaware of previous studies evaluating structured interdisciplinary day treatment programs for chronic migraine without concurrent aggressive medical management of headaches. In light of changing healthcare parameters, research is needed to evaluate if a time limited program results in substantial reductions in pain, inactivity due to pain, emotional distress, and improved functional life activities.

Methods: All patients admitted for inpatient treatment with IV medications for chronic migraine were evaluated by a psychologist and physical therapist to select patients appropriate for a 12 day outpatient interdisciplinary program. Sixty patients (90% female; mean age = 43) with significant distress or impairment were enrolled. Treatment consisted of 60 hours of integrated physical therapy, occupational therapy, and cognitive behavioral therapy at an estimated cost of $12,000. Baseline data was collected upon admission to the program and after thee weeks of treatment. Domains evaluated included pain severity, interference by pain, depression, anxiety, activity levels, and patient perception of ability to self manage pain. Global measures of health were obtained using the 12-Item Short Form Survey (SF-12) the RAND Medical Outcomes Study.

Results: Nine paired-samples *t* tests were conducted to evaluate changes in biopsychosocial outcome measures with the Bonferroni Method employed to control for Type I error (Bonferroni $\alpha = .006$). Nine of nine outcome measures were statistically significant ($p < .001$). Furthermore, large effect sizes were found and ranged from .82 for decrease in pain level and improved perception of control over pain to 2.05 on the Canadian Outcomes Performance Measure.

Conclusions: Preliminary evidence supports that brief, cost-effective interventions for migraine sufferers can

improve biopsychosocial outcomes in the areas of pain perception, distress and performance measures.

Measure	Mean (SD) Pre	Mean (SD) Post	*p* Value	Effect Size d	n
Hours Resting	4.06 (2.91)	1.57 (1.27)	< .001	.87	35
Pain Rating	7.94 (2.70)	5.54 (2.86)	< .001	.82	35
Helpfulness of Pain Mgmt Techniques	3.60 (2.20)	8.17 (1.84)	< .001	1.47	35
Percpetion of Control of Pain	6.46 (2.73)	8.80 (2.17)	< .001	.82	35
Beck Depression Inventory - II	22.89 (11.47)	9.77 (9.30)	< .001	1.56	35
Beck Anxiety Inventroy	19.03 (12.29)	9.80 (9.11)	< .001	1.10	35
Perception of Physical Health	27.60 (8.11)	40.23 (10.83)	< .001	1.53	35
Perception of Mental Health	31.79 (7.94)	43.21 (8.53)	< .001	1.45	34
Canadian Outcome Performance Measure	2.85 (1.17)	6.93 (1.86)	< .001	2.05	40

P49

Day Hospital Withdrawal for Chronic Migraine with Medication Overuse: Results at 3 Years Follow-Up

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Objectives: Purpose of this study was to determine the clinical course of a sample of chronic migraine patients with medication overuse 3 years after day hospital withdrawal.

Background: Patients with chronic headache and medication overuse are particularly difficult to treat, with no one approach being universally accepted. Some type of withdrawal program, however, is typically implemented before beginning a pharmacological prophylaxis treatment. Different withdrawal modalities have been performed for managing these patients: at first step, in-patient withdrawal has been confirmed effective in preceding clinical experiences. In recent years new modalities for withdrawal have been developed as day-hospital setting withdrawal.

Methods: A group of 202 patients were treated. Patients were suffering from chronic migraine with medication overuse according with IHS criteria. All patients were submitted to a day hospital withdrawal and then they were followed with meetings every 3 months until the first year and then every 6 months until the last follow-up 3 years after withdrawal.

Results: Eighty patients achieved the last follow-up meeting 3 years after withdrawal. Patients clinically improved: days of headache per month decreased significantly from 22.8 (SD 5.8), at baseline to 7.8 (SD 4.9); consumption of medications per month decreased significantly too from 26.7 (SD 19.9) to 7.4 (SD 5.0) at the last follow-up.

Conclusions: From these results the day hospital setting for withdrawal, followed by periodic clinical meetings, seems to be effective for this category of patients to improve significantly at long-term headache frequency and analgesics intake.

P50

Association of Brain Volume and Cognition in the Chronic and Episodic Migraine Patients

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Objectives: To study the association of the Brain Volume and Cognition in the Chronic and Episodic Migraine Patients.

Background: There are controversies about migraine's benign nature and chronic migraine's damage to the central nervous system. All these questions lead us to study the correlation between cognitive functions and cortical-subcortical brain volume in migraine patients.

Methods: Forty patients (20 episodic migraine and 20 chronic migraine), diagnosed according to ICHD 2004, and 20 control cases are included in the study. Neuropsychological tests were applied and bilateral cranial subcortical volumes were measured with automatic segmentation method in all cases.

Results: Left hippocampus and right amygdala were atrophic while left lateral ventricle volume was larger in

chronic migraine group as compared to episodic group and control. The attention test scores were statistically lower in the episodic and chronic migraine patients than the control cases. Decreased brain volume and low scores in neuropsychological tests in migraine patients showed positive correlation with the duration of migraine disease and number of days with pain.

Conclusions: There is no study in the literature about brain volume using automatic segmentation method in migraine patients and its association with cognition status. Our findings about presence of brain volume changes and attention deficits are in line with the previous literature findings stating attention problems and brain volume changes in the migraine patients.

P51

Low Vitamin D Levels in Migraine

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Objectives: Assessing the levels of vitamin d in patients with migraine.

Background: Vitamin D is a lipid soluble vitamin that acts as a hormone, it is involved in the regulation of cell growth and metabolism, insulin resistance, endothelial dysfunction, modulation of immune function, and inflammation reduction. Hypovitaminosis D has been linked to several disorders including hypertension, diabetes mellitus, depression, multiple sclerosis, metabolic syndrome, and cancer. Low levels of 25 (OH) vitamin D have been found in chronic pain disorders such as musculoskeletal pain, headaches, fibromyalgia, but limited information in migraine is available.

Methods: Migraine patients and controls were consecutive recruited from June 2011 to December 2012, 298 individuals were included, and signed informed consent. Individuals were divided in 3 groups: healthy controls (79), episodic migraine (128), and chronic migraine (91), diagnosis were made according to the International Classification of Headache Disorders. Serum 25-hydroxy-vitamin D levels were obtained in chemiluminescent immunoassay. Mean 25(OH) vitamin D levels were compared between groups, 2x2 analysis of different vitamin d cutt offs in 10 ng/ml, 20 ng/ml, and 30 ng/ml.

Results: Migraine patients overall had low 25(OH) vitamin D levels compared to controls (25,1 ng/ml +- 11,7 vs 27,3 ng/ml +- 8,6, p=0,03). Chronic migraine patients (22,9 ng/ml +- 11,2) had low levels compared to episodic migraine (26,1 ng/ml +- 11,0, p=0,004) and controls (27,3 ng/ml +- 8,6, p=0,003). Significantly more chronic migraine patients were below 20 ng/ml, compared to episodic migraine and controls ($p<0,001$), as well as episodic migraine vs controls ($p<0,001$).

Conclusions: Migraine is linked to hypovitaminosis D, Chronic migraine patients have even lower levels. Decrease in Vitamin D may be cause or consequence of migraine. Further studies are necessary to verify the role of vitamin D in migraine and other headache disorders.

P52

Increased CGRP Levels in Peripheral Blood as a Biomarker for Chronic Migraine

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Objectives: To test CGRP levels outside migraine attacks in peripheral blood as a potential biomarker for CM.

Background: In terms of frequency, migraine can be divided into two types: episodic (EM) and chronic (CM, $\geq$15 headache days/month). Around 2% of the population suffers from CM. During a migraine attack, activation of the trigemino-vascular system releases of vasoactive neuropeptides, especially calcitonin gene-related peptide (CGRP), and CM seems to be the result of sensitization of the pain pathways by repeated episodes of trigeminal activation. There is no available biomarker for any of the primary headaches, including migraine.

Methods: Women older than 17 and diagnosed as CM were recruited. Matched healthy women with no headache history and women with EM served as control groups, together with a series of patients with episodic cluster headache in a pain-free period. CGRP levels were determined in blood samples obtained from the right antecubital vein by ELISA outside a migraine attack and having taken no symptomatic medication the day before. Due to ethical reasons, preventatives were not stopped.

Results: We assessed plasma samples from 103 women with CM, 31 matched healthy women, 43 matched women with EM and 14 patients with episodic cluster headache matched for age. CGRP levels were significantly increased in CM (74.90 pg/ml) as compared to control healthy women (33.74 pg/ml), females with EM (46.37 pg/ml) and

episodic cluster headache patients (45.87 pg/ml). Thresholds of 43.45 and 58.22 pg/ml optimize the sensitivity and specificity to differentiate CM from healthy controls and episodic migraine, respectively In the CM group, CGRP levels were increased in women with a history of migraine with aura vs. those only experiencing migraine without aura. Variables such as age, analgesic overuse, depression, fibromyalgia, vascular risk factors, history of triptan consumption or kind of preventative treatment did not significantly influence CGRP levels.

Conclusions: Increased CGRP level measured in peripheral blood outside migraine attacks and in the absence of symptomatic medication seems to be a reliable marker for CM.

P53

Somatosensory High-Frequency Oscillations in Chronic Migraine

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Objectives: To assess how migraine chronification changes the activity of thalamo-cortical connections.

Background: The pathophysiology of chronic migraine (CM) is not completely clarified, but a crucial role was attributed to central sensitization mechanisms. Altered thalamo-cortical connections characterize migraine when still episodic and between attacks.

Methods: Seventeen episodic migraineurs (MO) between attacks and 18 chronic migraine (CM) patients underwent median-nerve somatosensory (SSEPs) (right stimulation, 500 sweeps, 4.4 repetition rate, 1.2 motor threshold). Patients groups were compared to a group of 20 healthy volunteers (HV) of comparable age and gender distribution. Digital filter (band-pass 450-750 Hz) was employed to extract 600Hz high-frequency oscillations (HFOs) superimposed on the conventional broad-band N20 SSEPs. Two phases of the HFOs were identified: an early which reflects the activity of the thalamo-cortical fibers, and a later which probably is generated by cortical pyramidal cells located in somatosensory area 3b.

Results: In CM the reduced early HFOs amplitude found in MO between attacks disappeared, showing a pattern similar to HVs. This early HFOs normalization was accompanied by a significant shortened latency of the negative oscillatory maximum ($p=0.01$). The amplitude of the late HFOs was significantly greater in CM than in HV ($p=0.01$).

Conclusions: Our data document that migraine chronicity alters thalamo-cortical connections by shortening response time and enhancing amplitude of the thalamocortical loops and by increasing primary cortical activation. These findings may be electrophysiological fingerprints of the somatosensory system central sensitization process that is thought to be the underlining mechanism of headache chronification. Whether this electro-functional behaviour is primary or secondary to daily headache remains to be determined.

P54

Treatment of Chronic Migraine: A Three-Month Comparator Study of Naproxen Sodium vs. SumaRT/Nap (Treximet™)

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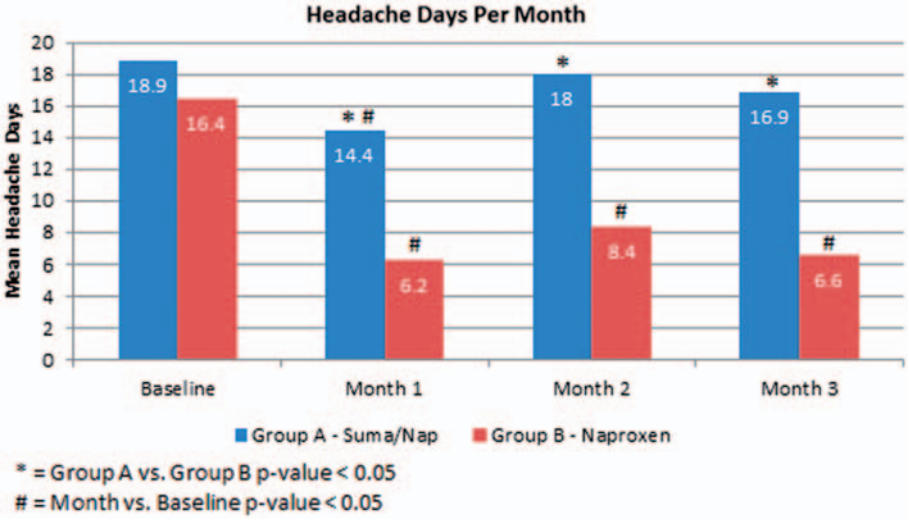
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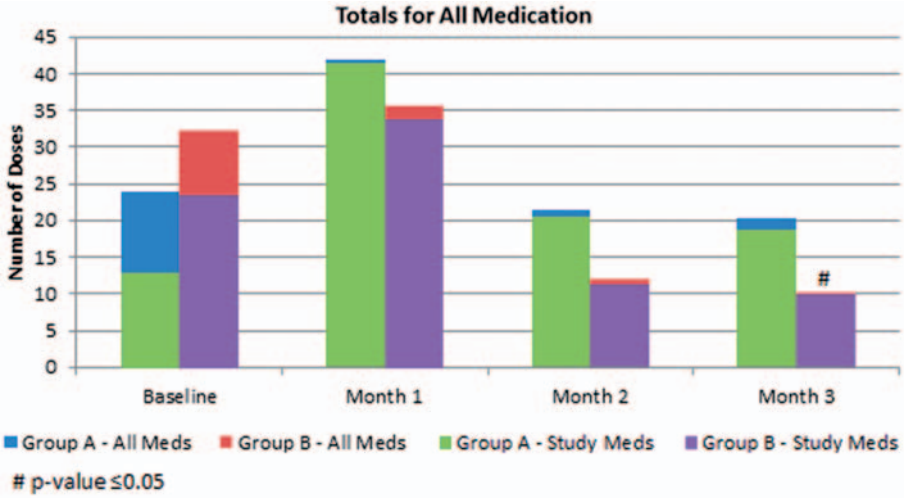
Objectives: This exploratory pilot study compared SumaRT/Nap (Group A) and naproxen sodium (Group B) as both a daily preventive treatment and an episodic acute treatment in patients with chronic migraine (CM).

Background: Acute medications have not been thoroughly studied in chronic migraine, yet critical to patient management. Many acute medications have demonstrated efficacy as both acute and prophylactic medications.

Methods: A double-blind, randomized comparator trial of 28 subjects, 18 to 65 years of age, with IHS defined chronic migraine was conducted at 2 US headache centers. Study medications were utilized as a daily preventive treatment and if needed, an acute treatment during Month 1. In months 2 and 3 subjects were allowed to treat migraine attacks of migraine for up to 14 days per month.

Results: There was a reduction in migraine headache days from baseline to month 3 in both groups. This reached statistical significance for Group B, but not Group A at month 3 for per protocol completers:





Primary endpoint, p=0.02 vs. 0.25, respectively. There were more dropouts for lack of efficacy in Group B compared to Group A (5/12 vs.1/16, respectively). Duration of migraine from treatment to pain-free was better for naproxen than SumaRT/Nap throughout the active phase of the study. There was a significant reduction of acute medication for Group B from baseline to month 3. MIDAS scores improved in Group A, from 77 to 56 and Group B, from 81 to 16. Both treatments were well tolerated with no subject withdrawals due to AEs or MOH.

Conclusions: This study suggests there is a role for acute medications in the treatment of chronic migraine. There may be a subset of subjects with CM who are highly responsive to high doses of naproxen sodium when provided as a daily preventive for 1 month followed by aggressive episodic treatment for 2 months. This subset may be identifiable early in an empirical trial of naproxen. Group A had fewer dropouts for lack of efficacy than Group B, suggesting subjects favored SumaRT/Nap as acute treatment. There was no evidence SumaRT/Nap reduced headache days.

P55

Chronic Migraine in Children Associated with Blunted Cardiovascular Autonomic Reflexes with Orthostatic Stress Despite Increased Sympathetic Activation (A Pilot Study)

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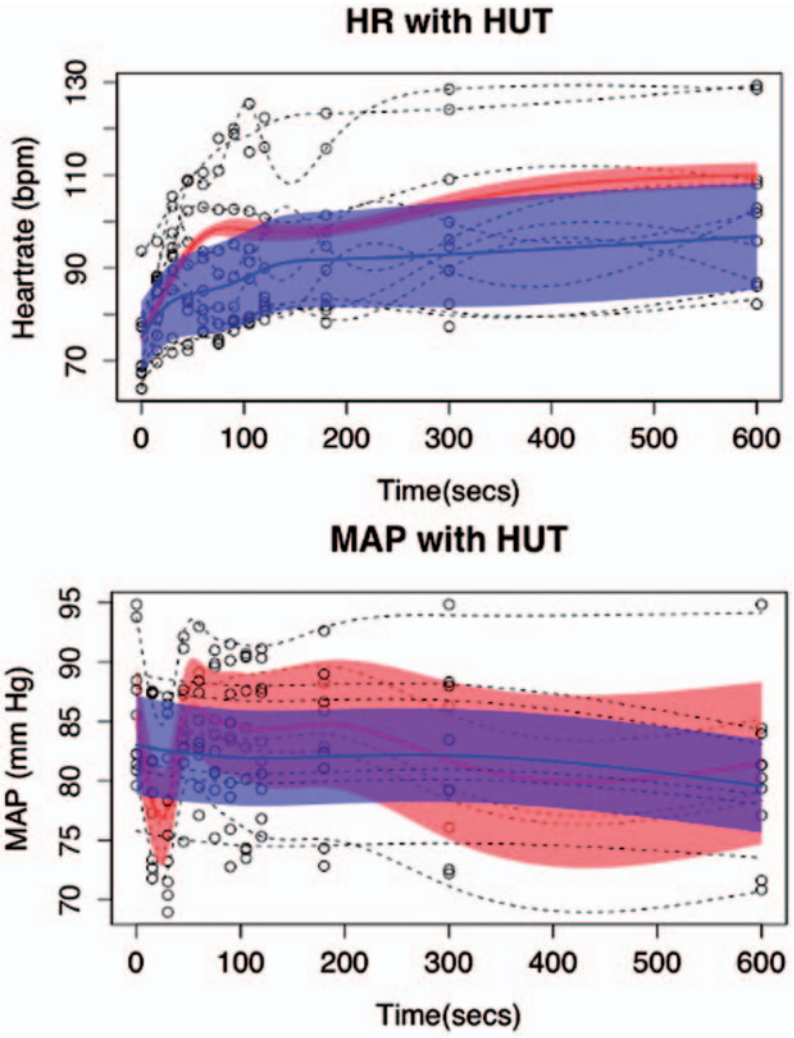
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Objectives: Assess subjective and objective differences in symptoms and cardiac autonomic reflexes comparing episodic and chronic migraine.

Background: Migraine in children often progresses to chronic migraine. Orthostatic intolerance (OI) refers to the development of symptoms like dizziness or lightheadedness on standing an chronic OI is associated with many symptoms including headache. Based on clinical observations, children often report symptoms of OI when presenting with chronic migraine. We tested the hypothesis that the chronification of migraine is associated with objective changes in cardiovascular responses to orthostatic stress, deep breathing, and Valsalva.

Methods: This pilot study included participants aged 8-17 years with episodic or chronic migraine based on ICHD-II. The average migraine days per month, PedMIDAS, and OI symptoms were documented. The primary outcome measures were heart rate (HR) and mean arterial pressure (MAP) in response to head-up tilt (HUT) for 10 minutes, deep breathing at 6 breaths/min for 8 breaths, and Valsalva to 40 mm Hg for 15 seconds. HR and BP were recorded using continuous electrocardiogram and non-invasive blood pressure (Finopress®) sampled at 250 Hz. Heart rate variability (HRV) frequency domain analysis during HUT was performed. Participants were analyzed in two groups: (1) episodic migraine (EM; < 15 days/mo; i.e. episodic and frequent migraine) and (2) chronic migraine (CM; > 15 days/mo). Smooth splines mixed effects models were fit to the data and used to estimate the mean response and 95% confidence interval (CI).

Results: Frequent migraine (7-14 migraines/month) were the predominant subgroup in the EM group (n=4/5). Symptoms of OI were higher in the CM group, but not significantly different. During HUT, the CM group had a significantly lower early heart rate (HR) (Figure 1) and remained lower during the HUT. The MAP pattern in the CM group was linear and qualitatively different from the normal EM group. Low-frequency HRV (LF-HRV; a



marker of sympathetic activation) was significantly lower in the CM group during HUT (p=0.03). Responses to deep breathing and Valsalva were not significantly different.

Conclusions: Children in the CM group had a significantly lower early HR in response to orthostatic stress and the pattern of MAP was blunted in comparison to the EM group. These observations may be due to alteration of cardiosympathetic responses in the CM group despite increased activation. Our pilot data are limited by sample size and over representation of frequent migraine. Alteration of the autonomic nervous system may serve as a biomarker of migraine progression and support alternative therapeutic strategies.

P56

Frequency and Severity of Cutaneous Allodynia in Migraine and Chronic Migraine

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Objectives: To evaluate the presence and severity of cutaneous allodynia (CA) in patients with migraine and chronic migraine and to compare the severity classification among them.

Background: The relationship between migraine and CA have been arousinginterest once it was recently recognized as a sign of central sensitization during migraine attacks, suggested as a negative influence on the migraine pharmacological treatment and pointed out as a risk factor for migraine chronification. The 12 item Allodynia Symptom Cheklist (ASC-12) is the only tool available that can detect CA and also assess its severity. Although the investigation about CA with the ASC-12 has been already done[1], we do not know how it occurs in brazilian population.

Methods: The presence and severity of CA were assessed by the Brazilian version of the ASC-12[2] in 64 volunteers, 32 in each group, from a tertiary outcome headache service. The migraine diagnoses were given by expert neurologists according to ICHD-II (2004). The ASC-12 scores range from 0-24 points and classifies the CA as none, mild, moderate and severe. Subjects with a diagnosis of other concomitant headaches, fibromyalgia, trigeminal neuralgia and systemic diseases with neuropathy peripheral sensory were excluded. The X^2 test was applied, using SPSS® 16,0, to compare proportions between groups.

Results: The migraine group (M) was composed with 91% of woman and mean age of 42 (SD=10) and the chronic migraine group (CM) was composed with 94% of woman and mean age of 39,7 (SD=11). Eighty four percent of the M had CA, while this proportion on the CM was eighty one percent (figure 1). In general, no difference between the proportions of the classifications was found (p>0,05). The relative frequency of the severity in the sample with any kind of allodynia showed a greater proportion of severe CA in CM (p<0,05) (figure 2).

Conclusions: The frequency of CA in brazilian patients with migraine is high, although it seems that migraine

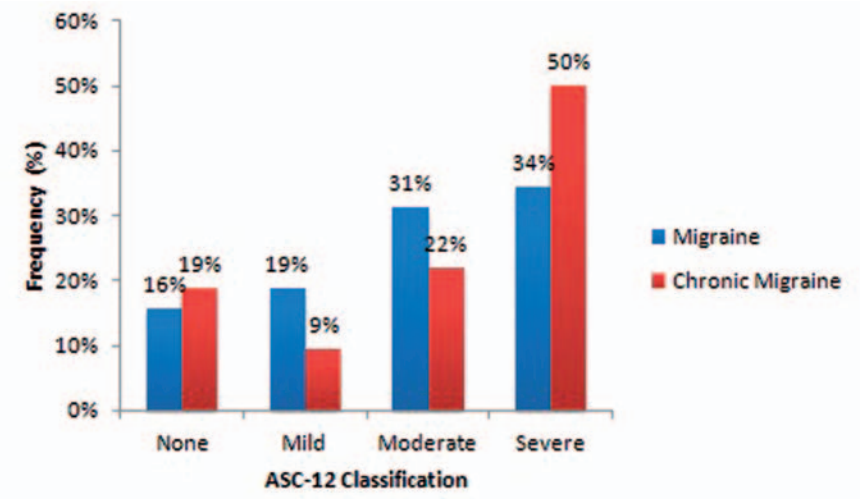


Figure 1. Frequency of cutaneous allodynia classification in migraine and chronic migraine assessed by the 12 item Alldynia Symptom Cheklist.

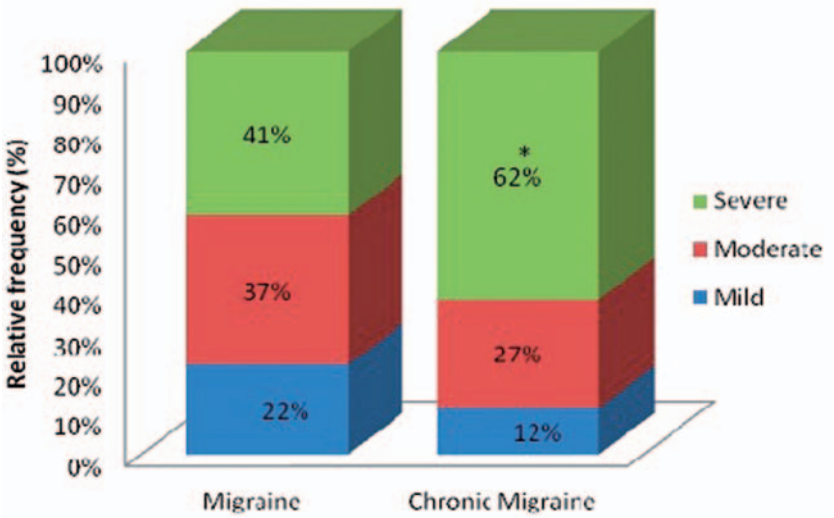


Figure 2. Relative frequency of cutaneous allodynia classification in migraine and chronic migraine among patients with allodynia. * $p<0,05$ for X^2 value

attacks frequency do not influence in CA presence, but it can influence in its severity.

P57

Predictors to Treatment Response in Patients with Chronic Migraines: Can the Course of the Disease Be Changed?

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Objectives: To estimate the remission rate and to identify predictors of remission from MC to ME in a cohort of patients managed by neurologist headache specialist.

Background: It has been recognized multifactorial evolutionary pattern that leads to chronic migraine (CM) and probably refractory migraine (RM). The remission rate to an episodic pattern and factors that allow prediction of therapeutic response are still unknown.

Methods: We performed a retrospective study of an estimated sample of adult patients with CM based on the classification criteria ICHD-2 who were treated by a headache specialist for a year, selected by simple random sampling of medical records of a neurological institution in Medellin (Colombia). We evaluated clinical characteristics, comorbidities, treatment and therapeutic response and we compared those between responders (pattern change from CM to EM) and non-responders using a multivariate logistic regression model.

Results: We evaluated clinical records of 224 patients with CM. The average age was 47 years (SD: 13.7), 87.5% were women. Average HA onset was at age 29 (SD: 16.9) and the average HA evolution time was 17 years (SD: 14.4). At first consultation by headache specialist (HASp), average HA days/month was 25 (SD: 5.7), 38.8% had analgesic overuse and 69.2% had symptoms of anxiety or depression. After one year, 59.8% of patients remitted to episodic pattern (n = 134), on an average 5 months after first visit (SD: 3.5) decreasing HA days/month from 25+5.8 to 6+4.1; 67.2% of them with low frequency EM (0-9 days/HA/month). Comparing responders and non-responders there was statistically significant difference in overuse (33.6% vs. 46.7%) but lost significance in the multivariate analysis, which showed sleep complaints (OR 2.28, 95% CI 1.2 - 4.3), fibromyalgia or chronic pain (OR 2.33, 95 % CI 1.03 - 5.3) and use of preventive medication (OR 2.15, 95% CI 1.05 - 4.4) to be associated with bad prognosis; prior to HASp treatment, significant difference in the frequency of use of TCA (58.2% vs. 80%p 0.001), SSRIs (56% vs. 70% p 0.03), dual antidepressants (1.5% vs. 14.4% p <0.0001), opioids (61.2% vs. 74.4% p 0.02), topiramate (6.7% vs. 18.9%, p 0.005) and triptans (6.7% vs. 18.9% p 0.005), and during the year of following, in the use of Botox® (21.6% vs. 53.3% p <0.0001), antipsychotics (12.7% vs. 24.4% p 0.01), dual antidepressants (23.9% vs. 42.2% p 0.003), gabapentin (15.7% vs. 46.7% p <0.0001), naratriptan (14.2% vs. 33.3% p 0.001), propranolol (21.6% vs. 11.1% p 0.03) and TCA (67.2% vs. 48.9% p 0.005).

Conclusions: Sleep complaints, fibromyalgia and chronic pain, preventive medication are independent predictors of

no return to episodic pattern. We recommend that patients with CM should be evaluated early by HASp.

P58

Evidence for Long-Term Efficacy of Peripheral Nerve Stimulation of the Occipital Nerves in the Management of Chronic Migraine

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Objectives: Provide evidence to support long-term efficacy of PNS of the occipital nerves in the management of chronic migraine.

Background: Chronic migraine is a debilitating disorder with few treatment options. Recent studies have shown the utility of PNS of the occipital nerves in the management of chronic migraine.

Methods: In this IRB-approved, prospective, multicenter, double-blinded study, patients were implanted with a neurostimulation system (St. Jude Medical, Plano, TX) and randomized to an Active or Control group for 12 weeks. Patients continued in an open-label phase of the study which lasted an additional 40 weeks. Outcomes collected during this phase included headache day reduction (duration $>$ four hours with moderate/severe peak intensity), migraine-related disability and distress as assessed by the migraine disability assessment (MIDAS) questionnaire and the Zung Pain and Distress (PAD) scale, headache pain relief, and satisfaction. All statistical testing was conducted to assess change from baseline to 1 year post-implant. Analyses were performed using paired *t*-tests. An intent-to-treat (ITT) analysis that included all patients (N=133) as well as an analysis of only patients that met the criteria for intractable, chronic migraine (ICM; N=105) was performed for all variables.

Results: For the ITT population, headache days were significantly reduced by 6.7 ($\pm$8.4) days ($p<0.001$), MIDAS scores were significantly reduced by 50.9 ($\pm$71.9) points to a mean score of 106.7 ($\pm$85.4) points ($p<0.001$), total PAD scores were significantly reduced by 10.3 ($\pm$14.8) points from a mean baseline score of 66.8 ($\pm$13.6) points ($p<0.001$). In addition, 65.4% of patients reported excellent or good headache relief and patient satisfaction was also high among this patient cohort. Slightly improved results were noted for the ICM population in which headache days were significantly reduced by 7.7 ($\pm$8.7) days ($p<0.001$), MIDAS scores were significantly reduced by 57.9 ($\pm$71.8) points from a baseline score of 169.7 ($\pm$70.6) points ($p<0.001$), total PAD scores were significantly reduced by 11.2 ($\pm$15.2) points to a score of 57.4 ($\pm$16.2) points. In addition, 67.9% of ICM patients reported excellent or good headache relief and patient satisfaction was also high among this patient cohort.

Conclusions: The results provide long-term evidence to support efficacy of PNS of the occipital nerves for the management of chronic migraine.

P59

Therapeutic Effect of Nasal Oxytocin in Chronic Migraine: Dependence on Cytokines

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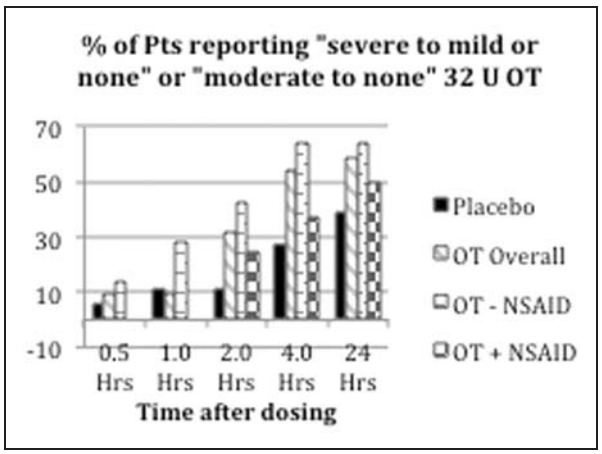
Objectives: Oxytocin receptor (OT-R) expression is known to be driven by cytokines, and particularly by IL-6, for which there are early response elements on the OT-R gene promoter.

Background: As OT-R are on trigeminal nerve neurons, their level should thus be enhanced by IL-6 as should the analgesic effect of OT for trigeminally mediated pain wherein there is an inflammatory component, including chronic migraine.

Methods: This study included a single-dose, placebo-controlled, double-blind, parallel study of the effects of 32 U of nasally-applied oxytocin in patients with chronic migraine. The primary inclusion criteria included an incidence of migraine-type headache of at least 15 days/month and the presence of a headache for at least 10 hours prior to dosing (to ensure OT-R upregulation) and patients were washed out of other medications for at least 4 hours. Patients were asked to rate their pain on a standard 4-point categorical scale (severe, moderate, mild, or none) just prior to and at 0.5, 1, 2, 4, and 24 hrs after dosing; nausea, photophobia, and phonophobia were also recorded.

Results: Figure 1 demonstrates that, nasal OT reduced pain by 2 categories in 42% of pts at 2 hrs and 55% at 4 hrs.; compared to 11% and 28% for placebo. Pts that had taken a NSAID, which blocks IL-6 production, within 24 hrs prior to dosing showed a strong decrease in effect. Photophobia and Phonophobia were also decreased compared to placebo.

Conclusions: These results suggest that nasal oxytocin may be a viable alternative for the treatment of chronic migraine headache.



P60

CaMEO (Chronic Migraine Epidemiology & Outcomes) Study: Design, Methodology and Baseline Cohort Characteristics

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Objectives: To describe the methodology and characterize the source population for the CaMEO study.

Background: Understanding the clinical and epidemiological characteristics of migraine provides a foundation for optimizing patient treatment paradigms. CaMEO is a prospective, web-based cohort study that utilized longitudinal and cross-sectional data collection to characterize migraine clinical course and to assess aspects of family burden, barriers of care and endophenotypes and comorbidities among those with migraine.

Methods: Study population included migraine subjects recruited from a large (2.4 million members) web-based panel. Sampling quotas were used to match the demographics of the study population to the demographic characteristics in the general population. People with migraine were identified using ICHD-2 criteria and subdivided based on headache days per month into episodic (EM) and chronic migraine (CM). Migraine subjects will complete surveys every 3 months over the course of one year beginning in the Fall of 2012. Baseline data includes headache features and frequency, comorbid depression and anxiety, medication use, healthcare consultation, disability, quality of life. Additionally, subjects will be asked to recruit family members (spouse and children) living in the household in order to assess migraine-related burden and impact within the family unit.

Results: Of 489,537 invitees, 80,783 responded to the screening survey (16.5%) and 16,789 (3.4%) eligibly completed the initial survey. Eligible respondents were at least 18 years old, spent an appropriate amount of time ($\geq$10 minutes) completing the survey, screened positive for ICHD-2 migraine provided data on headache frequency and consistently reported age, gender. Eligible respondents had EM (n=15,313; 92.1%) or CM (n=1,476; 8.8%) and were invited into the 12-month longitudinal assessment. Additionally, compared to non-responders, responders were significantly older (average $p<0.0001$), more likely to be female ($p<0.0001$), more likely to be Caucasian ($p<0.0001$), more likely to be married ($p<0.0001$), less likely to be employed full/ part time ($p<0.0001$), and less likely to have incomes exceeding $50,000 ($p<0.0001$).

Conclusions: CaMEO was designed to characterize the course of EM and CM over 1 year using assessments every 3 months in a community-based web panel of persons with migraine. Future data will allow for quantification of variations in headache frequency, disability, comorbidities, and medication use with repeated assessments over the course of 1 year. CaMEO will also generate data on the impact of migraine on the family unit, including the perspective of the spouse and child. Data can be used to define migraine endophenotypes for future genetic studies.

P61

Sociodemographics, Disability and Employment Differences between Persons with Chronic and Episodic Migraine: Results of the CaMEO (Chronic Migraine Epidemiology & Outcomes) Study

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Objectives: To characterize sociodemographics, headache-related disability and employment status among individuals with chronic migraine (CM) and episodic migraine (EM) in a large, US sample.

Background: Previous research suggests that individuals with CM and EM vary on sociodemographics, headache-related disability and employment status in addition to headache frequency.

Methods: CaMEO is a prospective, web-based cohort study. Questionnaires were sent via e-mail to a survey panel constructed to be sociodemographically representative of the US population beginning in the Fall of 2012. Of 80,783 respondents, 16,789 subjects met an ICHD-2 based case definition for migraine and were eligible for inclusion. CM and EM were distinguished based on headache days per month (CM= ICHD-2 migraine diagnosis and $\geq$15 headache days/ month; EM= ICHD-2 migraine diagnosis and $<$15 headache days/month). Survey data includes sociodemographics and headache-related disability (using the Migraine Disability Assessment Scale [MIDAS]). Herein, we use descriptive and inferential statistics to contrast those with EM and CM based on responses to the baseline survey.

Results: Of the 16,789 eligible participants meeting ICHD-2 criteria for migraine, 1,476 (8.8%) had CM and 15, 313 (91.2%) had EM. Respondents with CM showed a greater female preponderance than those with EM (81.1% vs. 73.8%; $p< 0.001$) although mean ages did not differ significantly (40.6 vs. 41.0; p=.32). The sample was predominately Caucasian and more so for CM (87.5% vs. 83.3%, $p<0.001$). Compared to EM, those in with CM completed fewer years of education; 34.9% vs. 45.9% had bachelor's degrees or higher ($p<0.001$). Individual incomes were more likely to be below the median for CM than EM (69.1% vs. 59.1%; $p<0.001$). Household incomes (59.8% vs. 49.5%; $p<0.001$) were also lower for CM, as well, the CM group was less likely to be employed full or part time (56.4% vs. 66.0%; $p<0.001$). Headache-related disability was significantly higher for CM than EM (mean MIDAS 60.5 vs. 13.1; RR=4.6, $p<0.001$).

Conclusions: In comparison with EM, persons with CM are more burdened financially and occupationally as seen in the higher levels of headache-related disability, unemployment and underemployment with corresponding reductions in personal and household income. Ongoing data collection will allow us to characterize the longitudinal course and consequences of CM and EM in the US population.

P62

High Prevalence of Right to Left Shunt in Women with Chronic Migraine Is Independent of Aura Status

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Objectives: To study the prevalence and characteristics of right to left shunt (RtLS) in a series of women with chronic migraine (CM).

Background: The prevalence of RtLS is estimated as 25% of the general population (1). Prevalence of shunt has been shown to be increased in migraine with aura and one study has found a high prevalence of shunt in CM (2).

Methods: This series includes 84 women (age 43 years, range 16-61) meeting diagnostic criteria (IHC-II revised 2006) for CM. There were 41 women with migraine with aura attacks. We carried out a transcranial doppler study (AplioXG, model SSA-790A, Toshiba) following the CODICIA study protocol (3).

Results: Forty-eight patients (57%) showed some degree of RtLS. Twenty-three (53,5%) out of the 43 patients without aura had shunt while twenty-five (61%) out of the 41 patients with migraine with aura had shunt. There was no difference in RtLS prevalence in those CM who fullfil aura criteria versus those without (61% versus 53,5%; odds ratio 1.358, 95% confidence interval 0.57 to 3.235, p=0.636). Nineteen (39,5%) of the total detected shunts were massive and detected at rest. In patients with aura, ten (40%) of the 25 shunts were detected at rest and nine (36%) of them were massive. In patients without aura, nine (39%) of the 23 shunts were detected at rest and ten (43,5%) of them were massive. There was no difference in RtLS appearance (detected at rest or with Valsalva maneuver) in CM who fullfil aura criteria and those without (40% versus 39%; odds ratio 1.037, 95% confidence interval 0.325 to 3.302, p=0.851). There was no difference in RtLS degree in those with CM who fullfil aura criteria and those without (36% versus 43,5%; odds ratio 1.367, 95% confidence interval 0.428 to 4.364, p=0.815).

Conclusions: Prevalence of RtLS in women with CM was higher than expected for the general population and there were not differences according to aura status. There were no differences in RtLS, both in terms of degree or appearance at rest or after Valsalva, between patients with or without aura. The clinical implications of our findings needs to be determined, though they suggest a relationship between the presence of shunt with an increased frequency of migraine attacks.

P63

Transient Exacerbation of Headache in Patients Receiving Intravenous Dihydroergotamine for Inpatient Management of Chronic Migraine

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Objectives: To examine for any association between transient headache exacerbations some patients experience with an inpatient course of intravenous dihydroergotamine (DHE) and medium term outcome.

Background: Clinical experience suggests a proportion of patients experience transient headache exacerbations with administration of intravenous dihydroergotamine (DHE). This may dissuade some clinicians and patients from completing a full course of inpatient treatment.

Methods: We examined prospectively collected diary data in patients havingDHE for inpatient management of chronic migraine, and examined the presence of common side effects associated with intravenous (IV) DHE, as well as the qualitative medium term outcome.

Results: A total of 19% of 212 chronic migraine patients had a documented headache exacerbation related to IV DHE. Of these, 66% went on to have a degree of improvement in the medium term, in comparison to 82% of the patients without a headache exacerbation related to DHE. The difference was not significant ($p = 0.066$). There was no difference in associated nausea ($p = 0.059$). Qualitatively, headache exacerbations were more likely to occur during infusions early in the inpatient course, as well as being related to a faster rate of infusion.

Conclusions: Transient headache worsening associated with inpatient IV DHE is a common occurrence. Interestingly, it is also associated with triptan use. The data support pushing on with treatment in patients with early transient nausea after DHE since it is likely to settle and outcomes remain good.

P64

Modified Spinal Accessory Nerve Blocks for Effectively Treating Refractory Migraine

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Objectives: To retrospectively review our clinical experience with modified spinal accessory nerve (SAN) blocks for very effectively treating refractory migraine.

Background: The current standard care for migraine is often unable to cure Refractory Migraime, or control and prevent its episodes very well. Long term of using headache medications has also brought drug side effects. We have used the modified spinal accessory nerve (SAN) blocks to very effectively treat the patients with refractory migraine headache.

Methods: Author did an retrospective chart review of his 62 refractory migraine patients, who received SAN block injections in author's Pain Clinic from 2009-2011. The patients migraine diagnoses were all confirmed by their neurologists and author. Twelve patients lost tracks. Total 50 cases were available for this study. They were: 17-67 years old, 40 women, 10 men, history of refractory migraine for 1 to 30 years, no current neck pain history, having daily headaches or 1-20 episodes of headache per month, usually at moderate or severe level based on a VAS pain scale (>5/10), each headache duraton from a few hours to 2-3 days.

They tried the standard care treatment for their chronic refractory migraine, that included several prescription headache medications, and /or Botox injections. The treatments they had were either unable to cure and prevent relapses of their headaches, or unable to control migraine very well. 90% of the patients were found to have mild tenderness at the ipsilateral spinal accessory nerve point, the junction of the upper and middle thirds of the sternocleidomastoid (SCM) muscle.

All patients had modified spinal accessory nerve block injections, 1% Lidocaine 1 ml at the ipsilateral spinal accessory nerve point, either one or both sides, using 27G 1'' needle. The each patient received 3-10 sessions of injections in 2-3 weeks apart.

Primary outcome: After finishing inection course, the patients have either no migraines or more than 50% improved migraine in frequence of headache episode, pain level (based on VAS pain scale), pain duraton, and decreased pain medication doses for a long period of time.

Results: From begining of 2009 to the end of 2012, eleven patients either had no significant improvement after 5 sessions of injection. Thirty nine patients(78%), after finishing 3-10 sessions of injection, either have had no headaches or more than 50% migraine headache improvement at least for more than one year, some of tem more than three years, so far in the end of 2012. The patients have discontinued routine prescription headache medications. They

just take OTC pain medications as needed, such as 400 mg ibuprofen or two tablets of Eccedrin migraine.

Conclusions: The modified spinal accessory nerve block injection is very successful in the treatment of Refractory Migraine Headache. It can significantly improve refractory migraine headache for a long period of time. It is also easy to do and has no side effects.

P65

Barriers to Chronic Migraine Care: Results of the CaMEO (Chronic Migraine Epidemiology & Outcomes) Study

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Objectives: To describe patterns of healthcare consultation and diagnosis among a large, US population-based sample of chronic migraine (CM).

Background: CM is burdensome to the individual, society, and healthcare systems; yet it remains largely undiagnosed and under-treated.

Methods: CaMEO is a prospective, web-based cohort study. Questionnaires were sent via e-mail to a survey panel constructed to be sociodemographically representative of the US population, beginning in the Fall of 2012. Of 80,783 respondents, 16,789 met ICHD-2 criteria for migraine. Respondents with migraine were divided into an episodic migraine (EM) group and a CM group with $\geq$15 headache (HA) days/month. Collected data includes healthcare visits, medical diagnoses, current and past treatment, satisfaction with treatments and knowledge, attitude and behaviors that may be barriers to optimal care. A "doctor" was defined as a prescribing health-care provider (HCP). "HA Specialists" included all neurologists, HA or pain specialists. A "non-prescribing HCP" was defined as any HCP that cannot prescribe medicine (e.g., chiropractor, psychologist).

Results: Of the participants, 1,476 (8.8%) met criteria for CM and 15,313 (91.2%) had EM. Self-reported medical diagnoses in the entire sample with CM included migraine (59.6%), CM or transformed migraine (13.6%) or chronic daily headache (11.4%). Of those with CM, 20.5% reported at least one of CM/TM/CDH. Although not mutually exclusion, of those with CM, 13.6% reported currently seeking care from a HA Specialist, 41.8% from a doctor and 43.4% from a non-prescribing HCP. Refer to Table 1 for HA diagnosis rates for CM and related disorders by HCP type.

Conclusions: Among persons with CM, just one fifth report an appropriate medical diagnosis (CM/TM/CDH). Adequate diagnostic rates are highest in individuals treated by headache specialists, intermediate among those consulting doctors and lowest among those seeking headache care from a nonprescribing HCPs. This is a barrier, as proper diagnosis is necessary for an optimal treatment plan.

P66

Chronic Migraine (CM) Patients Should Be Screened for Pseudobulbar Affect (PBA)

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Objectives: To report a case series of pseudobulbar affect (PBA) in patients with chronic migraine (CM).

Background: Pseudobulbar affect (PBA) is an underrecognized neurologic condition characterized by uncontrollable, inappropriate outbursts of laughing and/or crying that are incongruous or disproportionate to the patient's emotional state; PBA occurs secondary to a variety of neurologic conditions, but it has not previously been reported in patients with chronic migraine (CM). CM shares many pathophysiological features with other diseases affecting the central nervous system, yet it was not included in the recent point-prevalence epidemiological data from the PBA Registry Series (PRISM) of 5,290 neurologic patients. PBA is screened for using the Center for Neurologic Studies – Lability Scale (CNS-LS), the first self-report measure of PBA to be established and validated; it consists of subscales for laughter (4 items) and for crying (3 items), with each item scored on a 5-point scale (1 = applies never; 5 = applies most of the time) for a total score ranging from 7 (no symptoms) to 35 (maximum). In the clinical trials leading to the FDA approval of fixed dose combination dextromethorphan/quinidine (DM/Q) for the treatment of PBA, more patients treated with placebo had headache than patients treated with DM/Q (15.6% vs 14.0%). This led to our use of DM/Q for the treatment of headache; we previously reported a patient with >20 year history of refractory chronic migraine who responded dramatically (reduction of headache frequency and severity) to DM/Q. It is unclear, however, whether the therapeutic effect of DM/Q in CM is due to its efficacy in PBA.

Methods: Retrospective analysis of 5 consecutive chronic migraine (CM) patients, all of whom completed both the CNS-LS to screen for PBA symptoms and the Beck Depression Inventory -II (BDI-II) to screen for depression. The CNS-LS subscores for laughing and crying were also analyzed separately, as was the crying specific question of the BDI-II.

Results: All 5 CM patients were women, between the age of 40 and 65 years (mean/median age = 50 years). The mean number of headache days per month was 26 and 4 patients met criteria for PBA (CNS-LS≥13), while the other patient had a CNS-LS = 12. Mean CNS-LS was 15 and median was 14. Mean BDI-II was 15 and median was 13. There appeared to be some correlation (Pearson coefficient, 0.54) between CNS-LS and BDI-II scores, but depression alone did not explain the presence of PBA.

Conclusions: PBA has not previously been described in patients with chronic migraine (without other underlying neurologic conditions, such as multiple sclerosis, amyotrophic lateral sclerosis, stroke, traumatic brain injury, parkinson's diseases or Alzheimer's dementia). This case series suggests that PBA (in addition to depression) should be screened for in patients with CM. Further research should be conducted to estimate the prevalence of PBA in CM patients and to ascertain whether the response of CM to DM/Q is independent of the effect of DM/Q on PBA.

P67

An Exploratory Study of Calcitonin Gene-Related Peptide in Chronic Migraineurs Receiving OnabotulinumtoxinA: Implications to Pathophysiology and Treatment Responsiveness

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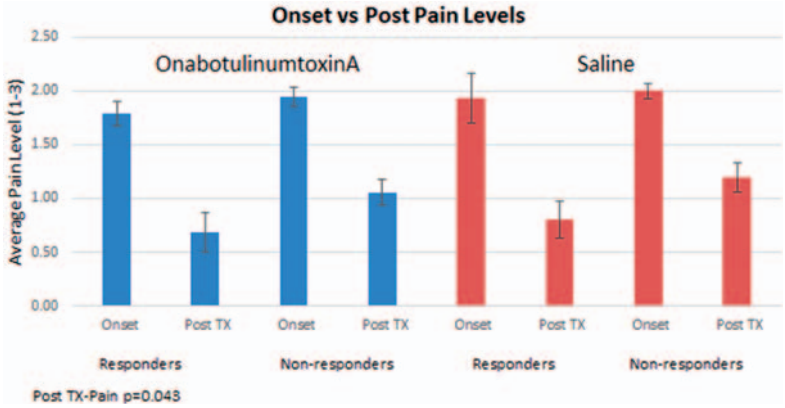
Objectives: To further the understanding of mechanisms of onabotulinumtoxinA in the treatment of chronic migraine (CM) and implications of response to acute treatment.

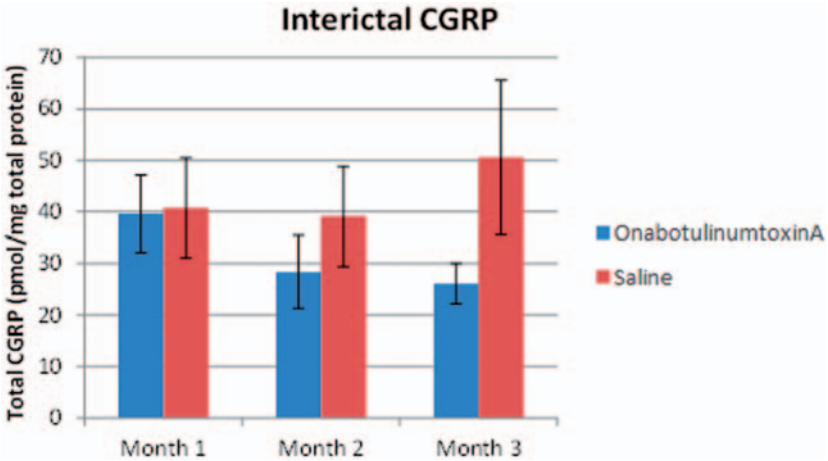
Background: CGRP plays a pivotal role in the pathogenesis of episodic migraine but its role in chronic migraine is less understood. OnabotulinumtoxinA has shown to inhibit the release of CGRP while triptans inhibit release of CGRP during attacks of acute migraine.

Methods: A randomized, placebo-controlled, crossover pilot study was conducted at 2 headache centers. Following a 30-day baseline period to define the frequency of headache days and document the diagnosis of CM, 20 patients were randomized 1:1 to receive onabotulinumtoxinA or saline injection and followed for 3 months. After a 1-month washout period, the groups were crossed over, treated, and followed for an additional 3 months. All subjects received 0.1 cc of onabotulinumtoxinA or saline in 31 sites as described in the PREEMPT Study. Saliva samples were collected at monthly intervals and analyzed for CGRP. Treatment response to onabotulinumtoxinA and acute medication was monitored via daily diary records.

Results: Saliva CGRP levels declined from baseline for subjects receiving onabotulinumtoxinA regardless of response compared to subjects receiving saline injections. Response to subjects' usual acute interventions improved for onabotulinumtoxinA responders (>50% reduction in headache days) compared to onabotulinumtoxinA non-responders (p=0.08) and saline non-responders (p=0.04). There were no significant changes observed in saliva CGRP during intensification of migraine headache or post treatment with a triptan.

Conclusions: This small exploratory study was underpowered for definitive conclusions. It appears that onabotulinumtoxinA is associated with reduction of interictal saliva CGRP levels. Because CGRP level did not change during intensification of migraine or post treatment with triptan treatment, there may be a unique difference in pathophysiology between episodic and chronic migraine.





Subjects responding to onabotulinumtoxinA had an improved response to usual acute interventions.

P68

Severity of Cervical Functional Disability in Subjects with Headache

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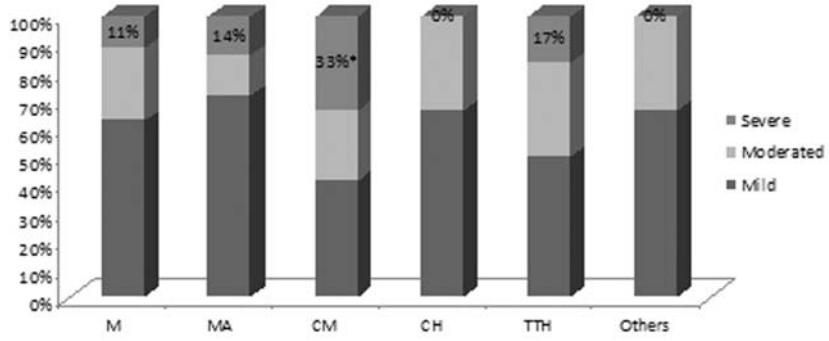
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Objectives: To evaluate severity of functional disability in subjects with different types of headache by the Neck Disability Index (NDI).

Background: Neck pain is one of the most frequent complaints in the general population and can be associated with temporomandibular disorders, fibromyalgia and headache. Despite of the association between headache disorders and cervical structures, the headache repercussion on cervical spine function are unknown.

Methods: We evaluated 77 subjects from a tertiary outcome hospital, diagnosed by neurologists according to ICHD-II, with the following diagnosis: 38 migraine without aura (M), 12 migraine with aura (MA), 13 chronic migraine (CM), 3 cervicogenic headache (CH), 7 tension-type headache (TTH) and 6 other headaches. Only volunteers with one type of headache were included, with no history of cervical lesions and other comorbidities. The NDI is composed by questions about cervical disability and functionality and the items are scored according to the level of difficulty to perfom each task or pain severity. The NDI classification levels are: no disability (0-4), mild (5-14), moderate (15-24), severe (25-34) and complete disability (>34). For statistical analysis the chi square were used.

Results: Only 13% of the total sample showed no cervical disability, 9% for group M, 2% MA, 1% MC, 0% CH, 1% TTH and 0% Others. The relative frequency of cervical disability was higher in the CM (33%) when compared to the other headache groups, M (11%, p <0.001), MA (14%,



p <0.001), CH (0%, p <0.001), TTH (17%, p <0.001) Others (0%, p <0.001).

Conclusions: The frequency of cervical disability, regardless of level, is present in all types of headache examined, but the severe level is higher in chronic migraine.

P69

Prolonged Efficacy of OnabotulinumtoxinA on Migraine-Related Disability Over 8 Consecutive Treatment Cycles

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Objectives: To retrospectively analyze patients with chronic migraine(CM), who were OnabotulinumtoxinA (OnabotA) responders in regard to a sustained reduction in migraine-related disability over a prolonged period in our community-based, out-patient headache center.

Background: Chronic migraine (ICHD-II 1.6) is an extremely disabling condition that affects approximately 1-2% of the population in North America. The PREEMPT study that led up to FDA approval for OnabotA for the treatment of CM showed a significant decrease in headache frequency and duration. We have previously reported that a sustained decrease in migraine-related disability exists over approximately 3 treatment cycles with OnabotA. Whether this is a prolonged effect or transient in nature has been open to question.

Methods: We queried our electronic records system at our community-based headache center to review CM patients who were treated with OnabotA over 8 consecutive treatment cycles at 12-13 week intervals from January 2010 through January 2013. All patients had been injected with OnabotA with doses ranging from 155-195 units per the PREEMPT protocol. Migraine Disability Assessment Scores(MIDAS) were routinely collected at each treatment visit and compared to baseline. The average scores for the entire cohort were then calculated for each treatment cycle.

Results: 35 patients were found to meet the above criteria. Average MIDAS scores showed a sustained decrease over the approximately 2- year period of regular treatment with OnabotA 155-195 units from approximately 65 at baseline to 39 at the 4-week interval. At the last treatment cycle, the average MIDAS score was decreased to 23.

Conclusions: The effect of OnabotA on migraine-related disability in chronic migraine is sustained in patients with chronic migraine who are regularly (12-13 week intervals) treated with 155-195 units in our community-based, outpatient headache center retrospective review. Whether or not this is true when patients return at less regular intervals has not been determined.

P70

Restoring Pain Modulation for Chronic Migraine; by Mild Stimuli of Stretching Tender Points of the Neck

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Objectives: The purpose of the study is to reveal the tender point in the back of the neck in patients with chronic migraine and to know the effect of stretching exercise by turning the shoulder around the neck axis on the pain in the tender point. The effect of daily stretching exercise on the chronic migraine was also investigated.

Background: Chronic migraine is reported to be 2% of the adult population, but the doctor attendance rate is much higher than episodic migraine. Among other preventive treatment the benefit of the occipital nerve stimulation is closely assessed, but its basic concept of treating central sensitization via the trigeminal-cervical convergence theory is giving rationale to other treatments. It indicates the possibility for other types of stimulation may be effective to treat chronic migraine.

Methods: Patients with chronic migraine of ICHD2R (n=128) and age & sex matched normal volunteers (n=100) were studied. Tender point elicited by finger pressure was evaluated by double blind methods. Examiner, blind physiotherapist, palpated the tender point without knowing the diagnosis or treatment. Tenderness was reported by the patients using VAS method. Headache diary was kept for three months prior to and after, to count and check the headache days.

Results: On palpation and applying pressure by the examiner's finger, intense pain in the C3 region was elicited in 118 patients (92%) with chronic migraine. Pain radiated to the head in 67%. After neck stretching exercise for 2 minutes, 98% of the patients reported disappearance of tenderness on palpation from 10 to 3.6 +/- 2.2 (p<0.01). Neck stretching exercise for 2 minutes daily over 3 months period reduced the headache days from 24.2 to 13.6 (p<0.01). Normal volunteers did not show significant

tender point in the corresponding region in the back of the neck.

Conclusions: A strong tender point seen at the C3 region on the back of the neck in chronic migraine seems to have referred from the central sensitization through the trigemino-cervical convergence. Disappearance of tender point by turning the shoulders and stretching the tender point may indicate that a good stimulation was sent to caudate trigeminal nucleus and modified pain control system. Physiotherapeutic intervention helps patients restore pain modulation and improve chronic migraine. NA.

P71

Improvement in Aura and Prodrome in Chronic Migraine (CM) Following Treatment with Botulinum Toxin Type A (Botox). A Prospective Analysis

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Objectives: Prospective study performed to assess the change in frequency, duration, and disability with social life, work or activities of daily living (ADL) by aura and prodrome following treatment with Botox.

Background: Botulinum Toxin A (Botox) is a licensed preventive treatment in CM recommended by National Institute of Clinical Excellence (N.I.C.E) in UK. The prevalence of Aura and prodrome in Chronic Migraine is unknown. Studies have shown improvement in headache days, severity and quality of life following Botox in CM[1]. However, we are not aware of the impact of this treatment in aura or prodromal symptoms and its impact on quality of life.

Methods: Patients with CM with prodrome or aura or both who received treatment with Botox as per PREEMPT protocol were prospectively interviewed through structured questionnaire. All patients maintained a headache diary for at least 30 days before and after receiving treatment. Data were collected for the presence of aura and prodrome; its frequency, duration and severity and impact on social life and ADL before and after treatment. The Data was statistically analysed using SPSS 17.

Results: Data of 35 patients with chronic migraine were available for analysis. Males=5 (mean age 56.4, median-55; range 33-77 years). Females=30 (mean age -44.1, median-45 & range 19-70 years). Overall 28.6% did not suffer any aura, 71.4% suffered both aura and prodrome, however 100% suffered prodrome. The result has been tabulated in table 1.

Table 1.

						Improvement by	
Paired differences	Mean	Median	Std Dev	paired t score	p value	>70%	>50%
Aura frequency(day)	8.86	8	8.31	5.33	0.0001	66.7	75
Aura Duration(Hour)	3.24	0.88	9.67	1.64	0.114	54.2	66.7
Social Life(day)	6.24	4	7.84	3.98	0.001	83.3	88.9
Work/ADL(Day)	5.52	3	7.33	3.76	0.001	83.3	88.9
Aura Severity change	1.52	2.0	7.33	6.56	0.0001		
Prodrome frequency(day)	9.63	11	8.01	7.110	0.0001	42.9	62.9
Prodrome duration(hour)	21.06	12	26.97	4.65	0.0001	48.6	65.7
Social life(day)	9.31	8	9.06	6.09	0.0001	59.3	81.5
Work/ADL(day)	8.4	7	9.05	5.49	0.0001	60	80
Prodrome severity change	1.4	1.0	1.03	8.01	0.0001		
HIT-6 Paired difference	11.4	10.50	9.25	6.08	0.0001		
HIT-6 Impact change	1.04	1	0.96	5.23	0.0001		
Grade improved by	3	2	1	0	worse		
Aura severity change	24%	28%	28%	16%	4%		
Prodrome severity change	14.3%	34.3%	31.4%	17.1%	2.9%		
HIT-6 IMPACTGRADE change	7.7%	23.1%	34.6%	34.6%			

Conclusions: This is the first observational study looking at 35 patients who received treatment with Botox for prevention of CM. Our data shows that Botox improves symptoms of aura and prodrome and has a positive impact on quality of life. The exact mode of action of Botox remains unknown although it is possible that Botox directly or indirectly affects cortical or sub-cortical areas involved in the generation of aura or prodrome.

P72

Evaluation of Cerebral Hemodynamics of Patients with Chronic Migraine: Effects of Amitriptiline

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Objectives: Amitryptiline is a serotonin-nor-epinephrine reuptake inhibitor. Amitryptiline is used in migraine prophylaxis if attacks occur 2 or more times in a month and if increase of attacks is present.

Background: Its mechanism of action is largely through serotonin. Inspired from the vascular theory of migraine pathophysiology, the aim of our study was to research the effects of amitryptiline on the blood vessels of the brain.

Methods: The study included 11 patients with chronic migraine and a control group of 11 participants with compatible gender and age characteristics. With a transcranial Doppler machine with temporal insonation the blood flows of booth MCA and PCA, pulsatile indexes and VMR's were measured. The VMR's were three times remeasured with breath holding indexes (BHI). The patients received 10 mg of amitryptiline prophylaxis. The tests performed with transcranial Doppler were repeated on the 1st month of the treatment. The results before and after the treatment were compared among the patients and with the results of the control group.

Results: The average age of the patient group was 40,4. Statistically significant increase of the right MCA BHI was detected after the treatment ($p=0,043$). No significant difference was detected in other pre and post-treatment data ($p>0,05$). The BHI's of the patient group were significantly decreased compared to the control group. Eventhough with treatment, the right MCA BHI data were close to the control group, after the treatment they were found to be decreased again. No statistically significant difference was detected for other data ($p>0,05$).

Conclusions: The effect of amitryptiline on migraine headaches through serotonergic action is known. In our study we found amitryptiline to increase the BHI of MCA and the data was close to the data of the control group. Amitryptiline may have an effect on migraine treatment by affecting the vascular bed in the migraine pathophysiology and partially improving the VMR. There is a need of larger studies researching the effect of higher amitryptiline doses on cerebrovascular structures.

P73

Withdrawn by the author.

P74

Botulinum Toxin A for Treatment of Chronic Migraine

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Objectives: As the significant population of chronic migraine patients, refractory to common therapeutic prophylaxis, BoNT has been used in our clinical experience for treating patients referring to our headache centre and suffering from chronic migraine with medication overuse.

Background: Chronic migraine is a common and debilitating headache syndrome.

Botulinum neurotoxin (BoNT), a potent toxin produced by the anaerobic bacterium clostridium botulinum, used for treatment of disorders associated with increased muscle tone and hyperidrosis, has been recently employed for patients suffering from chronic migraine.

Methods: Ten patients have been submitted to a withdrawal from medications in a day hospital setting and after that, they have been treated by BoNT A injection in multiple sites according to the protocol of the PREEMPT study at the dosage of 150 U for 31 sites. Every session of local injection (150 U per 31 sites) was repeated every three months for a period of one year. A second group of 8 patients, after withdrawal, was treated by BoNT A injection, multiple sites, at the dosage of 100 U; every session of local injection has been repeated every three months for a period of one year. Number of medication intake and days of headache per month were recorded by an headache daily diary.

Results: Data concerning the first group of patients evidenced that days of headache / month decreased during the period of treatment at 150 U (pre 21.4+7.9 post

13.8+10.9 p< 0.01). Also medication intake decreased (pre 19.6+8 post 11.7+9.5 p<0.01).

In the second group of patients, treated with 100 U, results were not significant: only 3 patients completed the treatment with 4 sessions; 5 patients dropped for different reasons (side effects, no benefit, low compliance).

Conclusions: Although these results are preliminary they led to intense efforts to evaluate analgesic properties of BoNT A and to assess their clinical applicability.

The pharmacological profile of BoNT A makes it a good candidate for migraine prevention at the adequate dosage of 150 U as proposed in the PREEMP study. Its long duration of action (3 months) makes it particularly attractive for patients who are not compliant with the daily use of preventive medications, or if they cannot tolerate it or when they are refractory to preventive medications. On the other side we cannot confirm the efficacy of lower dosage (100 U) for patients with chronic migraine after withdrawal.

P75

Comorbidity of Migraine and Affective Disorders among Substance Dependent Inpatients

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Objectives: To examine comorbid migraine and psychiatric disorders among inpatients with substance use disorders.

Background: Psychiatric comorbidities among migraineurs compound negative impact of migraine (Saunders et al., 2008; Guidetti et al., 1998), and inpatients with substance use disorders (SUDs) are at increased risk for affective disorders (Compton et al., 2003). Data are limited, however, regarding associations between migraine and these comorbidities within inpatient clinical settings.

Methods: Data were collected from 181 substance-dependent inpatients in residential substance abuse treatment. Participants were assessed for substance dependence and other Axis I psychiatric disorders using the Structured Interview for the DSM-IV (SCID-IV; First et al., 1996) and completed two validated screeners for migraine (ID Migraine; Lipton et al., 2003; Brief Headache Screen; Maizels & Burchette, 2003). Inpatients screening positive for migraine on both measures were classified as migraineurs. Participants also completed self-report measures of anxiety sensitivity (ASI-III; Taylor et al., 2007), depression and anxiety symptoms (DASS – 21; Lovibond & Lovibond, 1995), and substance use (DUQ; Lejuez et al., 2007). Standardized mean differences were used to quantify differences between inpatients with and without migraine across four theoretically-organized domains of predictors (demographics, psychiatric disorders, SUDs, and self-reported symptoms). Predictors within each domain that best discriminated between groups were identified using a classification tree with Bonferroni corrections. Candidate predictors were entered into a multivariate logistic regression to predict migraine status, and replicated using bootstrapping of 500 samples.

Results: Forty-four (24.3%) participants met criteria for migraine. Migraineurs were more likely to be female (34.8% vs. 18.3%) and reported higher levels of current anxiety symptoms on the DASS (M = 19.7 [11.0] vs. 11.3 [10.3]). Having a lifetime diagnosis of generalized anxiety disorder (GAD) or a current diagnosis of alcohol dependence was associated with greater than three-fold increased odds of migraine (OR = 3.47 and 3.79, respectively). These 4 predictors were forced into the final multivariate model, which differentiated well between those with and without migraine (area under ROC curve = 0.81; 95% CI: 0.73 to 0.88).

Conclusions: Lifetime GAD, current anxiety symptoms, and current alcohol dependence are the strongest psychiatric predictors of migraine among substance dependent inpatients. Migraine was also associated with elevated rates of several other SUDs, but addition of these SUDs did not improve the final model. Future research should focus on further clarifying relations of migraine with specific substance categories. Implications for migraine screening and management in SUD treatment settings are discussed.

P76

Treatment and Social Impact of Cephalic Hypersensitivity Syndrome Relating to Migraine

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Objectives: In this cohort study, we will report: 1) social impact of Cephalic Hypersensitivity Syndrome (CHS) and 2) that pertinent use of triptan agents reduce risk of incidence of CHS, which has been disseminated concept of CHS in Japan lately.

Background: Pathophysiology of migraine has been commonly explained by trigeminovascular theory, although recent studies have suggested that the cause of the migraine stems from cortical hyperexcitability.

Methods: In this study, observation items are: 1) demographics of subjects, 2) medical magnificent, 3) treatment status, 4) laboratory test: Varicella-zoster virus (VZV) antibody. This study was conducted in compliant with Japan ethic guideline for epidemiological study which was established by ministries of HEALTH, LABOUR, AND WELLFARE and EDUCATION AND SCIENCE, JAPAN.

Results: Of 1000 subjects, the proportion of female in analyzable subjects (n=964) whose mean age are 46.3±16.0 yrs**,** were approximately 73.3%.

To identify factors relating to migraine onset, we performed multivariate analysis using the logistic regression model. Gender, age pre-photophobia and tinnitus were suggested onset of migraine attack.

Conclusions: We hereby proposed diagnostic criteria of the "CHS" below [Fig]. Here we defined a new syndrome, "cephalic hypersensitivity syndrome" as a subliminal cortical hyperexcitability which itself is invisible but apparently seen as some symptoms such as dizziness and cephalic ringing. The cephalic hypersensitivity syndrome should be treated to attenuate the excitability by an appropriate triptan medication during attacks so as to exhibit its recurrence.

Fig. diagnostic criteria of the "Cephalic Hypersensitivity Syndrome (CHS)" According to statistics on number of patients, those who complain with dizziness and tinnitus suffering from CHS and now presenting migraine headache consult headache clinics, were markedly increased lately in Japan because concept of CHS has been disseminated in multiple Japan medical communities. Furthermore, triptan agents' sales in Japan were dramatically increased as compared before and after our presentation of CHS on basis of a sale statistics.

Table. Logistic Regression Model of Migraine To Explore Relating Factors

			95% CI of OR	
	P value	OR	Lower	Upper
Gender	0.0005	0.2508	0.1158	0.5435
Age	0.0000	0.9500	0.9273	0.9733
Photo(pre)	0.0189	0.2273	0.0657	0.7830
Photo(post)	0.4508	0.6570	0.2204	1.9581
Tinnitus +	0.0118	0.0569	0.0061	0.5293
Tinnitus -	.	.	.	.

OR: odd ratio

P77

Chronification of Migraine Headache and Cervical Abnormalities

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Objectives: Despite of therapeutic approaches with pharmacological and nonpharmacological strategies, some migraineurs have progression to chronic course (choronification). The Chronification of migraine disturbs the quality of patient's life. Chronic migraine headache is an enormous burden to individuals and societies due to high prevalence and considerable direct and indirect economic costs.

Generally speaking there are no abnormal findings in laboratory tests in migraineures according to the second edition of the International Classification of Headache Disorders.

Background: In practice chronic migraineurs show some abnormalities in cervical spine. There are no references

Of the following items to meet at least one entry.
- have a history of chronic headache and migraine in the past*
- within 2 degree, there are those with chronic headache and migraine
Of persons who meet the above, A ~ C satisfies the following items.(Incidentally, in the treatment of irritable brain syndrome, headaches may occur in the past)
A. About the following symptoms interfere with daily life and social life meet three or more
- unilateral or bilateral tinnitus head
- insomnia
- increasing anxiety
-Transient impairment of higher brain functions -
- heaviness of the head
-labile and rotating dizziness
B. Observed suggesting abnormal EEG findings of generalized hypersensitivity
C. Independent of other disorders
**Migraine should be diagnosed n accordance with the ICHD-*

that chronic migraineurs have any abnormalities in cervical spine.

Methods: The procedure was performed during the physical examination from Jan 2009 to Nov. 2012 at Dept. of Neurology, Busan National University Hospital. The 200 patients with migraine without aura, who complained of chronic headache for more than 3 years without other neurological or systemic diseases, were included in this study.

Cervicogenic headache and neck problems were excluded using criteria of International Headache Classification. The exact location may be good clue or guide to improve diagnostic accuracy, we applied Korean Hand Therapy Method to confirm migraine headache using the location of tender points on the head and neck.

Cervical spine study was included during routine laboratory tests.

Results: Among 200 chronic migraineurs, number of female was 148, that of male was 52. Mean age was 48 years old.

The X-ray finding of cervical vertebrae in migraineurs (200 persons) were various as followings, normal pattern 42, loss of normal lordortic curvature of c-spine 57, diffuse spondylosis with osteopenia 66, mild degenerative cervical spondylosis 51, mild disc space narrowing C3/4, C4/5, C5/6, C6/7 90, neural foraminal narrowing 75.

The right side of neck pain (110) is more than left side (90).

Conclusions: The chronic migraineurs having chronic progressive course and long periodic cycles for more than 3 years have some abnormalities on the radiological study.

It may be helpful to include the cervical spine study in the chronic migraineurs and to consider the correction of cervical abnormalities for prevention of chronic processes.

P78

Correlation between the Level of Disability the Cervical Spine and Pressure Pain Threshold in Patients with Migraine and Chronic Migraine

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Objectives: The aim of this study was to determine the correlation between Neck Disability Index (NDI) and the Pressure Pain Threshold (PPT) of cervical muscles in patients with migraine and chronic migraine.

Background: The correlation between NDI and cervical mobility was weak in patients with neck pain, but is not established it how disability is correlated with the cervical muscle PPT, especially in migraine patients, since this population showed muscle hypersensitivity and reduced cervical mobility[3].

Methods: Of 32 volunteers, 16 had migraine 38 (SD=9) years and 16 chronic migraine 38 (SD=10) years, diagnosed by neurologists acccording ICHD-II (2004). We excluded women with other concomitant headache, use painkillers in the last 24 hours, overuse of any medication, systemic degenerative diseases, history of trauma in the cervical region and diagnosis of neuropathic pain. The NDI questionnaire was used as interview and PPT was random assessed the in sternocleidomastoid, trapezius and suboccipital muscles with an algometer (Kratos, modelo DDK-10). The correlation was by verified Pearson correlation coefficient to a α=0.05 by SAS 9.2.

Results: There were moderate correlations for the migraine group, r (-0.53, -0.46 and -0.46) and weak correlations for chronic migraine group, r (-0.26, -0.16 and -0.18) for regions of the sternocleidomastoid, trapezius and suboccipital muscles, respectively.

Conclusions: NDI is correlated to the PPT in patients with migraine, emphasizing the importance of physical and functional assessment.

Table 1: Correlation between pain threshold for pressure and Neck Disability Index in migraine and chronic migraine groups.

Groups		NDI	ECM	TRAP	SUB
Chronic migraine (n=16)	NDI	1,000	-0,269	-0,163	-0,280
Migraine (n=16)	NDI	1,000	-0,534	-0,469	-0,469

NDI: Neck Disability Index, ECM: Sternocleidomastoid, TRAP: Trapezius, SUB: Subocciptal.

P79

The Effectiveness of the Injection of Botox in the Treatment of Transformed Migraine (TM)

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Objectives: The objective of this study is to evaluate the effectiveness of the injection of Botox in the treatment of transformed migraine (TM).

Background: Transformed migraine (TM) is a chronic, daily headache, with vascular quality. It usually occurs in people during their 20s and 30s with long history of migraines. Additionally, patients usually use large doses of analgesics and experience withdrawal headaches.

Methods: 40 patients were evaluated at the Pain & Headache Center, IMC, KSA according to IHS classification. Patients were allocated to receive either Botox injection which was perfomed as per the PREEMPT protocol [155-195 units] every 12 weeks for two cycles. Patients were not required to quit analgesics causing TM. The primary efficacy end point was mean change in headache days as per 28 days from baseline to weeks 21-24 post-treatment); or bridge therapy (N=21) as per patients' preference. (Dihydroergotamine; Valporic acid; Magnesium sulfate; Lornoxicam; and Granisetron) was provided as per protocol over 3-5 days. Oral bridge therapy (Eletriptan and Etoricoxib) was administered daily for 15 days. This was followed by Topiramate 100mg daily for 6 month as a preventive therapy. Inclusive criteria: 19 males, 21 females; ages 20-50 years, with a mean of 34. Exclusive criteria: pediatrics; patients older than 50, with uncontrolled diabetes, blood pressure, other neurological deficits; or pregnancy.

Results: Average symptomatic improvement of 79%, according to numeric pain scale, was recognized in patients receiving Botox therapy and appreciated within 10-15 days of therapy. However, an average improvement of 60% was recognized by patients receiving oral bridge therapy and appreciated within one month of therapy.

Conclusions: Patients who received Botox injection as per PREEMPT protocol showed more rapid and significant symptomatic improvement of their headache after the treatment as compared to the oral bridge therapy.

P80

Migraine with Visual and Sensory Aura after Atrial Septal Defect Closure

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Objectives: To describe a patient with atrial septal defect (ASD) closure presenting with migraine with visual and sensory aura and to review literature of similar cases.

Background: Patients with migraine prior to ASD closure commonly report a decrease or resolution of their headaches after surgery. However, 0.2 to 12% of patients experience new occurrence of migraine with aura (MA) or worseningof previous migraines after ASD closure. Ostium secundum comprise about 90% of all septal defects, and closure is via open-heart surgery or with less invasive cardiac percutaneous transcatheter closure devices. MA is reported more frequently in younger females undergoing percutaneous transcatheter closure. Most auras in these patients are visual and sensory auras are not commonly reported.

Methods: This is a case report and review of literature.

Results: A 22-year old woman presented to our clinic with complaints of new onset severe headaches associated with visual symptoms, one day after ASD closure via percutaneous transcatheter Amplatzer septal occluder. A 1.3 cm secundum type ASD had been diagnosed during workup of shortness of breath. Prior to surgery a transthoracic echocardiogram revealed 60% ejection fraction and a severely dilated right ventricle. Patient reported severe generalized throbbing headaches twice daily lasting over 4 hours. Her visual symptoms including zig zagging lines, a large fixed blank spot in her vision, photophobia, phonophobia, nausea, difficulty concentrating, and lightheadedness during these episodes. She also reported two episodes of numbness of the right cheek and right arm preceding her headache lasting less than an hour. She did not have a prior history of headaches and family history was unremarkable for migraine. Neurological examination and MRI of brain were unremarkable. A diagnosis of chronic MA was made and she was placed on daily preventative treatment for migraine. She reported that her migraine symptoms were much more disabling than her previous ASD related symptoms. Various etiologies leading to pathogenesis of migraine following ASD closure have been postulated including paradoxical embolism, paradoxical transfer of headache provoking neurotransmitters, changed intra-atrial pressure, platelet activation on the surface of the device, nickel allergy, or release of atrial natriuretic peptide associated with the stretch of the atrial septum caused by

the device. Presence of atrial shunts together with migraine with aura may be infrequently familial. We hypothesize that in our patient, increase in cardiac output and overall volume to the left side of the heart may have triggered migraines.

Conclusions: Young patients with valvular surgery should be counseled extensively regarding the risk of developing MA and its long-term implications. Migraine is a chronic neurological condition, however contrary to migraine without aura, MA is emerging as a specific entity with clear-cut risk among women of both symptomatic and asymptomatic strokes, and is associated with a higher cardiovascular morbidity and mortality. More research is necessary to confirm our findings.

P81

Withdrawn by the author.

P82

Resolution of Refractory Migraine with Sodium Oxybate

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Objectives: Is Sodium Oxybate (Xyrem) a possible treatment for refractory migraine headaches.

Background: There are very few treatment options available for patients with refractory headache. Many patients with chronic headache experience difficulty in initiating and maintaining sleep, along with a lack of quality sleep. We attempted to assess the efficacy of Sodium Oxybate (Xyrem) in a 25 year old female with an 18 year history of headache and an 8 year history of Chronic/Refractory Migraine Headache. The patient had been seen at numerous academic headache centers in the USA and tried on multiple abortive and preventative medications, undergone inpatient treatment and had a marginal response to a dual neuro-stimulation trial.

Methods: Retrospective case analysis using a visual analog pain scale and headache diary. Endpoints included the decrease in number of headache days, decrease in migraine days, and decrease in headache intensity at 24 weeks (VAS), decrease in overall disability (VAS). Epworth and pre and post poly-sonograms were used to measure sleep efficiency, latency to sleep, latency to REM, amount of REM sleep and alpha intrusion into stage 2 and 3 sleep.

Results: 24 weeks after initiating Sodium Oxybate our patient experienced improvement in the total number of headache days (-18), Migraine days (-12). Headache intensity was decreased and there was a marked improvement in overall disability. Improvements in sleep efficiency, latency, REM latency, and an improvement in the amount of REM sleep, along with a decrease in the amount of alpha intrusion into stage 2 and 3 sleep were also seen.

Conclusions: Sodium Oxybate may be an effective treatment for Chronic and Refractory migraine headaches in patients with underlying issues with sleep. Further controlled studies are needed.

P83

First Experiences with Onabotulinumtoxin A (Botox) in Patients with Chronic Migraine in Czech Republic-Preliminary Data

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Objectives: This is the first experience to assess efficacy, safety and tolerability of onabotulinumtoxin A (BOTOX) as headache prophylaxis in adults with chronic migraine in Czech Republic.

Background: Several studies have demonstrated a effect of onabotulinumtoxin A in patient with refractory chronic migraine.

Methods: ICHD-II criteria for chronic migraine were applied to symptoms described by patients headache. Diagnosis was made by ICHD-II criteria for chronic migraine. MIDAS and HIT-6 was applied in all patients at week 0 and at follow-up, three month and six months after first injection. Patients diary was provided for six months for documentation of headache episode frequency. All patients had poor headache control, poor quality of life, high disability scores and high acute medication intake.Subjects were treated to injections every 12 weeks of onabotulinumtoxin A (150 U). The primary endpoint was mean change from baseline in headache episode frequency at week 24. The second endpoint was mean change from baseline in HIT-6 and MIDAS at week 24.

Results: We reported preliminary data of 7 patients (2 males and 5 females), mean age 56 years (median 48 years), who fulfilled ICHD-II criteria for chronic migraine Mean score on a pain scale of 0-10 were 8 (standard deviation 2) at week 0, MIDAS grade IV (severe disability) at week 0 and HIT -6 mean score 65 (median 66) at week 0. Two patients (1 male and 1 female) interrupted treatment for lack of efficiency at

week 12. The rest of patients still take the treatment. The subjects had not any adverse event.

Conclusions: We need to treat more subjects with onabotulinumtoxin A. Unfortunately, health insurance not covered the treatment of chronic migraine with onabotulinumtoxin A (Botox) in Czech Republic.

P84

Ending Emesis: Use of Aprepitant To Manage Nausea Associated with Intravenous Dihydroergotamine (DHE)

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Objectives: To assess the efficacy and tolerability of oral aprepitant in controlling nausea associated with intravenous dihydroergotamine (DHE) administered for medically-refractory migraine.

Background: Intravenous DHE is effective in the treatment of medically-refractory migraine, particularly when nausea is well-controlled. Many patients have severe nausea despite the use of multiple anti-emetic medications. Aprepitant is a selective, high-affinity antagonist of the neurokinin-1 (NK_1) receptor that mitigates the emetogenic mechanisms associated with substance P. It is used in the prevention of postoperative and chemotherapy-induced nausea and vomiting, but has not been previously studied in the prevention of DHE-related nausea.

Methods: We reviewed prospectively collected inpatient data on nausea in patients with migrainous disorders admitted to the UCSF Headache Center for a five-day course of intravenous DHE and who received oral aprepitant as adjunctive anti-emetic therapy due to refractory nausea. Peak and average daily nausea scores were determined pre- and post-aprepitant from patients' hourly dairies (rating headache and nausea on a ten-point visual analog graph) and were categorized as mild (0-3), moderate (4-6), or severe (7-10). The efficacy of aprepitant was assessed via the following parameters: reduction in either average or peak daily nausea score, cessation of emesis following administration of aprepitant, and $\geq$50% reduction in the number of PRN anti-nausea medications.

Results: A total of twenty-three cases were identified, with admission diagnoses of chronic migraine with or without aura, medication overuse, and New Daily Persistent Headache of a migrainous type. In all twenty-three cases, aprepitant was found to be effective in reducing nausea in at least one of the three outcome measures; this was also reflected by patients' subjective report of effectiveness. Ten of these twenty-three patients (43%) demonstrated a response in all parameters. In all patients who developed emesis (n=10), the addition of aprepitant resulted in complete cessation of emesis. In the subgroup of patients withdrawing from cannabis (n= 6), nausea was noted to be particularly severe and all patients demonstrated a response in at least two of the three outcome measures. No side effects from aprepitant were reported by any patients.

Conclusions: Oral aprepitant appears to be a novel, effective, and well-tolerated treatment for controlling nausea and vomiting related to intravenous DHE administration. Confirmation of our findings through further prospective studies would improve current intravenous DHE protocols for the treatment of refractory headache.

P85

Interventional Therapies at the C1-C3 Nerve Roots for Headache Disorders

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Objectives: The objectives of this study are to characterize the pain referral patterns at the C1-3 levels through multimodal stimulation, and to investigate the potential efficacy of a novel, brief low temperature radiofrequency rhizolysis (BLT-RF) as a therapy for patients with occipital pain.

Background: The upper cervical structures are viewed as important targets for the interventional treatment in primary and secondary headache disorders. The specific role of the C1-3 nerve roots in the pathophysiology of headache remains uncertain. Cadaveric studies have shown the presence of dorsal root ganglia at the C1 level, which suggests a previously unrecognized sensory function. An increased understanding of the role of C1, C2 and C3 in head pain is important for the advancement of therapeutic interventions.

Methods: This study is a retrospective review of data from 12 patients with occipital pain (8 of whom also had migraine) who underwent multi-modal provocation at the C1, C2, and C3 levels under fluoroscopic guidance, followed by nerve root block with anesthetic and steroid. 9 patients underwent subsequent BLT-RF of the C1 spinal nerve and C2 and C3 dorsal root ganglia.

Results: All patients with migraine reported their typical periorbital or orbital pain with C1 stimulation. Patients

without migraine reported occipital or cervical pain with stimulation at the C1 level. Stimulation of the C2 and C3 level evoked pain in occipital and cervical distributions, consistent with previous reports in the literature. Patients who had temporary relief from the nerve block reported sustained pain relief of >50% from the BLT-RF for up to 11 months.

Conclusions: The periorbital or orbital pain produced by direct stimulation of the C1 spinal nerve suggests that the C1 nerve root level might be pertinent in headache disorders where pain occurs in the occipital and periorbital regions. Therefore, C1 may represent a therapeutic target for migraine and cluster headaches. The BLT-RF technique appears safe and effective with a longer duration of pain relief than nerve block with steroids.

P86

Evaluation of the Typical Duration of Migraine Aura: A Clinically-Based Study

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Objectives: To evaluate the distribution of the duration of each individual symptoms of non-hemiplegic migraine aura (NHMA) and of the whole NHMA in a clinically-based population of patients. We also analyze intra- and inter-patient variability of the duration of the aura.

Background: In the ICHD-II, NHMA duration is considered normal when it lasts between 5 and 60 minutes, whereas hemiplegic migraine aura can be longer. A recent systematic review of the topic (Viana et al., Cephalalgia, 2013 *in press*) did not find any article exclusively focusing on the duration of the aura. The pooled analysis of data from the literature on aura duration showed the prevalence of patients in whom the whole NHMA lasted for more than one hour varies between 11.6% and 31%.

Methods: We recruited 73 consecutive patients affected by NHMA at the Headache Center of Pavia and of Trondheim (55 and 18, respectively), with the intention to include a total of 100 patients. The study received the approval by the local Ethics Committees and all patients signed an informed consent form. All the patients prospectively recorded the characteristics of three consecutive attacks in an *ad hoc* aura diary that included the the time of onset and the end of each aura symptoms and the headache. The patient had to describe briefly each aura symptoms, the main characteristics of headache attacks and the timing of the analgesic intake. We also collected demographic and clinical data on each patient.

Results: Of the 73 patients recruited so far, 14 completed the diaries during three consecutive auras for a cumulative number of 42 auras recorded. Three patients dropped-out. Visual aura lasted for more than one hour in 13 out of 40 auras (32%), somatosensory aura in 5 out of 15 auras (33%), aphasic symptoms in 1 out of 4 (25%) and the whole aura duration in 15 out of 42 auras (35%). One patient out of 14 experienced one aura with visual symptoms lasting for 30 minutes in 2 episodes, 90 minutes in a third one.

Conclusions: Our preliminary data seem to indicate that the duration of NHMA, whether single symptoms or the whole aura, may be longer than one hour in a significant proportion of migraineurs.

P87

State Depression during the Migraine Cycle: A Prospective Study

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Objectives: Study the temporal relationship between timing of migraine attacks and depressive symptoms.

Background: Migraine patients have a three times more increased risk of depression. No studies have examined the temporal relationship between attacks and depressive symptoms.

Methods: We performed a prospective diary study in a large cohort of migraine patients (n=504). Migraine diagnoses were based on ICHD-II criteria. Participants filled out a daily diary on migraine status and depressive symptoms during a 1-month period. We randomly selected one whole migraine cycle per participant. A migraine cycle consisted of a continuous period of 1 inter-ictal day, 3 pre-ictal days and 1 migraine day. Also a recovery day was counted, as the first headache free day after a migraine cycle. In patients with one migraine day the recovery day followed directly after the first migraine day. In patients

with more than one migraine day the recovery day was the first headache-free day after a number of migraine days. Severity of depressive symptoms was defined using 5 questions, covering 5 items from the DSM-IV classification for depression. On each of these items participants indicated on a 5-point scale (0-4) to what extent this symptom was present on the current day (total scoring range from 0-20). Primary analysis was performed using a repeated measurements model with post-hoc testing. In a secondary analysis we tested whether the presence of depressive symptoms during the migraine cycle is influenced by lifetime depression.

Results: On the migraine day, participants scored significantly higher on the depressive symptoms scale (which does not indicate that they fulfil the criteria for a depression) than on all different days of the migraine cycle ($p<0.001$). The total score on the migraine day ranged from 0-18 (median 3). Persons with a lifetime depression scored significantly higher on all days of the migraine cycle than participants without a lifetime depression ($p<0.001$). No differences between participants with and without a lifetime depression were observed in the change of the depressive symptoms scores between the days of the migraine cycle.

Conclusions: Migraine patients report significantly more depressive symptoms during their migraine day than on all other days of their migraine cycle. This does not necessarily indicate that they fulfil the criteria for a depression. Migraine patients who fulfil the criteria for a lifetime depression have higher scores on all days of the migraine cycle.

P88

Association of History of Migraine with Aura and Larger Infarct Volume in Acute Stroke

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Objectives: To determine wither patients who have a history of migraine or aura develop larger infarcts in acute stroke.

Background: A history of migraine, particularly with aura, is a risk for stroke. Cortical spreading depression (CSD) is believed to occur both in acute stroke and migraine aura. Animal models suggest that CSD concurrent with ischemic stroke may be associated with larger infarcts. Individuals with migraine may be predisposed to CSD and therefore larger acute infarcts.

Methods: Patients able to communicate presenting to a single tertiary-care hospital with possible or confirmed acute stroke were interviewed to determine the presence and nature of current or past headache as well as any headache occurring within 24 hours of stroke symptom onset. Volumes of confirmed acute infarcts were measured from diffusion weighted and apparent diffusion coefficient images. A path model was hypothesized based on potential predictors of infarct size including stroke location, prior history of migraine, prior history of aura, and presence of peri-stroke headache.

Results: Data from 139 patients were analyzed using IBM SPSS v 20 with alpha set at $p < 0.05$. Results of the path analysis revealed that history of aura had a significant direct affect on infarct volume. The re-specified model indicated that without controlling for location, the geometric mean (GM) of the infarct volume for those without prior aura was 4.04 cm3 while the GM for those with prior aura was 10.89 cm3 (2.69 times larger) ($p < 0.0001$). After controlling for stroke location, the GM for those without prior aura was 1.22 cm3 while the GM for those with prior aura was 3.96 cm3 (3.24 times larger) ($p = 0.004$).

Conclusions: These data show, for the first time, an association between history of aura and larger infarcts. Further studies are needed to confirm this finding and explore its implications.

P89

Reliability of Assessing Lifestyle and Trigger Factors in Patients with Migraine

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Objectives: To compare the assessment of lifestyle and trigger factors in retrospective questionnaires to that in daily diaries, to analyse the correlation between these two ways of assessment and to examine how often possible trigger factors actually are followed by headache.

Background: Many lifestyle factors are blamed as triggers for migraine and headache. But most studies on triggers used patients' retrospective self-report and may suffer from recall bias.

Methods: Patients with migraine or probable migraine (without or with aura, without or with co-existing episodic

tension-type headache) filled in two questionnaires, one on lifestyle in general and one on trigger factors and then kept a diary. The questionnaires and the diary included the same set of 45 items possibly related to migraine. The questionnaires covered the previous three months and the diary had to be kept for the subsequent three months. In the diary, the patients had to assess each item every day irrespective of the presence of headache and they had to record the occurrence of headache as well as all headache characteristics required for diagnosing migraine and tension-type headache according to ICHD-2. We analysed the agreement between questionnaires and diaries and correlated the frequency of each variable of the lifestyle questionnaire to its frequency on all diary days and the frequency of each variable of the questionnaire on trigger factors to its frequency on day -1 as well as on day -2 and day 0 of headache onset.

Results: Of 415 patients screened, 327 patients with completed questionnaires and diaries were analysed (283 female, 44 male, mean age 41.9 years). We found a statistically significant correlation between lifestyle questionnaire and diary in 91% of the variables. In contrast, the questionnaire on trigger factors and the diary entries on days before headache onset correlated in 33% of the variables. Only 25 – 36% of all days with a certain possible trigger factor actually were followed by headache on the next day. Similar results were found for the days 0 and -2 of headache onset.

Conclusions: Comparing retrospective questionnaires to prospective diaries in patients with migraine, retrospective assessment of lifestyle is reliable, but headache triggers are overestimated when assessed in questionnaires. Therefore, prospective diary recordings should be used for assessing reliably the influence of headache triggers.

P90

Premonitory Symptoms as a Predictor for Migraine Attacks; a Cross-Sectional and Prospective Study

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Objectives: To assess whether migraine attacks can be predicted by migraine patients based on premonitory symptoms.

Background: A number of migraineurs might be able to predict their attacks with some degree of accuracy based on premonitory symptoms, which are reported by over 70% of patients and show large clinical heterogeneity. It is unclear whether groups of patients with specific premonitory profiles can be distinguished, elucidating possible distinctive pathophysiologic mechanisms involved in attack initiation. We aimed to investigate i) how well patients can predict their next migraine attack, based a) on occurrence of premonitory symptoms, and b) on subjectively assessed chances; ii) if a subgroup of well-predicting patients can be identified.

Methods: Prospective premonitory data were collected from migraineurs (n=711) via the LUMINA website by a web-based diary study in n=711 migraineurs. Data on occurrence and severity of 43 different premonitory symptoms were collected during one month. Patients scored each of the symptoms, and rated overall chance (0-100%) of getting a migraine attack the next day. General Linear Mixed Models were used to perform prediction analyses.

Results: In the prospective study, n=711 migraineurs reported 1,775 migraine attacks (mean±SD: 2.7±1.5 per person). In total, 88.8% of migraineurs reported premonitory symptoms, of which hypersensitivity and fatigue complaints were most common, followed by gastro-intestinal, affective and thermoregulation symptoms. Overall, premonitory symptoms (PS) were predictive of a migraine attack in the next three days (OR 4.04; 95%C.I. 0.46-35.81). A subgroup of migraineurs (10.8%) was classified as predictors, since they were able to well predict the occurrence of a migraine attack the next day based on an overall 0-100% score.This subgroup was able to predict a migraine attack within three days very accurately (OR 15.6; 95%C.I. 1.73-139.71).

Conclusions: Migraine patients can, overall, moderately well predict their next migraine attack, whilst a subgroup are very good predictors. Prediction of migraine attacks based on occurrence and severity of individual premonitory symptoms is comparable to a prediction based on an overall assessed chance.

P91

Autonomic Dysfunction in Migraine: Comparison between Migraine Populations with and without Orthostatic Intolerance

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Objectives: (1) To characterize any autonomic dysfunction in a population of migraineurs suffering from orthostatic intolerance (OI) and compare it with a population not suffering from OI, and

(2) To assess clinical neurocardiac physiological parameters and morphometrics of small fiber anatomy, including sudomotor innervation, on skin biopsy, in both populations.

Background: OI is defined by any combination of the following symptoms that arise when a patient assumes an upright posture: tachycardia and chest discomfort, fatiguability and exercise intolerance, lightheadedness and near syncope, inattention, anxiety, visual obscuration, acral symptoms and lower extremity weakness. OI is a manifestation of autonomic imbalance and may arise from central and/or peripheral nervous system dysfunction. The presentation of a migraine patient with OI is under-recognized and frequently misdiagnosed.

In phase I of this study, 37 male and female adults between 18 and 75 years, suffering from migraines with and without auras, as defined by the IHS, and who complained of symptoms of OI were studied with head upright tilt-table (HUT) testing, clinical autonomic reflex testing, quantitative sudomotor axon reflex testing (QSART), and punch skin biopsy for morphometric evaluation of small fiber density.

In phase II an age-matched population of 22 migraineurs with and without auras was studied in identical fashion, and the two populations were compared with respect to laboratory features and biopsy evidence of small fiber sensory neuropathy (SFSN).

Methods: Statistical analyses were both descriptive and comparative. Associations between quantitative results were estimated with Pearson and Spearman coefficients. Group comparisons for qualitative data were performed using chi-square or Fisher's exact test and comparisons of quantitave data were performed using T-test or Wilcoxon rank sum test.

Results: Phase 1 and 2 populations were demographically similar and overwhelmingly female.

In Phase I 36/37 patients (97%) had a positive 45 minute HUT (HUT45) [POTS +/- orthostatic hypotension (OH) +/-vasovagal response (VVR)] while 15/36 (42%) had a positive 10 minute HUT (HUT10). 21/37 (57%) phase I patients had a positive skin biopsy for SFSN while 16/37 (43%) had a negative skin biopsy.

Among Phase II patients HUT45 was positive in 15/22(68%) and negative in 7/22(32%). Positive and negative skin biopsies were distributed equally between both HUT45 positive and HUT45 negative groups.

Conclusions: Using clinical laboratory methods, including 45 minute HUT testing, detection of POTS, OH and VVR is common among migraineurs with and without symptoms of OI.

Biopsy presence of SFSN fails to significantly differentiate migraineurs symptomatic or asymptomatic of OI nor does it distinguish migraineurs with positive HUT45 from those who are negative.

Peripheral autonomic dysfunction, as measured by morphometric analysis of skin biopsies, fails to fully explain the cause of OI in migraine sufferers. Central nervous system dysfunction may also play a role.

P92

Evaluation of Balance in Vestibular Migraine and Migraine Patients without History of Vertigo

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Objectives: To assess and compare balance and gait between vestibular migraine (VM) patients and migraine patients without history of vertigo.

Background: VM is the second most common diagnosis in dizzy clinics. In addition to vertigo attacks, patients with VM might complain being off-balance causing some difficulties in their daily activities. A few studies show that migraine patients, even without history of vertigo, have subtle balance problems.

Methods: 30 definite VM patients, 26 migraine patients without history of vertigo (migraine only) and 30 subjects without migraine were studied. Twenty-six migraine only patients and 30 subjects without migraine were the control groups. Vestibular migraine patients were diagnosed according to Neuhauser criteria afer neurootological examination including bithermal caloric tests. Balance and gait were assessed by using of Clinical Test of Sensory Interaction and Balance, Berg Balance Scale, Dizziness Handicap Inventory, Falls Efficacy Scale and Dynamic Gait Index. Motion sickness susceptibility questionnaire short-form (MSSQ) was also given.

Kruskal–Wallis one-way analysis of variance was done for statistics using SPSS 15 software.

Results: VM patients demonstrated worse scores in all balance tests compared with two control groups. Migraine only patients showed significantly worse balance scores than migraine-free controls. VM patients and migraine only patients had significantly worse MSSQ

childhood section scores than controls, but there was not any difference between VM and migraine only patients, VM patients had significantly worse scores in MSSQ adult section than both migraine only patients and controls.

Conclusions: 1-VM patients have problems in static and dynamic balance and they have increased risk of falling and motion sickness intolerance. VM patients need vestibular rehabilitation for a better quality of life.

2-Migraine only patients also showed some significant balance problems. They might need vestibular rehabilitation for better daily activity performance. Migraine only patients had compansation in MSSQ adult section interestingly.

P93

Characteristics of Migraine with Aura in a Prospective Clinical Trial

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Objectives: To describe the clinical presentation of migraine with typical aura in a large group of patients enrolled in a clinical trial, and to compare self-reported migraine symptoms to prospective recordings of attacks in the same patients.

Background: About a third of migraine patients have attacks with aura, usually one or more neurological symptoms arising from the cortex or brainstem. The clinical presentation of aura can vary considerably and many descriptions of the clinical characteristics are based on purely retrospective studies.

Methods: 267 patients with migraine with typical aura according to current ICHD criteria were enrolled from 16 centers for a clinical trial. We reviewed data collected for this trial regarding the clinical presentation of migraine aura, headache, and associated symptoms. Baseline characteristics provided by patients on inclusion were compared with migraine symptoms collected prospectively during the study. Only attacks starting with a migraine aura were recorded.

Results: The majority of patients (70%) reported that more than 50% of migraine attacks were preceded by aura. Visual aura symptoms were reported by all patients, the most prevalent symptoms being dots or flashing lights (70.4%), wavy or jagged lines (46.8%) and blind spots (42.3%). Non-visual aura was less prevalent, reported by around half the patients. The most prevalent non-visual aura symptoms were somato-sensory(29.5%), difficulty in recalling or speaking (25.8%) and changes in smell (18.7%). Symptom intensity for migraine related symptoms (pain, nausea, photo- and phonophobia) was mainly ($\geq$70%) graded moderate to severe. Patient reported data prior to the trial indicated a consistently higher symptom score (more severe phenotype) than in the prospectively collected data, ($P<0.01$ for all) (figure 1).

Conclusions: Based on this large clinical collection of data exclusively from MA attacks, we show that visual aura symptoms are more prevalent than non-visual aura symptoms. The severity of self-reported migraine symptoms was great than that recorded in the prospective data set.

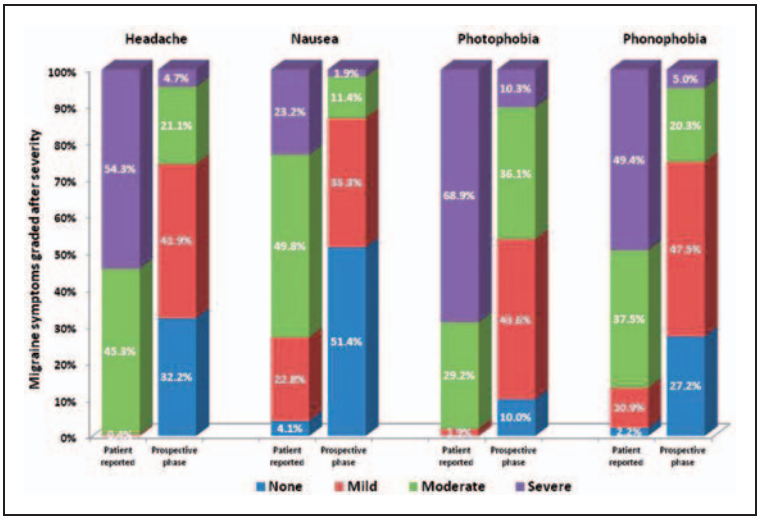


Figure 1. Columns on the left for each symptom are patient-delivered data (N=267 attacks) and columns on the right are from the prospective recordings (N=365 attacks).

P94

Resource Utilization and the HIT-6 Score in Migraine Patients

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Objectives: This study examines the association between migraine patients' HIT-6 score and their resource usage as measured by phone contacts and unscheduled visits with the University of Pittsburgh Headache Center, as well as emergency department visits.

Background: The Headache Impact Test-6 (HIT-6) score is simple questionnaire that headache patients can complete while waiting for their headache provider. It assesses six aspects of a patient's headaches: pain, daily activities, social impact, energy level, emotional impact, and concentration. The HIT-6 score has been validated as a measurement of the impact of headache and its treatment on an individual's functional health and well-being. However, no studies have been performed that examine the HIT-6 score's ability to predict resource utilization among migraineurs.

Methods: The study was a retrospective cohort study. Patients visiting the UPMC Headache Center from April 1, 2010 to August 31, 2010 diagnosed with migraine headaches were recorded into the data set. A total of 627 patient visits were recorded with each record representing a unique patient. Patients' HIT-6 scores were recorded along with all contacts with the UPMC Headache Center over the following six months. Cochran-Mantel-Haenszel X^2 statistics, single variable ANOVA models, and logistic regression models were used to test the HIT-6 score's association with other variables in the data set.

Results: The HIT-6 score was associated with many aspects of lifestyle disturbance, both relating to the patients' migraines and not. Positive correlation was seen between the HIT-6 score and all levels of migraines recorded in the data set (total, severe, and incapacitating). Additionally, association was seen with other markers of migraine impact such as ED visits in the previous six months, presence of insomnia, and medication usage over the previous 30 days. Positive correlation was also seen with depression rating and anxiety rating (both a 0 – 10 self-assessed rating). Most importantly, HIT-6 scores were statistically associated with the number of unscheduled contacts a given patient had with the UPMC Headache Center over the 6 months following the visit where the HIT-6 questionnaire was administered.

Conclusions: The HIT-6 score is a simple questionnaire, yet a high score clearly paints a distinct portrait of a patient struggling with high migraine burden. A high HIT-6 score reveals a patient who may be using significant medication but is still suffering from debilitating headaches. This patient is more likely to suffer from depression and anxiety, and is more like to be sleeping poorly. Additionally, these patients are much more likely to have repeat contact with their headache provider, defined as either a telephone call or unscheduled visit to the office. Identification of these migraineurs and devotion of additional education regarding care plans could potentially reduce costs associated with office contacts.

P95

Cluster Headache and Depression: A Case-Control Study

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Objectives: To investigate the comorbidity of cluster headache and depression.

Background: Cluster headache is often called suicide headache, and suicidal tendencies have been reported in 25-55% of patients. However, the comorbidity of cluster headache and depression has not been extensively studied.

Methods: We performed a large case-control study within LUCA (Leiden University Cluster headache neuro-Analysis programme). CH diagnoses were based on ICHD-II criteria. Depression was assessed using validated depression questionnaires (HADS and CES-D) and supplementary questions on lifetime depression. Data were analyzed with logistic and linear regression models.

Results: Cluster headache patients (n=462) had an almost three times higher odds for lifetime depression than healthy controls (n=177) (OR 2.8; 95% CI 1.7-4.5). Furthermore, having chronic cluster headache and having active attacks (last attack < 1 month) were associated with current depression. The latter seems to be explained by sleep disturbances (presumably due to nocturnal cluster headache attacks).

Conclusions: Cluster headache patients have an almost three times increased risk for lifetime depression. Active depression is presumably explained by sleep disturbance due to current nocturnal attacks.

P96

Pain Rehabilitation: Can It Help Patients with Intractable Headache?

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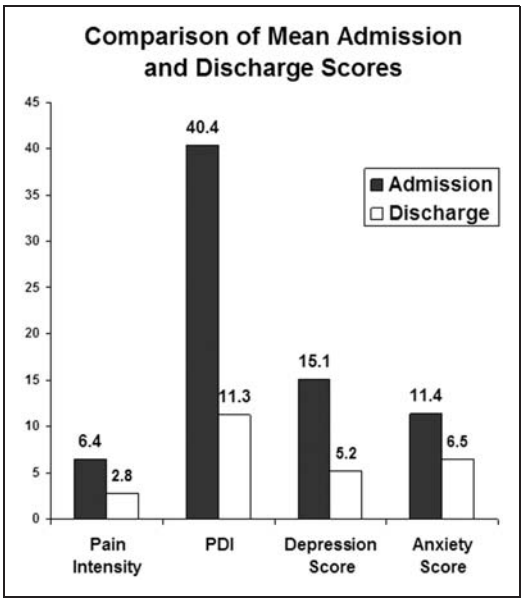
Objectives: To assess the efficacy of chronic pain rehabilitation programs in treating headache as an alternative to primary or tertiary standard care.

Background: Incapacitating headaches can have a significant impact on people's lives. Studies have investigated both prevalence and medical treatment of chronic headache, but few have reported on the efficacy of treating these disorders within a comprehensive, intensive interdisciplinary chronic pain rehabilitation program (CPRP). CPRPs provide team based comprehensive treatment of headache, focusing not only on physical pain, but also its association with impaired mood and function.

Methods: Retrospective analysis of 200 patients (80% female), ages 19 to 75, who completed the CPRP at the Cleveland Clinic, January 2007 - December 2011, diagnosed using International Headache Society (IHS) criteria with migraine or headache as a major complaint. Outcome measures included: pain intensity scores (0-10/10), Depression Anxiety Stress Scale (DASS) scores, (measuring mood), and Pain Disability Index (PDI) scores, (measuring function). Data were collected at admission, discharge, 6 months, and 12 months following discharge. Repeated measures T-test were used.

Results: There was a significant difference in pain intensity scores between admission (M=6.59, SD=2.34) and discharge (M=3.54, SD = 2.67); $t(122)=11.83$, $p<0.001$. Pain intensity scores decreased by 3.6 points from 6.4 to 2.8, which is clinically significant.Similarly, there was a significant difference in admission (M=42.4622, SD=11.62317) and discharge (M=17.6218, SD=13.27496) scores for PDI; $t(118)=18.406$, $p<.001$. PDI scores decreased by an impressive 29.1 points, shifting from 40.4 (severe disability) to 11.3 (mild disability). There was also a statistically significant difference between depression scores at admission (M=19.4837, SD=13.17862) and discharge (M=6.2480, SD=8.25102); $t(122)=10.873$, $p<.001$. An average decrease by 9.9 points for depression indicates a shift from a score of 15.1 at moderate to 5.2 at normal levels of depression. Admission (M=14.2724, SD=10.07518) and discharge (M=7.0325, SD=7.59415) scores for anxiety were also significantly different; $t(122)=8.409$, $p<.001$. Anxiety scores dropped an average of 4.4 points from 11.4 to 6.5, which is a shift of one category from moderate to mild. Results indicate that individuals had statistically and clinically significant improvement in pain, mood, and function at all time points.

Conclusions: An interdisciplinary chronic pain rehabilitation approach for patients diagnosed with headache can be effective in helping to decrease pain, as well as in normalizing mood and function. Thus, CPRPs may serve as an alternative treatment to primary and tertiary standard care, and interventional pain anesthesia.



P97

Migraine and Benign Paroxismal Positional Vertigo

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Objectives: The aim of our study was to determine one-year prevalence of migraine in patients with Benign paroxysmal positional vertigo (BPPV) compared to an age- and sex- matched orthopedic control group.

Background: BPPV is most common cause of episodic vertigo. Pathophysiological or statistical links between vestibular migraine/Meniere's disesae and migraine were documented. A potential link between migraine and BPPV was also suggested.

Methods: A prospective study was conducted on a consecutive series of 184 patients (68 male, 116 women, aged from 14 to 85) with idiopathic BPPV. The diagnosis of BPPV was based on typical findings of vertigo and nystagmus by Dix-Hallpike maneuver and head turning in supine position. The diagnosis of migraine was made on a personal interview with structured questionnaire according to the International Classification Headache Disorders (ICHD-2).

Results: The prevalence of migraine was not higher in the BPPV (5.4%) group compared to the control group (10.8%; p=0.09). All of the 10 patients with BPPV and migraine were migraine without aura.

Conclusions: One year prevalence of migraine is not increased in patients with BPPV. It is unlikely that migraine and idiopathic BPPV is interrelated.

P98

Presence and Disability Related Dizziness in Migraine Patients with and without Aura

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Objectives: To evaluate the presence and disability related dizziness using the Dizziness Handicap Inventory (DHI) in migraine patients with aura (MA), without aura (M) and control group (CG).

Background: The relationship between vestibular disease and dizziness in migraineurs is well established, showing an increased risk of presenting vertigo and balance problems. The DHI it's feasible to measure the self-perceived level of handicap associated with dizziness assessing physical, emotional and functional tasks. Higher scores are associated with functional deficits in physical examinations and history of falls. Nonetheless, the impact of dizziness in migraneurs is unexplored, especially in patients with aura.

Methods: Women were selected in an outpatient headache clinic and were diagnosed with MA or M by neurologists experts on headache according to ICHD-II (2004). Exclusion criteria included history of vestibular problems, systemic disorders or other primary headaches. Based on a sample size calculation (α=5%, β=80%) were selected 92 volunteers, 31 with MO (38±10), 31 with MA (37±8) and 30 CG (33±9), witch were matched to patients by age. To compare dizziness between groups, logistic regression and odds ratios were calculated. Results of the DHI test were contrasted using the Kruskal Wallis test to a α<0.05, using SAS 9.2.

Results: A total of 80% of those with MA, 65% of M and 6.5% CG reported dizziness (p<0.0001). MA increased risk of dizziness by 58 times relative to controls, and M increased the risk by 25 times. Also DHI scores were significantly higher in those with migraine relative to controls (p<0.01). Both migraine groups had average scores classified as moderate impact for all three aspects (physical, psychological, and functional) compared to controls (p<0.001). The migraine groups were different to CG on the levels of severities.

Conclusions: The disability related dizziness is greater in migraneurs than controls, without influence by aura. Presence of migraine, especially with aura, increases the

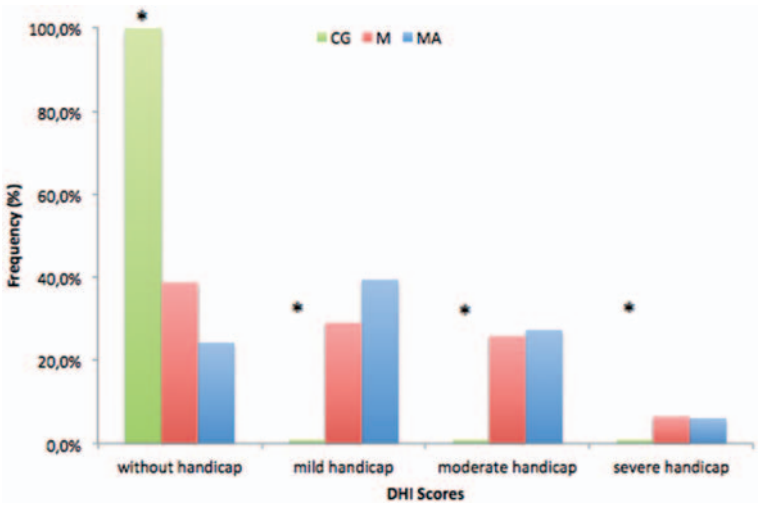


Table 1 –Prevalence and Relative risk for symptoms of dizziness in individuals with migraine, relative to controls.

	CG (n=30)	M (n=31)	MA (n=31)
Report of Dizziness (%)	6,5%*	65%**	80%
Relative Risk (*r*/CI)[a]	ref	25 / 5-127	58 / 10-315

[a]Relative risk and Confidence Interval.* $p<0,0001$ CG *versus* M e MA.** $p<0,001$ M *versus* MA.

risk of developing dizziness. The dizziness is prevalent in individuals with migraine, impacting several aspects of daily life.

P99

Clinical Predictors of Migraine Evolution in Elder Age

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Objectives: The study was focused on revealing clinical predictors of M evolution/outcomes in M patients after the age of 50.

Background: It is known that migraine (M) could have different evolution pathways in elder age including total cessation, partial cessation (M aura without headache - late-life M accompaniment or Fisher's syndrome) and M continuation/persistence with typical attacks. M evolution in elder age as well as factors determining M outcomes were not previously studied.

Methods: M patients suffering both from MO and MA (n=54, F-51, M-3, 50 to 75 y.o.) were divided according to outcome of the disease into 4 groups: 1) total cessation during $\geq$1 year of both pain attacks and aura (n=11, m.age 60), 2) partial cessation (Fisher's syndrome) - the loss of pain attacks during $\geq$1 year but with M aura preservation (n=8, m.age 54), 3) M regress when M attacks became less severe (n=20, m.age 57.5) and 4) M persistence with typical and severe attacks comparable to those in the middle age (n=15, m.age 55). All patients underwent clinical interview with careful history focused on clinical manifestations during illness course and filled in headache diary.

Results: According to the data obtained **predictors of favorable M outcomes** (total cessation and regress, groups 1 and 3; $p<0,05$) included: initial form "M with aura", low attack frequency in active disease period (at age 30-40) and complete stabilization of hormonal state by the time of observation (menopause). **Predictors of unfavorable outcomes** (persistence, group 4): initial form "M without aura", high attack frequency in the middle age and fluctuating hormonal state by the time of observation (for females active menstrual cycle or premenopause). For group 2 with the cessation of pain and preservation of M aura only one predictor was revealed - initial form "M with aura".

Conclusions: Main clinical predictors of M outcomes in the elder age include initial (in active disease period) form of M and attack frequency and the hormonal state (for female patients presence/absence of hormonal fluctuations).

P100

The Use of the Lamotrigine for Treatment of Migrainous Headache in Missouri Veterans with Comorbid PTSD

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Objectives: The study was performed to assess the possible utility of lamotrigine for management of headache in the veteran population with PTSD.

Background: Lamotrigine has been shown to have little value for headache management outside of SUNA/SUNCT or perhaps migraine with aura. Migraine without aura has not been found to respond well to lamotrigine. It has been shown, though, to be effective for the treatment of psychiatric disturbances such as bipolar disorder and PTSD.

Methods: The nature this study was a chart review and retrospective analysis initiated after it was noticed serendipitously that when lamotrigine was used to treat the psychiatric symptoms of PTSD in the veteran population in mid-Missouri some patients diagnosed with migraine headaches without aura reported decreased headache frequency. Initial headache frequency was compared to frequency after approximately 6 months of treatment. The final dose of lamotrigine ranged from 100mg/day to 200mg/day with the average being 121mg/day.

Results: Of the initial 15 patients evaluated, 13 reported greater than 50% reduction in headache frequency, which was the cut-off we used to define a good response to therapy (84.7%). None of the patients noted a dramatic decrease in headache intensity. The initial headache frequency ranged from 13 a month to daily with an average of 25.4 headaches per month (standard deviation 6.9). The final headache frequency ranged from one or less per month to one per day, the average final frequency being 7.2 per month (standard deviation 8.3), a 75.7% improvement in headache frequency (standard deviation 22.4).

Conclusions: Our findings indicate that there may be a place to use lamotrigine for the management of headache with co-morbid PTSD.

Patients n=15	Number	Percent	Standard deviation
non-responders	2	13.3	N/A
responders	13	86.7	N/A
Headache days /mo. ave. at treatment onset	25.4	84.7	6.9
Headache days/mo. ave. at 6 months	7.2	8.3	8.3
Average Headache day reduction	18.2	22.4	22.4

P101

Blood Pressure and Heart Rate during a Migraine Attack

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Objectives: To analyse the behavior of blood pressure (BP) and heart rate (HR) during the headache of a migraine attack.

Background: There are controversies concerning the relationship between blood pressure and headache. Moreover, there are no detailed studies on the behavior of BP and the HR during the headache of a migraine attack.

Methods: Ten patients (nine women), 21 to 43 years-old, with migraine diagnosis were selected. They had from 3 to 11 days of headache a month, no other health problem, or use of any medication other than analgesics. Hypertension was ruled out through 24-hour ambulatory BP monitoring (Dyna-MAPA ABP-Monitor, Cardio Sistemas Coml. Indl. Ltda, Brazil). The patients were trained to use a home blood pressure monitoring (HBPM) device (Dyna Klock, I.E.M. GmbH, Germany). To obtain the measurements from pain-free period, they were asked to measure their BP from 4 to 5 consecutive days, 6 times a day (2 in the morning, 2 in the afternoon, 2 at night) and to write in a card, simultaneously, if they were symptoms-free or not. We only considered the measures made on symptoms-free period. To obtain the measurements from headache period, the patients were asked to perform the HBPM from the beginning to the end of the headache. During the first two hours of pain, they measured the BP each 10 minutes, and after that each 15 minutes until the end of the headache. Patients completed a headache diary in the beginning of headache and once per hour until the end of the pain in order to certify the migraine attack. Due to ethical issues, the use of 400 mg of ibuprofen was allowed from the end of the second hour of pain. To statistical analysis, the mean values of systolic (SBP), diastolic (DBP), mean blood pressure (MBP) and HR from pain-free period were compared with the mean values of these variables from headache period.

Results: Comparing the mean values of BP from pain-free period to those from headache period (SBP 119,09 vs 108,77 – IC95% 7,25-11,58; DBP 76,68 vs 70,35; IC95% 3,94 – 7,10; MBP 90,69 vs 83,15; IC95% 5,24 – 9,85), we observed a statistically significant reduction in BP during headache ($p \leq 0{,}01$). Comparing the mean values of BP from pain-free period with those from headache period divided hourly for the first four hours of pain, we observed a progressive reduction in BP (SBP, DBP and MPB) between the first and second hours of pain and a sustained reduction between the second and fourth hours. With regard to HR, we observed a statistically significant increase in the mean values during the first hour of headache with no differences in the remaining hours.

Conclusions: We observed a progressive reduction in BP during the headache of a migraine attack, and an increase in HR in the first hour of pain.

P102

Optimization of Headache-Patient Satisfaction with an ICHD-II Based Exhaustive Questionnaire

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Objectives: To optimize forms and/or implementation procedure of an exhaustive headache questionnaire (**ExQ**) to maximize patients' satisfaction.

Background: An ExQ is a valuable means of exploring the relationship between the patients' symptoms and headache diagnoses. However, it can also be frustrating because of its length and complexity. In the worst case, that frustration may precipitate the patients' withdrawal from a headache specialty outpatient clinic.

Methods: This study was approved by the ethics committee of our hospital. **Participants:** 441 associates of our institution (287 females). **The ExQ**: From the complete ICHD-II we extracted 247 questions which could be answered by participants' statements. These items and additional symptom-related questions not derived from ICHD-II were subdivided into 16 categories and then arranged in the following order: Patient information, Headache Impact Test 6 (**HIT-6**) (1), Migraine Disability Assessment Scale (**MIDAS**) (2) and the questions we created. Participants with headache were asked to base their answers on their own headache experience and then to evaluate the ExQ whereas those without headache were asked only to evaluate it 'objectively'. **Evaluation of the ExQ:** We created an interview form to help standardize evaluation of the ExQ. It comprised; i. The time required, ii. Impression of time required to apply the ExQ, iii. Sufficiency (**SF**: this indicated whether the ExQ was able to identify adequately the headache characteristics. iv. overall satisfaction (**OS**). The latter three items were measured using a visual analogue scale (**VAS**) with verbal anchors. Two copies of this interview form were inserted, one in a random position and the other at the end of the ExQ section. This randomization enabled us to determine the correlations between the number of questions and the VAS values. Provisional headache classification was determined based entirely on ExQ. **Statistics:** We evaluated the correlations by Spearman's rank correlation coefficient (ρ) because no normal distribution was shown. The comparisons of first and second interview form values were expressed by the Wilcoxon signed-rank test.

Results: 224 participants had headache (migraine: 59, tension type headache: 123). In the first interview form, the headache group's OS did not correlate with the number of questions, time required or impression of amount, but did correlate with SF (ρ=0.6560, $p<0.0001$). HIT-6, MIDAS and headache types didn't affect this correlation. The first and second interview values showed no significant difference. Only OS correlated with SF. Objective evaluation of the non-headache group didn't show any correlation between OS and SF.

Conclusions: OS is improved only if the headache patient feels sufficient empathy. The answer to "How many questions are enough" 'is individually diverse. Multiple questions don't always lower the patients' satisfaction. However, in this study, any modifiable factor which defines SF could not be identified. For now, it is appropriate to use the ExQ unchanged and allow patients to answer in sections as inclined.

P103

The Presence of Osmofobia Improves the Diagnosis of ID-Migraine?

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Objectives: The advent Migraine extended-ID aims to compare the ID-Migraine with ID-Migraine plus question about osmophobia for greater accuracy in the diagnosis of migraine.

Background: Migraine causes a great impact on health of their patients, affects about 18% of women and 6% of men, with peak prevalence between 25 and 55 years of age. The advent Migraine extended-ID aims to compare the ID-Migraine with ID-Migraine plus question about osmophobia for greater accuracy in the diagnosis of migraine.

Methods: It was included in this study a total of 269 patients waiting for neurological evaluation at the neurologic clinic. Willingly, they completed the questionnaire ID Migraine with an extra question about osmophobia, considered positive for the diagnosis of migraine when they responded positively to at least two of the four questions total. Then, in consultation with the neurologist, we used the criterias of the International Classification of Headache for the diagnosis of migraine, enabling, in this way, the comparison between the test result and diagnosis of the specialist. We calculated the Kappa coefficient, rates of sensitivity, specificity and accuracy to verify the statistical significance.

Results: The results confirm the relationship of migraine diagnosed clinically with gender (females are more frequent among patients) and at the age of study participants (persons <40 years are more frequent among patients). The results also show that brings osmophobia small gain in sensitivity and little loss in specificity of ID-Migraine in the diagnosis of migraine, ie without osmophobia is more than sufficient to diagnose preliminarily migraine.

Conclusions: The question osmofobia didn't improve the sensitivity and specificity of the ID-Migraine.

P104

Headache Prevalence and Clinical Features in Patients with Idiopathic Intracranial Hypertension (IIH)

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Objectives: Aim of this study was to investigate the prevalence and the main headache features in patients with IIH and to explore possible correlations with body mass index (BMI) and intracranial pressure (ICP) levels.

Background: Idiopathic intracranial hypertension (IIH) is the syndrome of elevated intracranial pressure in the absence of space occupying lesions or other brain disorders. Although IIH may be heterogeneous as far as clinical presentation headache is one of the most common symptoms.

Methods: Aim of this study was to investigate the prevalence and the main headache features in patients with IIH, and to explore possible correlations with body mass index (BMI) and intracranial pressure (ICP) levels. Differences for age, BMI and ICP between patients with and without headache, as well as differences between those with and without obesity for ICP, were assessed with Mann-Withney U test.P-value $<.05$ was used to set statistical significance. A consecutive clinical series of IIH patients with demonstration of increased ICP by lumbar puncture in the recumbent position were enrolled.

Results: Among a total of 40 patients (9M, 31 F mean age at observation 39,8 yrs.), headache was reported by 30 (75 %). Considering the headache features at least one of which is required for diagnosis of headache attributed to IIH according to ICHD-II, daily or nearly-daily was present in 73,3 %; diffuse/non-pulsating pain in 80 %; aggravation by coughing/straining in 56.6 %. The three headache characteristics were all present in 36,6 %. In 26,7 % headache was pulsating, in 20 % unilateral, and migrainous associated symptoms (nausea or photophobia-phonophobia) were described in 43,3 %. No differences were found for age, BMI and ICP between patients with and without headache; no differences were found between those with and without obesity for ICP, and between those with and without severe intracranial hypertension for age and BMI.

Conclusions: These results confirm the strong association between headache and IIH. They indicate that further studies are warranted in order to assess the possible relationships between this key symptom and other IIH features, and propose possible changes in the current ICDH-II criteria for headache attributed to IIH, considering the high frequency of migrainous symptoms as well as the recently proposed association between chronic migraine and IIH without papilledema.

P105

Dream-Enacting Behaviour in Migraine Patients: Association with Impaired Sleep and Severe Headache-Related Disability

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Objectives: To investigate the clinical correlates of dream-enacting behaviours (DEB) in migraine patients.

Background: Sleep disorders, nightmares and visual hallucinations have been reported in migraine patients, which may suggest the involvement of rapid eye movement (REM) sleep regulation in migraine. However, the association betweenmigraineand REM sleep behaviour disorder (RBD) has never been studied.

Methods: We performed a cross-sectional, case-control study including episodic migraine patients ($n = 161$, mean age 33.1 years) and headache-free control subjects ($n = 140$, mean age 33.1 years) under 50 years of age. The Japanese version of the RBD screening questionnaire was used, and subjects scoring 5 or higher were defined as having DEB.

Results: A significantly increased frequency of DEB was observed in migraine patients compared to controls (24.2% vs. 14.3%). Migraine patients with DEB showed higher scores on the Migraine Disability Assessment and Pittsburgh Sleep Quality Index and an increased rate of smoking compared to migraine patients without DEB. Duration of migraine and headache frequency and intensity were not different between migraine patients with or without DEB.

Conclusions: DEB was associated with impaired sleep and severe headache-related disability in migraine patients. We suggest that DEB may reflect brainstem dysfunction and increased brain excitability in migraine patients.

P106

Preliminary Data from a Headache Prevention Program in a Brazilian Public Financial Institution

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Objectives: The purpose of this study is to evaluate the first 25 patients treated for chronic headache in a Brazilian non-medical public institution.

Background: Chronic headaches patients commonly present with low scores in quality of life questionaries, loss of job opportunities, absenteeism, presenteeism, psychiatric and non psychiatric comorbidities, social isolation and are unemployed[1-3]. The medical literature gives us many examples of the efficacy of medical programs dedicated to the trreatment of chronic headaches, even when implemented in primary-care non-medical institutions[4]. Chronic headaches are highly prevalent in Brazil[5]. In a study performed in the city of Florianópolis (Santa Catarina State, Brazil), the one-year prevalence of headache was 80.8% in the general population. The prevalence of migraine, tension-type headache (TTH) and chronic daily headache (CDH) were, respectively 22.1%, 22.9% and 6.4%[6].

Methods: This is a retrospective analysis of the medical records of the first 25 patients followed in our Medical Outpatient Clinic for the treatment of chronic headache.

Results: Twenty five patients presented for the treatment of headache. Nineteen (76%) were female. The median age was 39.6 years (range 26-67). Thirteen patients (52%) presented with typical migraine. Eight (32%) had migraine in association with psychiatric disorders and TTH. Overall, 84% of the patients were migrainous. Tension-type headache was observed in 10 patients (40%). In two cases of the TTH group (20%), this was their only diagnosis. In eight patients of the same group (80%), TTH was associated with migraine and mental illness. Two patients (08%) were diagnosed as having CDH and analgesic abuse. One patient (4%) had a cervicogenic headache, and one was diagnosed as having Glioblastoma Multiforme. Nine patients (36%) were treated with Beta-blockers and 07(28%) with Topiramate. Non-pharmacological interventions were used when appropriate. Eighteen patients (72%) reported an improvement of at least 50% of their symptoms. Three patients (12%) abandoned treatment. The follow-up visits of the five most recent patients are still pending.

Conclusions: Preliminary data from the first 25 patients treated for chronic headache in our Institution showed that the most common diagnosis was migraine with or without aura. This is consistent with the medical literature that indicates that migrainous patients are usually those who look for prevention programs more often. Our small-scale study also demostrates that even in a primary-care non-medical institution, programs dedicated to the prevention of chronic headaches can be truly effective and should be implemented.

P107

Decubitus as Aggravating Factor of Headache in the Crisis Migrainous

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Objectives: 1) Check in a sample of patients migraneurs, the percentage of those who complain of worsening headache during the crisis, by recumbency. 2) Check if there are differences with respect to worsening by recumbency between the gender.

Background: The migraine attacks are often disabling. The physical activity and movements of the lower head are recognized factors of transient increase in pain intensity during crises. For this reason, many patients seek rest. In clinical practice, it appears that some patients complained of worsening headache by lying down, during migraine attacks, preferring to remain seated or reclining position. This finding, to our knowledge, not been studied.

Methods: A retrospective analysis of medical records. We evaluated the clinical history of 734 consecutive patients with a chief complaint of headache, attended in a tertiary clinic since it started using the program Hypatia (tutorial and database headache). Using the search filters, we selected patients who received a diagnosis of migraine in any of its forms (1.1 to 1.6 Classification of IHS 2004) a total of 563 (76.7%). All patients were questioned about the factors worsening headache, during the crisis, including the decubitus. The who reported worsening by recumbency were recorded and divided according to gender.

Results: Of the 563 patients (482 women - 85.6%, 81 men - 14.4%) diagnosed with migraine, 20.8% (n = 117) complained of aggravation by recumbency.

Of these, 89.7% (n = 105) were women and 10.3% were men (n = 12).

Conclusions: The worsening of headache by recumbency is more frequent in females, as well as migraine. We believe that the increased venous return in the decubitus and, consequently, the pulse pressure is possibly one of those responsible for the aggravation of headache by recumbency



Figure 1 - Percentage of the patients with migraine who complained of headache by recumbency

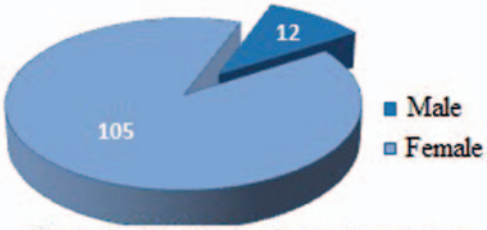


Figure 2 - Distribution by gender among patients who complained of headache by recumbency

P108

Decreased Affective Response and Increased Perceived Exertion to Aerobic Exercise in Migraine Patients

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Objectives: We aimed to study affective response and perceived exertion to aerobic exercise (AE) in M patients.

Background: Migraine (M) patients have low physical activity levels and often fail to comply with aerobic exercise and other prescribed treatment recommendations, but little is known about its mechanisms. Affective response to aerobic exercise is positively correlated to exercise intensity and predicts 6 and 12-months exercise compliance.

Methods: Ten migraine patients taking no preventive medicine (1m/9f; age: 37,1±14,2; BMI: 26,9±5,6) and 10 matched control subjects (1m/9f; age: 35,1±10,1; BMI: 24,3±2,2) were included in the study. All subjects signed informed consent. Cardiopulmonary exercise test (CPET) was performed for determination of peak oxygen uptake (VO2Peak) and ventilatory threshold (VT). An AE session was conducted for 30 min at workload corresponding to VT. The Feeling Scale was applied before (FS pre), during (FS dur; at 15') and just after termination of AE (FSpos). For perceived effort assessment, Borg's Scale was applied at the last minute of AE. All measurements were undertaken in the interictally period (headache-free day).

Results: M patients and controls had not headaches along the AE session. Clinical features and maximal CPET parameters were equal in both groups. M patients had significantly lower VE/VO2 at VT [$F(1, 18) = 4{,}807$; $p = 0{,}042$] and lower affective response than controls, FSdur [$F_{(1, 18)} = 5{,}737$; $p = 0{,}028$]. M patients presented a higher exercise effort perception, Borg's Scale [$F_{(1, 18)} = 4{,}469$; $p = 0{,}049$]. There were main effect of time and group [$F_{(2, 17)} = 5{,}664$; $p = 0{,}013$], but no interaction.

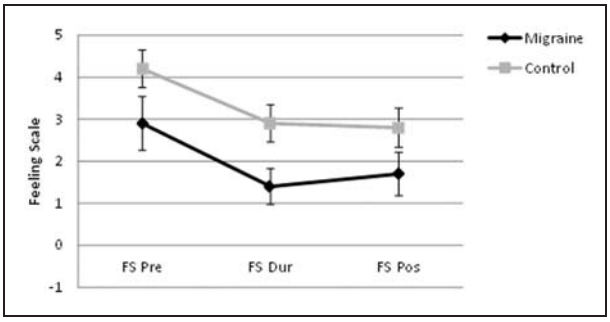
Conclusions: M patients have decreased affective response and increased perceived exertion response to AE. The AE prescription should be revisited in M patients regarding the current recommendations for a better compliance.

Characteristics	Migraine (n=10)	Control (n=10)
Sex(%)		
Male	1(10)	1(10)
Female	9(90)	9(90)
Age(y)	37,1±14,2	35,1±10,1
BMI(Kg/cm^2)	26,9±5,6	24,3±2,2
MwA	7	-
MwoA	3	-
M Dur (y)	12,1±9,4	-
Days with M	10,5±5,5	-
M Freq	8,4±4,4	-
Disability (0-3)	1,56±0,4	-
Cardiopulmonary Data		
VO_2Peak	29,1±6,8	32,0±3,7
HRmax	177,9±17	185,9±8,6
VT (%VO_2Peak)	58,6±9,5	52,9±6,0
HR at LV	127,9±21,0	123,6±13,9

(continued)

Continued

Characteristics	Migraine (n=10)	Control (n=10)
VE (L/min) at VT	30,2±5,3	29,4±4,9
VE/VO_2 at VT	23,1±2,9 *	25,6±2,2
VE/VCO_2 at VT	29,6±3,7	31,7±2,1
Affective Response		
FS Pre	2,9±2,0	4,2±1,4
FS Dur	1,4±1,3 *	2,9±1,4
FS Pos	1,7±1,6	2,8±1,5
Perceptual Response		
Borgs Scale	12,3±1,3 *	11,1±1,2



P109

A 14-Months Study of Change in Disability and Mood State in Patients with Chronic Migraine Associated to Medication Overuse

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Objectives: The aim of the study was to evaluate changes in disease severity, disability and mood state in group of patients with CM associated to MO (CM+MO) who underwent detoxification followed by prophylaxis.

Background: Chronic migraine (CM) and medication overuse (MO) cause a relevant burden on sufferers and on society, as demonstrated by several studies with disease specific tools (namely MIDAS), and by recent data with a standardized generic disability measure based on the international classification of functioning concepts (WHO-DAS-2).

Methods: Patients were enrolled at hospital admission and re-evaluated after >12 months. MIDAS was used as a proxy of disease activity, WHO-DAS-2 to assess disability DBI-2 for mood state. Data from study completers were analysed: longitudinal differences were tested with ANOVA and effect size. T-test was used to assess differences in WHO-DAS-2 and BDI-2 between those with MIDAS ≤21 and ≥22 at follow-up. Differences between baseline and follow-up were calculated; correlation between MIDAS, WHO-DAS-2 and BDI-2, using Pearson's index; linear regression was used to assess change in WHO-DAS-2, using MIDAS and BDI-2 change as predictors.

Results: 69 patients (56 females, age 42.2±12.6) completed the study. Mean follow-up duration was 14±1.7 months: MIDAS was significantly lower at follow up (101.9±79.3 at baseline, 52.0±54.3 at follow-up, P<001). Effect size was moderate for MIDAS, small for WHO-DAS-2 and BDI-2. In 27.5% of the sample, MIDAS fell below 21 at follow-up: these patients had significantly lower WHO-DAS-2 (14.5±13.0 Vs. 31.0 ±18.4, P=001), while BDI-2 was not different. WHO-DAS-2 change was little correlated to MIDAS change (R=.28, P<05), and strongly correlated to changes in BDI-2 Somatic (R=.73, P<001), Cognitive (R=.69, P<001) and Summary scores (R=.76, P<001). 57.1% of WHO-DAS-2 change variance is explained by change in BDI-2 and MIDAS scores.

Conclusions: Our study showed a clear clinical improvement 14 months after detoxification in CM+MO patients: only one-fourth achieved a MIDAS score≤21 (i.e. below severity threshold), but mean MIDAS reduction was around 50%. Improvement in functioning was demonstrated by decrease in WHO-DAS-2 score: this reduction, although modest, is largely explained by reduced disease activity and improved mood state. Our findings indicate that appropriate treatment (detoxification+prophylaxis) is likely to reduce CM-MO burden, and that recognition and treatment of mood problems may be a key factor in disability reduction.

P110

Changes in Sodium Valproate Prescription for Migraine Prophylaxis after Approval of Japanese Insurance Coverage

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Objectives: To compare migraine prophylaxis associated with sodium valproate (VPA) as a migraine outpatient prescription at the Department of Neurology in 2008 and 2012, i.e., before and after Japanese insurance coverage of VPA.

Background: VPA is widely used for the treatment of epilepsy, and has received approval for several new indications for the treatment of bipolar disorders and neuropathic pain and migraine prophylaxis. VPA was approved by the Japanese insurance system for coverage of migraine prophylaxis in 2011.

Methods: The subjects were 200 consecutive migraine patients followed at the migraine outpatient service of our department of neurology in 2008 and 2012, i.e., before and after insurance coverage of VPA. We assessed migraine prophylaxis with 5 frequently used drugs (VPA, clonazepam [CZP], amitriptyline hydrochloride, lomerizine hydrochloride [approved only in Japan], topiramate).

Results: Of the 200 patients receiving these 5 drugs, there were 66 before insurance coverage of VPA and 148 after insurance coverage of VPA. Among the 66 patients before insurance coverage, 8 used VPA, 37 CZP, 27 amitriptyline hydrochloride, 5 TPM, and 17 lomerizine hydrochloride. Among the 148 patients after insurance coverage, 62 used VPA, 54 CZP, 48 amitriptyline hydrochloride, 36 TPM, and 29 lomerizine hydrochloride. Prior to insurance coverage, VPA was used by 8 (4%) of migraine prophylaxis patients and after insurance coverage by 62 (31%). Monotherapy was CZP (17 patients) and lomerizine hydrochloride (9) before insurance coverage, and VPA (28 patients), amitriptyline hydrochloride and lomerizine hydrochloride (17) after insurance coverage. Reduction of 4-week migraine frequencies in patients receiving VPA and topiramate was the same, at 43%, after insurance coverage. The average daily dose of VPA was 209 mg after insurance coverage.

Conclusions: Our results indicate that the frequency of VPA use for migraines has increased significantly since insurance coverage of VPA for this indication in Japan. Administrations of VPA and topiramate are equally effective for decreasing headache frequency in migraine patients.

P111

Expert Consensus Recommendations for the Performance of Peripheral Nerve Blocks for Headaches: A Narrative Review

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Objectives: To describe a standardized methodology for the performance of peripheral nerve blocks (PNB) in the treatment of headache disorders.

Background: Peripheral nerve blocks (PNBs) have long been employed in the management of headache disorders, but a wide variety of techniques are utilized in literature reports and clinical practice.

Methods: The American Headache Society Special Interest Section for PNBs and other Interventional Procedures (AHS-IPS) convened meetings during 2010-2011 featuring formal discussions and agreements about the procedural details for occipital and trigeminal PNBs. A subcommittee then generated a narrative review detailing the methodology.

Results: PNB indications may include select primary headache disorders, secondary headache disorders, and cranial neuralgias. Special procedural considerations may be necessary in certain patient populations, including pregnancy, the elderly, anesthetic allergy, prior vasovagal attacks, an open skull defect, antiplatelet/anticoagulant use, and cosmetic concerns. PNBs described include greater occipital, lesser occipital, supratrochlear, supraorbital, and auriculotemporal injections. Technical success of the PNB should result in cutaneous anesthesia. Targeted clinical outcomes depend on the indication, and include relief of an acute headache attack, terminating a headache cycle, and transitioning out of a medication overuse pattern. Reinjection frequency is variable, depending on the indications and agents used, and the addition of corticosteroids may be most appropriate when treating cluster headache.

Conclusions: These recommendations from the AHS-IPS members for PNB methodology in headache disorder treatment are derived from the available literature and expert consensus. With the exception of cluster headache, there is a paucity of evidence, and further research

may result in the revision of these recommendations to improve the outcome and safety of these interventions.

P112

Cabernet Sauvignons from France Do Trigger Migraine More Often Than Those from South America: An Open Prospective Study

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Objectives: The aim of this study was to evaluate whether cabernet sauvignon wines from the left margin of the Gironde river, specifically from the Medoc area, would trigger migraine differently from those made in South America (SA).

Background: Red wines are known migraine attack triggers. This is may occur because of the high content of vasoactive substances, like condensed tannins. Wines can also take on tannins from the oak or other woods used in wine barrels for storage. Different woods as different *terroirs* in different countries affect the type and concentration of tannins as well as the quality of the wine. French Bordeaux area wines are rich in tannins. Those from the left side of the Gironde river have more cabernet sauvignon (minimum 75%) compared to those from the right side margin, which have more merlot. In addition, it seems that South American (SA) wines made of cabernet sauvignon have less tannin compared to those of France.

Methods: Twenty eight (14 women, 14 men, ages 25 to 67 years, mean 54,5) regular patients with migraine according to the International Classification of Headache Disorders (ICHD-II) from a tertiary center, who were self-considered regular wine drinkers and who pointed a clear-cut relationship between wine intake and migraine attacks, were prospectively studied. They were asked to drink half bottles (375ml) of a SA cabernet sauvignon and a French cabernet sauvignon from the Medoc or Haut Medoc regions, at their discretion (order, winemaker, time of the day and presence or absence of food) with a minimum interval of 4 days between the wine types. In addition, they were asked to avoid any other type of alcoholic beverages during the time of the study. The patients had to fill out a detailed headache calendar.

Results: Twenty three patients (13 women, 10 men) completed the study and had the two half bottles of different cabernets. Among them, the patients reported a migraine attack within 12 hours of having the French cabernet in 60,9% of the times (14 out of 23) compared to 39,1% (9 out of 23) who pointed the SA cabernet as a clear migraine attack trigger. Four patients among the 23 didn't present migraine attacks after having the wines, whereas 4 presented attacks after both wines and 5 reported that the SA cabernet, but not the French, triggered an attack of migraine.

Conclusions: Despite the open methodology, which challenges definitive conclusions, we concluded that even among migraineurs who point the red wine as a migraine trigger, SA cabernet sauvignons triggered migraine attacks in nearly one third of the times it was consumed. As for French cabernets, it may trigger attacks in more than half of the times it is taken. Although the reasons are unclear, one may speculate that the tannin and flavonoid content, which are higher in French wines, are the most responsible for triggering migraine attacks. Controlled studies are necessary to confirm these observations.

	n=10 French CS	n=10 male South American CS	n=13 female French CS	n=13 female South American CS
Migraine attack	4	6	10	3
NO migraine attack	6	4	3	10

P113

Headache and Stroke

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Objectives: To establish realtions between headache and stroke.

Background: The etiology of headache in stroke is not known, and its relation to migraine and tension-type headache is unclear. The aim of our study was to investigate and classify headache appearing in stroke patients prospectively, using the headache classification as determined by the Headache Classification Committee of the International Headache Society (1988).

Methods: Thirtyfive consecutively admitted patients aged younger than 75 years with acute stroke were examined and questioned about headache and prior headache complaints; 30 (85%) were able to communicate.

Results: Nine (~27%) of the 35 patients experienced headache from 3 days before to 3 days after stroke.

Headache occurred in 50% of patients with intracerebral hemorrhage, in 26% with infarction, and in 15% of patients with lacunar infarction. The headache in thromboembolic stroke was classified as tension-type headache (3 patients), migraine-like headache (2 patients), and other headache (10 patients). Migraine was more frequent in vertebrobasilar stroke. In patients with unilateral headache and unilateral stroke lesion, the headache was ipsilateral in 4 of 7 cases. In infarction, severity of headache showed no relation to lesion size or lesion localization. Patients with previous tension-type headache and migraine experienced reactivation of known headache equally often.

Conclusions: (1) Headache occurs in one fourth of patients with acute stroke. (2) Unilateral headache is usually ipsilateral to stroke lesion. (3) Headache severity is not related to size of ischemic stroke lesion.

P114

Grey Zones of Migraine without Aura Diagnosis

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Objectives: To evaluate the diagnostic value of clinical characteristics of MwoA in ICHD-II in a clinical dataset for obtained grey zones and possible reasons of this distribution have been discussed.

Background: Concerning migraine without aura (MwoA), the second edition of the International Classification of headache Disorders (ICHD-II), did not introduce any major changes to before (ICHD-I). However still many patients fail to meet the criteria's such as location, pulsating quality, pain intensity, aggravation with physical activity, nausea, vomiting, phonophobia and photofobia. Difficulties of fulfilling the criteria in some patients may lead to locate them in a so called "grey zone".

Methods: This study was a tertiary based retrospective clinical study including 1365 patients with MwoA, after exclusions "possible" diagnosis, known comorbidities and missed clinical variables, in a dataset including 3286 patients with migraine. The patients meet all of the criteria of ICHD-II named as Full-MwoA. When specialist diagnosis accepted as gold standard, one, two, three or more failed criteria named as Zone I, Zone II and Zone III, respectively. Statistical powers and variables of the zones calculated and discussed.

Results: Out of 1365 patients 351 (25.7%) were Full-MwoA, 546 (40%) located in Zone I, 327 (23.9%) located in Zone II and 141 patients (10.3) located in Zone III. Most important differentiating features of the zones are previous history of migraine equivalents as periodical vomiting, infantile colic, or motion sickness before puberty and triggering by menstrual cycle after puberty. Most important determinates of criteria are severity of the pain and associated photophobia or phonophobia in all zones.

Conclusions: This study showed us strict criteria of migraine diagnosis have to be supported by the grey zones definition in all age and gender groups even in MwoA as a most simple type of migraine.

P115

Withdrawn by the author.

P116

What Does the Headache Patient Want?

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Objectives: The purpose of this study was to know what the headache patient wants when he comes to the doctor.

Background: Headache is an extremely common condition. It is estimated that globally, among the adult population, 46% have current headache in general, 11% have current migraine, 42% have current tension-type headache, and 3% have current chronic daily headache. (1) The average rate of medical consultations due to headaches is 30.3 per 1000 men and 55.4 per 1000 women. However, only 64% of patients with migraine and 45% with tension-type headache had previously sought medical attention, and of these, only 32% returned for ongoing care. (2). A previous study found that "Pain relief" and "an explanation of what was causing the pain" were listed with higher frequency among the reasons to have a medical consultation by both physician and patient groups. (3)

Methods: Consecutive outpatients were asked to fill out a survey form prior to their first appointment at the headache clinic. The questionnaire includes specific information including age, sex, duration of headache, frequency of headache, how many doctors they had seen previously about headache. No attempt was made to select patients as to specific headache type. In the second part, patients were asked to choose the most important reason to have that medical consultation among five options: a. To have an explanation; b. To have a complementary exam; c. A doctor to follow him/ her for their headache; d. be worried about having a serious disease;

e. Relief of pain. If none of these options was the reason, there was an open question regarding the patient's reasons for seeking medical attention for headaches. The Hospital Anxiety and Depression Scale was used. The diagnoses of headaches were registered.

Results: Five hundred thirty-two patients were interviewed, 82.5% were women, the mean age was 42.3 years (SD=16.1). They had seen previously a mean of 2.5 (DP =3.5) doctors because of headache; 32%, more than 2 doctors. They have had headache for a mean of 14 years (DP=12.5); 60% for more than 5 years. Mean frequency of headache = 16 days per month (DP= 11.2), 48.1% had chronic daily headache; 23.4% had tension-type headache; 71.2%, migraine. Reasons to have a medical consultation: To have an explanation (18.9%); to have a complementary exam (22.2%); A doctor to follow him/ her for their headache (13.2%); be worried about having a serious disease (26.2%); Relief of pain (19.5%). There was no association between be worried about having a serious disease/ have a complementary exam and the gender, years of study, had been in more than 2 doctors, migraine, tension-type headache, depression, anxiety or had chronic daily headache.

Conclusions: The most frequent reasons to have a medical consultation because of headache were "be worried about having a serious disease" and to "have a complementary exam". No variables studied were associated with these reasons.

P117

Botulinum Toxin A for the Treatment of Greater Occipital Neuralgia: Pathophysiological Considerations for Efficacy

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Objectives: To evaluate efficacy of botulinum toxin A in refractivegreater occipital neuralgia.

Background: Greater occipital neuralgia (GON) is rare but can be responsible for severe intractable headache. Failure of medical treatment as well as injection therapy with corticosteroids or anaesthetics is not unusual. Botulinum toxin A (BTx A) or surgical procedures have been already tested as an alternative tool. Results with BTx A are heterogeneous authorizing Linde et al (2001) to recommend its use in grade C of recommendation. We make the hypothesis that the effect of BTx A depends on the presence of a pathological focal dystonia in the trapezius or semi-spinalis muscles when the nerve become superficial. We evaluate 4 cases of refractive GON fulfilling the IHS criteria for diagnosis uncontrolled by usual therapy treated with BTx A preceded by electromyography evaluation.

Methods: 4 women were referred for the treatment of refractive GON. They met International Classification Headache Disorders Criteria for the Greater Occipital (code 13.8) but have no pain relief with recommend therapy. The mean age was 61 yo, the duration was over 14 months. All have unilateral GON. NSAIs, anti-epileptic drugs, analgesics or corticosteroids were inefficient. Brain MRI and cervical radiolography were unremarquable. BTx A Injection was unilateral with a minimum of 30 UI in the trapezius at the same site of the pain preceded by electromyographic detection and completed if needed by injection in the splenius capitis. Reduction of pain was evaluated by percentage of improvement at 10 days and 3 months. Toxicity was also evaluated systematically. All cases gave their acceptation before treatment.

Results: All case have abnormalities in electromyography evaluation before injection. Improvement of pain was of 60% compared with the pain before and maintain at one month. No side effect was declared. No significant reduction of rescue therapy was observed in one case.

Conclusions: This preliminary work propose to considerateBTx A as an alternative and safe treatment for GON. We suggest that before injection an electromyography evaluation is needed. If observed abnormal activities in trapezius muscles and in case of refactory GON, BTx A might be an effective treatment and must be tested. We recommend conducting a double blind controlled trial to validate this proposition.

P118

Chiropractic Spinal Manipulative Therapy for Cervicogenic Headache: A Single Blinded, Randomized, Placebo-Controlled Study

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Objectives: The purpose of this study was to highlight and validate chiropractic spinal manipulative therapy for cervicogenic headache (CEH).

Background: The prevalence of CEH varies between 0.4-4.1 % in different studies. Pharmacological management usually has none or minor effect on CEH, while cervical spinal manipulative therapy has been reported to have an effect. We conducted a randomized single blinded controlled clinical trial on CEH applying chiropractic spinal manipulative therapy.

Methods: A single blinded, randomized, placebo-controlled trial of 16 months duration. The trial consisted of 1

month baseline, 3 months treatment and 3, 6, 12 months follow up. Fifteen participants aged 18-70 years with CEH completed the trial. Participants were randomized into 1 of 3 groups: (i) chiropractic spinal manipulation, (ii) sham chiropractic manipulation, (iii) control group, not receiving treatment. Primary outcome was reduction of headache days while secondary outcomes were reduction in headache intensity, duration, headache index and medication from initial baseline to post treatment and follow up using headache diaries.

Results: Results are currently being analyzed and will be presented at the congress.

Conclusions: To be presented at the congress.

P119

Electron Microscopic and Proteomic Comparison of Terminal Branches of the Trigeminal Nerve on Patients with and without Migraine Headaches

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Objectives: The purpose of this study was to compare the ultrastructural appearance and protein expression of the zygomaticotemporal branch of the trigeminal nerve (ZTBTN) in patients with and without migraine headaches (MH).

Background: After obtaining IRB approval and diagnosis of MH by a neurologist, a 5mm segment of the ZTBTN that is routinely removed during migraine surgery was compared to a similarly sized nerve segment obtained from patients without a history of MH who underwent an endoscopic forehead lift.

Methods: The detailed cytoarchitectural differences between nerve segments were examined on the electron microscope. Additionally, using multidimensional label-free LC-MS platform, nerve segments obtained from 15 migraine and 15 control subjects were snap frozen at -80°C for the proteomics analysis. Frozen nerve tissue samples were appropriately prepared and processed for quantitation and statistical analysis.

Results: Control nerves contained longitudinally oriented myelin sheaths that had a characteristic wavy appearance compared to migraine nerves which revealed a more linear organization. Furthermore, in migraine derived nerves, the neurofilaments were strikingly discontinuous and poorly registered with the myelin sheaths. Large regions of the nerve contained axons with patchy neurofilament interspersed with an apparent absence of neurofilaments, suggesting axonal pathology. Transverse sections through normal nerves revealed the characteristic arrangement of myelinated and unmyelinated axons. Throughout the migraine derived nerves, however, the organization of a significant number of the myelin sheaths and their target axons was disrupted. The most striking feature was the excessive amount of myelin surrounding the axon. Frequently this myelin was folded and constricted the axon, leaving little axonal cytoplasm. Analysis of LC-MS/MS datasets identified 170 differentially expressed proteins in an initial study and 77 differentially expressed proteins in an independent verification analysis that are correlated with migraine diagnosis. Protein analysis identified significant networks comprised of highly connected molecular modules potentially related to migraine specific biology. In migraine nerve samples, molecules that are essential for the establishment of normal axonal calibers including clusters of neurofilaments, and proteins that are involved in myelination of axons are down regulated. On the other hand, up regulation of clusters of proteins that are involved in free radical scavenging suggests that oxidative insult is also part of migraine pathogenesis, and functions to protect proteins and lipids against oxidative damage.

Conclusions: This study offers electron microscopic and proteomic evidence of axonal pathology and deregulation of the myelination process in patients who have MH compared to those who do not. This study offers the rationale for the peripheral component of the migraine cascade.

P120

Pain Location of Migraine Headache Is Closely Related with Gold Meridian System of Korean Hand Therapy

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Objectives: The diagnosis of primary headache has not been sufficient for appropriate treatment. We mainly depend on the history taking and criteria of International Headache Classification. The criteria are well described but they are not well interpreted. The location of headache might be crew to diagnosis. The sites of Botox injection sites are nearly same and the dosage of injection is more than 100 units. We emphasized to manage the

patient individually as personalized medicine. The location is important to treatment of Botox injection.

Background: If the location is determined accurately, the dosage of Botox might be reduced. There are no standardized methods to decide the location in clinical practice. In Eastern Asian Medicine, there are Meridian and Acupuncture Points on the body including on the head. It is well described but it is complicated to use in practice easily. We need simplified Meridian and Acupuncture Point system. We propose to use Gold Meridian and Acupuncture Points of Korean Hand Therapy to determine the location.

Methods: This procedure was performed during physical examination based on well performed history taking at department of neurology, Pusan National University Hospital from March 2011 to Feb. 2012. The 200 migraine headache patients who have no other neurological or systemic diseases were included. We checked pain location on both sides and sites of head using 20 New Modified Acupuncture Points on Gallbladder Meridian (CM1-12) and Urinary Bladder (CI1-8) each one side.

Results: The headache points are grouped such as Gallbladder and Urinary Bladder Gold Meridian System, the migraine headache patients belonged to Gallbladder, mixed type headache belonged to various combined Gallbladder and Urinary Bladder Meridian. The pure migraine groups are three, and mixed form headache group are nine.

Conclusions: The pain location of intractable headache patients presented as mixed form headache. The location of pains of such headache should be considered for Botox injection. We can inject small dosage of Botox injection depending on right or left exact side and sites.

P121

BMS-927711 for the Acute Treatment of Migraine: A Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Trial

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Objectives: To determine an effective and tolerable dose range of a new oral calcitonin gene-related peptide (CGRP) receptor antagonist, BMS-927711, for the acute treatment of migraine.

Background: CGRP has been closely linked to the pathophysiology of migraine. CGRP receptor antagonists may be effective in treating migraine by blocking the activities of CGRP in trigeminal neurons without the vasoconstrictor liability of triptans and ergotamine derivatives. BMS-927711 is a potent, selective, competitive human CGRP receptor antagonist that has shown *in vivo* efficacy without vasoconstrictor effects. It has been shown to be generally safe and well tolerated at single ($\leq$1500 mg) and multiple ($\leq$600 mg) doses for 14 days in healthy volunteers.

Methods: In this randomized, double-blind, parallel-group, placebo-controlled, dose-ranging study, patients (N=885) were allocated, using an adaptive design, to one of the following dose groups: BMS-927711 10, 25, 75, 150, 300, or 600 mg; sumatriptan 100 mg (active control); or placebo. Patients were treated for a single migraine attack. The primary endpoint was pain freedom at 2 hours post-dose using a four-point numeric rating scale (no pain, mild pain, moderate pain, severe pain).

Results: Of 1026 enrolled patients, 885 were randomized, and 799 were evaluable. BMS-927711 doses of 75, 150, and 300 mg were more effective than placebo (15.3%) for pain freedom at 2 hours post-dose (31.4%, $p=0.0018$; 32.9%, $p=0.0005$; and 29.7%, $p=0.0024$, respectively). BMS-927711 doses of 10, 25, and 600 mg were not statistically different from placebo. The difference in 2-hour post-dose pain freedom between the sumatriptan group (35.0%) and the placebo group was also statistically significant ($p<0.0001$). For the secondary endpoint of sustained pain freedom from 2 to 24 hours post-dose, BMS-927711 doses (25–600 mg) were statistically significant compared with placebo ($p<0.05$). Overall, BMS-927711 doses offered an acceptable tolerability and safety profile within a single-headache, single-treatment paradigm.

Conclusions: BMS-927711 was effective and generally well tolerated for acute treatment of migraine at doses of 75, 150, and 300 mg.

P122

Double-Blind, Placebo Controlled, Randomized Clinical Trial Comparing Melatonin 3 mg, Amitriptyline 25 mg and Placebo for Migraine Prevention

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Objectives: To test the efficacy and tolerability of melatonin 3 mg and amitriptyline 25 mg compared to placebo in migraine prevention.

Background: Melatonin has been linked to migraine mechanisms in several ways. Previous reports have shown therapeutic effects on migraine and other headache disorders. Amitriptyline has been widely used for migraine prevention, but its unfavorable side effect profile limits its use. Better tolerable options in migraine prophylaxis are necessary.

Methods: A randomized, double-blind, placebo-controlled multicentric study was carried out. Men and women, aged 18-65 years, with migraine with or without aura, experiencing 2-8 attacks per month, were recruited from the general population. After a 4-week baseline phase, 196 subjects were randomized to receive either placebo, amitriptylne 25 mg or melatonin 3 mg for 3 months. The primary outcome was migraine frequency in number of headache days per month. Secondary endpoints were migraine intensity, duration, and analgesic use. Tolerability were also measured in the three groups.

Results: One hundred seventy nine subjects completed the study. Mean reduction in headache frequency was 2.7 in the melatonin group, 2.18 for amitriptyline, and 1.18 for placebo. Melatonin significantly reduced headache frequency compared to placebo (p=0,009), but not to amitriptyline (p=0,19). Melatonin was as tolerable as placebo and better tolerable when compared to amitriptyline.

Conclusions: Our study shows that melatonin 3 mg is better than placebo for migraine prevention, and better tolerable than amitriptyline 25 mg.

P123

Co-Morbid Recurrent Headaches and Major Depressive Disorder: An RCT of Cognitive Behavior Therapy

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Objectives: To carry out the first RCT of cognitive behavior therapy (CBT) designed for individuals suffering from both recurrent headaches and major depressive disorder.

Background: Meta-analytic reviews have shown that the average reduction in both migraine and tension-type headache with behavioral treatments to be 33% to 55%. In one of our studies, CBT achieved a 68% reduction. However, 35% to 50% of recurrent headache sufferers fall into the mildly or moderately depressed categories, and elevated scores on pre-treatment depression scales predict negative outcomes for behavioral treatments. Also, numerous epidemiological and clinical research studies have reported elevated risk of mood disorders in migraine and chronic daily headache. Presence of psychiatric disorders predicts poorer outcome for headache treatment. Hence, there is a need for developing treatments for individuals who suffer from both recurrent headaches and depression.

Methods: 100 participants were recruited who were over 18 years of age and diagnosed as migraine or tension-type headache (TTH) with a minimum of 6 headache days per month, a minimum chronicity of 12 months, and a stable pattern over last 6 months; as well as major depressive disorder. A stratified randomization procedure was used to allocate participants to an intervention group (CBT for chronic headache and co-morbid depression, 12 sessions) or a control group (Routine Primary Care, RPC). Stratification within groups was on the basis of headache diagnosis (migraine vs TTH), and whether patients also had, or did not have, an anxiety disorder. Measures included diaries for recording headaches and medication, Beck Depression Inventory (BDI II), Patient Health Questionnaire (PHQ-9), and Beck Anxiety Inventory (BAI).

Results: The average decrease in headaches in the CBT group from pre- to post-treatment was 45.0%, compared to a 0.4% increase for the RPC group. The CBT group was associated with a 57.1% decrease in depression, compared to a 13.4% decrease for the RPC group (BDI II). The mean BDI scores of the CBT group were 30.6 ('severe depression'), 13.1 ('mild depression'), and 10.2 ('mild depression'), at pre-treatment, post-treatment and 4-month follow-up, respectively. On an alternative measure of depression (PHQ-9), the CBT group was associated with a 61.5% decrease compared to a 27.5% decrease for the RPC group. Anxiety decreased by 49.4% in the CBT group compared to 13.9% in the RPC group (BAI), and medication consumption decreased by 42.1% in the CBT group compared to 15.9% in the RPC group. All the differences between the CBT and RPC groups were statistically significant except for one which was a trend.

Conclusions: Reported here is a new treatment for a co-morbid group who suffer from two very disabling disorders that in combination are highly refractory to treatment. This treatment resulted in substantial reductions in both headaches and depression, as well as medication consumption and anxiety.

P124

Effectiveness of Brief Intervention Performed by GPs for Medication Overuse Headache in Primary Care – A Double-Blinded Pragmatic Cluster Randomised Parallel Controlled Trial

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Objectives: To evaluate the effects of a brief intervention (BI) versus business as usual (BAU) in the management of medication-overuse headache (MOH) in primary care.

Background: MOH in the general population can be identified through screening for headache frequency and using the Severity of Dependence Scale (SDS). BI is a method that has successfully been applied for detoxification from overuse of alcohol and illegal drugs.

Methods: A double-blinded pragmatic cluster randomised parallel controlled trial of BI vs. BAU. Intervention was performed in primary care by general practitioners (GPs) trained in BI. GPs were recruited from continuing medical education (CME) groups. A MOH screening questionnaire was sent to all the GPs' 18-50 year old patients. Suspected MOH patients were cluster-randomised based on their GP. Half of the GPs were trained in BI, which was applied to suspected MOH patients as follows: SDS was scored by the GP and individual feedback was given of the score and relationship between this, medication overuse and headache. Finally, advice was given regarding measures to be taken, how the patient should proceed, possible difficulties and gains. Patients were followed-up after three months with a clinical interview and neurological examination by a headache expert. The patients also completed a prospective headache diary before intervention and before the three-month follow-up.

Results: Ten CME groups with altogether 50 GPs were recruited. The screening questionnaire was sent to almost 27000 patients aged 18-50 year on these GPs' list. Responder rate after two reminders was 42% for the screening questionnaire. 191 patients were invited to the main study. One-hundred-and-nineteen patients were recruited, 29 MOH-patients in the intervention arm and 44 MOH-patients in the BAU-arm. In addition, 17 population controls with chronic headache without medication overuse and 29 healthy population controls without chronic headache were recruited.

Simple analgesics were most commonly overused, followed by triptans and combination analgesics. Medication overuse was significantly more reduced by BI than BAU (69% versus 27%, $p<0.001$), and significantly more patients in the BI arm (41%) than in the BAU arm (18%) were free of both medication overuse and chronic headache ($p=0.03$) in the intention-to-treat analysis. More results are currently being analysed and will be presented at the meeting.

Conclusions: BI represents a simple and effective instrument for treating MOH patients in the general population by GPs.

P125

Meditation for Migraines: A Pilot Randomized Controlled Trial

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Objectives: To assess the safety, feasibility, and effect of Mindfulness Based Stress Reduction (MBSR) in adults with migraines.

Background: Stress is a well-known trigger for headaches. Research supports the general benefits of mind/body interventions for migraines, but there are few rigorous studies supporting the use of specific standardized interventions. MBSR is a standardized 8 week mind/body intervention that teaches mindfulness meditation/yoga. Preliminary research has shown MBSR to be effective for chronic pain syndromes, but it has not been evaluated for the treatment of migraines.

Methods: We randomized adults who met International Classification of Headache Disorders-II criteria for episodic migraine with or without aura to either MBSR or usual care. In addition to safety and feasibility, our primary outcome was change in migraine frequency from baseline to follow-up immediately post-intervention. Secondary outcomes included change from baseline to follow-up in migraine severity, duration, and scores on instruments of headache impact/disability (Migraine Disability Assessment, MIDAS; Headache Impact Test, HIT-6), self-efficacy (Headache Management Self-Efficacy Scale), and mindfulness (Five Facet Mindfulness Scale). Mann-Whitney U tests were performed to compare changes seen from baseline to follow-up in the intervention vs. control group. To estimate effect size,

we ran independent t-tests on the change scores and report the differential change and 95% confidence intervals (CI).

Results: 19 adults were randomized to either MBSR (n=10) or usual care (n=9). In the intervention group, no adverse events were reported and MBSR participation was high, with average daily home practice of 34 +/- 11 minutes and average attendance of 6/8 classes. There was no statistically significant difference in migraine frequency between those in the MBSR vs. control groups from before to after the intervention (p=0.14). At follow-up, those in the MBSR group had less severe (by 1.26 points/migraine on a 0-10 scale, [-2.6, 0.07], p=0.05) and shorter migraines (by 2.9 hours, [-6.2, 0.53], p=0.04). The MIDAS and HIT-6 scores were lower after the intervention compared to before in the MBSR vs. control groups (by 13 [-24, -2], p=0.02 and by 5 [-10, 0.4], p=0.04, respectively). Measures of self-efficacy and mindfulness improved in the MBSR vs. control group from baseline to follow-up (by 13 points each [-3, 29], p=0.04 and [1, 25], p=0.03, respectively).

Conclusions: MBSR is a safe and feasible intervention for adults with migraines. Although the small sample size of this pilot trial did not provide power to detect changes in headache frequency, secondary outcomes demonstrated this intervention had a beneficial effect on migraine duration, severity, disability, self-efficacy, and mindfulness. Future studies with larger sample sizes are warranted to further evaluate this intervention for adults with migraines.

P126

Double-Blind, Placebo-Controlled, Crossover Study of Early-Intervention with Treximet in (Truly) Episodic Migraine

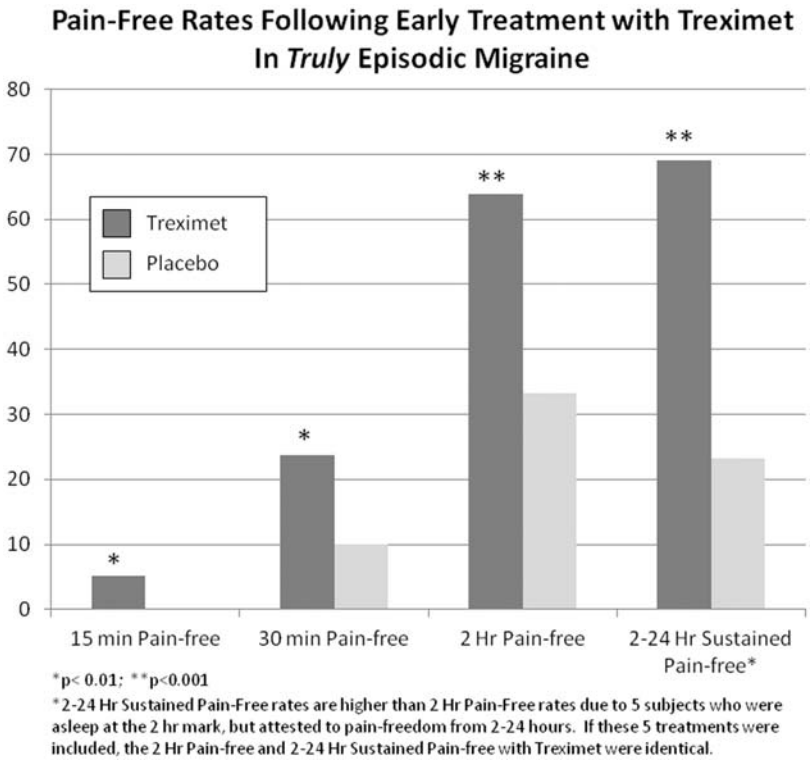
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Objectives: Believing that neck pain in migraineurs is integrally related to migraine, we sought to ascertain whether early treatment with Treximet in *truly* episodic migraineurs (those with fewer than 15 days a month with *either* headache or neck pain) is more robust than previously published rates.

Background: We have established the high prevalence of neck pain in migraine and reported its consistent linear correlation with increasing headache frequency. We have further shown that its presence is a marker for poorer treatment outcome and disability.

Triptans have shown relatively disappointing 2-hour pain free rates ranging from 18-58%, with sustained 2-24 hour pain freedom rates ranging from 17-25%. We believe that many



subjects in these studies are not truly episodic but rather discount days with mild headache and ignore neck pain.

Methods: Successfully screened adult migraineurs who returned baseline diaries that recorded 2-7 migraine attacks/mon and <15 headache &/or neck pain days/mon were eligible. Each received a blister pack containing 4 pills (3 Treximet, 1 placebo in random order) to be dispensed for treatment of 4 migraines. Subjects were instructed to treat within 30 mins of onset of mild headache or neck discomfort on the first day of discomfort.

Results: 78 subjects were successfully screened and issued baseline qualification diaries; 20 were disqualified for excessive frequency of headaches &/or neck pain. An additional 22 subjects were lost to follow-up, leaving 43 qualified and randomized subjects. Pain-free response to treatment and onset of pain-freedom was much more robust in this population than in previous triptan trials.

Conclusions: These results support a fundamental re-evaluation of the role of neck pain in migraine. Results are distinctly better than those published in conventional trials in which neck pain is not considered and support the hypothesis that neck pain in migraine may represent hyperalgesia or allodynia. It is notable that in this carefully selected population of subjects who had twice attested to their episodic pattern, the greatest reason for disqualification was excessive frequency of head or neck pain in their baseline qualification diary.

P127

The Prophylactic Treatment of PEMF in the Refractory Migraine Headache, Double-Blind, Parallel Placebo-Controlled Study

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Objectives: The aim of the study was to investigate the effect of PEMF therapy on the refractory migraine (RM).

Background: According to the enigmatic etiology of migraine, a comprehensive treatment that affected all contributing factors in the migraine with minimal side effects is not provided yet. PEMF as non-pharmacological treatment of migraine had good effect with weak evidence in the control of migraine.

Methods: 30 RM kept 2 weeks, baseline log of headache activity prior to being randomized to having placebo or active treatment of PEMF for 30 minutes per session and 3 days per week, for 2 weeks. The 16 patients of the active group also were exposed to added 2 weeks and kept the migraine dairy log for 4 follow-up months. The parameters of PEMF were squared electromagnetic pulses with 10 Hz frequency and 5 mT intensity.

Results: The results showed an improvement in the headache days ($P<0.000$), duration of headaches ($P<0.002$), missed work ($P<0.000$) and numbers of sedative drug ($P<0.001$) in the active to compare with placebo group after 2 week. Whiles the intensity of headache did not differ significantly. To analyze the persistency of treatment in the active group, repeated measurement indicated significant improvement in the days and duration of headaches ($P<0.000$) (Figure 1) missed work ($P<0.01$) and numbers of sedative drug ($P<0.006$). The menstruated dependency only had interaction in the intensity of headache. Then the PEMF decreased the intensity in the non menstrual migraine patients. MIDAS scores was significantly decreased after treatment ($P<0.000$).

Conclusions: PEMF (10 Hz, 5mT) had high beneficial prophylactic effect with good persistency in the treatment of refractory migraine. The important note is to control the appropriated dose and response of patient that should be to evaluate

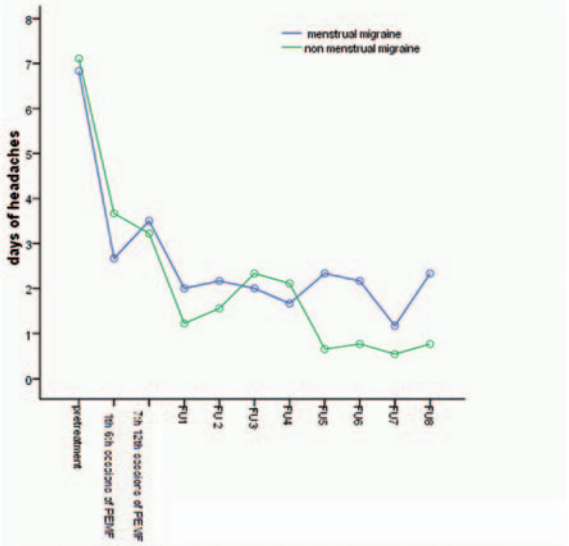


Figure1: the sum of days with headache in the RM related and non related to menstrual condition. each time frame was two weeks consisted pretreatment, 1th-6th sessions of treatment,7th-12th sessions of treatment, 1th-8th follow up (FU) after treatment in the active tratment group. results showed the days of headache significantly decreased after treatment and the improvement remained after 4 months follow up.

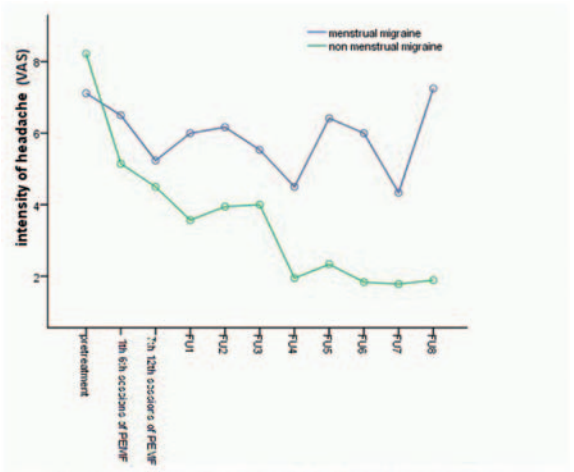


Figure 2 The intensity of headache in the RM related and non related to menstrual condition. each time frame was two weeks consisted pretreatment, 1th-6th sessions of treatment,7th-12th sessions of treatment, 1th-8th follow up (FU) after treatment in the active tratment group. results showed the intensity of headache significantly decreased after treatment and the improvement remained after 4 months follow up only in the RM related to menstrual condition.

P128

Rapid Rollout of a Pediatric Migraine Prevention Study Conducted in Academic Research Centers

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Objectives: This study provides a pathway for investigators and institutions who are seeking a successful route for rapid startup of a multicenter pediatric migraine research study. We detail the infrastructure, strategic decisions and processes employed in the startup of an investigator initiated pediatric migraine prevention study funded by NINDS, based at an academic research institution.

Background: Creation of the study infrastructure included recruitment of a committed trial team at the central coordinating center(CCC), development of a collaborative relationship with a co-investigator statistician at an experienced data coordinating center(DCC), recruitment of site investigators committed to migraine research with established research sites and adequate potential subjects, partnering with the funding group to meet the agency's criteria, and recruitment of experienced consultants to provide guidance during planning.

Methods: The principal investigators created ongoing collaboration among the CCC, DCC, the research site investigators and internal and external consultants. This included: weekly teleconferences, clear timelines /accountability for deliverables, project management, IND regulatory, budget management, legal contracting, recruitment/ retention/ marketing, site management, data base development, and a novel statistical plan. Site investigators received frequent updates regarding study development. They contributed opinions regarding study design and became stakeholders. Detailed pre-work resulted in a clinical package that included a complex protocol based upon a novel statistical design allowing for three trials in one. Biweekly contact with the research sites maintained momentum at the sites.

Results: The timeline from date of clinical package delivery to first patient in was 13 weeks. The timeline from delivery to site activation of the initial group of 5 sites was 13-20 weeks, compared to the reported 36 weeks for academic centers. The second group of 10 sites achieved activation at 21 weeks. The remaining 13 sites were activated by 31 weeks, 5 weeks ahead of the industry average. To date, 84 % of site have been activated and open to enrollment, with 50 % of the sites open to enrollment at 24 weeks. The overall average time to site activation was 26 weeks.

Conclusions: A diverse research team in frequent communication with site investigators and complex pre-work with clinical package development enabled the rapid roll out of a multicenter pediatric migraine prevention study. The timeline to site activation for this pediatric migraine prevention study is ahead of industry standards.

P129

Randomized, Placebo-Controlled Pilot Trial of a Novel, Noninvasive EEG-Based Intervention, *HIRREM*, for Alleviation of Episodic Migraine

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Objectives: To pilot test high-resolution, relational, resonance-based electroencephalic mirroring (HIRREM™) for reduction of headache (HA) frequency and severity in episodic migraine (MI) and to estimate effect sizes for use in a larger trial.

Background: Studies have identified altered proportionation of power across broad-band bins of the EEG

frequency spectrum in MI. HIRREM is a novel, noninvasive technology designed to facilitate relaxation and auto-calibration of neural oscillations. HIRREM involves collection of EEG data from 2-channel recordings, analysis of the data at high spectral resolutions (0.001 hertz), and delivery of auditory tones for resonance in near real time with dynamically varying dominant EEG frequencies.

Methods: Sixty-three subjects were screened, 33 enrolled, and 30 (16 HIRREM, 14 placebo; mean age 51 ± 11, 26 women) completed an IRB-approved, randomized, single-blind, placebo-controlled, pilot trial. Individuals assigned to active HIRREM underwent a series of 90-minute sessions (mean 10.0, range 8-12) over a mean of 2.7 weeks (range 1-5), each of which consisted of listening to near real time auditory feedback derived from their own dynamically varying EEG activity. Individuals assigned to placebo had a comparable number of visits but listened to randomly generated musical tones. Subjects maintained a daily HA diary prior to undergoing intervention (2 weeks), during intervention, and for 2 months afterward. Primary outcome was defined as a joint distribution of HA frequency and intensity during the post-intervention follow up period. Analysis used a mixed effects, mixed distributions model to predict probability of an attack, and, when present, intensity of the attack. Using random effects, the model considers the hierarchical data structure of multiple diary days nested within a person.

Results: Three subjects had malfunctions in electronic daily diary tools and were excluded from analysis. Before the intervention, the HIRREM group tended to have greater likelihood of HA compared to placebo, OR 1.56 (95% CI: 0.97 to 2.53, $p = 0.064$). However, during the post-intervention period, the HIRREM group had a reduction in the likelihood of experiencing headache compared to controls, OR 0.74 (95% CI: 0.55 to 1.03, $p = 0.077$). This clinically meaningful effect size did not reach statistical significance in this pilot sample. No adverse events occurred. A comparable number of subjects in each group (50%) guessed that they received active HIRREM.

Conclusions: In this pilot trial, a promising effect size for reduction in headache frequency was observed for the HIRREM intervention beyond that observed for a placebo condition. The effect size associated with HIRREM as well as its safety and lack of side effects suggest that larger controlled trials are warranted.

P130

Atopic Disorders Are More Common in Childhood Migraine Than TTH

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Objectives: In order to determine and investigate the correlates of atopic disorders in a specific dataset, we performed this retrospective cross-sectional clinical based study.

Background: There are supportive clinical and pathophysiological data about the relationship between migraine and atopic disorders far from a coincidence.

Methods: Data set was composed from three tertiary center web based data (www.childhoodheadache.org). Headache diagnosis and differential diagnosis had been made according to ICHD-II and DSV-IV. Migraine (MwA, MwoA and chronic migraine) and TTH (episodic TTH and chronic TTH) patients included and all other causes of headache disorders also comorbid headache disorders like migraine plus TTH or "possible" causes of headache had been excluded.

Results: Out of 765 patients, identical age and gender distributed 293 migraine and 178 TTH, totally 471 patients included the study. After descriptive statistics accordingly, 49 migraine (16.7%) and 3 TTH (1.7%) reported specific atopic disorders ($p=0.000$). Among migraine sufferers MwA (21.6 %) were more frequent association than MwoA and CTTH ($p=0.000$). Most common types of atopic disorders were seasonal rhinitis, conjunctivitis and asthma. There were also a close relationship between atopic disorders and generalized anxiety disorders of the patients and positive atopic disorders or migraine history of the families, especially mothers.

Conclusions: Atopic disorders are common pathophysiological mechanisms with migraine. Although ICHD-II did not require, atopic disorders have to be questioned in all patients and relatives, not only accurate diagnosis but also planning to prophylactic medications such as beta blockers.

P131

Anticephalgic Photoprotective Premedicated 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 bryonia 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 premedicated 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 bryonia 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.

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 bryonia and rhus toxicodendron.

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 bryonia 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 bryonia and rhus toxicodendron.

P132

Stimulation of the Sphenopalatine Ganglion (SPG) for Cluster Headache (CH) Treatment - Pathway CH-1, a Randomized, Sham Controlled Study

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Objectives: The pain and autonomic symptoms of CH result from activation of the trigeminal parasympathetic reflex, mediated through the SPG. We aimed to investigate the safety and efficacy of on-demand SPG stimulation for the treatment of chronic CH.

Background: CH is a highly disabling neurological disorder. A multi-center, multiple CH acute treatment study of a novel SPG neurostimulation therapy has been completed.

Methods: All patients met the ICHD-2 criteria for chronic CH with a minimum of 4 attacks/week. Patients were implanted with a miniaturized neurostimulator which, along with a controller, provides on-demand SPG stimulation. During the blinded experimental period (EXP), each attack was randomly treated with one of three therapies: full, sub-perception or sham stimulation using a random insertion of placebo design. Pain relief at 15 minutes (decrease from "moderate" or "severe" to 'none' or 'mild' on the 5-point scale), rescue medication use and CH frequency reduction were analyzed. Responders were defined as acute (pain relief in $\geq$50% of treated attacks), and/or frequency ($\geq$50% reduction in attack frequency vs. baseline, with no increases in preventive medications).

Results: 43 patients were enrolled, 38 completed the EXP. The average baseline CH frequency was 17 attacks/week. Pain relief was achieved in 55% of full stimulation treated attacks (N=260) compared to 8% with sub-perception (N=254) and 8% with sham stimulation (N=255).

Rescue medications were used in 42% of full stimulation treated attacks compared to 73% of attacks treated with either sub-perception or sham stimulation. 11 (29%) of the 38 patients were acute responders, and successfully treated 81% of their CH attacks with SPG stimulation. 16 patients (42%) were frequency responders with an average reduction of 88% at the end of the EXP compared to baseline.

Clinically significant improvements occurred in 63% (24 of 38) of patients. Of these 24, 8 (33%) were acute responders only, 13 (54%) were frequency responders only, and 3 (13%) were both acute and frequency responders. 10 of the 13 frequency only responders (77%) did not treat enough attacks to be evaluated for acute response. Of the 37% (N=14) non-responders, half (N=7) did not treat a sufficient number of attacks for evaluation of acute response.

Most patients (77%) experienced transient, mild to moderate sensory disturbances within the first 30 days following implant. Most sensory disturbances remained mild or resolved at three months post-implant.

Conclusions: Acute, on-demand SPG stimulation using the ATI Neurostimulation System is an effective and safe novel therapy for chronic CH.

P133

New ICHD-III Cluster Headache Criteria in the LUCA Population

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Objectives: We evaluated the presence of 'ipsilateral sense of aural fullness' and 'ipsilateral facial flushing' in our LUCA (Leiden University Cluster headache Analysis programme) population in subjects: 1) fulfilling the ICHD-II criteria[1] for the diagnosis CH (cluster headache) and 2) most probably CH (clinical characteristics fulfill all ICHD-II criteria for the diagnosis CH except one criterion).

Background: The forthcoming ICHD-III criteria for cluster headache will add 'ipsilateral sense of aural (ear) fullness' and 'ipsilateral forehead/facial flushing' as possible accompanying autonomic symptoms.

Methods: In this cross-sectional cohort study a sense of aural fullness and facial flushing during cluster headache attacks were investigated, using web-based questionnaires.

Results: Of the 1139 subjects who entered our web-based recruitment system, 864 subjects (75,9%) returned all necessary questionnaires. According tot the ICHD-II criteria 535 subjects of the 864 subjects were diagnosed with CH, 205 additional subjects as most probably CH (missing 1 ICHD-II criterion) and 124 subjects as no CH. In 1,5% of these 205 probably CH subjects no autonomic symptoms was the missing criterion according to the ICHD-II. Of all CH subjects 33.3% reported an 'ipsilateral sense of aural fullness' and 20.0% 'ipsilateral facial flushing' during a cluster headache attack. According to the new ICHD-III criteria 2 out of 205 probably CH subjects would be diagnosed as having cluster headache.

Conclusions: Although 'ipsilateral sense of aural fullness' and ' ipsilateral facial flushing' was often reported in our CH subjects, modification of the ICHD-III criteria of cluster headache with these autonomic symptoms led to a diagnosis of cluster headache in only 2 more patients.

P134

High Doses of Corticosteroids and Verapamil in Cluster Headache

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Objectives: A short course of corticosteroids is considered the most fast-acting prophylactic therapy of cluster headache (CH), rapidly suppressing attacks during the time required for verapamil (V) to have effect. However, it is common experience that the current use of both drugs is often unsatisfactory.

Background: We report our preliminary results of an open clinical study on a series of patients (P) affected by episodic cluster headache (ECH) treated with high doses of iv methylprednisolone (MP) and verapamil (V) per os.

Methods: Upon informed consent, a consecutive series of 20 P (6 female, 14 male, 41.1 $\pm$ 13.2 years), affected by ECH (ICHD-II 2004) was followed during 29 active cluster periods (CP). EKG and blood chemistry, including cells count, glucose, electrolytes, liver enzymes, were performed routinely before and after 5 days since the start of therapy, and when deemed appropriate thereafter. P with controindications for steroids and/or V were excluded. P with at least two prior clusters were included

(cluster/year 1.3 ± 0.6; mean duration 20-40 days for 5 P, 40-90 days for 8 P and up to 300 days for 7 P; attacks/day 2,3 ±1.1). Most P were recruited within 2 weeks from the beginning and more than a month before the expected spontaneous end of CP. P received MP 250-500 mg/day iv for 5 days, then 120 mg im for 3 days, 80 mg im for 3 days and prednisone 25 mg per os for 2 days, tapered in the following 8 days. Concomitantly, oral V was started with progressive increments up to 320 and 600 mg/day, based on anamnestic data about its previous efficacy and tolerability.

Results: The 29 CP considered were interrupted within the third day from the start of MP/V administration. In 22/29 (76%) CP, no recurrence was observed during a 6 months follow up. V dosage was 320 mg/day in 11 CP, 360 in 3, 400 in 2, 480 in 3, 520 in 2, 640 in 1. In 7/29 (24%) CP, recurrence was observed within the first month. Among them, in 4 CP, the increment of V up to 400 mg/day in 1 CP, 520 in 2, and 560 in 1 blocked the attacks within a week, with no further recurrence during a 6 months follow up; whereas, in 3 remaining CP, a reduction of $>$ 50% in frequency and intensity and of $>$ 75% in the length of active phase was observed in comparison with previous anamnestic experience.

In all our P, V was gradually tapered in not less than a month, and at least 30 days after the last attack. Mild side effects were reported by 5 P (5 CP), mainly moderate anxiety, forunculosis (MP); constipation, transitory asthenia, bradicardia, isolated ankle oedema with no clinical signs of cardiac involvement (V).

Conclusions: To our knowledge this is the first report about efficacy of high doses of iv MP and V per os in ECH. If confirmed, our very satisfactory findings warrant the revaluation of the doses and timing of these drugs with appropriate clinical trials.

P135

Stimulation of the Sphenopalatine Ganglion (SPG) for Cluster Headache (CH) Treatment – Pathway CH-1, Impact on Quality of Life (QoL) and Headache Disability

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Objectives: We evaluated the impact of on-demand SPG stimulation on headache disability and QoL in chronic CH patients during the Pathway CH-1 study.

Background: CH is a highly disabling neurological condition in which most patients report substantial restrictions to their daily living and significant reductions in their QoL; disability is amplified in patients with chronic CH.

Methods: SPG stimulation was performed with the ATI Neurostimulator, a miniaturized implantable neurostimulator which, along with a controller, provides patient controlled SPG stimulation. At the completion of the blinded, randomized experimental period (EXP), headache disability and QoL were evaluated using the HIT-6 and SF-36v2 questionnaires. Changes from baseline were compared to the clinically significant differences (CSD) in the literature [1,2].

Results: 43 patients were enrolled, 38 completed EXP. One patient did not complete the HIT-6 survey following EXP. Mean age of these 38 patients was 42 years, with an average disease duration of 12 years (range: 2-36). At baseline, these patients averaged 17 attacks/week; all used triptans as acute therapy, 50% also used oxygen. 79% of patients used preventive therapy, with the majority (68%) using verapamil.

Mean baseline HIT-6 headache disability score was 66.2 (severe impact). 22 (58%) patients improved by greater than the HIT-6 CSD (-2.3 units) following EXP; average HIT-6 score after EXP was 59. Mean baseline SF-36v2 Physical (PCS) and Mental (MCS) Component Scores were 38.4 and 33.2, respectively. An improvement at end of EXP of greater than or within the SF-36v2 CSD (3-5 units) in PCS, MCS or both was observed in 76% (N=29) of patients.

63% (N=24) of patients experienced either acute pain relief at 15 minutes in $\geq$50% of treated attacks, reduction in attack frequency of $\geq$50% compared to baseline, or both during EXP. 83% of responders (20 out of 24) reported clinically significant improvements in either HIT-6 or SF-36v2. An additional 11 patients who were not considered efficacy responders demonstrated clinically significant improvements in HIT-6, SF-36v2 or both following EXP. Thus, 35 of 38 patients (92%) showed benefit from the therapy in terms of acute pain relief, decreased attack frequency, and/or improvement in disability or QoL.

Conclusions: Patient controlled, on-demand SPG stimulation using the ATI Neurostimulation System is a safe and effective therapy also associated with significant clinical

improvements in headache disability as well as physical and mental QoL metrics.

P136

Exacerbation of SUNCT and SUNA Syndromes during Intravenous Dihydroergotamine Treatment: A Case Series and Pathophysiological Considerations

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Objectives: We describe a series of patients with SUNCT and SUNA in comorbidity with chronic migraine (CM) or cluster headache (CH), treated with intravenous dihydroergotamine (IV DHE), who experienced dramatic worsening of their SUNCT and SUNA syndromes while on DHE.

Background: Several cases of SUNCT exacerbations with dopamine agonists in patients with prolactinomas have been described, suggesting that the dopamine-prolactin axis might play a role in SUNCT pathophysiology. DHE is an ergot alkaloid derivate with affinity for serotonin and dopamine receptors, known to be effective in migraine and CH.

Methods: An initial observation that patients with both CM or CH and SUNCT/SUNA receiving IV DHE had complained of dramatic worsening of their SUNCT/SUNA led to review of case notes of individuals assessed between 2008 and 2012, with CM or CH and SUNCT/SUNA, according to ICHD-2 criteria, who underwent at least a trial of IV DHE.

Results: Twenty-three patients with a diagnosis of SUNCT or SUNA in comorbidity with CM or CH, who were treated with IV DHE, were identified. Five patients had a mild improvement of the SUNCT/SUNA (22%), 12 patients had no appreciable effect (52%), whereas six patients had a dramatic worsening of the SUNCT/SUNA (30%). Moreover, one chronic CH patient developed a new onset SUNA during his first IV DHE infusion treatment. Of these seven, three patients had chronic SUNCT and four chronic SUNA. Four of them had CM in comorbidity; one had CM and sporadic hemiplegic migraine and two patients had chronic CH. Patients requiring repeated courses of IV DHE, consistently had exacerbations of SUNCT/SUNA whilst on treatment. All seven patients required a course of IV lidocaine for 7-10 days in order to obtain a reduction of the SUNCT and SUNA attacks. Patients 1-4 had normal MRI brain scans; patient 5 and 7 had ipsilateral vascular loops with the trigeminal nerve, whereas patient 6 had a pituitary non-secretory adenoma.

Conclusions: A significant proportion of our patients suffered severe exacerbation of SUNCT or SUNA whilst on IV DHE, whereas patient 5 developed a new onset SUNA syndrome during his first IV DHE course. We speculate that DHE might worsen SUNCT and SUNA syndromes through a perturbation in the dopaminergic system. Moreover the different effect of DHE in migraine and CH compared to SUNCT/SUNA, might suggest the involvement of different neurochemical pathways in the latter that require further investigations.

	Outcome of IV DHE for CM or CCH (duration)	Baseline attack frequency (SUNCT/SUNA)	Attack frequency during IV DHE (SUNCT/SUNA)
1	CM: pain free (7 weeks)	10-15/day	SUNCT status (from day 4)
2	CM: >50% improvement (6 weeks)	15-20/day	50-60/day (from day 3)
3	CCH: pain free (3 weeks)	20-30/day	60/day (from day 4)
4	CM: 70% improvement (3 weeks)	15-80/day	SUNA status (from day 3)
5	CCH: ineffective	none	New onset SUNA (from day 5)
6	CM: pain free (1 week)	10-30/day	50-60/day (from day 3)
7	CM: pain free (2 weeks)	40-50/day	>100/day (from day 4)

P137

Cutaneous Allodynia in Cluster Headache Patients in the LUCA Population

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Objectives: To investigate the prevalence and severity of cutaneous allodynia in a group of cluster headache patients.

Background: Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the skin, is considered as a marker for central sensitization, and has been described in various pain syndromes, including migraine. By contrast, the appearance of cutaneous allodynia in cluster headache patients is still subject of debate.

Methods: This is a cross-sectional study in participants with cluster headache from the LUCA (Leiden University Cluster headache neuro-Analysis programme) population. Cluster headache diagnoses were based on ICHD-II criteria. We assessed allodynia by using the 12-item Allodynia Symptom Checklist (ASC-12). In a multivariate analysis we controlled for gender, lifetime depression, cluster headache subtype (chronic vs. episodic), age at onset, and comorbid migraine.

Results: A total of 218 (36%) of 606 patients had allodynia; 107 mild, 62 moderate, and 49 severe allodynia. Cluster headache patients with comorbid lifetime depression had significantly higher odds for cutaneous allodynia (OR 1.64, 95% CI 1.08-2.51). Significantly higher odds were also found for female gender (OR 2.08, 95% 1.30-3.33) and comorbid migraine (OR 2.00 95% CI 1.05-3.82) and significantly lower odds for age at onset (OR 0.98, 95% CI 0.96-0.99). Chronic cluster headache did not attribute to the odds of having allodynia.

Conclusions: Cutaneous allodynia was present in more than one third of cluster headache patients. Future research is needed to unravel the mechanisms behind cutaneous allodynia in cluster headache.

P138

A Possibility To Predict Chronic Cluster Headache Refractoriness to Pharmacological Therapies and Deep Brain Stimulation

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Objectives: Our aim was to enlighten a possible way to predict refractoriness of chronic cluster headache (CH) to either pharmacological therapies and deep brain stimulation (DBS).

Background: Till today this question has no answer. Being stated that sumatriptan, the "king" of the drugs for CH attack, induces activation of central cholinergic system [1], we also used a pupillometric approach regarding cholinergic system.

Methods: We used an algorithm including family and personal history of responders and non responders. Algorithm is a procedure for automated establishing a final "output". We also used a pupillometric evaluation of instillation of 1% tropicamide, a muscarinic antagonist. Pupil diameter was evaluated in standard light condition before and at 0, 30, 60, 90, 120, 150, 180, 210 min following tropicamide eye drops instillation, the latter followed a 4-days wash-out period. Results derived from the comparison between a group of chronic CH classified as responders and a matched group of non responder chronic CH sufferers. On the ground of response to either prophylactic treatment administration or to surgical practice we can divide chronic CH sufferers in two groups: Group A) included 47 non responders (40 males, 7 females; mean age 34.4 $\pm$ 3.1 SD). Group A was compared to a matched group – Group B- of 85 chronic CH responding to therapeutic approaches (76 males, 9 females: mean age 34.3 + 2.9 SD). Pupillary changes were evaluated in 3 Groups of males: 12 chronic CH sufferers refractory to therapies (age 33.2 + 4.8SD), 12 chronic CH responding to therapeutic approaches (age 33.8 + 4.4 SD) and 12 controls (age 33.1 + 5.7 SD).

Results: Outcomes regarded either pupillopharmacological approach and an algorithm the output of which was refractory CH. Algorithm evidenced an higher ($p>0.0001$) link score regarding items of inheritance taken as input compared to data set of output. The peak of tropicamide-induced mydriasis was at 90: 5.5 mm $\pm$ 0.24 SD versus 3.1 $\pm$ 0.55 SD baseline $p>0.0001$ symptomatic side; 6.58 mm $\pm$ 0.54 SD versus 3.09 mm $\pm$ 0.57 SD non symptomatic side eye $p>0.0001$ in refractorgy CH sufferers. In chronic CH sufferers responding to therapeutic approaches 7.1 mm $\pm$ 0.37 SD versus 2.9 $\pm$ 0.6 SD baseline $p>0.0001$ symptomatic side; 8.2 mm $\pm$ 0.74 SD versus 3.0 mm $\pm$ 0.53 SD non symptomatic side eye $p>0.0001$. In healthy control group 7.7 mm $\pm$ 1.2 SD versus 3.2 mm $\pm$ 10.58 SD baseline $p>0.0001$.

Conclusions: Non responder chronic CH sufferers show the lower ($p>0.0001$) mydriatic response. The algorithm profile, giving a score of risk for refractoriness, mirrored the poorness of response to tropicamide and stressed the possible role of a neural abnormal trim inherited in some CH. Such an abnormal inherited trim, seemingly involving cholinergic system, is likely to determine refractoriness to therapies including DBS.

P139

Marijuana for Chronic Cluster Headache - Its Effect on Cluster Headache History and on Cholinergic Mydriasis

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Objectives: First question regards the effectiveness of marijuana in chronic cluster headache (CH) and the distinction between drug-induced pain tolerance and pain relief. Second question concerned possible effect on cholinergic system. Third question concerns the impact of marijuana on CH history.

Background: Hypothesis of cholinergic involvement flows from animal data indicating an inhibition of hippocampal acetylcholine release after acute and repeated cannabinoids.

Methods: Pain tolerance was evaluated as behavioral manifestations i.e. movements and vocalization measured by using electronic wrist ergometer and sound registration. Pain relief was evaluated on a 0-10 VAS. The parameters were applied to 4 subsequent CH attacks during which sumatriptan or majiuana were used. The cholinergic receptor function was observed by using a pupillometric approach following instillation of 1% tropicamide, a muscarinic antagonist. Pupil diameter was measured before and at 0, 30, 60, 90, 120, 180, 210 min after eye drops instillation. A 10 years perspective epidemiological study was performed in 2 groups of men matched for age: Group 1 included CH abusing (n= 100, mean age 31.3 + 4.8) marjiuana; Group 2 included CH sufferers (n= 100, mean age 31.1 + 5.2) never using other drug than sumatriptan.

Results: The drug does not abort CH attacks. Sufferers using marijuana have an higher pain tolerance rating 30% more than CH not using cannabis as shown by behavioral parameters. VAS score registered no significant decrease following majiuana consumption compared to baseline in 4 subsequent CH attacks. The peak of tropicamide-induced mydriasis was at 90: 5.8 mm $\pm$ 0.142 SD versus 2.09 $\pm$ 0.53 SD baseline p> 0.0001 symptomatic side; 6.5 mm $\pm$ 0.65 SD versus 3.09 mm $\pm$ 0.59 non symptomatic side eye p> 0.0001 in CH using marijuana. In chronic CH never using marjiuana 7.9 mm $\pm$ 0.173 SD versus 2.9 $\pm$ 0.54 SD baseline hp> 0.0001 symptomatic side; 8.5 mm $\pm$ 0.65 SD versus 3.1 mm $\pm$ 0.55 SD non symptomatic side eye p> 0.0001. In healthy controls 7.9 mm + 1.2 SD versus 3.3 mm $\pm$ 10.5 8 SD baseline p> 0.0001. Mydriasis of CH abusers was lower (p>000.1) than controls and non addict CH sufferers. Epidemiological observation evidenced that eighty-six marijuana abusers suffered from episodic CH from the beginning till to the end of the observation. The remainder started an history of chronic CH 2.1 years $\pm$ 1.6 SD after starting abuse. Whereas, in the group of sufferers never using cannabis, only two sufferers became chronic.

Conclusions: A different response to tropicamide challenge distinguishes controls and non drug user CH from marijuana CH abusers and suggests a defect induced by marijuana on central cholinergic system. It is not possible to discard that CH became chronic because of the use of marijuana. It seems noteworthy that marijuana seemingly only aids to better tolerate pain as shown by behavioral items and VAS.

P140

Testosterone Cypionate in the Treatment of Episodic Cluster Headache: A Case Series and Meta Analysis

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Objectives: To obtain preliminary evidence in support of the hypothesis that testosterone supplementation may be of utility in males with cluster headache.

Background: Cluster headache is a primary headache disorder in which several lines of evidence implicate a change in hypothalamic function. Kudrow, Stillman, and others have reported low or low-normal testosterone levels in patients with cluster headache, and have indicated benefit with testosterone supplementation. However, the data for this association with low testosterone, and support for the benefit of testosterone supplementation is still sparse.

Methods: This is an open-label, unblinded, retrospective case series of patients with the ICHD-2 diagnosis of cluster headache. Male patients with cluster headache between the ages of 19-65 were evaluated for testosterone levels. Those with low or low-normal levels of testosterone but without abnormally high PSA levels were given 400mg testosterone intramuscular injection. Repeat injections were given for subsequent cycles of cluster attacks, where available. We also analyzed the present data together with the previously published experience with testosterone.

Results: There were 23 patients initially evaluated with cluster headache, and 17 were evaluated with

testosterone and PSA levels. The median testosterone level was below normal, including 11 patients with low total testosterone levels, and an additional 4 that had low normal total testosterone levels. Of these 15 patients, 5 (29%) had a sustained headache-free response to a single injection of 400 mg testosterone. An additional 3 patients had a marked decrease in frequency and intensity prior to the resolution of the cluster cycle. An additional 6 patients received a second dose of 200 mg testosterone with complete resolution of the headache. A single patient had a complete resolution after a third injection, again with 200 mg testosterone. A total of 17 cluster cycles were treated with testosterone injection in this manner, and 14 (82%) of these cycles were aborted by this approach.

Conclusions: The present evidence suggests that total testosterone levels are below normal in those with cluster headache. Testosterone injection may be an effective way to abort the cluster cycle. Present evidence is supportive of a definitive prospective, randomized, placebo controlled trial.

P141

Non-Invasive Vagus Nerve Stimulation for the Treatment of Cluster Headache: A Cohort Study

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Objectives: The objective of this work is to undertake a preliminary clinical evaluation of treatment outcomes in patients with cluster headache using a non-invasive vagus nerve stimulation device, CE marked in Europe for the treatment of headache disorders.

Background: Cluster headache (CH) is a highly disabling primary headache disorder. Abortive therapy is currently limited by dose restrictions of triptans, and practicality issues of using oxygen. Preventive medications may not be entirely effective. Surgical interventions, in particular deep brain stimulation, carry additional risks.

A need therefore exists for a novel, safe and practical therapeutic approach. We assessed the usefulness of a new portable, non-invasive vagus nerve stimulation (nVNS) device, the GammaCore.

Methods: Patients with CH attending one of two headache centres were offered nVNS treatment in an unbiased fashion. After training, most patients were instructed to use the device both acutely to treat attacks, and twice daily as a preventive measure. A few patients used it for acute treatment only. Case notes were reviewed, and patients questioned during routine follow-up about their experience with the device and the impact they perceived it had.

Results: Of patients given the device, 21 of 25 (12 male; 12 chronic, 10 of who were considered to be medically intractable, and 9 episodic; median age 46, range 13-84) had sufficient data available during a median device use period of 12 weeks (range 1-26) to include in analysis. Eighteen reported an overall improvement in their condition, stating a mean estimated subjective improvement of 51% (SD 30) from baseline, while three remained the same. Ten patients were able to reduce significantly or stop their previous abortive treatment, seven reduced it and four required the same amount as before. Eight patients were very satisfied, ten satisfied and two equivocally satisfied after using the device. Only one patient felt dissatisfied. All 21 stated they would recommend this treatment to other patients with CH.

Patient feedback suggests that nVNS can both abort and significantly improve attack intensity, as well as reducing attack frequency when used prophylactically. In addition, prophylactic treatment may offer highly significant improvement in some patients with otherwise intractable chronic CH.

Conclusions: This is the first evaluation of an entirely new treatment modality for CH that appears to be well-tolerated and effective in both the acute *and* preventive treatment of CH. The significant improvement achieved in some patients with medically intractable chronic CH suggests that nVNS should be trialled before intracranial surgical procedures are considered.

These preliminary findings will serve to inform the design of clinical trials aimed at further clarifying the efficacy of this treatment.

P142

Naratriptan in Prophylactic Treatment of Cluster Headache; the 2nd Edition

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Objectives: The purpose of this study is to determine whether naratriptan would show efficacy in prophylactic treatment of cluster headache in Japan.

Background: Naratriptan, 5-hydroxytryptamine$_{1B/D}$ (5-HT$_{1B/D}$)-agonist, is an effective medicine for migraine. Naratriptan has also been reported to reduce the frequency of cluster headache (1-3).

Methods: We report 13 patients with cluster headache preventively treated with naratiptan. We used the International Classification of Headache Disorders; 2nd Edition (ICHD-II) for diagnosing of cluster headache. The study was conducted in 4 centers (Department of Neurology, Saitama Medical University, Saitama Neuropsychiatric Institute, Saitama International Headache Center and Saitama Medical University International Medical Center) and patients were recruited from these specialized headache outpatient centers. Naratriptan was taken before they went to bed.

Results: Eleven of 13 patients with cluster headache have shown no attack after naratriptan treatment. In one case, the frequency of attacks was decreased by naratriptan. But naratriptan had no effect for her headache in one case.

Conclusions: It has been suggested that naratriptan might be preventive medicine for cluster headache because biological half-life of naratriptan is longer than that of other triptans.

P143

No Olfactory Deficit in Episodic Cluster Headache

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Objectives: To determine whether patients suffering episodic cluster headache have a nasal chemosensory performance deficit.

Background: Cluster headache (CH) is a rare primary headache disorder, which is characterized by strictly unilateral severe headache attacks. Its pathophysiology is still obscure. Electrophysiological findings in episodic CH showed an asymmetric facilitation of trigeminal nociceptive processing which is predominantly located on brainstem level even in remission periods. But as in other headache syndromes, such as migraine, alterations and disregulation in other senses are in discussion. A diffusion tensor imaging study detected frontobasal alterations and the authors suggested an involvement of the olfactory system (Teepker et al.). Furthermore preliminarily data from a small study using olfactory testing even suggested alterations in olfactory performance and raised the question of clinical implications of this finding.

Methods: We investigated 30 patients (mean age: 46y; m:f = 24:6) suffering episodic cluster headache and currently being in a remission periods, using the commercially available 'Sniffin'Sticks' test battery testing nasal chemosensory performance. With this system based on pen-like odor dispensing devices olfactory performance was tested regarding odor threshold, odor discrimination and odor identification. Determined scores were then compared to the standardized reference values previously defined in a big control cohort.

Results: Neither in overall olfactory performance (TDI-Value), calculated as the sum of the subscores, nor in any of those we were able to detect alterations in olfactory performance. TDI Value (ref.: 30.5) was 31.39±5.49 ipsilateral and 30.47±4.76 contralateral to headache. Scores for threshold, discrimination and identification behaved comparable and will be presented as table.

Conclusions: No lack of olfactory performance was observed in the patient cohort regarding odor threshold, discrimination, identification or TDI-overall performance. Furthermore no lateralization in nasal chemosensory performance could be identified in side comparison in all domains. This is in contrast to previous findings and pulls CH apart from being a multisensory disorder.

P144

Botulinum Toxin Type A in the Treatment of Episodic and Chronic Form of Cluster Headache

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Objectives: The aim of the study was to evaluate safety and efficacy of botulinum toxin injections (in completely new, unchecked paradigm) in patients with chronic (CCH) or episodic (ECH) cluster headache.

Background: Cluster headache (CH), especially in its chronic form, is frequently resistant to hardly a few drugs available for this disease, like steroids, verapamil, valproic acid, lithium and topiramate. Another therapeutic option for resistant cases is specifically desired. As recently botulinum toxin has been successfully tried in chronic migraine – another type of daily or almost daily headache type, it seemed to be worth trying this therapy also in CH. Until now there has been only 1 original publication on small doses (50 U) of botulinum toxin A in a group of 12 CH patients [1].

Methods: Twelve patients - 4 with CCH and 8 with ECH (2 women with ECH, with mean age of 51 years, and 10 men – 6 with ECH and 4 with CCH, with mean age of 50,1 years), with no other concomitant treatment, were injected i.m. with a total dose of botulinum toxin type A (Botox) of 200 U each, divided into 14-18 portions. The area of injections covered typical painful region, and was adjusted individually ("follow the pain"). Decision on re-injections after 90 days depended on whether a patient suffered from headaches or not, at that time. The effect of treatment was evaluated as comparison (before and after therapy) of: the number of headaches per 24 hours, number of headaches per month, mean duration of headaches, mean intensity of headaches, headache index (frequency x duration x intensity), number of days from injection to significant improvement and to remission.

Results: Ten out of 12 patients evaluated the treatment as beneficial. They reported improvement in most of estimated parameters, while headache index after 90 days was significantly lowered in all 10 cases ($p<0.05$). In "responders", the mean time to significant improvement was 15.8 days (11.8 days in ECH and 21.7 days in CCH) while average time to achieve remission in ECH was 25.3 days. CCH patients had temporal remissions lasting even several months. One patient with ECH had only partial and short-lasting improvement, while another ECH patient did not find the treatment helpful at all. No adverse effects (beside asymmetry of the forehead) were reported.

Conclusions: Botulinum toxin type A in the dose of 200 U injected i.m. in relatively small fronto-temporal area, evaluated in an open trial, is safe, well tolerated, and at least partially effective method of treatment in both forms of CH.

P145

Shunting the Diagnosis: A Case of Secondary Cluster Headache

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Objectives: The intent of this study is to demonstrate cavernomas as potential structural causes for secondary cluster headache.

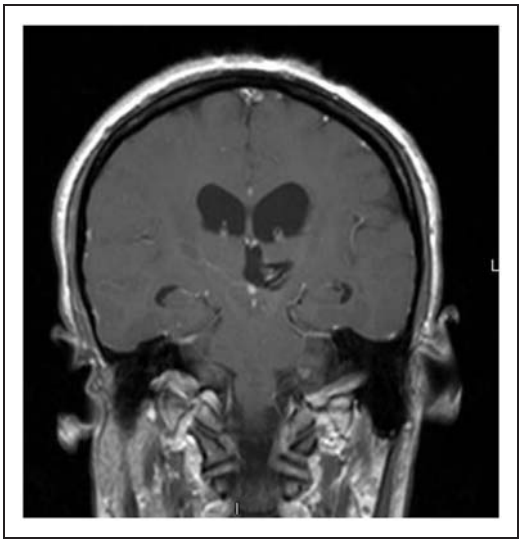
Background: Cavernomas are thin dilated vascular channels that lack smooth muscle or neural tissue. Their incidence is 0.3-0.5% and are usually discovered in young adults. The most frequent presentation is seizure, but can present with focal deficits or headaches. One case reported a tectal cavernoma causing hydrocephalus requiring shunting and subsequent surgical resection. Another case reported idiopathic hydrocephalus causing cluster headaches. Other than these cases, to our knowledge, there are no other reports of cavernomas causing hydrocephalus or such patients developing secondary cluster headaches.

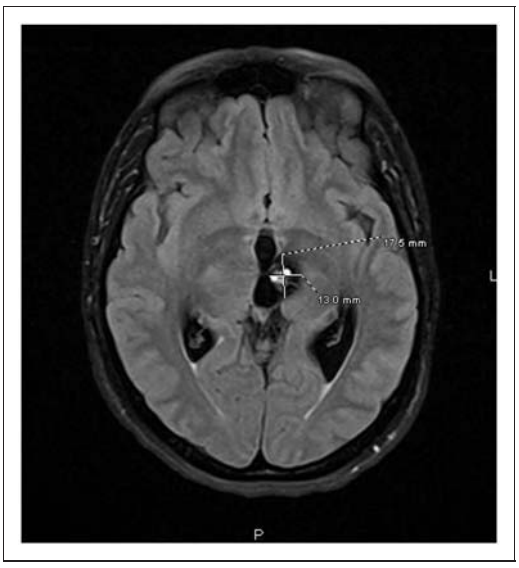
Methods: A 36 yo woman with history of right hemiplegia and hemisensory deficits since childhood presented with neck pain and falls. MRI revealed two cavernomas in the left thalamus extending to the midbrain and tectal region. Two years later, she developed chronic nausea and headaches. A repeat MRI demonstrated obstructive hydrocephalus, and a VP shunt was placed with resolution of hydrocephalus and improvement of nausea. Unfortunately, there was no improvement of headaches.

Results: Since onset, she had 3-4 headaches per day that occur around the same time daily. They are located around the left temporal/parietal area, lasting about 45 minutes. The headaches are throbbing, 7-10/10 with photophobia, phonophobia, nausea, vomiting, and cutaneous allodynia. During attacks she feels restless and unable to find a comfortable position. There is unilateral eyelid drooping with left sided congestion and some runny nose with headaches, but no other autonomic symptoms. She was started on a trial of verapamil, and reached a dose of 360mg daily. On this dose of verapamil, her headache frequency improved to 1 headache per day with a 5/10 intensity. For abortive therapy, she has used oxygen at 10 LPM

with a face mask, which typically terminates a headache within 10 minutes.

Conclusions: The patient's cavernomas caused obstructive hydrocephalus requiring intervention. Initially, it was unclear whether her hydrocephalus and/or cavernomas were contributing to her headaches with cluster features. Subsequent resolution of her hydrocephalus after VP shunt placement, did not lead to improvement of her cluster headache symptoms. Therefore, her cavernomas may be playing a causative role in her cluster headaches. In addition, this case suggests that verapamil and oxygen may be effective treatments for secondary cluster headaches.





P146

A Case of Cluster Headache with Polycythaemia Rubra Vera Responding to Venesection

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Objectives: First case report of polycythaemia rubra vera presenting with cluster headache which responded well to venesection.

Background: Cluster headache (CH) is the most frequent type of Trigeminal Autonomic Cephalalgias (TACs) with a prevalence of 0.1%. CH is more common in males who smoke. The episodic variant is 6 times more common than the chronic one. Majority of CH are primary although secondary cases have been described with intracranial pathologies such as pituitary macroadenoma, meningiomas, and intracranial large arteries aneurysms.

Headaches of non-specific nature is a presenting feature in a third of patients with Polycythaemia Rubra Vera (PRV) and other hyperviscosity disorders although presentation with CH has not been reported before. We report a case of PRV presenting with CH which responded well to venesection and recurrence of symptoms with a rise of haematocrit and haemoglobin (Hb).

Methods: A 52 year old gentleman, a lifelong smoker, presented with a 4 month history of recurrent right peri-orbital excruciating headaches on a background of continuous dull ache. The excruciating attacks would come on between 4-6 times a day, each lasting 30-75 minutes with ipsilateral autonomic features and extreme restlessness. The attacks were more common in early hours of morning. A diagnosis of CH was made and verapamil with a short course of steroid was commenced with oxygen and subcutaneous imigran as abortive treatment

Routine investigations showed Hb of 18.5, WBC 14, Platelets 520 with a haematocrit of 59. The alkaline phosphatase was 175 and B12 was 950. MRI head was normal

He was referred to haematology where he reported no benefit with verapamil and steroids although the abortive treatment was successful. Further investigations confirmed the diagnosis of PRV. He was subjected to venesection with complete resolution of cluster attacks and the background pain, however the attacks repetitively recurred with a rise of haematocrit and Hb levels and settled with further venesection. The patient went in remission on hydroxyurea and remained cluster-headache free.

Results: Non-specific headaches may be a presenting feature in a third of patients with hyperviscosity disorder. CH

has been reported in patients with haemochromatosis responding to venesection. As far as we are aware this is the first report of CH as a presenting feature of PRV.

Conclusions: The poster reviews literature to suggest plausible mechanisms for CH in PRV and other hyperviscosity disorders although we feel this may only be a trigger in those with an inherent tendency for a specific headache disorder.

P147

Recurrent SUNCT Following Prolactinoma Resection in a Pregnant Woman: A Case Report

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Objectives: To report the efficacy of peripheral nerve blocks in the treatment of short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT).

Background: SUNCT is a rare headache syndrome that has been associated with pituitary adenomas, especially those secreting prolactin or growth hormone. The observations of headache resolution following tumor resection and with the use of dopamine agonists suggest a role of the hypothalamo-pituitary axis regulation in the pathophysiology of the syndrome. No medical treatment has been universally effective and most agents used raise concerns during pregnancy. Cases in the literature of treatment with greater occipital nerve stimulation or blocks show either conflicting results or afford only temporary benefit.

Methods: A 32 year old woman with history of migraine since childhood developed amenorrhea and persistent galactorrhea immediately following her first pregnancy. She had elevated prolactin and was diagnosed as having a right-sided pituitary macroadenoma (prolactinoma). Upon initiation of cabergoline (0.25mg) she developed frequent ipsilateral attacks of SUNCT. The tumor was resected with immediate resolution of the headaches. Two weeks later she became pregnant again with almost immediate recurrence of the same, brief (up to 30 seconds) attacks of abrupt onset headache in the right periorbital, frontal and temporal regions with radiation to the neck, associated with conjunctival injection, tearing and nasal congestion. Evaluation for tumor recurrence with non-contrast MRI showed no gross postsurgical changes. The headaches were of increasing frequency and severity and by week 13 of gestation they recurred every 5 minutes and persisted during sleep. A series of peripheral nerve blocks were performed.

Results: Consecutive 0.5% bupivicaine nerve blocks of the right occipital, supraorbital, supratrochlear and auriculotemporal nerves, as well as an ultrasound guided occipital nerve block offered temporary (4-5 hours), but almost complete pain relief. Short courses of prednisone and use of oxycodone/ acetaminophen for breakthrough pain decreased the frequency, duration and severity of attacks. She underwent right occipital nerve radio frequency thermo-coagulation (RFTC) (120 second - 0.5 A pulses). One week later, and while off steroids and opioids, she experienced significant pain relief lasting one week and followed by an exacerbation. She is currently at 23 weeks of gestation and we will follow her clinical course to delivery, expected in May of 2013.

Conclusions: Our patient demonstrates the complex association between hypothalamo-pituitary hormonal changes and SUNCT, as well as the challenges in identifying optimal treatment. This is the first case report of ipsilateral greater occipital nerve pulsed RFTC under ultrasound guidance for SUNCT, offering substantial, but brief benefit.

P148

Cluster Headache in Brazil: Data from a Nationwide Survey

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Objectives: To determine the clinical features of cluster headache in Brazil.

Background: Although less common than migraine and tension-type headaches, cluster headache is nonetheless an important clinical entity, particularly given its pain being considered to be one of the most severe known to man. A nationwide survey may provide data about disease distribution according to gender, possible identification of risk factors, economic consequences, and social impact. Information about access to standard care may lead to public healthcare policies tailored to this specific headache population.

Methods: A comprehensive, self-applicable questionnaire was developed in Brazilian Portuguese and it has been made available over the internet since December/2010. Regardless of answering the questionnaire online, all subjects who had the chance to do so were offered a medical

consultation, when again the same questionnaire was applied by the authors. Test-retest and inter-rater reliability were calculated using Cohen's kappa statistic, Cronbach's alpha coefficient and Pearson's correlation coefficient. Only variables with statistically significant reliability were analyzed.

Results: As of February/2013, 246 subjects had answered the questionnaire online and fulfilled the CH diagnostic criteria according to the second International Classification of Headache Disorders (ICHD). The average age of the subjects was 37,97 $\pm$ 4,13. There were 158 male (64,75%) and 86 female (35,25%) patients. Considering the temporal pattern, 33 (13,41%) evolved into the chronic form of CH, while 213 (86,58%) presented the episodic form. Notably, 47 (19,10%) subjects had had pain attacks superior to 180 minutes and 50 (20,32%) had had more than 8 pain episodes a day. History of present or previous smoking habit was related by 132 (53,65%) subjects. Comorbid conditions were related by 229 (93,08%) patients, being anxiety in its several forms the most common with 175 (71,13%). Although 218 subjects had performed ancillary examinations (88,6%), only 114 (46,34%) were offered oxygen therapy at some point of their disease.

Conclusions: Despite being subject to some biases, our ongoing survey shows that most characteristics of CH in Brazil are similar to what is found in the scientific literature. However, the fact that almost 20% of the patients had presented pain attacks superior to 180 minutes and more than 8 pain episodes a day may contribute to further review of CH diagnostic criteria. Risk factors other than smoking habit should be investigated in our population. Furthermore, the disparity between the performance of ancillary examinations and the use of oxygen therapy suggests that CH is still under treated in Brazil.

P149

Non-Indomethacin/Nerve Block Approach to Patients with Hemicrania Continua

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Objectives: To describe a non-indomethacin treatment for hemicrania continua (HC) utilizing anesthesiologic procedures.

Background: HC is an indomethacin-responsive headache syndrome. On indomethacin patients feel normal, off they have disabling headaches. The risk of long-term indomethacin therapy is great. There are very few alternative treatments outside of indomethacin. There is data on occipital nerve stimulators but that can have considerable morbidities. We present 3 patients who had complete alleviation of HC with two distinct procedures: C2 ventral rhizotomy and sphenopalatine ganglion rhizotomy.

Methods: Case reports.

Results: Case 1: 30 year old woman with a daily headache from onset, 100% right sided in the occipitonuchal region. Baseline pain low intensity with pain exacerbation periods lasting several days with associated ispilateral conjunctival injection. On exam right upper cervical facet and GON tenderness. HC diagnosed as became pain free on indomethacin 50mg TID. She had a right C1-C2 facet injection with complete relief of headache. This was followed by a C2 ventral rhizotomy, providing pain freedom off indomethacin for one year. Procedure was repeated after HC recurrence and has now gone 18 months headache free without medication.

Case 2: 24 year old woman with a daily one-sided headache of 7 years duration. Pain in left temple, face and periorbit. She had congenital blindness in the left eye enucleated at age 18 for thoughts this was contributing to her headache. Had some improvement until teeth extraction one year prior to clinic presentation. Post procedure had extreme worsening of pain. She suffered from continuous low level head pain with exacerbation periods lasting days with associated agitation, left ptosis and infraorbital swelling. On indomethacin she became pain free at dose of 75mg TID thus diagnosis of HC. She underwent a left sphenopalantine ganglion block leading to pain freedom and ability to discontinue indomethacin. She had a left sphenopalatine rhizotomy which gave her 4.5 months of pain freedom. Pain returned on a daily basis requiring repeat radiofrequency. Now 3 months post she is almost headache free.

Case 3: 47 year old man, daily right frontotemporal headache for 27 years. He complained of persistent pain with exacerbations periods lasting days with associated agitation, ptosis, conjunctival injection, lacrimation and rhinorrhea. On indomethacin 75mg TID he became pain free. Due to extremity edema the medication was discontinued, HC recurred. He underwent a right sphenopalatine ganglion block allowing complete pain relief. This was followed by a rhizotomy and at one year's time he has had total alleviation of his headache without the need of indomethacin.

Conclusions: Three patients with indomethacin responsive HC who achieved pain freedom after sphenopalatine ganglion or C2 rhizotomy. As the risks of long-term

indomethacin administration are substantial alternative treatments are necessary. We now suggest non-indomethacin, non-stimulator options for patients with HC.

P150

Differential Diagnosis of Chronic Paroxysmal Hemicrania. After Unsuccessful Microvascular Decompression

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Objectives: Orofacial pain (OFP) often arises from non-odontogenic sources, and often mimics dental pain causing patients to seek dental remedies. Common sources of non-odontogenic orofacial pain include musculoskeletal, neuropathic or neurovascular disorders. In this case, we report a patient who was initially diagnosed with trigeminal neuralgia and who underwent unsuccessful microvascular decompression surgery. She was later diagnosed, and treated successfully for chronic paroxysmal hemicrania (CPH), classified as a trigeminal autonomic cephalgia (TAC) by the International Headache Society (IHS). She also incurred an iatrogenic atypical odontalgia/differentiation pain following an apicoectomy.

Background: A 54-year-old, Caucasian, female presented with chief complaints of moderate to severe pulsating and stabbing pain in the maxillary right gingiva and headache of the right side lasting 10-20 minutes. Symptoms also included nasal congestion and ptosis of the right eye during attacks. Her medical history includes apicoectomy on teeth number 4 and 5 3 years ago, which is not related to her current problem, except for the fact that she may have developed an iatrogenic atypical odontalgia/differentiation pain. However, this is not related to the problem for which she sought our evaluation. The patient underwent unsuccessful microvascular decompression as a treatment for trigeminal neuralgia (TN).

Methods: Based on the clinical complaints, observations, radiographic findings and the succcesful trial of indomethacin, the diagnosis was chronic paroxysmal hemicrania (CPH) and non-related, iatrogenic atypical odontalgia/differentiation pain following apicoectomy.

Results: Patient is currently undergoing successful prophylactic therapy taking 1 tablet of Indomethacin 25mg 4 times a day. This will be continued with gastro-protection with omeprazole (Prilosec ©) for one month and the medication will be withdrawn slowly to determine if additional therapy is necessary.

Conclusions: An accurate diagnosis of orofacial pain conditions requires a detailed examination and knowledge of pain mechanisms. Moreover, a precise identification of the source of pain is the most important factor leading to a correct diagnosis, successful treatment and prevention of unnecessary treatment.

P151

Sec-Butyl Propylacetamide (SPD) a Novel Valproic Acid Amide Analogue Has Anti-Migrain Properties

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Objectives: Evaluation of the antimigraine potential of a novel valproic acid (VPA) amide analogue, *sec*-butyl-propylacetamide (SPD).

Background: Migraine is a disabling disorder affecting 12-15% of people worldwide. Pharmacotherapy is the main treatment for migraine, and there is an urgent need for novel antimigraine drugs. *Sec*-butyl propylacetamide (SPD) is a novel amide analogue of VPA, with greater potency and more rapid pharmacokinetics. SPD has a wide range of activity in animal models of epilepsy and is also effective in models of neuropathic and inflammatory pain. Since migraine and epilepsy are comorbid diseases we evaluated SPD's anti-migraine potential in two mouse models for migraine, and evaluated its relevant mechanism of action in cell culture in-vitro.

Methods: C57BL6 male mice were used in a blinded randomized fashion in two models for migraine. We evaluated SPD's potential in reducing the number of cortical spreading depression (CSD) in-vivo, and evaluated its effect on NTG induced heat hyperalgesia and mechanical allodynia. SPD's ability to modify GABA, NMDA, Kainate and voltage dependent Na+ currents was evaluated in primary culture of dissociated cortical neurons, and neuroblastoma cell line.

Results: SPD significantly decreased the number of CSDs compared to control following acute dosing, from 8.3 (± 1.0.) to 4.75 (± 1.1.) in the control and SPD groups respectively. 60 mg/kg SPD increased the withdrawal threshold for both NTG induced heat hyperalgesia and mechanical allodynia compared to vehicle in both time points evaluated, indicating its protective effect for NTG induced hyperalgesia. SPD was able to increase GABA but

not NMDA or AMPA mediated currents in cortical neurons cell culture. SPD had no effect on voltage dependent sodium channel currents.

Conclusions: SPD, a novel amide analogue of valproic acid, robustly suppresses CSD frequency and elevates the threshold of both NTG induced mechanical allodynia and heat hyperalgesia. SPD may exert its anti-migraine effects through enhancing cortical inhibition. As a promising novel anti-migraine compound further evaluation of SPD's specific mechanism of action is warranted.

P152

A Case Series: Incobotulinumtoxin A - A Novel Therapy for Refractory Trigeminal Neuralgia

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Objectives: To discuss the potential benefits of using incobotulinumtoxin A in treating cases of refractory trigeminal neuralgia.

Background: The first patient is an 81 year old male with over 10 years of V1 distribution trigeminal neuralgia of the right hemifacial region. Patient reported pain that would "drop him to his knees" and was intractable to multiple oral medications. His pain was refractory to surgical interventions such as gamma knife surgery, microvascular decompression and nerve ablation. Patient was started on onobotulinumtoxin A (Botox) and after several rounds of injections, patient began to develop resistance to therapy and was subsequently transitioned to incobotulinumtoxin A at the same unit dose with >90% relief in the frequency and severity of his symptoms.

The second patient is a 36 year old male with a 4 year history of right V3 distribution trigeminal neuralgia. He had also failed multiple oral medications and gamma knife surgery on two occasions. Patient was started on incobotulinumtoxin A with an 80% reduction in pain intensity and a 90% reduction in frequency of his pain symptoms. This benefit was maintained for the duration of three months.

Methods: The first patient was seen every 12 weeks for onobotulinumtoxin A injections in a grid like pattern along the V1 territory. After several sessions of onobotulinumtoxin A patient was transitioned to incobotulinumtoxin A. Pain was assessed via patient pain scale that was administered at every appointment visit.

The second patient was started on incobotulinumtoxin A injected in a grid like pattern along the V3 territory. The patient's pain scale was assessed at 6 and 12week follow-up sessions.

Results: Despite multiple trials of medical and surgical management patient developed substantial relief with the use of onobotulinumtoxin A. Due to development of onobotulinumtoxin A resistance in the form of shortened duration of therapeutic activity, patient was transitioned to incobotulinumtoxin A with a beneficial result for a 12 week period of time. In the second patient an improvement in patient symptoms were seen with injections of incobotulinumtoxin A.

Conclusions: Botulinum toxin A has been used as a minimally invasive therapy for several neurological conditions such as cervical dystonia and blepharospasm, and has since transcended into being a mainstay therapy for migraines, tension, and occipital headaches. The cases we describe show that botulinum toxin A has the potential to become part of the treatment regimen for trigeminal neuralgia cases that are refractory to both medical and surgical intervention.

We can furthermore discuss that those patients whom develop resistance to onobotulinumtoxin A may be successfully transitioned to incobotulinumtoxin A. Incobotulinumtoxin A may also be used an additional medication in the management of trigeminal neuralgia. These cases, like other similar case reports and studies, show that botulinum toxin A, and in particular incobotulinumtoxin A, can become an integral part of trigeminal neuralgia therapy.

P153

Dedicated Headache Clinic Impact on Care and Cost in a Multispeciality Clinic

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Objectives: To measure the impact a dedicated Headache Clinic may have upon delivery of care in a multispeciality clinic.

Background: With the coming health care changes there many patients will now have access to services previously unavailable. How this care is delivered will come under greater scrutiny for its evidence base and cost effectiveness. Migraine is the second leading cause of disability in the USA so an individual with Migraine can be assured that there will be attacks that will on occasion require rescue. All too often today Migraine patients seek that care in an expensive Emergency Department setting. It is because of these episodes of disabling attacks that migraine patients

are greater consumers of health care resources than other patients.

Methods: In 2008, our institution started a dedicated headache clinic that offered "Headache rescue" for established patient suffering with their usual primary headache. A Family Medicine physician with an interest in headache was selected as the first director. The utility of offering headache rescue has been documented with demonstrated patient satisfaction and cost savings. In an attempt measure the impact of a dedicated headache clinic charts were reviewed from May 2011 – May 2012 and 690 patients established care in our clinic. Randomization for this review was done by selecting every 9th patient who established care in our clinic, yielding an n = 70. Of the randomized patients, 17 had visited the ED one or more times, 14 had CT imaging of the head, and 11 were using opiates for their headache care.

Results: Patients who established care in our clinic showed a reduction in ED utilization, CT imaging, and opiate usage by 75%, 93% and, 47% respectively.

Conclusions: Our review of the data suggests that a dedicated headache clinic can reduce Emergency Department utilization, imaging and opiate usage. Our experience suggests that initiating a headache clinic can be a means of providing appropriate care in a cost effective fashion. Our experience also suggests that appropriate therapies (prophylaxis, abortive, and rescue) can be delivered in a primary care or specialty setting.

Indicator	Before enrollment	After enrollment
ED Visits	17	4
CT Head	14	1
Opiate usage	11	6

P154

What Do Patients Know about Their Migraine Medications? An Analysis of Patient Knowledge about Triptans in Patients Using Triptans

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Objectives: To compare triptan users' self-perceived vs. actual knowledge about the triptans in patients receiving vs. not receiving triptan education.

Background: Patient education on triptan use is crucial for safe and effective treatment. It is unclear how knowledgeable triptan users are regarding their triptan, how much education is occurring at triptan prescription, and how much impact patient education has on actual patient knowledge of triptan use.

Methods: This was a multi-center prospective observational study of 207 migraine patients who use triptans and were seen as new patients at tertiary care headache clinics in the USA. It was conducted by the American Headache Society Headache Fellows Research Consortium via standardized questionnaires regarding self-perceived and actual triptan knowledge, and whether or not education was received at time of triptan prescription.

Results: Over 87% of subjects received education about when to take the triptan and number of doses allowed per migraine, 71.5% about triptan side effects, 64.3% for number of triptan doses allowed each week/month, 64.1% for taking other medications with the triptan, 49.3% for medical contraindications to triptans. Compared to subjects not educated about when to take triptans, subjects receiving education had greater actual knowledge for taking triptans immediately after a headache begins (p=.049), treating when pain is mild (p=.009), and not needing to fail treatment with over-the-counter (OTC) medications first (p=.001). Compared to subjects not educated about contraindications to the triptans, subjects receiving education were more knowledgeable that coronary artery disease (CAD) is a contraindication (p=.001). Subjects educated about the number of triptan doses allowed and about taking other medications with the triptans showed no significant differences in actual knowledge compared to those not receiving education, although positive trends for increased knowledge were seen. No differences existed in actual triptan knowledge amongst subjects who thought it is complicated to understand how and when to take the triptan vs. subjects who did not think it is complicated.

Conclusions: This study supports that education at time of triptan prescription leads to greater patient knowledge regarding proper triptan use. Triptan users receiving education better recognized the importance of taking triptans immediately after a headache begins, treating when pain is mild, not needing to fail treatment with OTC medications first, and understanding that CAD is a contraindication to use. Education on triptan side effects, number of doses allowed each month, taking other medications with triptans, and triptan contraindications requires improvement.

P155

Headache Hall of Fame - Through Philately

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Objectives: To review the literature through philately of famous people who suffered from headaches and migraines.

Background: Since time immemorial, headaches have affected millions of people. It is one of the oldest conditions affecting humans, with a distinguished and rich history.

Methods: Literature review. The original postal stamp display (issued by different countries) of famous people with headaches, is displayed, with a short biography of the nature of their headaches.

Results: The famous people who suffered or are strongly believed to have had headaches are classified into several categories according to their respective fields of excellence. The noted ***philosophers*** are Julius Caesar, Karl Marx and Friedrich Nietzsche. ***Statesmen and rulers*** include John of Arc, Napoleon, Robert Lee and Princess Margaret. ***Presidents*** include Thomas Jefferson, John Adams, Abraham Lincoln, Ulysses Grant, Woodrow Wilson, Harry S Truman and John F Kennedy. Eminent ***scientists*** include Blaise Pascal, Charles Darwin, Alexander Graham Bell, Alfred Nobel and Sigmund Freud. ***Musicians and composers*** include Elvis Presley, Gustav Mahler, Pyotyr Tchaikovsky and Frederic Chopin. Famous ***writers and authors*** were Leo Tolstoy, George Bernard Shaw, Lewis Carroll, Edgar Poe, George Eliot and Miguel de Cervantes. Famous ***artist*** include Vincent Van Gogh.

Conclusions: Having headaches does not hamper one's true genius. These impressive people have enlightened the world and have served as role models, inspiring people with headaches, who are neither geniuses nor celebrities.

P156

Brain Anatomy and the Expression of Head Pain in the Art of Michelangelo and Leonardo da Vinci

M.M. Valença

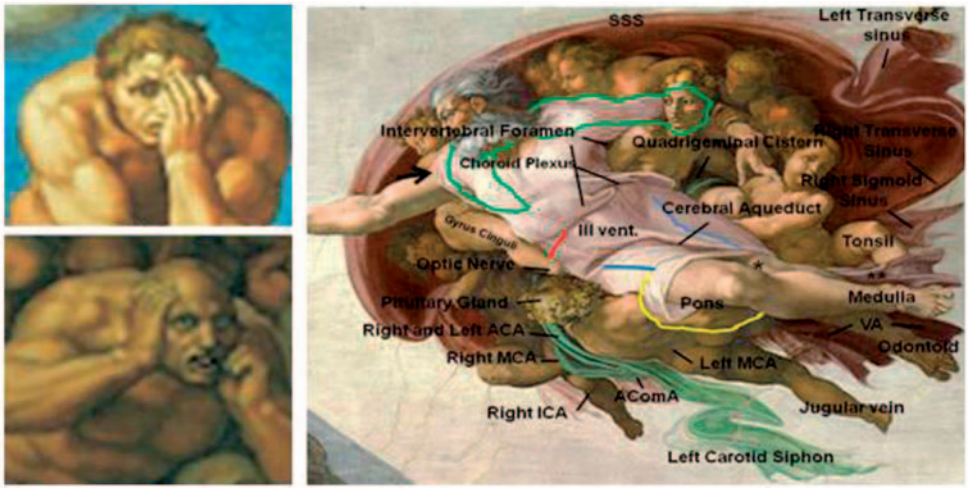
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Objectives: To show that Michelangelo painted the emotional expression of pain and different aspects of neuroanatomy in the Sistine Chapel.

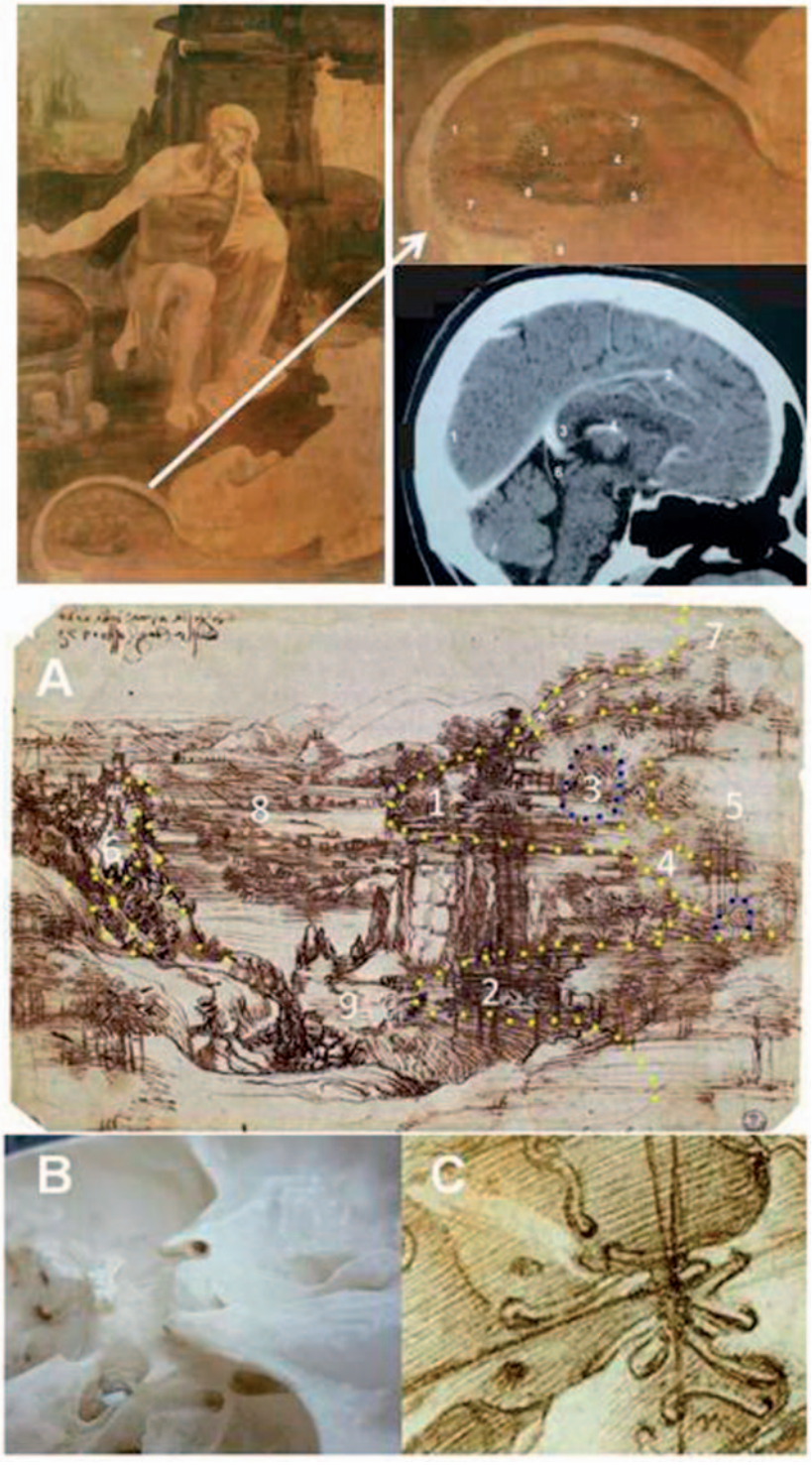
Background: Previous articles[1,2] have suggested that Michelangelo hid some brain illustrations inside the frescos he had painted.

Methods: The author conducted a meticulous search for anatomical features in the work of Michelangelo and Leonardo.

Results: Michelangelo painted human figures in the Sistine Chapel. Among them at least two may represent an attack of severe unilateral headache (note the hand over one of the sides of the head) occurring in young agitated men (*Last Judgment,* Fig 1). The author speculates that they represent a cluster headache attack. And if so, did Michelangelo believe the origin of the headache was in the brain, justifying his interest in brain anatomy and the painting of several anatomical details found in the Sistine Chapel? Many of these anatomical structures are camouflaged within his fresco *The Creation of Adam*, e.g. the



carotid siphon, the anterior communicating artery and the sagittal view of the brainstem (Fig 1). The intriguing interplay of art and science and the outstanding skills manifested in the drawing of neuroanatomical details, not yet described at the time, make Michelangelo one of the greatest neuroanatomists of the Renaissance period. Before Michelangelo, Leonardo had already used hidden anatomic imaging in his paintings and drawings, perhaps influencing Michelangelo regarding the method of painting he used in the Sistine Chapel. In Leonardo's earliest work (*Study of a Tuscan Landscape*) the present author realized that it was made over an illustration of the human *sella turcica* (Fig 2), indicating that he already had a particular interest in the anatomy of the skull. In *St Jerome in the Wilderness* the



intracranial content (deep venous system) of a hemicranium can be identified in the image of the lion's tail, indicating again the inclusion of hidden anatomical features within his paintings (Fig 2). In *Leda and the Swan* Leonardo also depicted the image of a brain camouflaged as a mountain.

Conclusions: In conclusion, in each face found in the Sistine Chapel Michelangelo purposely painted with different emotional expression, such as admiration, fear, repentance, tiredness, authority and pain, as in the case of the possible cluster headache. And the author cogitates that Michelangelo knew that all were the result of a particular brain status, hence his neuroanatomical curiosity.

P157

The Perception and Satisfaction of Patients Seen at a Rural Physician Assistant- Directed Headache Specialty Clinic

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Objectives: To examine the attitudes and satisfaction of patients seen at a Physician Assistant-directed headache specialty clinic in a rural setting.

Background: One of the greatest obstacles in preventing chronic headache sufferers from getting adequate care and higher quality of life is lack of access to specialty trained providers. It is estimated that there is one UCNS board certified headache specialist per 200,000 migraine sufferers. These specialists are almost all located in major urban centers and out of reach, geographically, from the majority of patients.

Some Physician Assistants (also known as Physician Associates) and Nurse Practitioners have had many years of high level training in major headache centers and are qualified to provide a very high level of specialty care in satellite or free-standing headache centers, thus increasing the accessibility of headache sufferers to that care. Being cost-effective they can also bring that level of specialty care to rural or other areas, which could not financially support a UCNS board certified neurologist.

There are several medico-social parameters that could, theoretically, limit the ability of PA or NP from providing this service. This study looks at one of those, patient attitudes and satisfaction.

Methods: An eighteen item questionnaire was given to 100 random patients via Internet survey or hard copy (for those who were computer literate) who had at least one completed visit at a PA directed headache specialty clinic. The results of this questionnaire was tallied and discussed.

Results: Of the 100 patients surveyed 38% of the patients had concerns about seeing a PA for their headache specialty care prior to the visit, however, almost 90% had no concerns after the visit was completed. In nine parameters measuring patient satisfaction with the the care given, almost 90% ranked the experience as a 8/10 or higher.

Conclusions: While there was a hesitation some patients about seeing a PA for headache specialty care prior to the first visit, most were very satisfied after at least one visit. This appears to support the premises that headache patients can be very satisfied by being seen at a PA directed headache specialty clinic. Other parameters that need to be explored include other barriers to this concept, including physician attitudes, medical-economic barriers as well as eventual patients outcomes. If this concept is developed at a national level as one avenue of meeting the needs of undeserved headache sufferers, it could be a significant contribution to headache care in general.

P158

Description of Headache Telehealth Users and Providers-Report of a Web Based Survey

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Objectives: 1) Describe the characteristics of headache patients who telephone their headache health care provider.

2) Describe the characteristics of telehealth headache providers.

Background: Telephone calls occur in all aspects of healthcare, headache being one of many types of healthcare that must manage incoming and outgoing communication with patients. Telephone communication must be provided in such a way to accomplish patient safety, quality care, and economic feasibility. There is limited documentation of the occurrence of telephone calls to a headache clinic. In order to promote safe, quality and economic telephone care of headache patients, the characteristics of those involved in the process of telephoning a headache clinic must be described.

Methods: Human research institutional review was obtained from Wayne State University. Two different surveys were developed to assess characteristics of those who telephone their headache clinic and those who make or receive telephone calls in a headache clinic. These two surveys were imported into a survey provider and hosted on a website. Advertisement for recruitment of subjects was accomplished by the website of the American Academy of Ambulatory Care Nurses and the facebook page of the Migraine Research Foundation.

Results: There was a total of thirty one (N=31) respondents to the surveys. Seventeen headache telehealth user's (HTU) responses were obtained and fourteen headache telehealth provider's (HTP) responses were obtained.

Conclusions: Most of the survey respondents were female. In the HTU group a diagnosis of migraine without aura or tension type headache was most frequent. It is interesting that half of the HTPs reported a personal history of headache. Both the HTU and HTP groups noted satisfaction with their current headache clinic telephone practices.

Table 1. Characteristics of HTU

HA Type	(N=17)
Migraine w/o aura	7
Tension	7
Migraine with aura	5
Other	3
Custer	2
Gender	(N=17)
Female	15
Male	2
Employment	(N=17)
Full time	12
Student	3
Homemaker	2
Part time	1
Age	(N=17)
50 and above	8
40-49	4
22-30	4
31-39	1
18-21	0
Education	(N=17)
College grad	6
Some College	5
Masters or higher	4
HS grad	2

Table 2. Characteristics of HTP

Gender	N=14
Female	12
Male	2
Practice type	N=14
Outpatient affiliated with a hospital	7
Private practice	5
Academic based clinic	3
Outpatient clinic	1
Inpatient hospital service	1
Other	0
Provider type	N=14
Nurse practitioner	5
Physician	4
Other	2
Nurse	2
Physician assistant	1
Psychologist	0
Administrative/office/clerical	0
Pharmacy/pharmacist	0
Receptionist	0
Medical assistant	0

(continued)

Table 2. Continued

Tenure	N=14
6 to 10 years	5
Greater than 10 years	4
Greater than 20 years	3
0 to 5 years	2
Educational level	N=13
Other	7
Masters degree	5
Trade school	1
Bachelors degree	0
High school diploma	0
Headache history	N=14
Yes	7
No	7

P159

Emergency Department Management of Headache: An Algorithm for Quality Improvement

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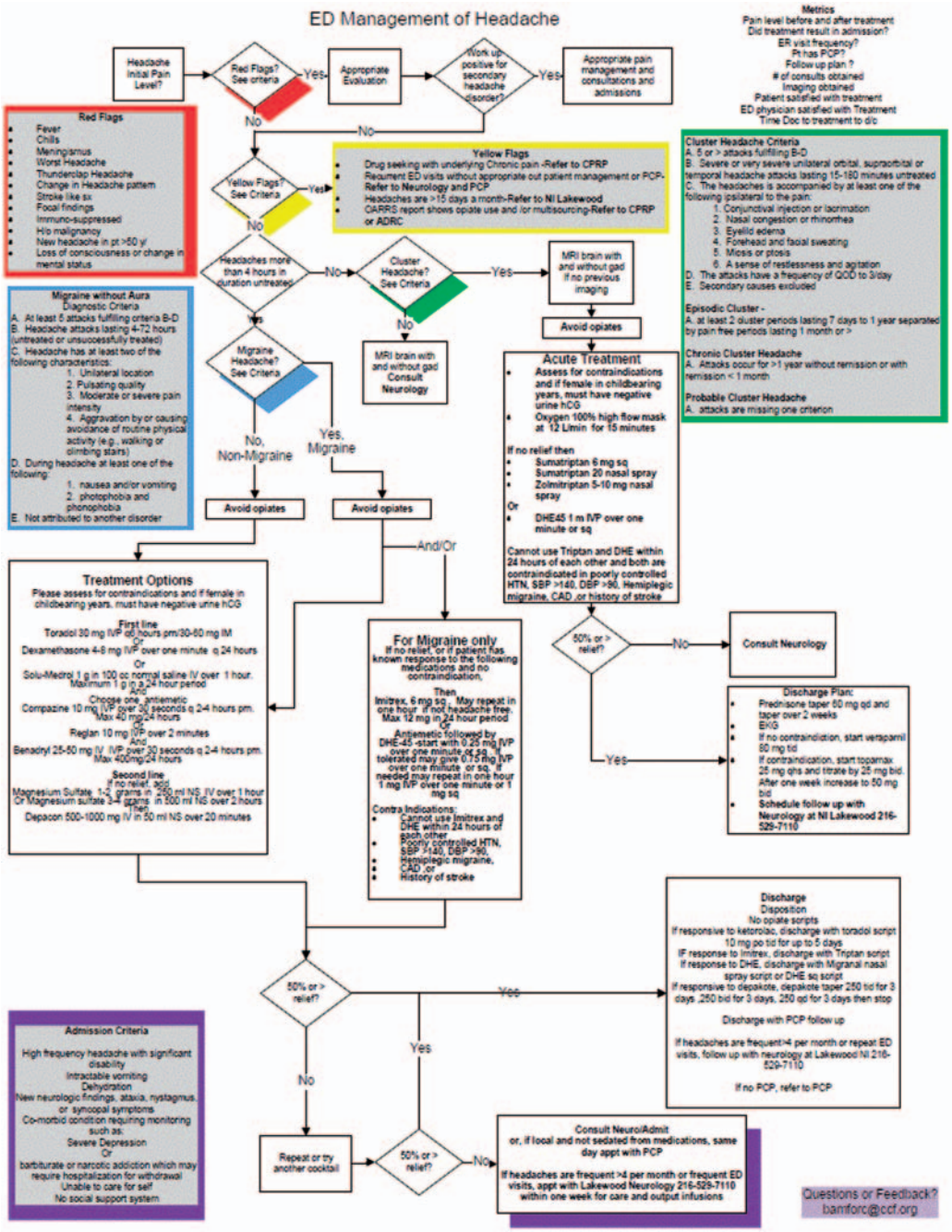
Objectives: To propose an algorithm for Emergency Department (ED) physicians to better evaluate, treat and discharge patients presenting with acute headache.

Background: Headache is the fourth leading cause of ED visits in the USA. In the case of primary headache, particularly migraine, prior studies demonstrate that medical treatment in the ED can be highly variable. At this time, there is no standardized management protocol directed at acute headaches presenting to the ED. In addition to initial management, discharge plans seldom include measures to prevent recurrence or instructions to re-treat if pain persists. An algorithm providing a step-wise approach on the evaluation and treatment of acute headache can potentially improve the efficiency of patient management.

Methods: We identified parameters in patients presenting with acute headache to the ER, that influence decision-making and treatment. These parameters were arranged in a tier system, and presence of absence of each parameter determined the next step in an easy to follow flow-diagram. The parameters included initial pain level, worrisome symptoms/signs ("red flags"), and drug seeking behavior ("yellow flags"). This was applied to the correct primary headache disorder as applicable. Clear treatment protocols and further instructions in case of suboptimal or non response were outlined for each headache disorder. Need for additional testing, neurological consultation and criteria for admission (McKesson Interqual admission criteria) were made readily identifiable. Finally, we outlined proper disposition plan for patients.

Results: An algorithm was created using the above parameters and the details are outlined in Fig 1. Checklists were made for "red flags" and "yellow flags" to refer those patients for appropriate evaluation. Criteria for diagnosis of migraine and cluster were included. Treatment for each using first line, alternative and second line medications were provided. Exact medications upon discharge along with follow-up plan were added to the algorithm. We will next be conducting a study piloting the use of this algorithm in our ED. Quality metrics including pain level, disposition, follow up, patient and provider satisfaction, and treatment time will be measured.

Conclusions: Headache management in the ED has been variable to date, despite it being a leading cause of evaluation in the acute setting. We propose an algorirthm to better standardize evaluation and treatment that potentially will improve efficiency of patient care. Once implemented, the results from our study will provide valuable information to guide efforts to further improve quality and cost of care for this population.



P160

Training of Physicians Who Treat Patients with Headaches

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Objectives: Evaluation and improvement of doctors' training in management of patients with headaches (HA).

Background: Headache is one of most common patients' complaints associated with significant limitations. For example, each patient suffering from migraine loses 6 working days a year. Total annual work time lost in 2010 to migraine was equal to 61.8 million man-days all over the country. Besides, there are expenses which have not been calculated yet, e.g. related to early retirement and reduced ability to perform domestic work. Hidden costs related to pain, suffering and poor quality of life have not been evaluated completely. Common belief of most healthcare

providers is that HA is an insignificant or trivial problem. HA-related physical, emotional, and economic problems are underestimated. HA management is subpar.

Lack of knowledge among primary healthcare workers is one of clinically relevant obstacles for effective management of HA. The problem begins in medical colleges where little attention is paid to the problem thus creating an impression of its insignificance.

Methods: Routine medical care for HA in 3 Moscow outpatient clinics and doctors' training system in 2 medical universities were evaluated.

Sociological study, questioning, expert examination and direct observations were the methods applied.

Results: Most HA patients seek medical advice in primary healthcare institutions consulting district physicians and general practitioners. Therefore, management of HA should start at this level. This approach contributes to early diagnostics of the disease and to better outcome of its treatment. Therefore, inclusion of HA management into primary care institutions should become the goal for healthcare policy both nationwide and locally.

The analysis of syllabi for primary care physicians demonstrated that little attention was paid to problems of HA diagnostics and management. The same refers to neurologists rendering specialized HA management. Therefore, new syllabi should be prepared based on educational standards for HA management. They were developed by the European Headache Federation (EHF) and should be adapted to the Russian healthcare system.

Conclusions: Strengthening of the role of primary healthcare in management of HA patients complies with modern trends in modernization of the Russian healthcare system, which include development of personnel policy and new syllabi based on international experience.

New syllabi should be worked out both for medical and postgraduate students. Postgraduate syllabus for primary care physicians should provide 8 hours of lectures and 26 hours of practical training with not less than 30% of class hours being dedicated to HA prevention. Syllabus for neurologists should provide 24 hours of lectures and 72 hours of practical training.

The syllabi should include up-to-date information and educational technologies, increase the significance and quality of practical training to improve doctors' skills in HA management and explain new diagnostic and treatment methods. The training in accordance with new syllabi will contribute to higher efficacy of medical care in headaches.

P161

Withdrawn by the author.

P162

Migraine and the Incidence of Ischemic Stroke in Taiwan: A Nationwide Population-Based Study

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Objectives: To evaluate the association between migraine and ischemic strokes in regard to status of aura, gender, and age subgroups.

Background: Migraine with aura (MA) has been associated with increased risk of ischemic stroke consistently; however, most studies do not find such an association with migraine without aura (MO) (1). Furthermore, no similar study has been done in Asia.

Methods: Retrospective cohort study of subjects aged 18-70 with neurologist-diagnosed migraine from 2005 to 2009 from a nationwide population-based administrative database were included. The comparison cohort consisted of subjects free from migraine or headache diagnosis, matched for age, gender, and comorbidities known as stroke risk factors. All subjects were followed till the end of 2010, death, or any stroke events. The main outcome was hospitalization with ischemic stroke.

Results: A migraine cohort was identified (n=150,615, F: 73.4%, M: 26.6%), and MA accounted for 10.7% (n=16,050). The migraine and the comparison cohorts were followed by a mean of 3.0 $\pm$ 1.5 years vs. 3.2 $\pm$ 2.5 years. In female subjects $\leq$ 50 years, MA was strongly associated with ischemic strokes (hazard ratio [HR]=2.548, 95% confidence interval [CI], 1.258-5.158, p=0.009), whereas MO was also associated with ischemic strokes (HR=1.564, 95% CI 1.144-2.137, p=0.005), but to a lesser extent (MA vs. MO, HR: 2.461, 95% CI, 1.595-3.797, $p<0.001$, adjusted for age and stroke related comorbidities). No association could be found in female subjects aged >50 years. In male migraine cohort, no association could be found in subjects aged $\leq$ 50 years;

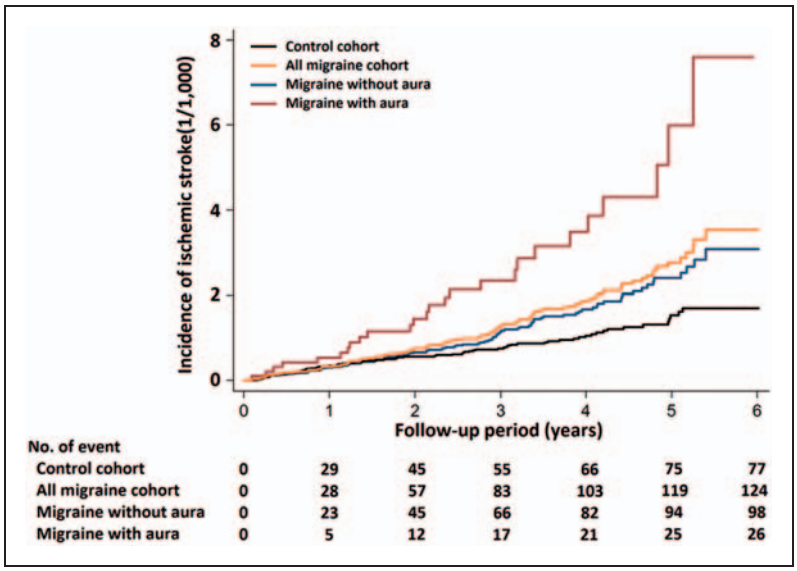


Figure 1. Cumulative incidence of stroke in female migraine cohort, aged $\leq$ 50 years.

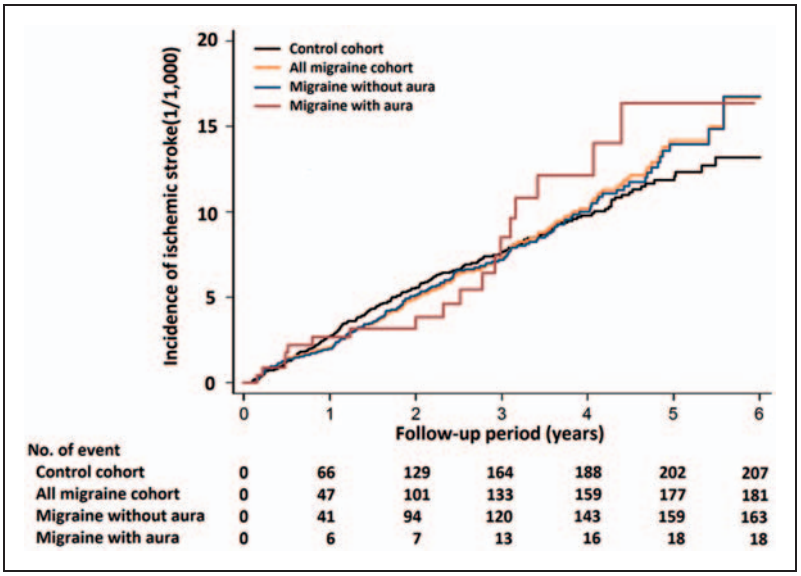


Figure 2. Cumulative incidence of stroke in female migraine cohort, aged >50 years.

however, migraine was associated with a decreased incidence of ischemic stroke in those aged > 50 years (HR=0.769, 95% CI, 0.605-0.978, p=0.032), especially in those with no stroke risk factors (HR=0.517, 95% CI, 0.315-0.849, p=0.009).

Conclusions: In this large cohort follow-up study, migraine in younger female subjects was associated with increased incidence of ischemic strokes, especially in those with MA. The reduction of stroke risk in older male subjects with migraine needs further confirmation.

P163

Migraine Is Associated with a Higher Risk of Transient Global Amnesia: A Nationwide Population-Based Study

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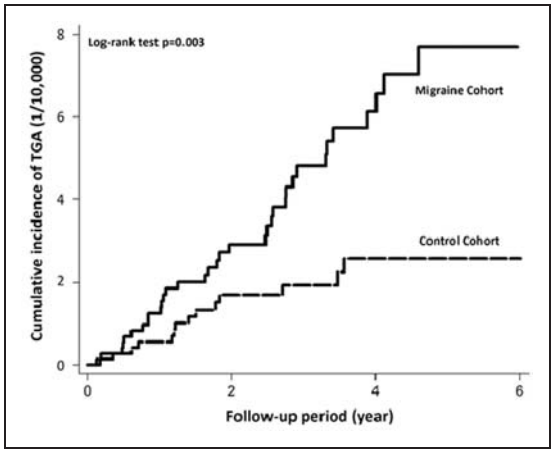
Objectives: This population-based study aimed to investigate whether migraine was associated with a higher risk of transient global amnesia (TGA).

Background: The pathogenesis of TGA is largely unknown. Several prior case-control studies revealed a higher frequency of migraine in patients with TGA.

Methods: We identified patients with migraine aged ≥40 years from the Taiwan National Health Insurance Research Database (NHIRD) between 2005 and 2009. Each migraine patient was matched with one randomly selected subject without migraine for age, sex, and cardiovascular comorbidities. Migraine patients with antecedent stroke, epilepsy, or TGA were excluded. Both cohorts were followed up until the end of 2010. We compared the incidence rates of TGA in the two cohorts and identified the risk factors.

Results: A total of 73,164 patients in the migraine cohort and 73,164 patients in the control cohort were enrolled with a mean follow-up of 3 years. The migraine cohort had a greater risk of developing TGA than the matched cohort (15.0 vs. 6.0 per 100,000 person-years, incidence rate ratio (IRR) =2.48 (95% confidence interval (CI) 1.30-5.00, p=0.003). The mean age of incident TGA patients were younger in migraine cohort than control cohorts (56.6 vs. 61.4 years, p=0.035). When compared to the matched controls, the association between migraine and TGA was significant for patients aged ≤ 60 years (hazard ratio [HR] =3.16, 95% CI 1.42-7.00, p=0.005), females (HR =2.54, 95% CI 1.30-4.96, p=0.006) and patients with migraine without aura (HR =2.86, 95% CI 1.44-5.68, p=0.003).

Conclusions: This population-based study demonstrates that migraine is associated with an increased risk of TGA.



P164

Prevalence of Chronic Headache and Its Association with Over-the-Counter Medication Overuse in Denmark

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Objectives: To estimate prevalence and associated demographic profile of chronic headache (CH) in the Danish population; and to compare the demographic profiles of those with and without overuse of over-the-counter analgesics.

Background: Previous cross-sectional surveys in Denmark showed prevalence of CH as 3.2% (24 of 740) among adults in 1989; 4.2% (23 of 549) in a follow-up of the same cohort in 2001; and 4.8% (10 of 207) in a representative sample of 25-36 year olds in 2001. There have been no previous large-scale prevalence studies on CH and no population-based data on medication-overuse headache.

Methods: The Danish National Health Survey of 2010 was used to gather data on chronic illness, including headache. Data from the self-administered questionnaire were linked with national statistical databases with information on respondents' socioeconomic status.

Results: Completed questionnaires were received from 68,518 individuals (53% of the targeted sample of 129,150) aged ≥16 years. The prevalence of CH was 3.0% (CI 2.9-3.2%), with a M:F ratio of 1:2.1. CH prevalence was almost evenly distributed in all age groups; but slightly higher among those 50-59 years (3.6%, CI 3.2-3.9%). There is a clear inverse relationship with socioeconomic position as determined by education, employment and personal income. Crude prevalence ratio (PR) was higher among non-western immigrants (PR 2.9, CI 2.5-3.3), although the ratio was attenuated among second generation migrants (PR 1.4, CI 1.0-2.1). Among those with CH, 51.8% (CI 49.7-54.0%) used over-the-counter (OTC) analgesics ≥15 days a month, suggesting medication overuse in 1.6% (CI 1.5-1.7%) of the population. Among those with chronic headache, subgroup analysis showed that those with OTC overuse were older (mean 52 vs. 49 years, p<0.001), had a higher proportion of women (70 vs. 64%, p<0.01), and short education (19% vs. 15%, p<0.05). Full-time employment was lower among those with OTC overuse (40 vs. 44%, p<0.001), likely owing

to the higher proportion of early retirees (16 vs. 8%, $p<0.0001$). Marital status, citizenship and personal income were not significantly different in these two groups.

Conclusions: The prevalence of chronic headache is 3.0% in the Danish population, among whom OTC analgesic overuse was seen in more than half, suggesting medication overuse headache in at least 1.6% of the population, pending analysis of prescription drug use. Prevalence of chronic headache and medication overuse were inversely associated with socioeconomic position.

P165

Associations between Lifestyle Factors, Chronic Headache and Overuse of Over-the-Counter Medication

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Objectives: To investigate associations between lifestyle factors, chronic headache (CH) and over-the-counter (OTC) medication overuse.

Background: In a related report, we estimated CH prevalence in Denmark at 3.0% based on a sample of 68,518 individuals. About half of those with CH took OTC analgesics $\geq$15 days a month. Lifestyle factors are known to be associated with CH, but may differ among those with and without medication overuse.

Methods: A representative sample of 129,150 individuals aged $\geq$16 years from two regions of Denmark were invited to participate in the Danish National Health Survey of 2010. Data on chronic illness (including headache frequency) and health-related behaviours were gathered using self-administered questionnaires. Respondents were categorized into three groups: no chronic headache (–CH), CH without OTC medication-overuse (CH–MO) and CH with overuse (CH+MO). Health behaviours of interest were compared across the groups (chi-square for proportions; anova for means). Crude and sociodemographically adjusted prevalence ratios (PR) were calculated to compare prevalence of CH–MO and CH+MO across categories of BMI and quintiles of Perceived Stress Scores.

Results: The response rate was 53%. There were 66,431 individuals classified as –CH; 1005 CH–MO; and 1082 CH+MO. The CH+MO group had the highest proportion of daily **smokers** ($p<0.0001$) and the lowest proportion of never-smokers ($p<0.0001$). This group also had the highest proportion of **sedentary** individuals ($p<0.0001$), highest mean **BMI** ($p<0.0001$) and proportion with BMI $\geq$ 30 kg/m^2 ($p<0.0001$). Compared to those with normal weight, the prevalence ratios of CH–MOand CH+MO were high not just for the obese but also the underweight even after adjustment for age, sex, low education and daily smoking. The prevalence of CH markedly increased with higher **stress** levels. More than half of the CH+MO group were in the highest stress quintile. **Alcohol** overuse was lower among those with CH ($p<0.0001$). Participants 16–34 years old were asked about **narcotics** use (response rate 13,851 of 14,231 individuals, 97%). There were no differences in recent use of cannabis ($p=0.16$) or narcotics ($p=0.36$), nor in lifetime use of narcotics ($p=0.15$).

Conclusions: In agreement with other population-based studies, we found associations between unhealthy lifestyle and CH, especially among those with OTC overuse, emphasizing the need for lifestyle interventions concurrent with medical management of medication-overuse headache. Dependence-related behaviours seen in alcohol abuse and drug addiction were not significantly higher among those with OTC analgesic overuse compared to the general population.

P166

Early Sexual Maturation and Recurrent Headache in Adolescents. The Young-HUNT 3 Study

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Objectives: To examine whether early sexual maturation is associated with migraine and tension-type headache in adolescents.

Background: Before puberty migraine affects boys and girls approximately equally, while after puberty there is an increasing prevalence of migraine in females. The mechanisms for this gender difference are not fully understood, but female sex hormones, in particular estrogens, are

believed to play a role. In support of this hypothesis early menarche, which is associated with a prolonged exposure to high estrogen levels, is associated with a higher prevalence of headache and migraine in girls. It has however not been established whether this association is related to female sex hormones, or rather to general changes occurring in puberty such as the pubertal growth spurt. To disentangle these effects, we examined the effect of the timing of sexual maturation on headache and migraine in boys and girls.

Methods: In the population based Young-HUNT 3 study (2006-2008) 3,001 girls and 3,206 boys attending secondary school in the Norwegian county of Nord-Trøndelag were assessed for the presence of migraine or tension-type headache, and for timing of sexual maturation by age at menarche (girls) or the Pubertal Developmental Scale (boys). Logistic regression was used to assess the effect of timing of sexual maturation on the prevalence of recurrent headache and migraine.

Results: Early sexual maturation in girls was associated with an increased prevalence of migraine (OR = 1.68, 95% CI 1.25 – 2.26, p=0.001) and tension-type headache (OR = 1.45, 95% CI 1.16 – 1.81, p=0.001), when adjusted for age. No corresponding association was found in boys (migraine OR = 1.01, 95% CI 0.67 – 1.52, p=0.97; tension-type headache OR = 0.97, 95% CI 0.76 – 1.24, p=0.79).

Conclusions: The effect of early sexual maturation on headache and migraine was specific to girls. This supports a mechanism involving female sexual hormones, rather than general changes occurring in puberty in both sexes.

P167

Impact of Migraine Burden on Prevalence of Symptoms of Irritable Bowel Syndrome

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Objectives: To examine the prevalence of Irritable Bowel syndrome (IBS) related symptoms (constipation/diarrhea) in migraine patients and determine the correlation between migraine frequency, disability and the presence of these symptoms.

Background: There are limited studies looking at the prevalence of IBS in migraine patients with none found in the literature looking at the impact of migraine burden on the prevalence of IBS symptoms of constipation and/or diarrhea. Based on our hypothesis that more frequent and disabling migraine leads to increased frequency of IBS symptoms, we examined the relationship between migraine frequency, disability measured by HIT-6 score, and prevalence of constipation/diarrhea symptoms in a migraine population.

Methods: This is a retrospective cross-sectional study of 498 migraine patients seen at the University of Pittsburgh Medical Center Headache clinic. Patients were seen consecutively between October 2011 and June 2012. Migraine was diagnosed based on ICHD-2 criteria. Migraine frequency, HIT-6 scores, and presence of symptoms of constipation/diarrhea were recorded for each patient during their initial visit. Based on HIT-6 score patients were divided in 3 groups: 1) HIT-6 of $<$60, 2) HIT-6 of 60-69 and 3) HIT-6 of 70-78. Based on migraine frequency patients were divided into 2 groups: 1) episodic migraine (patients with $<$15 headache days per month) and 2) chronic migraine (patients with $\geq$15 headache days per month). The prevalence of IBS symptoms of constipation/diarrhea were examined in episodic and chronic migraine groups, and in the 3 groups categorized by HIT-6 score and comparisons between IBS symptom prevalence in these groups were evaluated with the Chi-Square test.

Results: Mean age of subjects was 35.8 +/- 14.7 years with a gender distribution of 392 females to 106 males. Of the 498 patients, 219 were diagnosed with episodic migraine and 279 with chronic migraine. HIT-6 scores were available for 486 patients of whom 90 patients were in the $<$60 HIT-6 group, 300 patients in the 60-69 HIT-6 group, and 96 patients in the 70-78 HIT-6 group. One hundred and fifteen patients (23.1%) reported symptoms of constipation/diarrhea. Patients with chronic migraine had significantly more IBS symptoms versus those with episodic migraine (28.7% versus 16 %, p$<$0.01). Similarly, when compared across the 3 HIT 6 categories, patients had an increased frequency of IBS symptoms with increasing HIT 6 score (13.3% versus 22% versus 36.4%, p$<$0.01).

Conclusions: Our results demonstrate that not only is there a high prevalence of IBS symptoms in migraine patients; this prevalence is higher in patients with more frequent and disabling migraines. This relationship could suggest a common etiology between the two syndromes, perhaps through dysfunction of the serotonergic system. Furthermore, if the conditions possess some shared physiology, it may be possible to reduce IBS symptoms through management of migraine.

P168

Headache and Mental Health among Adolescents

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Objectives: To investigate the association between mental health symptoms (conduct difficulties, attention difficulties and anxiety/depressive symptoms) and recurrent headache in adolescents.

Background: The comorbidity of headache and psychiatric disorders is a well-recognized clinical phenomenon, but there are only limited data regarding this association among adolescents.

Methods: Young-HUNT 1, a population-based study of 8984 adolescents aged 12-20 years, was conducted in Norway from 1995 to 1997. A follow-up study, Young-HUNT 2, was conducted four years later and consisted of 2399 adolescents aged 16-20 years. In both studies the participants were interviewed about their headache complaints and completed a comprehensive questionnaire including self reported conduct difficulties, attention difficulties and anxiety/depressive symptoms.

Results: In adjusted multivariate analyses based on cross-sectional data from Young-HUNT 1, recurrent headache was associated with anxiety/depressive symptoms (OR: 1.7, 95%CI: 1.5-1.9, $p<0.001$), attention difficulties (OR: 1.3, 95%CI: 1.1-1.5, $p<0.001$) and conduct difficulties (OR. 1.2, 95%CI: 1.0-1.5, $p=0.035$). In the prospective part of the study we found that anxiety/depressive symptoms at baseline increased the likelihood of recurrent headache four years later (OR: 1.5, 95%CI: 1.1-2.0, $p=0.008$) and recurrent headache at baseline was associated with anxiety/depressive symptoms (OR: 1.7, 95%CI: 1.4-2.2, $p < 0.001$), attention difficulties (OR: 1.3, 95%CI: 1.1-1.7, p=0.018) and conduct difficulties (OR: 1.4, 95%CI: 1.1-1.8, $p=0.006$) at follow-up.

Conclusions: The results from the present study show that anxiety/depression, attention difficulties and conduct difficulties are associated with recurrent headache among adolescents. There seems to be a bi-directional association between recurrent headache and anxiety/depressive symptoms.

P169

Triptan Use and Overuse in the French General Population: A Regional Pharmaco-Epidemiology Database Analysis in 5.3 Million People

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Objectives: A population-based observational study was used to assess the prevalence, demographics, risk factors of triptan use and overuse.

Background: No data was available on triptan overuse in French general population.

Methods: The Provence-Alpes Côte d'Azur and Corse Health Care Insurance Database was analyzed for 18 months (from 05/01/2010 to 12/31/2011). Analysis included prescriptions for 5.3 million people (8 % of the total French population). Triptan overuse was defined as more than 30 (International Headache Society criteria) or 60 (stringent criteria) defined daily doses per 3 months.

Results: Triptans were used by 95549 (1.8%) people; of these, 9297 (9.7%) were overusers by International Headache Society and 2267 (2.4%) were overusers by stringent criteria. Considering stringent criteria, triptan overuse corresponded to 20% of the total triptan consumption. Prophylactic medication was more frequently dispensed in overusers, 57.4% of stringent overusers, than in non-overusers (29.0%). Antidepressants were more frequently dispensed in overusers, 50.3% of stringent overusers, than in non-overusers (26.3%). Benzodiazepines were more frequently dispensed in overusers, 70.6% of stringent overusers, than in non-overusers (50.6%). Sleep drugs were more frequently dispensed in overusers, 37.5% of stringent overusers, than in non-overusers (20.0%).

Conclusions: We could make use of a unique regionalHealth Care Insurance Database, which coveredthe medication use of 5.3 million people. Of these, 1.8% had used a triptan at least once in 18 months period and 0.04% (2.4% of all triptan users) were overusing triptans considering stringent criteria (60 DDD).

Overusers accounted for almost quarter of the totaltriptans consumption.

P170

Episodic Migraine and Obesity: The Influence of Age, Sex, and Race

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Objectives: To evaluate the association between episodic migraine (EM) and obesity and the influence of age, sex, and race on this relationship.

Background: Epidemiological and translational data have consistently identified age, sex, and racial differences in EM prevalence estimates as well as in adiposity volume and distribution in obese and non-obese states. Controversy exists as to whether the risk of EM is increased in those with obesity.

Methods: We conducted a cross-sectional study of 3,862 black and white adult participants interviewed in the National Comorbidity Survey Replicated. EM diagnostic criteria were based on the International Classification of Headache Disorders. Body mass index (BMI) was classified as underweight, ($<$18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese ($\geq$ 30 kg/m^2). Odds ratios (OR) and 95% confidence intervals (CI) for migraine were estimated using logistic regression and adjusted for demographics and health characteristics. Additional, models were stratified by age ($<$50/$\geq$50 years old), race (white/black), and sex (male/female).

Results: The mean BMI was greater in those with EM (27.8$\pm$0.30) as compared to controls (27.1$\pm$0.4), p=0.05. The unadjusted prevalence estimates of obesity were 32.2% among those with EM and 26.0% among controls, p=0.076. In all participants, the adjusted odds of EM were 81% greater in obese as compared to normal weighted individuals, (OR 1.81; CI: 1.27, 2.57; p=0.001). In addition, stratified analyses demonstrated that the odds of EM were greater in obese as compared to normal weighted individuals who were: 1) $<$50 years of age (OR 1.86; CI: 1.20, 2.89; p for trend=0.008), 2) white (OR 2.06; CI: 1.41, 3.01; p for trend=$<$0.001), or 3) female (OR 1.95; CI: 1.38, 2.76; p for trend=$<$0.001), and were not increased in those $\geq$ 50 years of age (OR 1.15; CI: 0.61, 2.18, p for trend=0.71) or men (OR 1.43; CI: 0.71, 2.89, p for trend=0.45). Due to the small number of black participants with EM, no conclusion could be drawn regarding the odds of EM in obese black participants alone. Similar findings were demonstrated in lower frequency EM subgroups.

Conclusions: The odds of EM are increased in those with obesity, with the strongest relationships among those $<$ 50 years of age, whites, and women.

P171

Headache in Olympic Athletes

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Objectives: To assess prevalence and clinical features of headache in Olympic athletes.

Background: Headache is a disabling disorder which may be triggered or worsened by physical activity. Therefore, headache may be a relevant clinical issue in athletes due to their commitment to intensive physical training and competitions, as well as the severe restriction in drug use.

Methods: We studied 331 Italian athletes participating to the 2012 Olympic Games. Detailed information on demographic, type of sport, training schedule and incidence of headache was gathered with self-administered questionnaires. Specifically, any correlation between the onset of headache and workout or competition was investigated.

Results: All athletes completed the questionnaire (n = 331; M/F = 212/119; mean age = 25.5 $\pm$ 6.6; engaged in endurance =142, power = 52, mixed = 28, skill =109 sport activities). Eighty-nine subjects (26.8%) reported headache (M/F = 44/45); namely, migraine without aura = 56, probable migraine without aura = 18; tension mimicking headache = 15. Forty-four athletes referred headache occurring either in association than outside physical workout/competition, 13 in association with physical workout/competition and 32 independent from sport

activities. We found no correlation between specific type of sport and incidence or clinical presentation of headache.

Conclusions: Headache is unexpectedly common observation in Olympic athletes (26.8%), with migraine/probable migraine being the most frequent clinical presentation. Workout or competition was associated with the attack in the majority of headache sufferers (64%). The large prevalence and the peculiar limitations in pharmacological treatment suggests that headache represent an emerging and relevant issue in athletes.

P172

Headache Management in Community Pharmacies: An Irish Study

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Objectives: To describe the population of patients who attend community pharmacies requesting acute therapy for headache management.

Background: There is a high prevalence of headache in the general population, with many people reportedly not receiving the most appropiate treatment. First line therapy for the treatment and prevention of headache depends on the diagnosis and severity of symptoms. Most sufferers are managed by general practitioners and or by community pharmacists, with a minority attending secondary care services (e.g. a neurologist). There is little information available on patients who attend their community pharmacist; therefore this project aims to describe those patients and their management.

Methods: A questionaire was formulated, piloted and refined. There were three main sections to the questionaire: (i) demographics, (ii) symptoms,and (iii) treatments. Questions related to symptoms allowed for diagnosis to be established (based on the ICHD-II guidelines). Treatment options and preferences were analyzed and compared to diagnosis.

Pharmacists throughout the Munster province of Ireland (n=367), were sequentially invited to participate and were asked to randomnly select 10 patients to complete the questionaire. Patients requesting a medication for a headache if aged 18 years or over were eligible to participate. The study was conducted over six months.Ethics approval was granted by the local ethics committee.

Results: 43% (158) of pharmacies participated with 1023 questionaires returned. 76.7% (765) of respondents were female, half of the cohort (51.8%) were aged between 18 and 39 years. The most common headache diagnosis was episodic migraine (32%; 327) followed by episodic tension type headache (30.3%; 327), probable episodic migraine (15.2%; 155),chronic daily headache (10.5%; 107).

Less then 50% (46.7%; 475) had a prior physician diagnosis. Patients were more likely to have had a diagnosis if the headache was considered severe, if there was a presence of vomiting and if the headache was a chronic daily headache ($p<0.05$).

The most commonly used preparation was paracetamol (71.3%; 729). Aspirin was underused in all diagnostic categories (85%; 860). Patients with migraine, who had previously used a triptan, considered it the most effective treatment available (68.6%; 166). Preventative therapies were prescribed for 28.7% (201) of patients for whom they were indicated.

Conclusions: This study has some important findings for the long-term management of headaches. In particular, it was evident that the types of headaches, patients present with to community pharmacies is largely underdiagnosed, and that treatment options are not optimized. Impovements need to be prioritized and provided for in the management of these patients.

P173

Relation between Vitamin D Receptor Gene Polymorphisms and Migraine without Aura in Iranian Population

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Objectives: The aim of this study was to investigate the association between migraine and two vitamin D receptor (VDR) polymorphisms (TaqI and FokI) and also relation between VDR polymorphisms and headache severity.

Background: Inflammation has a key role in migraine pathophysiology. Vitamin D is an effective anti inflammatory agent. To our knowledge there is no study to examine relation between VDR polymorphism and migraine.

Methods: In this case-control study we assessed the genotypic and allelic frequencies of TaqI and FokI polymorphisms in 103 patients with migraine without aura and 100 healthy subjects using high-resolution melt (HRM) assay. Patients filled Headache Impact Test (HIT-6) as a tool to assess headache severity.

Results: Genotype frequencies of vitamin D receptors were significantly different between control and migraine patients. Heterozygote genotypes (Ff and Tt) were statistically more frequent in the migraine patients than the control subjects both for TaqI gene (P=0.018; OR=1.81, 95% CI=1.03-3.18) and FokI gene polymorphisms (P=0.001; OR=2.91, 95% CI=1.47-5.77). Also f and t alleles were more frequent in the migraine patients and seem to be potentially the risk factor alleles for developing migraine according to our results. Total HIT-6 score was significantly different between FokI heterozygote and homozygote patients (60.32±1.87 vs. 49.87±2.69 respectively, P=0.004).

Conclusions: In conclusion our results showed that TaqI and FokI gene polymorphisms are associated with migraine without aura in Iranians patients. Also headache severity in FokI heterozygote patients was significantly more than the homozygote patients.

P174

Are Migraine and Tension Headaches Categorical Types or on a Continuum?

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Objectives: The purpose of this study was to reconsider clinical perceptions that there exist distinct headache types and to evaluate whether this distinction varies as a function of age and headache frequency.

Background: Although sophisticated systems have been developed for classifying headaches, controversy remains as to whether migraine and tension-type headache (TTH) disorders are separate entities or points on a continuum. If headache disorders represent a continuum, the utility of the current diagnostic system may be limited. If an individual headache sufferer experiences different types of attacks or a continuum of attacks, treatments might best be targeted based on the phenomenology of the specific attack rather than a diagnostic label.

Methods: A convenience sample of individuals meeting ICHD-II criteria recruited from headache clinics and community settings (n = 1,530) and undergraduate courses (n = 2,468) were combined (N = 3,999) for a taxometric analysis. A latent mode analysis was conducted to examine the dimensional structure of multivariate data for estimating the parameters of a two-group (migraine versus TTH) distribution. All diagnostic characteristics (eg, location, quality, secondary symptoms) thought to distinguish the two headache types were used in the analysis. The analysis produces a comparison curve fit index (CCFI) ranging from 0 (dimensional) to 1.0 (categorical).

Results: For episodic sufferers, two distinct classes of headache types were identified that were separated by 1.9 SD units on the latent scale (with the migraine class occurring at the higher end of the latent scale, CCFI = 0.48). However, chronic headache sufferers experienced headaches that differed only dimensionally (CCFI index = 0.23). Headache types were the most distinct at very low frequency (< 5 days/month) and among older adults, but could be placed on a continuum with increasing frequency and younger age (< 25 years). Increasing medication use was associated with an increasing fit of a continuum of symptoms.

Conclusions: This taxometric analysis supports viewing migraine and tension-type headaches as categorically distinct entities, but only at low headache frequency. The utility of a discrete diagnostic classification is greatly reduced with increasing headache frequency and/or abortive medication use. For these types of headaches, a continuum of symptoms may represent a better means of conceptualizing headache.

P175

Electronic Methods for Migraine Ascertainment in a Large Integrated Health Plan: Prevalence of Migraine in a Diverse Community

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Objectives: We sought to use electronic medical records (EMRs) to identify and characterize migraine in a large diverse integrated health plan in Northern California.

Background: One-year prevalence of migraine headache in the USA is estimated to range from 8-15% overall with women affected at approximately three times the rate of men. Current methods for migraine ascertainment from headache clinics are affected by clinic-ascertainment bias and population-based surveys are costly. With the growing use of EMRs, new methods must be developed and validated for identifying and tracking migraine prevalence over time.

Methods: From the Kaiser Permanente Northern California (KPNC) EMRs, we collected all migraine clinic and problem-list diagnoses from 2006-2010 and all migraine-specific prescriptions (MRX). We chart-reviewed a random sample to develop an electronic Migraine Probability Algorithm (MPA, scored 0-100), and tested it in a second independent chart review. Using the MPA and membership data, we calculated prevalence by age, race, and gender, and assessed utilization, measured by MRX.

Results: We identified 313,174 KPNC members with evidence of migraine from 2006-2010 (233,620 women, 79,554 men). Gender distribution varied by age group. From chart review of subjects with varied probability of migraine, at the lowest threshold, we estimated the algorithm to have positive predictive value of 94% and sensitivity of 85%. Specificity was back calculated to be >90%. Across all racial groups, the 5-year period prevalence of migraine among KPNC adults was 17.1% for women and 5.9% for men (ratio: 2.9). Among children, rates were the same by gender (<2%) until age 10, when prevalence rose to 5.8% for girls and 3.5% for boys. For women, prevalence climbed steadily with age, peaked at age 25-29, and then declined monotonically to 8% after age 85, while men experienced a nearly flat prevalence (range 5%-6%). Prevalence across ages followed similar patterns regardless of race. Overall, Caucasians had higher prevalence than Asians, but African Americans did not differ appreciably. MRX was higher among women than men, 45% and 30%, respectively, and lowest among Asian men (25%).

Conclusions: EMR techniques can be effectively used to capture migraine, and resulting prevalence patterns are similar to those reported in the population-based literature. Prevalence of diagnosed migraine in KPNC was three-fold higher in women than men, migraine peaked with age in women, but remained flat for men, and prevalence of migraine among Asian adults was roughly 2/3 that of Caucasians. These methods for ascertainment of migraine are inexpensive, easy to implement and can be combined with other EMR data to assess utilization. In addition, these methods have applications and implications that extend well to other institutions and as well as other debilitating chronic conditions.

P176

Validation of a Short Migraine Screener in Patients with a TIA or Stroke

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Objectives: To study the test-characteristics of a five-question migraine screener for diagnosing migraine in patients with a TIA or stroke.

Background: Migraine is an independent risk factor for stroke. To investigate the relation between migraine and stroke, reliable ascertainment of migraine history is crucial.

Methods: We included patients who were admitted to the Leiden University Medical Center with a TIA or stroke between January 2011 and April 2012 and answered a five-question migraine screener. A semi-structured telephone interview was carried out to validate the migraine diagnosis according to the ICHD-II criteria by a trained medical student under supervision of study physicians. In case of ambiguous symptoms, a headache specialist was consulted. All were blinded for the results of the screener. The test-characteristics of the screener were calculated with the final ICHD-II diagnosis as gold standard.

Results: Forty-nine (22.2%) of the 221 included TIA or stroke patients were diagnosed with life-time migraine. The sensitivity of all five questions combined was 0.47 (95% CI 0.31-0.62), the specificity 0.97 (95% CI 0.93-0.99), the positive predictive value (PV) 0.80 (95% CI 0.59-0.93) and the negative PV 0.87 (95% CI 0.82-0.92).The question with the best test-characteristics was on ever presence of severe headache accompanied by hypersensitivity to lights and sounds (sensitivity 0.96, 95% CI 0.85-1.00; specificity 0.89, 0.85-0.94; negative PV 0.99, 0.95-1.00; positive PV 0.71, 0.58-0.82). For assessing a history of migraine aura the question about visual disturbances lasting 5-60 minutes followed by headache had a good negative PV (0.99, 0.96-1.00), but a low positive PV (0.38, 0.24-0.53).

Conclusions: The short migraine screener can be used to rule out a history of migraine in patients with a TIA or stroke. To prevent misclassification in studies on the

relation between migraine and stroke, patients with a positive screener should be interviewed more extensively to verify the diagnosis.

P177

Do Migraineurs with Vertigo/Dizziness Display Some Common Characteristics? Results from a Population-Based Study

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Objectives: Our aim was to assses the frequency of vertigo/dizziness and to define the differences between clinical characteristics related to vertigo/dizziness in a community-based sample of migraneurs.

Background: Migraine and vertigo/dizziness are both common, distressing and interrelated. They occur together 3 times more than by chance, and both impact on quality of life, but their exact relationships were not well delineated in the migrainuers.

Methods: We designed a community- based prevalence study in adults, with face-to face interviews by specially trained general practitioners using a structured electronic questionnaire. Comprehensive interview form included diagnostic questions based on the ICHD-II criteria. The questionnaire assessed all diagnostic headache features, headache related impact, demographics, comorbidities and disability assessed by MIDAS questionnaire. Participants were asked to provide mean number of attacks and days with headache per month during last year and untreated duration of attack in hours. Descriptive statistics were applied and Chi-square test, t test and logistic regression test were used for comparisons.

Results: 5323 participants were reviewed. Vertigo/dizziness was significantly higher in migraineurs when compared to tension type headache sufferes. There were 534 migraineurs with vertigo/dizziness (MwVD) and 337 patients without vertigo/dizziness as controls. MwVD patients established 61.3 % of definite migraineurs. MwVD patients had significantly more nausea/vomiting, more headache aggravation with head motions and had more visual aura. Frequency of headaches and pain killers used per month were also significantly high in MwVD patients. MwVD patients reported significantly more motion sickness, allergy, allodynia and osmophobia, interestingly. Furthermore MwVD patients had significantly low quality of life.

Conclusions: Our findings showed that more than half of the migraineurs in the general population have vertigo/dizziness. These patients showed many significant differences in clinical characteristics and have low quality of life when compared to other migrainuers.

P178

Migraine, White Matter Hyperintensities (WMH), and Subclinical Brain Infarction (SBI) in a Race/Ethnically Diverse Older Cohort: The Northern Manhattan Study

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Objectives: Migraine, White Matter Hyperintensities (WMH), and Subclinical Brain Infarction (SBI) in a Race/Ethnically Diverse Older Cohort: The Northern Manhattan Study.

Background: Epidemiological studies suggest that migraine is a risk factor for WMH and SBI[1].

Methods: In the Northern Manhattan Study, stroke-free participants underwent quantitative assessment of WMH volume (WMHV) and SBI. We examined features of SBI and WMHV in those with migraine without aura (MwO) and migraine with aura (MA) in a subset of participants with information on migraine determined by self-report using questions based on the ICHD-2 criteria[2]. We examined the association between migraine overall (MO), MA, and MwO, with WMHV using linear regression, and with SBI using logistic regression.

Results: Of 546 study participants with imaging and headache data (41% men, mean age at MRI=71±8 yrs, 65% Hispanic, 18% black), 104 (19%) were classified as having migraines at baseline, 6% with MA, and 13% with MwO. When controlling for age, sex, race/ethnicity, insurance status, high school completion, time from baseline to MRI, those with MO at baseline had a 2.2-fold increased odds of SBI (95% CI 1.2-4.4). The association was stronger among those with MwO compared to those without migraine (OR 2.8, 95% CI 1.4-5.8). Adjusting further for hypertension, diabetes mellitus, smoking, mild-moderate alcohol use, BMI, the associations between SBI and migraine persisted for MO (OR, 95% CI=2.1, 1.0-4.3) and for MwO (OR, 95% CI=2.6, 1.2-5.7), compared to

those with no reported history of migraine. No association was observed between migraine and WMHV. The analysis for MA did not show a significant association, but was under-powered.

Conclusions: These results suggest that MwO is associated with SBI, but not WMHV.

P179

Productivity Impact of Headache on a Heavy-Manufacturing Workforce in Turkey

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Objectives: To measure productivity losses at a heavy-manufacturing company with a largely male workforce in north-western Turkey.

Background: Headache disorders are common and disabling and cause substantial productivity losses through absenteeism from work and impaired effectiveness at work (presenteeism). These losses are generally higher among women.

Methods: We used the HALT Index as the survey instrument. We first assessed productivity losses by surveying the entire workforce. Because we anticipated a high level of non-participation, we also applied HALT at the annual health checks provided to all employees by the company's on-site health clinic.

Results: Mean age of the workforce (n=7,200) was 31 yr. About two thirds (90% male) were manual workers rotating weekly through early, late and night shifts. One third (50% male) were clerical or managerial, working a standard 5-day week. Of 7,200 questionnaires distributed in the first assessment, 3,939 (54.7%) were returned with usable data. Absenteeism of $\geq$1 day in the previous 3 months was reported by 360 respondents (9.1%), of whom 4 (0.10%) reported absences of $\geq$45 days. Average absenteeism per worker in the entire workforce (*ie*, including those with and without headache) was 0.92 days/yr. Lost productivity through presenteeism equivalent to $\geq$1 day's absence in the previous 3 months was reported by 1,187 (29.4%) of respondents. Average presenteeism-related lost productivity per worker in the entire workforce was 6.0 days/yr. We estimated that 23,519 days' productivity was lost per year among respondents (2.3% of workforce capacity). In the first 6 months of annual health checks, 2,691 employees (37.4%) attended (94.4% male). Absenteeism was reported by 40 (3.4% of those reporting headache and 1.5% of the total sample), who recorded 74 days lost in total (mean/person 1.85). Presenteeism equivalent to $\geq$1 day lost was reported by 348 (29.9% of those reporting headache and 12.9% of the total sample), who recorded 1,240 days lost in total (mean/person 3.56). We estimated that productivity equivalent to 41,771 man-days/yr was lost in the entire workforce (2.4% of capacity; 94% due to presenteeism), closely matching the earlier estimate. A small minority (5.7%) of those with headache, who were only 2.5% of the workforce, accounted for >45% of presenteeism-related lost productivity.

Conclusions: These estimates were well above expectation informed by studies in Europe, suggesting a higher prevalence of disabling headache in Turkey than the European average. The high productivity losses in a largely male workforce were surprising. Possible factors were the nature of the work – manual labour for two thirds, often heavy – and rotation weekly through early, late and night shifts (schedule disturbances are a recognized migraine trigger). The high presenteeism to absenteeism ratio (16.6:1) was not unexpected: the unemployment situation in Turkey would make employees reluctant to be absent. There was a highly-disabled minority.

P180

Using an Opioid or Barbiturate Increases Disability and Nausea during a Headache Attack among Patients with Migraine

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Objectives: Evaluate the impact of using an opioid or barbiturate vs other acute medications on headache severity, associated symptoms, and disability during an individual attack across multiple attacks among patients who use opioids or barbiturates.

Background: Patients with migraine who use opioids or barbiturates for headache attacks experience higher migraine-related disability. It is unclear whether this is a function of the patient or the medication. There is a paucity of data regarding the impact of using an opioid or barbiturate vs other medications for individual headache attacks among patients with a history of using opioids or barbiturates for some attacks.

Methods: In this prospective, longitudinal study, patients with migraine who use opioids and/or barbiturates to varying degrees completed up to 6 months of daily web-based headache diaries collected in real/near-time (total days 16,855; total headache days 5,218; M = 9.3 headache

days a month). The diaries assessed headache and its characteristics (severity, nausea, vomiting, sensitivity to light/sound), timing (pain severity at initial dosing), acute medication(s) used, and disability during the headache (measured via Migraine Disability Index [MIDI]; 0-10 scale, higher numbers = higher disability). Medication was placed into three types: opioid and/or barbiturate (OB); migraine-specific medication (MSM); NSAID and/or simple analgesic (NSA). OB use at any point was classified as OB, otherwise grouping was based on first medication type. Log-linked GEE (for scaled outcomes) and logit-linked GEE (for binary/ordinal outcomes) evaluated the impact of medication type, pain severity at initial dosing, and their interaction while controlling for covariates. Sequential Bonferroni adjusted 95% confidence intervals were used.

Results: Medication use was; MSM (45%), NSA (32%), OB (23%). Pain severity at first dose was; mild (51%), moderate (37%), severe (12%). Regarding disability, GEE showed an interaction for medication X pain at dosing (Wald (4)=58.57, $p < .001$). Of note, at mild initial dosing, MSM (M= 2.5) and NSA (M = 2.6) had less disability during the headache than OB (M = 3.7, both $p < .001$). At moderate initial dosing MSM (M = 4.9) had less disability than OB (M = 5.8, $p < .001$). There were no significant differences at severe initial dosing. An interaction was also seen for nausea (Wald (4)=39.61, $p < .001$). Of note, at mild dosing, MSM (M =45%) resulted in less nausea than NSA (M=72%) or OB (M=73%, both $p < .001$). No significant differences between medication types were found at moderate and severe dosing levels. Results for photophobia, phonophobia, and severity replicated those for nausea.

Conclusions: Among persons who sometimes use an opioid or barbiturate, taking an opioid or barbiturate when pain is mild or moderate results in higher disability during individual attacks relative to using other acute medications. Increased disability appears to be a function of the medication and when it is used rather than the individual.

P181

Patients with Migraine Internalize Stigma More Readily Than Patients with Epilepsy

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Objectives: To characterize and compare the self-stigmatization process in episodic and chronic migraine, and in epilepsy.

Background: Enacted stigma is converted into internalized stigma through the self-stigma process, lowering self-esteem and causing psychological distress. We have recently shown that patients with migraine have a higher ratio of internalized to total stigma compared to epilepsy patients.

Methods: We studied 123 episodic migraine (EM) patients, 123 chronic migraine (CM) patients, and 62 epilepsy (Ep) patients in a clinical setting to investigate the extent to which stigma attaches to migraine, using epilepsy as a comparison. We used the stigma scale for chronic illness, a 24-item questionnaire suitable for studying chronic neurologic diseases, and various disease impact measures. The SSCI-Enacted includes 11 items and the SSCI-Internalized (SSCI-I) 13 items, dividing stigma into two domains. We analyzed the ratio of SSCI-I to total SSCI (SSCI-I/SSCI).

Results: Patients with chronic migraine had higher SSCI scores (54.0±20.2) on the stigma scale for chronic illness than either episodic migraine (41.7±14.8) or epilepsy patients (44.6±16.3) ($p<0.001$). Migraine patients reported less ability to work than epilepsy subjects. Stigma correlated most strongly with the mental component score of the short form of the medical outcomes health survey (SF-12), then with ability to work and migraine disability score for chronic and episodic migraine and the Liverpool impact on epilepsy scale for epilepsy. Analysis of covariance showed adjusted scores for the stigma scale for chronic illness were similar for chronic migraine and epilepsy, and lower for episodic migraine. Ability to work was the strongest predictor of stigma.

We then examined SSCI-I/SSCI, demonstrating that a higher proportion of the stigma reported by CM (0.634 ± 0.060) and EM (0.622 ± 0.059) patients could be attributed to internalized stigma than enacted stigma, compared to Ep patients (0.598± 0.074).

For each disease condition, SSCI-I /SSCI did not vary according to age, gender, income or education, but correlated negatively with ability to work for EM ($r = -0.236$, $p=0.008$), showed a trend for CM ($r=-0.174$, $p=0.055$), and did not correlate with Ep. There was no correlation of SSCI-I/SSCI with the physical component score of the SF-12, but there was a correlation with the mental component score of the SF-12 for EM ($r=-0.337$, $p<0.001$) and CM ($r=-0.259$, $p=0.004$), but not for Ep.

Conclusions: Patients with migraine process stigma differently than patients with epilepsy. The proportion of internalized stigma to total stigma correlated most strongly with inability to work for patients with EM than for the other diseases conditions studied, perhaps

because the expectation to work is greater for EM than for CM or EP.

P182

Migraine Treatment Optimization in Multiple Sclerosis

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Objectives: To determine adequate migraine diagnosis and predictors of treatment optimization in MS including demographics, socioeconomic status, depression, and MS characteristics.

Background: Migraine is under-diagnosed and under-treated in the general population. Patients with multiple sclerosis (MS) suffer from a higher incidence of migraine than patients without MS, but migraine diagnosis and treatment optimization has not been studied in MS.

Methods: We conducted a cross-sectional interview based study of 233 consecutive patients with MS using detailed questionnaires including the Migraine-Treatment Optimization Questionnaire (M-TOQ).

Results: Our cohort was predominantly female 156(67%), average age 44 years. 83 (36%) patients had migraine. Based on the results of (M-TOQ), acute migraine treatment was optimized in only 48 (58%) and was not influenced by race. However acute migraine treatment was better optimized in episodic 43(62%), rather than chronic migraineurs 5(36%). The majority of our patients 56(70%) were using non-specific acute abortive treatment for migraine headaches, of which non-steroidal anti-inflammatory medications were the most common. Preventative treatment was used infrequently 12 (14%), of which the most common were anti-epileptics or antidepressants. The use of complementary and alternative medications was quite high in this population 56 (70%), the most common modality of treatment reported being use of cold cloth/ice pack to forehead 47(57%).

Conclusions: As in the general population, the majority of MS patients with migraine are under-diagnosed. About half of MS migraineurs have non-optimized treatments regardless of migraine regimen, race, or walking ability. Depression and episodic rather than chronic migraine were positively correlated with optimized migraine medications. Socioeconomic factors predicting optimization of migraine treatment in MS patients include higher education and income, and private treatment setting. Optimized treatment usage was higher in private clinic. Alternative treatment was used more in public clinic and abortive treatment usage was similar in both public and private clinics.

P183

A Generalized Cost-Effectiveness Analysis of Interventions Against Migraine Using WHO-CHOICE Methodology

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Objectives: To identify how health resources may be allocated to an optimal mix of interventions against migraine by evaluating their cost-effectiveness (CE) in low, middle and high income countries in different world regions.

Background: CE analysis plays a crucial role in optimizing health-care resource allocation and clinical decisions. We identified 20 published CE analyses of migraine interventions. Most (17) applied intervention mix constraints, being focused on particular drugs (*eg*, triptans or specific prophylactics), which hindered comparisons with less costly and more accessible interventions. Further, all were performed in Europe or North America, with limited relevance to other regions in view of the large variations in development of health systems and overhead costs. None compared recommended acute and prophylactic interventions against doing nothing in real-world settings based on the epidemiological profile of migraine.

Methods: We modelled >20 interventional strategies, taking account of coverage and non-adherence. We included first-line acute and prophylactic drugs, and the expected consequences of adding public health-education and training of health-care providers. We used CostIt® software to standardize costing. Drugs were valued at the prices that would be incurred in the international market place, adjusting to include domestic margin. A health system perspective was taken, including all costs and the share of overhead resources that could be reallocated to other interventions. We used PopMod® software to estimate effectiveness of interventions. We took summary measures of sustained headache relief (for acute drugs) and reduced attack frequency (for prophylactics) from published evidence. We used age-standardized attack-incidence rates and ictal disability weights for migraine from the Global Burden of Disease 2010 study.

We expressed net health effects as disability-adjusted life years (DALYs) averted. We executed a first run of the model for India.

Results: Of the strategies considered, acute treatment only with an NSAID was the most cost-effective (US$ 46-47 per DALY averted, which represents a highly efficient use of health resources). Adding public health-education and/or training of health-care providers to acute self-management increased costs by US$ 0.03-0.04 per capita of the population. CE ratio then became slightly less favourable but still less than US$ 100 per DALY averted. Adding a triptan for stepped care increased the CE ratio 30-fold. For prophylaxis, amitriptyline was more cost-effective than propranolol or topiramate.

Conclusions: Self-management with an NSAID is by far the most cost-effective intervention for migraine in India, and this is most likely true for all world regions. Public education and health-care provider training are expected to accelerate progress towards desired coverage levels, cost relatively little to implement, and are therefore assumed to be economically attractive.

P184

Public Versus Private Care in Headache. Are There Differences?

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Objectives: This study aimed at comparing patient's profile, diagnosis, adherence, treatment strategies and response between headache sufferers attending two different services in Rio de Janeiro. A public and a private headache center.

Background: Countries with socialized medicine and/or with a free-of charge public system may deliver inferior quality care in comparison with private medicine environments.

Methods: Consecutive patients from both environments were prospectively compared regarding ages, sex distribution, diagnosis, treatment strategies, adherence, response (headache frequency decrease of higher than 50%) and requesting work releasing during the first and second consultations. Adherence was defined as returning for the following consultation and compliance with treatment prescribed.

Results: 500 patients from the Headache Center of Rio were compared to 227 patients from The Instituto de Neurologia Deolindo Couto (INDC). Adherence was identified in 73,1% of the public patients compared to 80,1% in the private center. Monotherapy was prescribed to 13,4% of the public system patients compared to 33% whereas 86,2% from the private center versus 67% from the public system received more than one drug for prevention. Requesting documentation for work releasing was seen in 2 (0,4%) of the private patients compared to 50 (22%) of those seeking for a public system care. Regarding decreasing of headache frequency of higher than 50%, it was presented by 62% of those returning (45% by ITT) in public system compared to 72,6% of those who adhered (58,2% by ITT) in the private setting.

Conclusions: Although most of the public services of Rio deliver poor quality care, the patients from the INDC did present similar profile of diagnosis, treatment approach and response when compared to those patients from the first and more comprehensive headache center of the State. Reasons for that may be the orientation provided to the attending physicians by the technical coordinator who is the same of the private setting. In addition, the geographical location of the public service, in this case better than that from most of the other services, may have contributed to the better standard of the patients. Interestingly, significantly more patients with TTH and requesting work releasing were noted in the public service.

		Private N=500	Public N=227
Gender	Female	71,8% (359)	75% (150)
	Male	28,2% (141)	25% (57)
Age (years)	Mean	38,7 (4-88)	39,8 (16-76)
Diagnosis	Migraine	58% (290)	45,4% (101)
	MOH	35,6% (178)	32,6% (74)
	TTH	1,8% (9)	15,4% (35)
	TAC	3% (15)	6,6% (15)
	Other	1,6% (8)	0,9% (2)
Headache frequency	(days/month)	17	16
Preventive therapy	None	0,4%(2)	0%
	1drug	13,4%(67)	33%(75)
	> 1 drug	86,2%(431)	67%(152)
Response	Adherent patients	72,6%(363)	62%(141)
	ITT	58,2%(291)	45% (102)
Adherence		80,1%(400)	73,1% (166)

P185

Reliability and Validity of the Persian Headache Impact Test (HIT-6) Questionnaire across Migraine and Tension Type Headache

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Objectives: The objectives of this study were to validate the Persian translation of HIT-6, compare the psychometric analysis of HIT-6 between migraine and tension type headache (TTH) patients, and evaluate the capability of HIT-6 to differentiate between TTH, chronic and episodic migraine.

Background: Headache impact test questionnaire (HIT-6) is a valid scale that measures the impact of headache in a one-month period. Up to this date there is no valid and reliable Persian translation of HIT-6.

Methods: Qualified participants, including 274 patients, diagnosed with migraine or TTH, were required to complete HIT-6, SF-36v2 and a symptoms questionnaire on their first visit. At third and eighth week from first visit participants completed HIT-6. Internal consistency (Cronbach α) and test-retest reproducibility (Pearson correlation coefficient) were used to assess reliability. Convergent validity was assessed through measurement of correlation between HIT-6 and headache days per month (HDPM), HIT-6 and numeric rating scale (NRS) and also between HIT-6 and SF-36.

Results: TTH, episodic migraine and chronic migraine included 24.5%, 61.9% and 13.6% of the participants respectively. Internal consistency among all patients, TTH and migraine in first visit was 0.74, 0.77 and 0.73 respectively. Test-retest reliability for HIT-6 between visit 1 and 2 showed a moderate level of correlation ($r=0.50$). The total HIT-6 score in the first visit was negatively correlated with both mental and physical components ($r=-0.39$ and -0.35 respectively, $P<0.001$). Also total HIT-6 score in first visit was modestly correlated with headache days per month (HDPM) and numeric rating scale (NRS) ($r= 0.14$ and 0.17 respectively, $P<0.001$). All questions were significantly correlated with total HIT-6 score (0.52 to 0.77, $P<0.001$). There was no significant difference in HIT-6 total score between TTH and migraine.

Conclusions: Persian HIT-6 is a valid and reliable questionnaire for evaluation of headache; however it cannot differentiate between chronic, episodic migraine and TTH in Iranian population.

P186

Difference in Dietary Patterns between Migraine with and Migraine without Aura

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Objectives: To evaluate the cross-sectional associations of dietary patterns between migraine with aura and migraine without aura in a large cohort of women.

Background: People with migraine often report that certain foods, including wine, chocolate, caffeine, cheese, and processed meats, "trigger" migraine attacks. However, epidemiologic evidence on migraine triggers or on the dietary patterns of migraineurs with specific focus on aura is limited. Using data from a large prospective cohort study of women, we aimed to examine whether intake of foods that have commonly been reported as migraine triggers was different between women with migraine with aura and women with migraine without aura.

Methods: We performed a cross-sectional study among 4946 women enrolled in the Women's Health Study who reported active migraine at baseline and completed a 131-item food frequency questionnaire. Women were classified as either having migraine with aura or migraine without aura. We compared women in the top quintile of average number of servings per day for each food item to those in the lower four quintiles using logistic regression. For these analyses, we examined intake of chocolate, caffeine, cottage cheese, cream cheese, other cheeses, bacon, hot dogs, processed meats, red wine, white wine, liquor and beer because these foods have previously been reported to be migraine triggers. Models were adjusted for age, total calories, body mass index, physical activity, smoking status, diabetes, history of hypertension, treatment for high blood pressure, history of high cholesterol, and treatment for high cholesterol.

Results: We had 2059 women who experience migraine with aura and 3115 women who experience migraine without aura. Migraineurs with aura were more likely to consume white wine (odds ratio (OR)=1.18, 95% confidence interval (CI): 1.00-1.39) and less likely to consume chocolate (OR=0.78, 95% CI: 0.65-0.95), bacon (OR=0.79, 95% CI: 0.68-0.93) and hot dogs (OR=0.74, 95% CI: 0.60-0.91) compared to those who experience migraine without aura. Results for red wine were marginally insignificant (OR=1.25; 95% CI: 0.99-1.58). We did not observe significant differences in intake for any other explored food item.

Conclusions: In this cross-sectional study, we observed different food intake patterns of common migraine trigger foods among migraineurs with and without aura. Future research needs to be performed to determine if migraineurs with and without aura may avoid eating difference food items in order to prevent migraine attacks and whether these food items truly cause migraine attacks.

P187

Prevalence of Chronic Migraine and Medication Overuse Headache in Eight Austrian Headache Centres

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Objectives: To evaluate the prevalence of episodic and chronic headaches in 8 Austrian headache centres with emphasis on chronic migraine and medication overuse headache (MOH).

Background: Lifetime prevalence of migraine is 10-18%, of tension-type headache (TTH) 16-59%. MOH shows a prevalence of 1-1.5%, in headache centres of 30-50%.

Methods: In April and September 2011 all patients who attended the headache centres for a first-time or control visit were screened for the study. Participants had to fill-in the Eurolight Questionnaire that covers demographic data, headache symptoms, information about medication, consultations of the health system, examinations due to headaches, questions about quality of life, depression and anxiety. Headaches were diagnosed according to ICHD-II.

Results: Of 598 patients screened, 121 refused participation or were excluded because of lacking knowledge of German. After excluding 36 patients due to incomplete data, 441 patients (348 women, 93 men, mean age 39.9 years) were analysed. The proportion of patients with migraine or probable migraine, TTH or probable TTH, MOH and other headaches was 68.5%, 12.7%, 16.1%, and 2.7% respectively. Headache was episodic in 59.6% and chronic in 40.4%. Of the patients with chronic headaches 42.0% had medication overuse headache, 42.0% had migraine or probable migraine, 14.2% had TTH or probable TTH and 1.8% had other headaches. Hospital Anxiety and Depression Scale Scores indicated a certain anxious state in 24.2%, a doubtful anxious state in 18.7% and no anxiety in 57.1%; it indicated a certain depressive state in 14%, a doubtful depressive state in 18.3% and no depressive state in 67.7%. Symptoms of anxiety were present in 55.8% of the patients with chronic headaches and in 34.4% of those with episodic headaches ($p<0.001$). Symptoms of depression were present in 45.2% of the patients with chronic headaches and in 22.2% of those with episodic headaches ($p<0.001$).

Conclusions: A substantial number of patients seen in specialised headache centres in Austria have chronic headaches. Among the latter chronic migraine and MOH account for more than 80% of diagnoses. These patients who frequently also show signs of depression or anxiety need a comprehensive and multidisciplinary treatment approach.

P188

Characteristics of Young Adults and Adolescent Presenting to a Headache Specialty Clinic

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Objectives: To describe the characteristics of young adults and adolescent with headache presenting in a multidisciplinary outpatient clinic for specialty headache treatment.

Background: As an individual develops from childhood into adolescence, the prevalence of migraine increases. Migraine is often under recognized in young patients and can have a significant impact on their lives. Young adults represent an underserved population whose needs are unique and challenging for providers who treat in solely a pediatric or adult setting. A young adult and adolescent multidisciplinary clinic was developed to meet the unique needs of this group while they transition to adulthood.

Methods: A retrospective analysis of 266 patients (ages 15-26) that have received a multidisciplinary evaluation and treatment for a headache disorders by a team comprised of a board certified Neurologist and Headache Medicine specialist, pain psychologist, nurse practitioner and registered nurse. Standardized questionnaires were completed by each patient providing information about the headache and health history as well as information pertinent to confirm diagnosis based on the International Criteria for Headache Disorders 2nd edition. This was accomplished through a semi-structured interview and a comprehensive neurological exam.

Results: The female to male ratio was 201:65. The mean age on evaluation was 16.9 $\pm$ 2.5 years old. The mean time from start of headaches to evaluation was 5.6 years. Average headache frequency was 18.7 $\pm$10.1 days per month with an average severity on a 0-10 numeric pain scale of 6.7 $\pm$ 1.7. The mean headache duration was 15.3 hours. Episodic migraine (<15 headache days/month) occurred in 31.2% of the patients evaluated with chronic migraine (>15 headaches/month) in 68% of the patients, including 40.2% reported an "always" or daily headache. The diagnosis of migraine without aura occurred in 96.6% of patients; status migrainosus 49.6%; migraine with aura 29.3%; medication overuse headache (MOH) 36.8%; menstrually related migraine without aura 19.5%.

Conclusions: Young adult patients presenting for care for intractable headaches are more likely to be females who have had nearly a 6 year history of headaches that they describe as moderate to severe in intensity. These patients are likely to present with chronic headaches that are primarily migraine without aura. Recognition of these patient characteristics should prompt early treatment and used as a tool in providing better outcomes.

P189

Adherence and Persistence to Triptans for Acute Migraine: A Systematic Literature Review

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Objectives: Evaluate adherence and persistence to triptan therapy for the acute treatment of migraine.

Background: Triptans are the most commonly prescribed treatment for patients with moderate to severe migraine. Clinical trials have demonstrated the safety and efficacy of triptans. However, observational studies have consistently reported low patient adherence and persistence over time.

Methods: A systematic literature review was conducted to identify all studies of patient adherence and persistence to triptan medications.

Results: 86 potentially relevant studies were identified, from which 6 articles met the inclusion and exclusion criteria and were included, along with an additional 3 articles identified from bibliographic review. This review found that over 2 years, approximately half of patients were persistent to the first prescribed triptan. 38% to 56% of patients filled only 1 prescription after starting their triptan therapy. Over 2 years, 14.8% of patients tried >1 triptan. In a study conducted in the UK, 9% switched to another triptan, and 41% of the 9% reported the switch as successful. In the US, 7.4% of those who discontinued the first prescribed triptan switched to another triptan, while 67.1% had switched to a non-triptan and 25.5% of patients had discontinued all therapy.

Conclusions: Triptans are a valuable treatment option for acute treatment of migraine. However, studies have shown that adherence and persistence to therapy is low. This, along with discontinuation and frequent switching behaviors, suggests that there is a significant proportion of patients not adequately treated with currently available triptans.

P190

Dementia Outcomes in Elderly with Self-Reported History of Migraine

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Objectives: To examine the risk of incident dementia in community residing adults over the age of 70 with migraine.

Background: Studies of the relationship of migraine and cognitive outcomes have been few and conflicting. Study sample characteristics, methods for identifying migraine, assessments of cognitive outcomes have varied widely. The Manitoba Aging Study reported that persons with migraine had a 5-fold increased risk of dementia.

Methods: The Einstein Aging Study (EAS) follows a systematically recruited, ethnically-diverse community residing sample of adults age 70+ with annual telephone screening and in-person assessments. Neurologic examination and comprehensive cognitive assessments are used to determine dementia status based on DSM-IV criteria at a case conference. Study subjects were said to have "migraine" if they reported a history of migraine or if they reported headache within the last 3 months at least "some of the time". Prevalent dementia cases were excluded. Cox proportional hazards models were used to model time to dementia with migraine status, demographic factors (sex, education, ethnicity) and APOE-e4 carrier status as predictor variables. Additional adjustments for overall baseline pain interference and pain intensity were included. Age was used as the time scale for these models in order to fully control for age effects.

Results: Of 974 eligible subjects, 136 met criteria for migraine. Among the 838 individuals without migraine, 76 developed dementia (9.1%). Of 136 with migraine, 8 developed dementia (5.9%). Cox model shows that migraine was not significantly associated with dementia onset (Hazard Ratio (HR)=0.60, 95% CI 0.29-1.25). Adjusting for sex, education, and ethnicity (HR=0.56, 95% CI: 0.27-1.18) and for APOE-e4 carrier status, baseline pain interference and pain severity did not materially alter the conclusion.

Conclusions: In this cohort, migraine was not a risk factor for incident dementia. Possible misclassification of migraine status due to remitted and forgotten migraine could attenuate the measured association. As migraine frequency, duration, disability and aura status were unknown, this does not exclude an effect on dementia risk of some migraine subgroups.

P191

Chronic Primary Headaches Are Different from Episodic Primary Headaches: Experiences from an In Patient Treatment in a Neurological Clinic

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Objectives: To compare clinical characteristics, therapeutics response and prognosis in subjects with episodic primary headaches (EPH) or chronic primary headaches (CPH) carried into an in-patient treatment in a headache unit from a neurological clinic.

Background: Primary headaches are frequent causes of consultation in the ER and hospitalization. Still there is a lack of guidelines with strong medicine-based evidence. There have been discussion about probable differences between episodic and chronic headaches, although there is not clear data from in-hospital. There are guidelines and medicine-based evidence for neuroimaging studies in PH, but still it is found high rates of prescriptions.

Methods: This is a retrospective cohort analytic study of patients with PH in a in-patient program from a headache unit from a neurological clinic. The results are presented comparing CPH against EPH according to de variable level measurement.

There was a retrospective information recolection, the evaluation of the outcome was prospective from clinical chart. The data was analyzed through the statistical tests chi square and frequency comparison.

Results: 198 patients were treated between 2009 to 2011. In the CPH, CM was the most common (88.1%), NDPH (9.8%) and CTTH (2.1%). In the EPH, EM was the main diagnosis (92.7%). in CPH the in-patient managment was need it because treatment refractoriness (49%), as in EPH was due to migranous status (69.1%). 38.9% of patients had neuroimaging abnormalities, but in just 7 patients (3.6%) with CPH LET to changes in treatment and diagnosis. 69.2% of patients were on prevention, and 91.4% used abortives. There was not possible to determine which IV meditacion had better efficacy and safety. During the in-patients treatment the average IV medications was 4.1+/-1.9; subjects with CPH needed higher numbers (4.6 +/-1.8 vs. 2.9+/- 1.4), prolonged infusions (7.5 days +/- 6.1 vs. 2.8+/-1.5). anxiety (58% vs 20%), deppression (57.3% vs 14.5%) and insomnia (48.3% vs 7.3%) were more frequently asociated with CPH. The in-patient period needed was significantly higher in patients with CPH ($p < 0.001$). At discharge, 74.9% were pain free or improved (AVS <3). Subjects with EPH had better response (87% vs. 70.2%; p= 0.0001 RR 3.62 CI 95% 1.8

– 7.04). CM was a risk factor for a bad in-patient response and prognosis (RR 4.0 CI 95%: 1.5 - 11).

Conclusions: The in-patient treatment is an effective option to treat primary headaches, the final results at discharge is directly related to the primary headache subtype. Although episodic and chronic headaches share clinical features, the differences in responses and prognosis suggest probably differences in pathophysiology and associated risk factors. Medicine-based evidence is need it, specially to cph patients. From our experience, an algorithmic approach is suggested.

P192

Sinus Pressure and Its Association with the Attack Frequency of Migraine and Tension-Type Headaches

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Objectives: 1) To determine if the prevalence of sinus pressure is greater in patients with migraine (M) and/or tension type headache (TTH) compared to controls, 2) To ascertain if the self-reported attack frequency of M or TTH differs between subjects with and without sinus pressure.

Background: Sinus pressure is a common complaint in headache patients and one that may contribute to the misdiagnosis of migraine as "sinus headaches".

Methods: Participants between ages 18-65 years were recruited from one allergy clinic consisting of rhinitis patients (n=655) and two control internal medicine (n=187) clinics in Cincinnati, Ohio. Rhinitis patients were categorized into allergic (AR; n=254), mixed (MR; n=279) and nonallergic (NAR; n=122) rhinitis based on allergy testing and responses to an irritant index questionnaire. Controls included patients that self-reported "rarely" or "never" experiencing rhinitis symptoms to specific allergic and non-allergic triggers. Subjects underwent a structured verbal interview to determine headache characteristics including the attack frequency (days/month) and presence/absence of sinus pressure. Subsequently, each subject was assigned an ICHD headache diagnosis by a blinded headache expert. Log binomial regression was used to determine if the prevalence of sinus pressure increased in those with M and TTH after controlling for rhinitis status, age and gender. Quantile regression was used to compare M and TTH attack frequency between those with and without sinus pressure at the 25th, 50th and 75th percentiles of these measures after adjusting for gender, age and preventive medication.

Results: Sixty percent of subjects were female; sinus pressure was reported by 80%, 68% and 33% of subjects with M, TTH and controls, respectively. The adjusted risk ratios (RRs) for sinus pressure prevalence were 1.2 (95% CI; 1.1, 1.4) for M and 1.1 (95% CI; 0.99, 1.2) for TTH. The RRs were significant for all the rhinitis subtypes (range for RRs: 1.6-1.7; all p values <0.01). For headache frequency analyses, the ratio of the means in patients with compared to those without sinus pressure were 2.0, 2.2 and 2.7 for M and 1.4, 2.1 and 2.0 for TTH at the 25th, 50th and 75th percentiles, respectively (p values <0.05).

Conclusions: Sinus pressure is more common in migraineurs than those without M even after accounting for rhinitis. The attack frequency of both M and TTH headache is significantly increased in patients with sinus pressure. Since sinus pressure commonly occurs in patients with rhinitis and rhinosinusitis, further work is needed to determine whether these disorders directly trigger headache attacks or if patients with more frequent headaches are more likely to experience pressure in the sinus regions.

P193

The Psychometric Properties of the Persian Migraine-Specific Quality of Life Questionnaire Version 2.1 (MSQ) in Episodic and Chronic Migraine

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Objectives: The aims of this study were linguistic validation of Persian MSQ questionnaire, analysis of psychometric properties between chronic and episodic migraine patients and capability of MSQ to differentiate between chronic and episodic migraine.

Background: Migraine specific quality of life (MSQ) is a valid and reliable questionnaire that consists of three dimensions; role restrictive (RR), role preventive (RP),

and emotional function (EF), which evaluates the patients in a one-month period.

Methods: Participants were diagnosed chronic or episodic migraine patients from four different neurology clinics. Baseline data included information from MSQ v. 2.1, MIGSEV, SF-36 and symptoms questionnaire. At the third week from the baseline, participants filled out MSQ and MIGSEV. Internal consistency (Cronbach alpha) and test-retest reproducibility (Pearson correlation coefficient) were used to assess reliability. Convergent validity of MSQ was assessed through measurement of correlation between MSQ scores (total score and each dimension of MSQ) and two components of SF-36 (mental and physical) scores. Discriminant validity was assessed through comparison between different grades of MIGSEV scale in each dimension and in total MSQ scores. Potency of MSQ to discriminate between chronic and episodic migraines was evaluated.

Results: A total of 106 participants were enrolled. Chronic and episodic migraine included 26.8 % and 73.2 % of the participants respectively. Internal consistencies of MSQ among all patients, chronic and episodic migraine were 0.92, 0.91 and 0.92 respectively. Test-retest correlation of MSQ dimensions between visit 1 and 2 varied from 0.41 to 0.50. All the questions were significantly correlated with total MSQ score ($r=0.44$-0.81, P-value<0.001). The total MSQ score in the first visit was correlated with SF-36 mental and physical scores (0.41 and 0.46 respectively, $P<0.001$). Comparison of the mean of MSQ scores between the three grades of MIGSEV showed significant differences ($P<0.001$). In all visits MSQ scores were lower in chronic migraine than episodic migraine; however the difference was not statistically significant.

Conclusions: Persian translation of MSQ is consistent with original version of MSQ in terms of psychometric properties in both chronic and episodic migraine patients.

P194

Is Neck Pain a Prodromal Symptom of Migraine?

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Objectives: The aim of our study was 1) to assess the prevalence of neck pain in migraineurs; 2) to evaluate the percentage of patients having neck pain as clear prodromal symptom of their migraine (neck pain outside the headache phase, without any migraine features, 2-24 h before their onset); 3) to describe clinical characteristics of neck pain.

Background: Although the pain of migraine is most commonly perceived in the ophthalmic distribution of the trigeminal nerve, a substantial percentage of migraineurs are reported to experience pain in the neck and occiput with their attacks.

Methods: An online questionnaire was set on the homepages of the Austrian self-helping group (www.shgkopfweh.at) and the headache medical center seilerstaette Linz (www.kopfschmerz-linz.at). Patients with a clear migraine (pre-diagnosed by a neurologist) were anonymously asked about the occurrence of neck pain during different phases of their attacks.

Results: 387 migraineurs, 311 females (80.3%) and 76 male (19.6%) responded. 261 (67.4%) reported to experience pain in the neck (189, 72.4% bilateral; 72, 27.6% unilateral): 157 (60.1%) with or immediately (within 2 h) before their attacks, 68 (26%) exclusively within 2 hours before their attacks and 36 (13.8%) 2-24 h before the attack. None of the patients showed neck pain before or within the attack without any additional accompanying signs or symptoms of migraine.

Conclusions: Neck pain is not a prodromal symptom of a migraine attack. There is support for neck pain being not simply a co-occurring condition in migraine, but rather related to the disorder itself.

P195

Comparing Electronic and Paper Diary Recordings of Headache among Adolescents in the General Population

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Objectives: (1) To develop and investigate the usefulness of electronic diary over the Internet (eDiary) of headaches among adolescents in the general population, and (2) to compare the response rate in eDiary versus paper diary posted to the investigator (pDiary), and (3) to investigate their response rates on weekdays versus weekends.

Background: Until recently, the use of pDiaries has been a common method to estimate the prevalence and temporal changes of headaches among children and adolescent in prospective recordings, primarily conducted in treatment outcome studies. The advances in information and

communication technologies have resulted in the development and use of electronic devices and diaries. To which extent this represents an improvement in evaluation of headache occurrence among adolescents in the general population is not yet known.

Methods: From a representative and stratified sample (by age, sex and location) of schools in a county in the midst of Norway, 380 adolescents aged 13-19 in 13 schools were recruited to report on headache occurrence at the end of the day for a three week period. Five schools (170 students) were randomized to eDiary recordings and six schools (210 students) to pDiary assessments. All the participants were asked to answer four questions daily. The eDiary students were instructed to log on to a PC or smartphone and fill out the eDiary every day. Daily reminders were sent out to the students via SMS to those who had not logged in after a particular time point in the evening. With the eDiary, retrospectively headache recordings were not allowed. An exploratory analysis was done.

Results: The pattern of responses for the e- and pDiaries differed. In the pDiaries, the students had responded either most days or $\leq$ 25%. Some of them admitted in free writing that they had supplemented data in retrospect if they forgot to answer for a particular day or two. The adherence rate in the eDiary group was high in that more than 70% of the students supplied data more often than every other day.

Complete non-participation (no information submitted for a single day) was high for the pDiary group (53/210 = 25%) compared to the eDiary group (14/170 = 8%).

There was no significant difference in adherence rates between students' eDiary recordings on weekdays (1370/2027 = 68%) compared to weekends (605/944 = 64%).

In a user evaluation some participants claimed that lack of Internet had been a problem for some days.

Conclusions: The eDiary was considered useful by most users. The documented post-registration in the use of pDiaries is a potential weakness and is likely to contribute to unreliable and biased estimates, which is overcome by the use of eDiary. Contrary to our expectation, the eDiary response rate on weekends and weekdays was similar.

P196

Claim for Medico-Legal Benefits by Patients Suffering from Headache: Results from a Multi-Centre Headache Clinic Survey

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Objectives: The aim of this study was to evaluate the rates, pattern, outcome, satisfaction with and presence of predictors of claim for medico-legal benefits in a clinical population of headache patients.

Background: No study have ever investigated the claim for medico-legal benefits in headache patients.

Methods: 317 consecutive patients attending three headache clinics (Pavia, Grottaferrata and Palermo) were asked to fill in a structured questionnaire designed to gather information about search for medico-legal protection.

Results: Only twelve% of the patients filling in the questionnaire has sought medico-legal benefits for headache. The most common reason for not claiming for medico-legal benefits was "I don't know about the existence of medico-legal protection for headache" (58%). Seventy-seven percent of the claims were motivated by the desire to obtain the recognition of the status of civil invalid, while the remaining ones were aimed at being granted a justified absence from work because of the headache attacks. Forty-five percent of the claims were done solely for headache. The most common source of information was the GP (39%). Fifty-five percent of the surveyed patients declared that the evaluation from the medico-legal committee lasted less than ten minutes and only 26% declared to be satisfied by the medico-legal visit. Seventy percent and 30% of the claims for justified absence from work and civil invalidity, respectively, were rejected. Sixty-five percent of the patients receiving the medico-legal benefits considered it as not useful. Predictors of claiming for medico-legal benefits were geographical area of provenience (OR 3.25, CI1.1-9.9, OR 3.51 CI 1.2-10), the severity of medico-legal impairment as proposed by the Lombardia Region (class A OR 0.09 CI 0.03-0.28, class B1 OR 0.6 CI 0.2-0.8) and having any other form of medico-legal protection (OR= 0.28 CI 0.12-0.65).

Conclusions: To our knowledge, this is the first study investigating the phenomenon of claiming for medico-legal benefits for headache worldwide. Our data indicate that claiming for medico-legal benefits is infrequent, mostly

because of the ignorance about the possibility of receiving such protection. Headache sufferers claiming for such protection were those more severely disabled and already benefitting other forms of medico-legal protection. Most of the claims for medico-legal benefits for headache are rejected after a superficial examination. Patients being granted the status of 'civil invalid' because of their headache, consider it as not really helpful for their needs.

P197

Restless Legs Syndrome in Migraine; More Prevalent and More Severe

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Objectives: Study the prevalence and severity of Restless Legs Syndrome (RLS) in migraine patients.

Background: RLS and migraine may have a pathogenic link. We aimed to evaluate i) the association between both migraine and RLS prevalence, as well as RLS severity, and ii) the correlation between premonitory symptoms and RLS.

Methods: We conducted a cross-sectional study in 2,383 migraine patients and 154 non-headache controls. Migraine and RLS diagnostic criteria were administered via a web-based interface. Detailed migraine characteristics were available, and severity of RLS symptoms were assessed using the International Restless Legs Syndrome Study Group rating scale. Determinants for RLS and RLS severity were calculated using multivariate adjusted regression models.

Results: Of the migraine patients, 16.9% reported RLS (fulfilling 4/4 essential criteria) compared to 10.4% of the controls ($p=0.034$), which remained a significant difference after adjusting for confounders ($p=0.045$). RLS severity was higher among migraineurs than among non-headache controls. Higher attack frequency, use of prophylactics and history of medication overuse were additional determinants. Migraineurs with RLS reported more premonitory symptoms (8.0 ± 4.2) when compared with migraineurs without RLS (7.1 ± 3.9; $p<0.001$).

Conclusions: Not only is Restless Legs Syndrome more prevalent among migraineurs, RLS severity is also higher compared to non-headache controls. Furthermore, migraineurs suffering from RLS report more premonitory symptoms.

P198

Patients' Perceptions of the Causes of Migraine in Flanders (Belgium): A Qualitative Study

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Objectives: The aim of this study was to obtain the views of patients in Flanders on migraine and to examine the ways they deal with it. Elucidation of patients' perceptions of what causes a migraine may facilitate its treatment and management. Ascertaining the sources that patients consult and seek advice will assist in the development of efficient patient education.

Background: The prevalence of migraine among the Belgian population is more than 10 per cent. In Flanders and Brussels migraine accounts for an estimated 1,150,000 days of sick leave every year. Despite its considerable impact qualitative studies of patients' perceptions of the causes of migraine, and their sources of information and advice are still scarce.

Methods: This was a qualitative study of 10 migraine sufferers that used semi-structured interviews. A systematic qualitative methodology was applied to the fully transcribed interviews. Close reading of each interview transcript was used to generate codes that formed the basis of a classification of potential domains and items that shaped the analysis as themes emerged.

Results: Younger patients most commonly related migraine to stomach, intestinal or bile problems and older patients to problems with cerebral perfusion. Respondents indicated that they obtained information from their general practitioner but also from popular views. Based on these beliefs and perceptions patients attempted to define the 'ultimate trigger' in order to reduce their migraine attacks. The study showed that false theories about the causes of migraine are rife among migraine sufferers and identified a need for earlier diagnosis and more reliable information.

Conclusions: This study raised awareness about the importance of health promotion and the need for concrete, practical information and well-organized patient education.

Respondent	Age cohort	Gender	Profession	Treatment
1	45-50	Female	Pedagogue	Neurologist
2	75-80	Female	Retired	GP
3	20-25	Female	Nursery teacher	GP
4	40-45	Female	Library assistant	GP
5	35-40	Female	Unemployed	GP/Homeopath
6	35-40	Male	GP	Himself
7	50-55	Female	Housewife	GP
8	50-55	Male	Writer	GP
9	25-30	Female	Teacher	GP
10	30-35	Male	Factory worker	GP/Dietician

P199

Association of Lower Level of Leisure-Related Physical Activity with Primary Headaches

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Objectives: The primary aim of the study was to assess the association of pure migraine, pure tension-type headache (TTH) and coexistent headache with the level of leisure-related physical activity. The secondary aim was to study the association between the level of leisure-related physical activity and episodic and chronic mixed headache.

Background: Low physical activity has been associated with higher prevalence of headaches.

Methods: Total of 1300 subjects was invited to participate in a cross-sectional population study. A total of 805 eligible subjects completed a diagnostic headache interview, provided self-reported data on neck pain and back pain, leisure-related physical activity, demographics and self-rated health. Levels of leisure-related physical activity were classified according to activities performed as low, medium and high (reference).

Results: Multinomial logistic regression analysis adjusted for gender, age, education, neck pain, back pain, poor self--rated health demonstrated that primary headache (mixed headache) was associated low physical activity (OR=2.54, 95% CI=1.47-4.39, p=0.001)followed by medium physical activity (OR=1.62, 95% CI=1.05-2.52, p=0.03). Low physical activity was significantly associated with pure TTH (OR=2.80, 95%CI=1.38-5.68, p=0.004) and coexistent headache (OR=2.97, 95%CI=1.27-6.99, p=0.01) in the adjusted analysis. Association of pure migraine with low (OR=1.95, 95% CI=0.86-4.43, p=0.11) and medium physical activity, and coexistent headache and pure TTH with medium physical activity did not reach statistical significance. Low activity level is highest in chronic headache (OR=2.97, 95%CI=0.94-9.44, p=0.07) compared to episodic headache (OR=2.42, 95%CI=1.37-4.28, p=0.002).

Conclusions: Lower level of leisure-related physical activity is associated with primary headaches. Furthermore, the association is strongest for coexistent headache followed by pure TTH and pure migraine. The causal the causal relationship of low activity level to headache chronicity cannot be assessed in our study.

P200

Real-Time Epidemiology of Migraine Attacks on Social Media

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Objectives: We sought to estimate the real-time impact of actual self-reported migraine attacks in the World Wide Web using twitter by analyzing the meaning of each single tweet message with the word migraine posted during an entire seven-day week.

Background: Social media is still underused as a powerful platform in science to help collect global free-style information regarding new patterns of patient behavior in Migraine. Nonetheless, measurements based on instant searching tools available in the internet for social media lead inexorably to misleading interpretations, due to the

diversity of postings that are not all directly related to patients suffering with the disorder.

Methods: A continuous cross-sectional sample of 21.741 Tweets that included the search term "migraine" was collected during 7 consecutive days in an arbitrary month of the year 2011. The data collected included only public information and all identifiers were coded to avoid linking the subject to the information gathered. Using different data sets, from the main database, two investigators developed a coding system. After developing the coding system, a portion of the undergraduate and graduate students* at the University of Michigan, School of Dentistry helped to categorize the data in specific variables, which are consistent with the International Headache Society classification for migraine.

Results: The data was examined using descriptive statistical analyses of 14.028 Tweets, which represents actual self-reports of migraine attacks in real-time (64.50% of the database). In general, the prevalence of migraine attacks, when reported, was 73.47% in females, 17.40% in males, and 0.01% transgender (two subjects self-reported being transgender). The impact of migraine was substantial in mood, with a prevalence of 43.91%. As a pain descriptor, the word "worst" (14.6%) was most commonly used, followed by the word "horrible" (6.97%) from the McGill Pain Questionnaire. Subsequently, in the profanity category, the remark "F-word" was the most frequently used (5.3%).

Conclusions: Twitter's limited length capacity permits users to post their messages in real-time, which is a unique source for epidemiological studies. The results show a novel method of research to investigate the real-time epidemiology of migraine attacks, taking advantage of a free form of expression via a new trend of communication.

*Full list of student co-authors will be displayed on poster/oral presentation.

P201

So Many Migraines, So Few Specialists: Analysis of the Geographic Location of United Council for Neurologic Subspecialties (UCNS) Certified Headache Specialists Compared to USA Headache Demographics

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Objectives: To compare the number of UCNS certified headache specialists in the USA to the population of each state, the expected migraine population, and the expected chronic migraine population.

Background: Migraine affects 11.79% of the US population in its episodic form and 0.91% of the US population in its chronic form. There are a limited number of United Council of Neurologic Subspecialties (UCNS) certified physicians in the field of headache medicine. As of 2013, a physician must complete an accredited fellowship program in order to sit for the UCNS exam. There is a dissociation between the number of certified providers and health care recipients in this area.

Methods: This study located each UCNS certified headache specialist geographically and compared that data to demographic data about state populations obtained from the U.S. Census. The expected number of migraine sufferers and chronic migraine sufferers were calculated based upon recent epidemiologic data. State by state ratios of UCNS certified physicians to the appropriate disease population were then compared.

Results: As of the 2012 exam cycle, there are 416 UCNS headache specialists that are currently practicing in the USA. The states with the highest number of headache specialists include New York (56), California (29), Ohio (29), Texas (25), Florida (24), and Pennsylvania (23). 6 states have zero headache specialists, 8 states have only 1 headache specialist, 5 states have two headache specialists. The total US population for ages 12 and over is 259,908,563 across 50 states + District of Columbia. The total expected migraine population for ages 12 and over (11.79% of the general population) in the USA is 30,643,219.58. The total expected chronic migraine population for ages 12 and over (0.91% of the general population) in the USA is 2,365,167.923. The states with the best ratio of provider to migraine patients includes the District of Columbia (1:31,419), New Hampshire (1:33,482), New York (1:34,907), and Nebraska (1:35,740). Besides states with 0 headache specialists, the states with the worst ratios includes Oregon (1:384,232), Mississippi (1:290,761), Arkansas (1:287,856), and Kansas (1:278,755). The states with the best ratio of headache specialists to expected chronic migraine population for ages 12 and over include District of Columbia (1:2,425), New Hampshire (1:2,584), New York (1:2,694), and Nebraska (1:2,758). Besides states with 0 headache specialists, the states with the worst ratios of headache specialists to expected chronic migraine population includes Oregon (1:29,656), Mississippi (1:22,442), Arkansas (1:22,217), and Kansas (1:21,515).

Conclusions: There is a significant association between expected migraine and chronic migraine population and the number of headache specialists in each of the USA. More UCNS certified headache specialists and more UCNS accredited fellowship training programs are needed in order to ameliorate this disparity.

P202

Influence of Tohoku-Pacific Ocean Earthquake on Headache Cases in the Affected Area

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Objectives: The aim of this study was to examine how Tohoku-Pacific Ocean Earthquake influenced the headache (HA) medicine at our hospital.

Background: On March 11, 2011, Tohoku-Pacific Ocean Earthquake with a magnitude of 9.0 occurred in East Japan, affecting a part of our hospital located in Sendai causing serious damage. The tsunami struck 4 km away from our hospital. This disaster caused considerable damage to various lifelines including food and medical supplies. Some transportation networks were also paralyzed for several weeks. Although there were such limitations, our hospital continued to conduct medical examination of patients including outpatients.

Methods: We compared the situation of outpatient consultation for HA cases, severity of pain, impact on daily life, and types of HA, which included migraine, tension-type HA (TTH), cluster HA (CH), and medication-overuse HA (MOH).

Results: The number of outpatient HA cases before the disaster was 9.5 persons/day, and the occurrence rates of the HA types were 62.2% for migraine, 38.6% for TTH, 3.0% for CH, and 10.6% for MOH. The number of HA cases decreased remarkably after the disaster (1.6 persons/day) in March, after which it increased gradually (8.1 persons/day) in July. After the disaster, although the severity of pain did not change, the impact on daily life because of migraine became significantly worse ($p < 0.001$). The occurrence rate of migraine increased and that of TTH decreased significantly ($p < 0.001$). The occurrence rate of MOH increased slightly, and no change was seen in the occurrence rate of CH.

Conclusions: After the disaster, although the HA outpatient consultation rate fell evidently, the occurrence rate of severe migraine increased at our hospital. Although it was difficult to visit a hospital due to difficulties as a result of the disaster, an HA patient particularly with the high impact on daily life visited hospital to seek help.

P203

Resource Utilization & Cost of Care for Patients Treated with CAMBIA Compared to Other Acute Migraine Therapies

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Objectives: To assess and tally resource utilization and cost of care for migraineurs managed with CAMBIA compared to management with other acute migraine therapies.

Background: Migraine is a costly and prevalent disorder, particularly when patients are poorly controlled, present to the ER, receive unnecessary imaging or transform into chronic migraine. By using an extensive database that captures millions of insured lives over several years, one could ascertain if treatment with one agent is associated with lower costs or better patterns compared to another regimen.

Methods: Retrospective cohort study, utilizing Pharmetrics Plus Health Plan Claims Database from January 1, 2009 through June 30, 2012. Inclusion criteria were patients who (1) presented a prescription for CAMBIA, a triptan, or an ergotamine between July 1, 2009 and December 31, 2011, (2) had 12 months of continuous benefits eligibility for review, and (3) during the 6 months prior to the prescription claim, had at least 1 inpatient claim or 2 outpatient claims with a primary diagnosis code of migraine (ICD-9 code of 346.XX). With the date of the first prescription as the index date, patients were followed longitudinally from 6 months prior to index to 6 months post index to evaluate their healthcare resource use and costs.

3 cohorts were compared: patients with a diagnosis of migraine and an index prescription for (1) CAMBIA, (2) a triptan, or (3) an ergotamine.

Outcome measures included mean number (total & migraine-related) of outpatient visits, ER visits, and hospitalizations, as well as mean number of migraine-related

procedures, acute migraine medications, and opioid prescriptions.

Cost-related outcomes were adjusted to 2012 US dollars using the medical component of the Consumer Price Index.

Pre-index variables described the study sample at baseline, and were used in statistical models as covariates when comparing outcomes. They included demographics, comorbidity measures, number of prescription classes and drugs dispensed and filled, all-cause healthcare costs, and use of prophylactic migraine medication.

All outcomes were compared using the CAMBIA cohort as the reference. Pairwise comparisons with the CAMBIA cohort and each of the other cohorts were performed adjusting for differences in the pre-index period variables. The threshold for a significant P-value was adjusted for multiplicity.

Results: Significant differences were observed for the CAMBIA cohort vs. other defined cohorts in multiple outcome measures. Additional sub-analyses will be performed to further explore difference within subgroups. The results of the retrospective claims analysis provide insights into the different classes of therapy and their impact on health-related economic outcomes and treatment of migraine.

Conclusions: Migraine treatment with Cambia is associated with significant differences in healthcare utilization and cost.

P204

Reliability and Validity of the Migraine Disability Assessment (MIDAS) Questionnaire among Migraine and Tension Type Headache in Iranian Patients

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Objectives: Linguistic validation of Persian MIDAS, assessment of psychometric properties between tension type headache (TTH) and migraine and evaluation of MIDAS capability to discriminate between (TTH), chronic and episodic migraine were the aims of this study.

Background: MIDAS is valid and reliable short questionnaire for assessment of headache related disability over a 3-month period that consists of three domains; school/job dimension, housework dimension and social dimension.

Methods: This was a multicenter study and the cases were diagnosed with migraine or TTH by a neurologist. First visit data included MIDAS, SF-36 and symptoms questionnaire. Patients filled out MIDAS in second and third visit within three and eight weeks after base line visit. Internal consistency (Cronbach α) and test-retest reproducibility (Pearson correlation coefficient) were used to assess reliability. Convergent validity of MIDAS was analyzed through the assessment of correlation between MIDAS and SF-36 scores. We evaluated the MIDAS capability to differentiate between chronic, episodic migraine and TTH.

Results: Episodic and chronic migraine and TTH included 61.9%, 13.6% and 24.5% of all 274 patients respectively. Internal consistency among all patients, TTH and migraine in first visit was 0.8, 0.72 and 0.82 respectively. Test-retest reliability for all questions between visit 1 and 2 varied from 0.55 to 0.69. All questions were significantly correlated with the total MIDAS score and the related dimension (P 0.001). Total MIDAS score in the first visit was negatively correlated with SF-36 mental and physical scores (r=-0.34 and -0.21 respectively, P 0.001). We found no significant difference in MIDAS scores between TTH and episodic migraine; however they both had significantly different scores than chronic migraine.

Conclusions: Persian MIDAS is a valid and reliable questionnaire for migraine and TTH that can differentiate between TTH and chronic migraine and also between episodic and chronic migraine.

P205

Identification of Subpopulations of Migraine Patients with a Favorable Cost Profile for Eletriptan

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Objectives: To characterize patient populations by total healthcare costs after initiation of eletriptan versus sumatriptan tablets for migraine.

Background: Identification of patient populations by total healthcare costs after treatment initiation may optimize management of migraine.

Methods: Patients (18–64 years) with ≥1 prescription claim for eletriptan or sumatriptan (index date=first prescription fill date) between January and December 2009 inclusive, were identified from a large nationally (US) representative, quality controlled, retrospective claims database. Continuous enrollment during the 12-month pre-index and 12-month post-index periods was required. Patients from each cohort were matched 1:1 for gender, age, total pre-index healthcare (outpatient + inpatient + prescription) costs, region of US, and comorbidities. Classification and Regression Trees (CART) analysis was used to identify populations with pre- to post-index differences in total healthcare costs. CART is a nonparametric data mining technique that uses binary decisions to construct decision trees for differentiating between groups with homogeneous response variables.

Results: 13,425 sumatriptan and 17,399 eletriptan patients were identified; 11,508 patients from each cohort were matched. 78% and 62% of patients, respectively were continuing users. Mean age (SD) was 48 (10) years; 85% was female. Pre-index (post-index) total annual healthcare costs were $8920 ($10,468) for sumatriptan and $8921 ($10,783) for eletriptan. An example decision tree constructed by CART is shown below. This decision tree was based on gender and number of pre-index office visits. Lower total healthcare costs for eletriptan (-$1,960 and -$3,392) were observed for male/female patients with a high number (≥18) of pre-index office visits.

Conclusions: Overall, at 1 year after the index date, total healthcare costs were similar between the two groups. However, lower total costs among eletriptan-treated patients were observed in those with greater resource use.

P206

Referral System for Chronic Headache: Profile and Utilities of the List of Doctors with High Concern in the Chronic Headache

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Objectives: To investigate the profile and utilities of the list of doctors with high concern in the chronic headache.

Background: Headache consultation rates in Japan are very low, and 69.4% of Japanese patients with migraine have never consulted a physician for headache (Sakai 1997). A lack of recognition of the existence of headache specialists among headache patients and practitioners might contribute to the low consultation rates (Imai 2010). In addition, the headache specialists were insufficient in Shizuoka Prefecture. For these reasons, we have managed a local medical network, or referral system, for chronic headache patients in Shizuoka prefecture. To manage the headache referral system, we listed the doctor who had zeal in the diagnosis and treatment of chronic headache.

Methods: Doctors who had a lot of chances to treat headache were invited to join this headache referral system. Start-up meeting was held on 9th September, 2010, and all participants were confirmed to the will of joining the list of doctors with high concern in the chronic headache.

	Male		Female	
Cohort	# pre index office visits <18	# pre index office visits ≥18	# pre index office visits <18	# pre index office visits ≥18
Eletriptan ($) post - pre	2430	3033	1910	−630
N (%)	1645 (14)	69 (1)	9211 (80)	583 (5)
Sumatriptan ($) post - pre	2669	4993	1267	2762
N (%)	1660 (14)	54 (1)	9323 (81)	471 (4)
Difference ($)	−239	−1960	643	−3392

Results: Although there were only 9 headache specialists in Shizuoka prefecture, 69 doctors agreed to the registration of the list and were widely distributed inside Shizuoka prefecture. Each doctor's work places were 78% in the clinic, and were 22% in the hospital. Among the 69 doctors, 52% were neurosurgeons, 38% were neurologists, 4% were general physicians and anesthesiologist, and 1% was dental surgeon. The list gave full details of what chronic headaches each doctors could diagnose and treat, what examinations each institution could do, and what medical supplies each doctors could prescribe. Eight months after making the list, questionnaire was sent to all doctors to evaluate the list and received replies from 49 doctors. Although only 15 doctors used the list, 52 referral patients had visited and 128 patients were referred to other institution.

Conclusions: Many non-headache specialists who had zeal in the diagnosis and treatment of chronic headache could join this headache referral system by making the list. Fifteen doctors used the list, and 180 patients were referred by the list. The list of doctors with high concern in the chronic headache diagnosis and treatment may be useful to promote headache referral system.

P207

Naturopathic Medicines for the Prevention of Debilitating Diseases in the USA of America: Knowledge among the Inhabitants of Houston within Texas

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Objectives: The studies were to interact with neighborhood naturopathic physicians as well as residents and document their knowledge on medicinal plants, their usage, and the types of debilitating diseases treated etc. The formulations mostly contained single medicinal plant instead of multiple medicinal plants. The knowledge evolved for along time through trial and error. Scientific studies conducted on the medicinal plants may lead to discovery of more effective drugs than in use at present.

Background: Naturopathic medicines are in great demand in both developed and developing countries in primary health care because of their great efficacy and no side effects. Today according to the World Health Organization, as many as 80% of the world's natives depend on naturopathic medicines for their primary health care needs. Houston is the largest city in the state of Texas, and the fourth-largest city in the USA of America, and the naturopathic healing systems are still popular here.

Methods: The studies were conducted during January 2011 to December 2012 using semi-structured questionnaires, open-ended questionnaires, informal interviews, and group discussions with neighborhood naturopathic physicians as well as residents having thorough knowledge about medicinal plants. The data such as local name of medicinal plants, plant parts used, application etc. were collected. The voucher samples of the medicinal plants collected during the studies were properly identified with help of floras.

Results: The studies were includes information on 29 medicinal plants used for wide range of debilitating diseases. Of these 12 medicinal plants are used against arthritis, 09 medicinal plants are used against chronic obstructive pulmonary disease, 06 medicinal plants are used against muscular dystrophy, 05 medicinal plants are used against snake-bite, 03 medicinal plants are used against dermatitis, 03 medicinal plants is used against paediatrics, and one medicinal plant is used for centipede poisoning.

Conclusions: An assessment of the scientific literatures revealed that preliminary studies conducted on some of the above medicinal plants justify their use to treat specific ailments as practiced by the naturopathic physicians as well as residents. There is enough scope of the amalgamation of these medicinal plants in the main stream of prenatal medicines suggest today after the medicinal plants drug are subjected to the phytochemical and biological screening, together with clinical trials.

P208

Metabolomics of Migraine: ^{1}H-NMR Study of Cerebrospinal Fluid

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Objectives: The objective of this study was to pinpoint diagnostically relevant biochemical or pathophysiological markers in CSF of migraine patients with an exploratory ^{1}H-NMR-based metabolomics approach.

Background: The diagnosis and thus adequate preventive treatment options of migraine are severely hampered by an incomplete pathophysiological understanding of the disease and the lack of objective diagnostic markers. As a body fluid in the closest proximity to the central nervous system, cerebral spinal fluid (CSF) should reflect the physiology of the central nervous system and as such is valuable for assessing the functional status of the brain.

Methods: After obtaining informed consent, CSF was obtained, interictally, via lumbar puncture from patients with hemiplegic migraine, migraine with aura, migraine without aura, and from healthy controls. CSF was immediately centrifuged at 4 °C, divided in aliquots, and placed on dry ice within 30 minutes and stored at -80 °C within one hour. CSF samples were prepared for NMR analysis and metabolite concentrations were measured by quantitative ^{1}H-NMR spectroscopy with a Bruker 600 MHz AVANCE II spectrometer. Unsupervised and supervised multivariate analyses were used for finding the optimal set of predictors before constructing a non-linear classification model. Univariate analysis (using Generalized Linear Models) was conducted to ascertain the differential significance of individual features.

Results: CSF was obtained from 136 subjects, 126 samples passed spectral and profile quality checks and were used in the analysis. Included in the data analysis were 18 patients with hemiplegic migraine (F:10, M:8), 38 with migraine with aura (F:27, M11), 27 migraine without aura (F:15, M12), and 43 healthy controls (F:22, M:21). Due to a significant gender effect found with PCA (principal component analysis) analysis, supervised multivariate modeling was carried out for males and females separately. We have shown that hemiplegic migraine patients can be best discriminated from controls by a set of five features in the NMR spectrum. Female migraine with aura patients can be best discriminated from female controls by a set of six features. Univariate analysis (GLM) showed that there are four features in the NMR spectrum that are significantly different between the four groups (hemiplegic migraine, migraine with aura, migraine without aura, and healthy controls).

Conclusions: Using an exploratory ^{1}H-NMR metabolomics analysis we have identified a set of features that discriminate migraine patients from controls. Replication of our findings on a new CSF sample set and detailed structural elucidation of the characteristic features are our next priorities.

P209

Exploring the Mechanisms Involved in CGRP-Induced Light Aversion in Mice

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Objectives: To use genetic, behavioral, and physiological methods develop new tools that uncover mechanisms involved in CGRP-induced light aversion in mice.

Background: Calcitonin gene-related peptide is known to play a critical role in the pathophysiology of migraine. Previously, our work has demonstrated a role for CGRP in light-aversive behavior in mice as a correlate to migraine-type photophobia. We have demonstrated that CGRP can induce light aversion in WT and *nestin/hRAMP1* mice, which are sensitized to CGRP based on conditional expression of hRAMP1 in the nervous system. WT mice show aversion only with bright light and following habituation to the chamber, whereas *nestin/hRAMP1* show light aversion at low light levels upon naïve exposure to the chamber. This work has illustrated a critical role for CGRP and its receptor in eliciting light aversion.

Methods: To further explore sites of CGRP action in light aversion, we generated a *synapsin/hRAMP1* mouse, which conditionally expresses hRAMP1 in neurons only instead of neurons and glia as with *nestin/hRAMP1* mice. Also we developed an assay to measure the blink reflex in mice by implanting a telemeter to record electromyography (EMG) of the orbicularis oculi. Air puff was used to induce a blink. EMG responses were assessed under various light conditions as well as after CGRP administration.

Results: Interestingly, *synapsin/hRAMP1* mice did not demonstrate CGRP-induced light aversion at low light levels upon naïve exposure as observed with *nestin/hRAMP1* mice. hRAMP1 expression in the nervous system of synapsin/hRAMP1 mice was similar overall as seen with *nestin/hRAMP1* mice. Initial studies with our new EMG blink reflex assay indicate that we can successfully record blink responses in mice. Bright light alone led to an increase in EMG activity in a *nestin/hRAMP1* mouse. Furthermore, bright light and CGRP increased EMG blink response induced by air puff in a nestin/hRAMP1 mouse.

Conclusions: The lack of CGRP-induced light aversion in *synapsin/hRAMP1* mice suggests that neuronal expression of hRAMP1 is not sufficient to sensitize mice to CGRP and light. Furthermore, pilot studies with an EMG blink reflex assay indicate that we have developed a new non-behavioral tool to study the role of light and CGRP in trigeminal sensitization and photophobia in mice.

P210

Polymorphisms in CGRP Receptor Genes Associated with Migraine in a Spanish Population

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Objectives: We performed a candidate-gene association study to determine whether 144 Single Nucleotide Polymorphisms (SNPs) in 39 candidate genes are related to migraine in a Spanish population.

Methods: 876 migraineurs and 801 healthy volunteers were recruited in a Headache Unit. Only unrelated Mediterranean Caucasian individuals were included. Polymorphisms were selected from the literature: genes involved in migraine pathophysiology and involved in pain pathways not previously described in migraine. TagSNPs were selected from Hapmap data using tagger pairwise selection with r2>0.8 in the CEU population. SNPs were genotyped with Veracode GoldenGate technology (Illumina). Statistical analysis for genetic association was performed using PLINK v1.07 and SNPTEST v2.2.0. Gene expression was assessed by qRT-PCR through a Taqman assay. Statistics of mRNA expression was performed using non-parametric tests with SPSS V15.0.

Results: 876 cases and 801 controls were successfully genotyped for 128 SNPs. Statistical analysis of genotype frequencies revealed nominal association for 9 SNPs in 5 candidate genes ($p<0.05$). Two of them, *CALCRL* and *RAMP1*, encode subunits of the CGRP receptor. Four SNPs in *CALCRL* and 2 SNPs in RAMP1 were associated with migraine. SNPs in CALCRL were found in allelic association with migraine ($p<0.05$): rs12621307 A allele OR=1.22 (1.07-1.4), rs6719550C OR=1.21 (1.05-1.39), rs17464221 T OR=1.24 (1.08-1.44) and rs2063505G OR=0.81 (0.70-0.94). SNPs in RAMP1 were associated in a genotypic recessive model: rs6741923CC OR=1.63 (1.16-2.29) and rs7578855CC OR=1.38 (1.01-1.74). Rs17862920 in *TRPM8*, previously reported to be associated with migraine in a GWAS study, was replicated. A SNP in *SPTAN1* (rs13299607) and another one in *EDNRB* (rs2329047) were also associated with the phenotype in our cohort. Analysis of qRT-PCR data from blood cells showed a correlation between the rs17464221 TT genotype and reduced *CALCRL* subunit expression and rs13299607 TT genotype and also with reduced *SPTAN1* mRNA levels. We did not observe any correlation between any genotype and expression of *RAMP1*. *EDNRB* and *TRPM8* expression was below the detection level of the assay.

Conclusions: We have found association between CGRP receptor gene polymorphisms and migraine. Furthermore, there is a correlation between the TT genotype in rs17464221 and a reduction in the expression of *CALCRL*. We have replicated an association for SNPs in *TRPM8*, *SPTAN1* and *EDNRB* genes. There is also correlation between a *SPTAN1* genotype and reduction of expression.

P211

A Single Nucleotide Polymorphism within the Glutathione S-Transferase Gene Is Significantly Associated with Migraine among Males Only

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Objectives: To investigate genetic factors involved in migraine.

Background: Migraine is a complex trait in which multiple genetic loci as well as environmental factors are likely to contribute to its clinical manifestation. Many of the reported genetic associations found in previous studies thus far have either not been replicated or have had only marginal statistical significance, likely due to the genetic heterogeneity of the common forms of migraine.

Methods: We have selected 50 genetic polymorphisms that have been implicated in previous studies to confer migraine susceptibility. From our DNA repository of individuals with migraine (the *Mayo Migraine Genomic Library* which includes age and gender matched controls), we have selected 1740 individuals ages 18-50, 1132 cases (240

males, 892 females) and 608 controls (258 males, 350 females).

Results: We have performed logistic regression analyses, and interestingly have found that a single nucleotide polymorphism within the Glutathione S-Transferase gene (rs1695) is significantly associated with migraine among males only (p=0.0019; OR=1.56), but not among female migraineurs (p=0.51; OR=1.06).

Conclusions: These findings could greatly impact the clinical management of migraine by suggesting possible underlying mechanisms of migraine susceptibility leading to development of rational, biologically based therapies.

P212

Genotyping the Risk of Migraine Chronification: The CHROMIG Study

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Objectives: We performed a candidate-gene association study to explore the genetic background of chronic migraine (CM).

Methods: We genotyped 128 SNPs in 39 candidate genes selected from the literature. TagSNPs were selected from CEU Hapmap data using a tagger pairwise tool with r2>0.8. CM patients were recruited in Barcelona (181 CM-801 controls) and Leiden (81 CM-2078 controls). The SNPs found associated were further tested in a group of high-frequency migraineurs (Barcelona: 116 HFM-801 controls; Leiden: 110 HFM-2078 controls) in order to identify SNPs with stronger association to chronification. These SNPs were replicated in a new sample (Barcelona: 70 CM-394 controls; Leiden: 210 CM-896 controls; Norway: 162 CM-495 controls) genotyped using a Taqman assay, and GWAS data from a Norwegian CM cohort (89 CM-706 controls). Statistical analyses were performed with PLINK v1.07 and SNPTEST v2.2.0. Meta-analysis was performed with GWAMA v2.1.

Results: Analysis of 128 SNPs in 262 CM patients and 2,879 controls revealed 30 nominally associated SNPs (25 SNPs in 12 genes and 5 intergenic polymorphisms) ($p<0.05$). These SNPs were then tested in a HFM study sample (226 cases and 2,879 controls) where only 8 SNPs remained associated. We hypothesized that these SNPs confer risk to migraine chronification and were further replicated in a cohort of CM and HFM (442 cases and 1,785 controls). Although there were some cohort-dependent weak associations, the meta-analysis of replication data performed in 531 cases and 2,491 controls did not confirm significant association between these genes and CM.

Conclusions: This is the first study that has tried to find a genetic predisposition to develop CM. Lack of replication might be explained by the difficulties of finding comparable cohorts, the the size of the cohorts and the use of the current IHS CM criteria. Chronic migraine deserves further examination in more comprehensive and better-powered studies.

P213

The Diagnostic Value of Visual and Auditory Evoked Potentials in Migraine: A Retrospective Multicenter Study

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Objectives: To pool the VEP and IDAP results in episodic migraineurs (EM) and healthy voluteers (HV) from several centers, and to determine their usefulness for the diagnosis of migraine.

Background: The diagnosis of migraine is made by history and based on ICHD criteria. There are at present no reliable diagnostic tests. Some patients may, however, provide information that is not reliable or incomplete because of recall bias or a tendency to exaggerate or, on the contrary, to minimize their symptoms. Many studies have found that migraine patients are characterized between attacks by a habituation deficit of visual evoked potentials (VEP) and/or increased intensity dependence of auditory evoked potentials (IDAP).

Methods: We analyzed electrophysiological recordings from 360 HV and 624 EM, part of them blindly. Recordings in EM were performed at least 3 days after or before an attack: VEP composed of 5 sequential blocks of 50 responses in 77 HV and 231 EM, VEP with 6 blocks of 100 responses in 240 HV and 280 EM, IDAP in 86 HV and 328 EM. Some subjects were tested both for VEP and IDAP. We used Bonferroni-corrected Mann-Withney tests to compare results between HV and EM. Thresholds were calculated by Receiver Operating Curve (ROC) analysis based on a 15% prevalence value for migraine, and used to calculate sensitivity, specificity, predictive values and efficacy of each test.

Results: Mean percentage habituation of VEP-5x50 were –6.2±22.3 in HV and + 8.0±28.0 in EM (p=<0.0001), and VEP-6x100 –10.5±17.9 in HV and 7.1±25. 9 in EM (p=<0.0001). Mean IDAP amplitude stimulus function slopes were 0.45±1.0 in HV and 1.2±1.1 in EM (p=<0.0001).

For VEP-5x50 sensitivity was 61.0 %, specificity 77.9 %, positive predictive value (VP+) 89.2 %, negative predictive value (VP-) 40.0 % and efficacy 65.3 %. For VEP-6x100 sensitivity was 61.4 %, specificity 77.9 %, VP+ 76.4 %, VP- 63.4 % and efficacy 69.0 %. For IDAP sensitivity was 45.7 %, specificity 87.2 %, VP+ 93.2 %, VP- 29.6 %, efficacy 54.3 %. In subjects who underwent both VEP and IDAP recordings, abnormality of at least one of them had a sensitivity of 83.4 %, a specificity of 66.7 %, a VP+ of 94.1 %, a VP- of 38.6 % and an efficacy of 81.1 %.

Conclusions: Taken alone, none of VEP or IDAP has sufficient diagnostic efficacy to distinguish EM from HV. However, when both tests are combined in the same patient, abnormality of at least one of them is highly predictive of migraine, suggesting that VEP and IDAP may be useful for the diagnosis of migraine.

P214

Withdrawn by the author.

P215

Methylation of Migraine-Related Genes in Different Tissues

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Objectives: The aim of our study was to investigate the methylation of different genes in different tissues both relevant to the pathophysiology of migraine and to examine the role of 17β-estradiol in the methylation. In addition, we investigated methylation in blood and aorta as a peripheral control.

Background: Migraine is – at least partly – genetic in nature. However, genes have only clearly been identified for familial hemiplegic migraine. GWAS studies have identified genes that may be relevant for the more common forms of migraine, but an additional influence of environmental factors is likely. Interestingly, the prophylactic effectivity of valproate, a DNA methylation inhibitor, may point to the involvement of epigenetic mechanisms in migraine. Migraine is much more common in women of the fertile age than in men, pointing towards a role for 17β-estradiol, which is known to be involved in epigenetic mechanisms. Also, CGRP can be regulated via epigenetic mechanisms. Methylation is often examined in blood, which can easily be obtained, but it is not sure whether these results can be compared to other tissues.

Methods: Female SD rats (n=11-12 per group) were ovariectomized or sham-operated and treated with 17β-estradiol or placebo. DNA was isolated from blood, aorta, dura mater, trigeminal caudal nucleus and trigeminal ganglion. DNA methylation of 10 migraine-related genes (MTHFR, eNOS, ESR1, GPER, CGRP, USF1, USF2, RAMP1, CRCP and CRLR) was assessed through bisulphite treatment and sequenom mass spectrometry.

Results: In none of the genes, we observed a significant effect of estradiol treatment. Tissue-specific methylation was seen in the CRCP, CRLR, ESR1 and NOS3 genes. The methylation in blood was not correlated to that in the rest of the tissues. Interestingly, the variation in methylation in some genes in some of the tissues was very high (e.g., mean: 41%, 5%-95% percentile: 18 to 67% methylation for the CRCP gene in caudal nucleus), while in other genes or tissues this variation was very small (e.g., mean 4%, 5%-95% percentile: 2 to 6% methylation for the ESR1

gene in blood). These different variations were specific for the combination of gene and tissue.

Conclusions: From our results we conclude that (i) DNA methylation is tissue specific and that methylation of DNA from blood cannot automatically be extrapolated to methylation of DNA from other tissues; (ii) certain genes in some tissues are prone to epigenetic regulation, while in other genes or tissues the methylation is conserved, being less influenced by environmental factors; and (iii) the variation in methylation that is present in some genes is likely to have reduced the power of our study when studying effects of estradiol treatment. Thus, we cannot categorically exclude that the methylation of the genes that we have studied may be influenced by estradiol.

P216

Genetic Susceptibility in High-Frequent Migraineurs – A Report from LUMINA

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Objectives: To investigate whether high-frequent migraineurs have a higher genetic susceptibility to migraine, reflected in a higher familial occurrence of migraine.

Background: Migraine is a heterogeneous disorder, in which many genetic variants contribute to its susceptibility.

Methods: We included migraineurs from the LUMINA (Leiden University Migraine Neuro-Analysis programme) cohort, recruited via a validated self-reporting, web-based questionnaire. All migraineurs who had either low attack frequency ($\leq$5 severe headache days/month) or very high attack frequency ($\geq$15 severe headache days/month) were selected. We calculated the population relative risk (PRR) in both groups, using the reported proportion of first-degree relatives with migraine and lifetime prevalence of migraine in the general population (33% for women, 13.3% for men). Children were excluded from the first-degree relatives, because unaffected children may still develop migraine. We used linear and logistic regression models to calculate associations between migraine frequency and the proportion of affected family members. Migraine subtype, gender and age were included as covariates.

Results: The PRR for female relatives was 1.29 (95% CI 1.17-1.41) in low-frequent migraineurs (n=1693), and 1.37 (95% CI 1.19-1.55) in high-frequent migraineurs (n=195). For male relatives, the PRR was 1.45 (95% CI 1.33-1.57) in low-frequent migraineurs (n=1693) and 1.63 (95% CI 1.26-2.01) in high-frequent migraineurs (n=194). These differences between PRRs in low- and high-frequent groups were not statistically significant. Migraine with aura ($p<0.001$), but not attack frequency, was associated with higher familial occurrence of migraine.

Conclusions: In LUMINA, genetic susceptibility to migraine was not higher in high-frequent migraineurs. Having migraine with aura was associated with higher familial occurrence of migraine.

P217

Genetic Polymorphisms of the Interleikin-6 Receptor (IL-6R) in the Patients with Chronic Headache

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Objectives: The aim of this study was to investigate theinterleikin-6 receptor (IL-6R) gene polymorphism in chronic headache. We analyzed a polymorphism Asp-358-Ala in exon 9, which carries have the change of soluble IL-6R corresponding to the proteolytic cleavage site of IL-6R, strongly influences the soluble IL-6R level.

Background: There are some hypotheses that an immunologic dysfunction has been involved in migraine pathogenesis. It is not yet clearly understood what immunological mechanism leads to migraine headaches. We preliminary demonstrated that the serum interleikin-6 levels in the patients of migraine with aura were higher than normal controls.

Methods: Genotyping for IL-6R Asp-358-Ala polymorphism was performed in 65 patients with migraine with aura (MA; 21 males and 44 females, average age: 32.6 years), 138 patients with migraine without aura (MO; 27 males and 111 females, average age: 36.8 years) and 77 patients with tension type headache (TH; 18 males and 59 females, average age: 49.8 years) on leukocyte genomic DNA samples by polymerase chain reaction – restriction fragment-length polymorphism (PCR-RFLP) analysis. One hundred eighty three normal healthy volunteers composed the control group (CTL; 55 males and 128 females, average age 58.1 years). The differences in the frequency of IL-6R alleles and genotypes between groups were evaluated by

the gene-counting method and comparison of groups by the chi-square test. The level of significance was set at $p<0.05$.

Results: The distribution of IL-6R genotypes in patients and CTL did not deviate significantly from Hardy-Weinberg equibrium. The 358-Ala allelic frequency of MA patients was significantly higher than that of CTL. There was the genotypic difference between MA patients and CTL.

Conclusions: Our results indicate that IL-6R Asp-358-Ala polymorphism is a genetic risk factor for patients with MA.

P218

α-Fodrin Is One of the Candidate Molecules for Migraine Diagnostic Biomarker

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Objectives: The diagnosis of migraine can sometimes be difficult because some patients do not fulfill the International Headache Society's criteria for migraine. Hence, an accurate and reliable diagnostic marker for migraine is required. In this study, we investigated the diagnostic utility of α-fodrin in migraine.

Background: We previously verified that the expression of α-fodrin, which was 1 of the 15 genes that were differentially expressed in lymphoblasts originating from patients with migraine with aura patients (MA) using cRNA microarray analysis, increased after cortical spreading depression in an animal model.

Methods: All patients were carefully interviewed and examined, and diagnosis was made using the ICHD-II. The patient serums were prepared from peripheral blood samples obtained from 8 MA, 11 migraine without aura (MO), 6 tension type headache patients (TTH), and 4 healthy controls (C). The serum samples were collected under the condition that migraineurs and TTH patients had been free of attack for the preceding one week. We performed Western blot analysis using anti-α-fodrin, anti-matrix metalloproteinase (MMP) 9, and anti-calpain antibodies for the serum samples.

Results: In MA, both of 240kDa (full length) and 150kDa (the fragment after catalysis) protein expressions of α-fodrin were significantly higher than those of C. However, there was no significant difference on the ratio of 150kDa to 240kDa proteins of α-fodrin between both groups. In MO, the expression levels of both 240kDa and 150kDa proteins of α-fodrin tended to be higher compared with C. As for TTH, the expression levels of α-fodrin didn't differ from C. Meanwhile, the protein expression levels of cytoskeletal proteinases, MMP9 and calpain, in MA and MO, tended to increase compared to C.

Conclusions: α-fodrin might play an important role in the pathophysiology of migraine, and the molecule can serve as a migraine biomarker superior to MMP9 and calpain.

P219

The Role of Nociceptin in Medication Overuse Headache – A Pilot Study

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Objectives: We aimed to test whether patients with MOH have decreased levels of nociceptin before withdrawal therapy compared with healthy volunteers, and further, to test if the nociceptin level would increase and normalize after withdrawal in parallel with the decrease in headache frequency and normalization of pain perception seen after withdrawal.

Background: Medication overuse headache (MOH) is a chronic, secondary headache caused by an excessive intake of symptomatic medications for an underlying headache, most often tension-type headache (TTH) or migraine. The mechanisms behind MOH are unknown and diagnostic as well as progrognostic biomarkers are searched. Nociceptin is found in the human trigeminal ganglion colocalised with calcitonin-gene related peptide (CGRP), substance P, nitric oxide synthase and Pituitary Adenylate Cyclase-Activiating Polypeptide (PACAP). These are all substances involved in migraines. PACAP and CGRP are capable of initiating delayed migraine-like attacks in human and nitric oxide can induce both migraine and TTH. Previously, decreased levels of nociceptin have been found in patients with migraine between attacks and the nociceptin concentration was even more decreased during attacks.

Methods: We drew blood samples on 18 MOH patients before withdrawal and 6 months after withdrawal start and, to reduce the influence of an eventual seasonal bias, also twice with a 6-month interval on 30 healthy volunteers of matching sex and age. The subjects were all part

of a study to test pain sensitivity in MOH before and after withdrawal therapy for MOH.

The blood plasma was collected and kept at -80°C until analysed. The plasma was acidified and freeze dried and then analysed for nociceptin in a radioimmunoassay. The analyses were done blinded to subject group.

Results: The nociception concentration was 10.13 pg/ml in MOH patient before withdrawal and 9.74 pg/ml in healthy volunteers (p=0.81). After withdrawal, the nociceptin level rose to 10.25 in MOH patients (p=0,67).

Surprisingly, the nociceptin level tended to be lower in MOH patients who had more than 50% reduction in headache frequency compared with the patients with less headache frequency reduction, both before (8.4 vs 10.3 pg/ml, p=0.38) and after withdrawal (7.7 vs. 10.9 pg/ml, p=0.06).

Conclusions: The similar levels of nociceptin between healthy volunteers and MOH patients and in MOH patients before and after withdrawal suggests that nociceptin is an unspecific biomarker for headache and that MOH may differ in response from migraine. The interesting tendency to a lower nociceptin level in responders before withdrawal in this pilot study suggests that biomarkers predicting the outcome of MOH must be searched.

P220

Genetic Association between Matrix Metalloproteinase MMP9 Polymorphism and Japanese Patients with Migraine

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Objectives: The pathophysiology of migraine is not yet fully understood but may involve painful vasodilatation of cerebral blood vessels. To investigate the role of the matrix metalloproteinase MMP9 genotyping in migraine, we analyzed a polymorphism -1562 C>T in the promoter region of the MMP9 gene.

Background: The MMP9 -1562 C>T polymorphism was previously reported to be associated with severity of the atherosclerosis.

Methods: This study consisted of 57 patients suffering from migraine with aura (MA), 135 from migraine without aura (MO), and 168 non-headache healthy controls. Genotyping for MMP9 -1562 C>T polymorphism was performed on leukocyte genomic DNA samples by polymerase chain reaction – restriction fragment-length polymorphism (PCR-RFLP) analysis. The PCR fragments were electrophoresed in 3% agarose gels and stained with ethidium bromide. The differences in the frequency of MMP9 alleles and genotypes between groups were evaluated by the gene-counting method and comparison of groups by the chi-square test. The level of significance was set at $p<0.05$.

Results: The distribution of MMP9 genotypes in patients and controls did not deviate significantly from Hardy-Weinberg equibrium. We found no difference in the allelic and genotypic distribution between migraine patients and controls.

Conclusions: Our results support the conclusion that MMP9 -1562 C>T polymorphism is not a genetic risk factor for Japanese migraineurs.

P221

Psychophysical Properties of Throbbing Pain in a Human Experimental Model of Pain

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Objectives: We tested the hypothesis that the psychophysical properties of throbbing pain could be modeled experimentally in healthy human subjects.

Background: Pain can have a throbbing pulsatile quality, especially when it is severe and disabling. A throbbing pain quality is associated with a wide range of acute and chronic pain conditions, is an important diagnostic factor in common clinical conditions such as migraine, and is the target of presumptive therapy and clinical management. However, despite its enormous clinical significance there is scarcely any empirical data to support our fundamental understanding of it. An experimental model of this clinically relevant pain quality, in healthy human subjects, would likely be of great utility in understanding the processing of pain experiences in human health and disease.

Methods: We elicited throbbing pain experiences using the cold pressor (immersion of the hand in cold water), an experimental model of pain with established relevance to clinical pain, in an otherwise unselected population of

healthy adult subjects. Subjects continuously recorded their subjective pain experiences into a digital recording system, while we simultaneously monitored their physiological responses. The measured psychophysical properties of throbbing pain included rate of throbbing, latency to onset, and duration of throbbing. Subjects also described pain qualities more generally using the Short Form McGill Pain Questionnaire. We also developed and applied normative standards, using a haptic stimulus control task.

Results: A throbbing pulsating sensation was recorded by 36 (38%) of the 94 study subjects. The psychophysical characteristics of their throbbing experiences corresponded closely to those found in other clinical settings, such as chronic migraine and acute dental pain. Accordingly, the rate and rhythm of the recorded throbbing experiences did not correspond to that of the subjects' arterial pulsations. Pain qualities elicited by the cold pressor were otherwise similar between those with and without throbbing sensations, with the exception of the quality of shooting pain.

Conclusions: The present findings support the cold pressor as an effective stimulus for eliciting the throbbing quality of pain. This experimental model of throbbing pain will provide an experimental platform from which build a better understanding of this clinically significant pain quality, and to determine a brain signature, or biomarker, of throbbing pain.

P222

Migraine and Endothelial Dysfunction: An Investigation of Urine Albumin Leakage in Migraineurs, the HUNT Study, Norway

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Background: The pathology of migraine constitutes both environmental and genetic factors and the disorder has been associated with an increased risk of cardiovascular events. Vascular endothelium regulates numerous vascular functions and abruption of endothelial cell function is often observed in cardiovascular disease. Interestingly, some studies have also found endothelial dysfunction in migraine patients. The excretion of small amounts of albumin in urine is believed to represent endothelial dysfunction and we therefore investigated the urine albumin to creatinine ratio (ACR) as an indicator of endothelial dysfunction in 304 subjects with migraine.

Methods: The association between migraine and ACR was investigated in the second Nord-Trøndelag Health Study (HUNT-2). ACR was measured in 304 subjects with migraine, 1025 subjects with non-migraine headache and 5428 headache free subjects. The study was originally designed for investigating ACR in cardiovascular disease and cases were therefore initially selected based on either 1) self-reported hypertension/diabetes (morbid sample) or 2) a random sample. Analyses were performed using analysis of covariance.

Results: There was no association between headache status and ACR in either the morbid sample (p=0.57, mean ACR: migraine: 3.31, non-migraine headache: 4.22 and no headache: 3.70.) or the random sample (p=0.90, mean ACR: migraine: 1.71, non-migraine headache: 1.51 and no headache: 1.76.) when adjusted for age, sex, self-reported diabetes and hypertensive medication. Similarly, we did not observe any differences in ACR score between individuals with migraine, non-migraine headache or no headache when morbid and random groups were combined (p=0.57, mean ACR: migraine: 3.08, non-migraine headache: 3.43 and no headache: 3.14.). Furthermore, in the combined sample, no significant differences in ACR scores were found among the headache sub-types migraine with aura (MA), migraine without aura (MO), headache and no headache (mean ACR: MA: 2.70, MO: 3.17, non-migraine headache: 3.43 and no headache: 3.14.).

Conclusions: Urine albumin leakage was not more frequently occurring in migraineurs than in other headache- or headache free subjects. This study did, therefore, not support the hypothesis of endothelial dysfunction in migraine.

P223

Evaluating the Utility of Salivary Biomarkers as a Clinical Tool in Diagnosing Patients with Temporomandibular Disorder-Related Pain

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Objectives: The purpose of this study was to evaluate the use of the salivary neuropeptides substance P (SP) and serotonin (5-HT) as a clinical tool to assess chronic pain in individuals with unresolved TMD.

Background: Chronic temporomandibular disorder (TMD), head, neck, jaw, and orofacial pain is estimated to affect at least 12% of the U.S. population.As the exact symptoms of pain in various TMD conditions may not be easily distinguishable, the diagnostic accuracy of current testing methods is contingent upon subjective measures. This renders differential diagnoses particularly complicated and challenging to assess. Saliva analysis may offer an alternate insight into the patho-physiology of TMD conditions.

Methods: Ten symptomatic patients from The Craniofacial Pain Center at TUSDM and 11 asymptomatic controls from the local community volunteered for this study. Unstimulated saliva was collected from Wharton's duct during the fasting state between 8:30-10:30 AM. At the time of sampling, subjects' ratings of pain intensity according to the 11-point Numerical Graphic Rating Scale (0-10) were obtained. Samples were analyzed using enzyme-linked immunosorbent assay (ELISA) to quantitatively determine the levels of SP and 5-HT. Student's *t*-test, Mann-Whitney U test, Spearman's rank-order correlation, and Pearson's correlation were used for statistical analyses.

Results: The amount of SP and 5-HT were elevated in saliva samples from patients when compared to that in control. However, the mean levels for either SP (37.48 pg/ml in patients, 27.06 in controls) or for 5-HT (26.16 ng/ml in patients, 19.20 in controls) were not statistically significantly different. When the overall pain score values were compared to SP or 5-HT, there was no observed correlation (rho=0.120, p=0.605; rho=0.285, p=0.211, respectively). We also did not observe a correlation between the two neuropeptides (r=-0.026, p=0.910).

Conclusions: Although salivary SP and 5-HT were increased in patients versus controls, the difference was not statistically significant. Studies using a larger sample size are warranted to further determine if these neuropeptides can be used for TMD-related pain disorders diagnosis.

P224

The Importance of Lactic Acid in Migraines and Fibromyalgia

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Objectives: To determine the relationship between migraine and fibromyalgia and levels of lactic acid in the blood.

Background: Lactic acid is a byproduct of both muscle metabolism and the central nervous system. Changes in metabolism are related to various physiological and pathological conditions.

Methods: The study of 113 patients was divided into six groups: 1) healthy subjects (n = 20); 2) patients with fibromyalgia (n = 20); 3) episodic migraine (n = 20); 4) chronic migraine (n = 20); 5) episodic migraine and fibromyalgia (n = 13); and 6) fibromyalgia and chronic migraine (n = 20). Blood levels of lactic acid were measured at four different time points: at rest, during aerobic exercise, during anaerobic physical activity and while resting after anaerobic exercise.

Results: Lactic acid increased in all groups during anaerobic physical activity without predominance for either group. During aerobic physical activity, all groups increased lactic acid levels, but the increase was more expressive in the chronic migraine group (p = 0.048) and the chronic migraine with fibromyalgia group (p = 0.042).

Conclusions: Patients with chronic migraine, with or without fibromyalgia, may have a disorder involving the metabolism of lactic acid during aerobic exercise.

P225

Emergency Consultation for Acute Headache in the Antepartum and Postpartum Periods

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Objectives: To contrast acute headache in antepartum and postpartum patients to further characterize the clinical trends, risk factors, and headache diagnoses in these populations.

Background: Antepartum and postpartum women are at high risk for acute presentations of primary and secondary headache disorders because of hormonal, physiological, and procedural factors. The clinical suspicion for various headache disorders may differ between pregnant and postpartum patients, and rates of headache diagnoses in these populations are not commonly reported.

Methods: Consecutive inpatient neurology consultations for acute severe headache in pregnant and postpartum women at an urban, tertiary hospital setting were captured in an interim analysis from 7/1/09 through 1/31/12 in a retrospective chart review.

Results: We identified 68 antepartum and 21 postpartum patients (mean age 29.2 +/- 6.4 years and 31.1 +/- 6.9 years). A secondary headache diagnosis was more common in both antepartum (57.4%) and postpartum (61.9%) patients, although migraine was still the most common overall diagnosis. In pregnant patients migraine was the cause in 42.6%, followed by preeclampsia/eclampsia in 25.0%. Similarly in postpartum patients, migraine was found in 38.1% and preeclampsia/eclampsia in 33.3%, but post-dural puncture headache was also prevalent (23.8%). Most patients (73.5%) who presented with headache during pregnancy had a previous history of headache, in contrast to postpartum patients (38.1%). Imaging was performed in 80.9% of pregnant and 85.7% of postpartum patients. The only significant findings noted in postpartum patients were Chiari type I malformation (n=1), pituitary macroadenoma (n=1) and subarachnoid hemorrhage secondary to reversible cerebral vasoconstriction syndrome (n=1), of which subarachnoid hemorrhage was the only new diagnosis.

Conclusions: Antepartum and postpartum patients similarly feature migraine and preeclampsia as the most common etiologies for acute headache. Postpartum headache patients frequently have post-dural puncture headache. Compared to pregnant patients with acute headache, postpartum patients differ remarkably by their lack of previous headache history, which implies anesthesia, labor and delivery are risk factors for subsequent new onset acute headache.

P226

Changes in the Threshold for Potassium Induced Cortical Spreading Depression Occurrence during the Natural Estrous Cycle in Mice

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Objectives: We explored the change in the threshold for cortical spreading depression (CSD) occurrence in response to potassium stimulation during the natural estrous cycle in C57BL/6J mice.

Background: CSD is known to be implicated in a variety of disease conditions, including migraine aura. Although several studies reported hormonal effects, few studies have examined the alterations in neuronal excitability with respect to CSD induction in naturally estrous cycling female animals.

Methods: The natural estrous cycle of mice was divided into 4 phases, which are proestrus, estrus, metestrus and diestrus. We compared minimum potassium concentrations necessary to evoke CSD in each phase of the natural estrous cycle. Initially, 0.025 M potassium was applied to the cranial window, and potassium concentration was gradually increased by 0.025 M until CSD was induced. We also measured the serum concentrations of estradiol and progesterone in the four stages of the estrous cycle by liquid chromatography.

Results: The minimum potassium concentrations to evoke CSD were 0.20 $\pm$ 0.05 M in proestrus($n = 7$), 0.26 $\pm$ 0.05 M in estrus ($n = 7$), 0.24 $\pm$ 0.09 M in metestrus ($n = 9$) and 0.11 $\pm$ 0.05 M in diestrus ($n = 7$). In diestrus, the minimum potassium concentration required to evoke CSD was lower compared to the other three phases, such that significant differences were observed against estrus and metestrus ($P < 0.05$). The serum concentration of estradiol was 4.82 $\pm$ 4.88 pg/mL in the proestrus stage ($n = 5$), 1.55 $\pm$ 1.96 pg/mL in the estrus stage ($n = 5$), 1.47 $\pm$ 0.80 pg/mL in the metestrus stage ($n = 5$) and 2.26 $\pm$ 2.63 pg/mL in the diestrus stage ($n = 5$). The serum concentration of progesterone was 0.73 $\pm$ 0.91 ng/mL in the proestrus stage, 1.78 $\pm$ 1.54 ng/mL in the estrus stage, 0.95 $\pm$ 0.67 ng/mL in the metestrus stage and 0.49 $\pm$ 0.48 ng/mL in the diestrus stage.

Conclusions: Our results demonstrated that neuronal excitability relevant to CSD induction differs among the natural estrous phases in mice. Although we found that the susceptibility of CSD was increased in the diestrous stage, the serum estrogen concentration did not reach the maximal level. We therefore infer that endogenous estrogen does not seem to be a principal determinant of the threshold for evoking CSD in wild-type mice. The serum concentration of progesterone was most reduced in the diesterus stage, at which time we observed the lowest threshold for evoking CSD, and it reached its peak value in the estrus stage, which showed the highest threshold for evoking CSD. These data raises for the possibility that decreased progesterone may lower the threshold for evoking CSD during the diesterus stage. These findings provide important insights regarding the susceptibility to the development of CSD in the estrous cycle in female mice.

P227

Patients with Menstrually-Related Migraine Lack the Trigeminovascular Menstrual Cyclicity of Healthy Women

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Objectives: We investigated the effect of the menstrual cycle on trigeminally-induced vasodilation in women.

Background: Transient receptor potential vanilloid type 1 (TRPV1) receptors on sensory nerve endings of the trigeminal track are important in mediating migraine attacks by releasing the vasodilator calcitonin gene-related peptide (CGRP). Variations in female sex hormone levels during the menstrual cycle may influence the sensitivity of the TRPV1 receptor, the amount of CGRP in perivascular nerve terminals and hence CGRP release, and/or the response of the postsynaptic CGRP receptors.

Methods: Capsaicin, the active ingredient of hot chili peppers, stimulates the TRPV1 receptor and causes CGRP-dependent vasodilation. We set up a novel model to study trigeminally-induced vasodilation in humans. Using a laser-Doppler imager we compared the vasodilator effects of capsaicin application and electrical stimulation on the forehead skin, a trigeminal nerve-innervated dermatome. Women with menstrually-related migraine (MRM, n=22, age 21 to 45) and healthy women (n=20, age 19 to 45), not using hormonal contraceptives, were studied on day 19-21 of their cycle and on day 1-2 of their menstruation. 0.06 mg/ml and 6.0 mg/ml capsaicin solutions were applied to the forehead skin. Electrical stimulation of the skin was used as a TRPV1-independent stimulus. Blood samples were collected to measure serum female sex hormone levels.

Results: Healthy women showed a higher dermal blood flow (DBF) response to capsaicin during day 1-2 of their menstruation (E_{max} 203±28 a.u. and 497±25 a.u. for 0.06 and 6.0 mg/ml) than during day 19-21 of their cycle (E_{max} respectively 156±27 a.u. and 456±24 a.u., $P<0.05$). In contrast, MRM women showed no difference in DBF responses during their cycle (day 1-2; E_{max} respectively 148±20 a.u. and 470±17 a.u., day 19-21; E_{max} respectively 154±20 a.u. and 465±20 a.u.). No difference in DBF response to electrical stimulation of the forehead skin between healthy women and MRM women was present at either occasion. Surprisingly, estradiol levels in healthy controls (75±8 pg/ml) were higher than in MRM patients (52±4 pg/ml, $p<0.05$) on day 19-21 of the menstrual cycle, whereas estradiol levels on day 1-2 of the menstruation did not differ (respectively 21±4 pg/ml and 25±5 pg/ml). Levels of progesterone between healthy controls and MRM patients did not differ at either point of the cycle.

Conclusions: Women with menstrually-related migraine have a compromised cyclicity in both the trigeminovascular system and estradiol levels during the menstrual cycle. Furthermore, the cyclic-related difference in capsaicin, but not in electrical stimulation dilator responses, suggests that the observed differences in healthy women are due to changes in the sensitivity of the TRPV1 receptor, likely sex-hormone related.

P228

Efficacy and Safety of Frovatriptan+Dexketoprofen in Menstrual Related Migraine (MRM)

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Objectives: To assess the efficacy and safety of frovatriptan +dexketoprofen in two different dosages (25 or 37.5 mg; FroDex 25 or FroDex 37.5) compared with frovatriptan alone (Frova) in the subgroup of women with MRM.

Background: Drugs for migraine attacks include triptans and NSAIDs; their combination could provide greater symptom relief. The association of headache with menstrual cycles is common. These migraine attacks are particularly difficult to treat and more disabling than non-MRM migraine attacks.

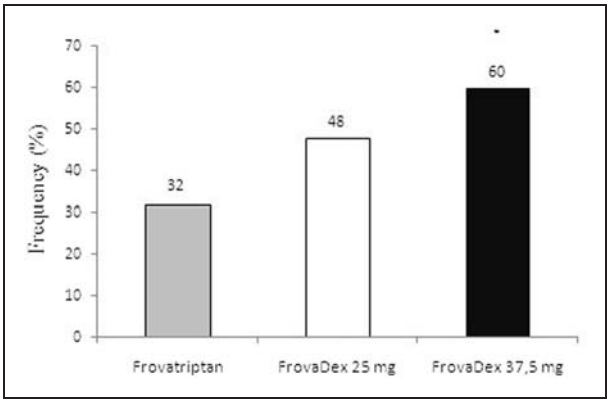
Methods: This analysis was carried out in women with regular menstrual periods who were randomized to any of the three treatment sequences, and who treated one MRM (ITT). Of the 258 females in the main study population 76 had a regular menstrual cycle and were randomized to Frova, FroDex 25 or FroDex 37.5. This was a pre-defined sub-group analysis of a multicenter, randomized, double-blind, parallel-group, pilot study. The primary end-point was the proportion pain-free (PF) at 2 hours. Secondary end-points included pain relief (PR) and sustained pain-free (SPF).

Results: Frequency (%) of PF at 2 h with Frova, FroDex 25 and FroDex 37.5 in the 76 females with MRM.* p=0.05 Frova vs FroDex 37.5. Secondary end points.* p=0.05

Drug-related adverse events were equally low between different treatments.

Conclusions: Combining frova+dexketoprofen resulted in impressive PF and PR rates at 2 and 4 hours compared to frova alone, whilst maintaining efficacy at 24 and 48 hours. The safety profiles were comparable. The intrinsic pharmacokinetic properties of the two single drugs contribute to this improved efficacy profile. The combination of a long lasting triptan together a NSAID with rapid onset of action might be a good and safe therapeutic strategy for MRM.

	Frova N=28	FroDex 25 N=23	FroDex 37.5 N=25
PF at 4 hour	43%	61%	80%*
PR at 2 hours	52%	81%	88%*
PR at 4 hours	80%	90%	96%
Sustained Pain Free at 24 hours	21%	35%	44%
Sustained Pain Free at 48 hours	21%	30%	32%



P229

Comorbid Medical Disorders and Migraine: Does Gender Make a Difference?

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Objectives: 1) To determine if the prevalence of comorbid medical and psychiatric disorders is increased in male and female migraineurs as compared to controls and 2) To ascertain if the types of associated comorbid disorders differ between men and women.

Background: Past studies have demonstrated that certain medical and psychiatric disorders are more common in migraineurs than controls, but few have determined if these associations are influenced by gender.

Methods: Consecutive patients that were 18-65 years of age presenting to the offices of two primary care physicians in Cincinnati, Ohio, were eligible for participation in the study. Each participant underwent a structured verbal interview to determine the presence/absence of headache and their clinical characteristics if present. They were later assigned an ICHD headache diagnosis by a blinded headache expert. Comorbid medical and psychiatric disorders were determined by validated written questionnaires, a physician diagnosis or medication usage. Univariate analyses were first performed separately for each gender to determine which

comorbid disorders were associated with the prevalence of migraine. To adjust for multiple collinearities, those disorders with p values <0.20 were used as independent variables in multivariate log binomial models along with age, obesity (BMI ≥ 30) and current smoking status. The dependent variable was the prevalence of migraine (ICHD 1.1-1.6). Separate multivariate models were performed for each gender.

Results: The study population was comprised of 1272 patients of which 55% were female and the mean age was 46. The prevalence of migraine was 57% in women (398/694) and 25% in men (145/578). The prevalence ratios (PRs) for migraine were significantly increased for rhinitis, gastroesophogeal reflux and sleep apnea in separate multivariate models for men and women (p values <0.05). In contrast, the PRs for hypertension and anxiety were only significant in the men's model while those for depression and smoking were only significant in the women's model. (Table 1)

Conclusions: The types of medical and psychiatric disorders associated with migraine differ between men and women. These results suggest that future studies of migraine comorbidities should include gender specific analyses. In addition, those patients with a greater number of comorbid medical disorders have an increased prevalence of migraine regardless of gender.

Variable	Women-Prevalence Ratios (95% CI)	Men-Prevalence Ratios (95% CI)
Age (+10 yrs)	0.92 (0.87, 0.96)	0.80 (0.71, 0.90)
Rhinitis (yes)	1.20 (1.04, 1.38)	1.43 (1.05, 1.95)
Diabetes (yes)	1.11 (0.99, 1.24)	—
Hypertension (yes)	—	1.43 (1.06, 1.94)
Depression (yes)	1.21 (1.09, 1.34)	—
Anxiety (yes)	1.08 (0.97, 1.22)	1.96 (1.53, 2.52)
GERD (yes)	1.26 (1.12, 1.41)	1.51 (1.16, 1.97)
Current Smoking (yes)	1.11 (1.01, 1.22)	0.91 (0.69, 1.19)
Obesity (BMI>30; yes)	—	0.77 (0.59, 0.99)
Sleep Apnea (yes)	1.13 (1.00, 1.27)	1.47 (1.07, 2.01)

P230

Imploding, Exploding and Ocular Migraine Headaches in a Women's Health Clinic – Prevalence and Comparison of Methods To Determine Pain Directionality

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Objectives: Determine the prevalence of imploding, exploding and/or ocular headaches in women with migraine and investigate the concordance between physician assignment and patient self-assignment of pain directionality.

Background: The direction that migraine headache pain is felt, imploding vs. exploding, may be due to differences in underlying mechanisms leading to the headache and may predict response to migraine treatment. The proportion of migraine patients with imploding, exploding, and/or ocular pain and the best methods of determining this pain characteristic are largely unknown.

Methods: 198 patients with migraine presenting to a Women's Health Clinic participated with structured clinician-administered interviews and completed written questionnaires. Following the interview, clinicians classified the directionality of migraine pain for each patient as imploding, exploding, and/or ocular. Patients determined the directionality of their own migraine pain by responding to a written question ("Is your headache pain pushing in or pushing out of your head or is it located within your eye socket (ocular)? Check all that apply.") and by choosing amongst three pictures that graphically represented imploding, exploding, and ocular pain. Descriptive statistics were used to determine the prevalence of each headache direction and kappa coefficients were calculated to determine the concordance between the clinician assignment of directionality, patient self-assignment via the written question, and patient self-assignment via selection of the most representative pictures.

Results: Subjects were females between the ages of 18 and 77 years (mean 48 years). Depending upon the method used to assign directionality, 34%-41% of migraine patients had imploding headaches with or without ocular pain, 18%-45% had exploding headaches with or without ocular pain, 7%-40% had ocular pain only, and 8%-13% had imploding and exploding headaches with or without ocular pain. The concordance (Kappa coefficient) between physician assignment of headache directionality with patient response to the written question was 0.33 (weak to moderate), between physician assignment and patient assignment via selection of representative pictures was 0.35 (weak to moderate), and between patient assignment via written question and via selection of representative pictures was 0.35 (weak to moderate).

Conclusions: The prevalence of imploding, exploding, and/or ocular migraine headaches varied substantially depending upon the method of determination. The

concordance between clinician assignment, patient-self assignment via answering a written question, and patient self-assignment via choosing a representative picture was low. Improved methods of determining pain directionality are needed.

P231

Headaches, Menstruation and Aspects of Reproductive Life in Young Women

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Objectives: To classify headaches as a function of the menstrual cycle according to the Second Edition of the International Classification for Headache Disorders [1], in college students.

To contrast aspects related to women's reproductive cycle as a function of headache type.

Background: Although migraine and several other headache types disproportionally affect women, and that migraine has a well described hormonal influence, headaches that occur during the menstruation are often not migraine. Furthermore, it is yet little explored whether migraine, migraine types, or headache frequency are linked to specific events of the reproductive cycle. Since particular migraine subtypes seem to be risk factor for more serious diseases[2], the topic is of relevance.

Methods: Sample consisted of 422 college students. A structured questionnaire were responded and allowed the classification of the headaches according to the ICHD-II[1]. Aspects of reproductive life were asked (age of menarche, use of contraceptives pills, headaches during pregnancy). We contrasted findings as a function of headache type.

Results: Of a sample of 422 students, 334 (79.1%) had headaches, and 134 (31.8%) had headaches associated to the menstrual cycle. Of them, most were menstrually related headaches (prevalence of 30.8%).

Overall, median age of menarche was 12.3 years. Women with migraine with aura (MA) were significantly more likely to have had their menarche at earlier ages than women without migraine ($p = 0.03$). Use of hormonal contraceptive pills was strikingly similar as a function of having or not migraine headaches, having or not aura, and of number of headache days per month (around 73% for all groups). Interestingly, during pregnancy, MA and CDH responded to a significantly higher proportion of the headaches, relative to outside of pregnancy ($p < 0.01$).

Conclusions: Most female college students are affected by menstrualheadaches. Although migraine without aura responds by the vast majority, other headaches such as tension-type headaches, idiopathicstabbing headaches, and migraine with aura also happen.

The fact that women with MA are equally likely to receive hormonal contraceptives relative to others raise the question whether providers are assessing risk of cardiovascular outcomes in some of these women (particularly the obese or those who smoke).). Furthermore, MA and CDH being relatively more common during pregnancy that outside pregnancy is an issue that needs to be explored. Finally, mechanisms to explore menarche happened earlier in women with MO should also be explored since our study is cross-sectional. It would be of interest to define whether earlier menarche age is associated with increased risk of MO, if the opposite is true, or if an unidentified association or pre-disposition would explain the finding.

P232

Impact of Widespread Chronic Pain Report on Health-Related Quality of Life

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Objectives: The aim of this study was to assess the health-related quality of life (HRQoL) of women with episodic (EM) or chronic migraine (CM), as compared to women without headaches. We also assessed the relevance of widespread chronic pain (WCP) on HRQoL scores.

Background: Migraine and WCP are prevalent and more common in women than men. The prevalence of WCP in migraine is increase by twofold. Nonetheless WCP is characterized by a decreased threshold for pain often reflected by dysfunction in the ascending endogenous modulatory pain systems. Although its relevance as a risk factor for migraine progression has been documented, the influence

of this condition on the HRQoL of individuals with episodic and chronic migraine is poorly understood.

Methods: Women with age from 18 to 65 years and a first diagnosis of EM or CM seen in an outpatient headache clinic from September of 2006 to September of 2008 were invited to participate. They were asked to bring a woman of similar age, not suffering from headaches, to the initial visit. Migraine was diagnosed as per the ICHD-2. Questions about WCP followed the protocol of the American College of Rheumatology. HRQoL was assessed using the Short-Form 36 (SF-36). ANOVA was used to compare groups with respect to age. Multivariate analysis modeled SF-36 total scores and specific domains as a function of headache status and WCP using quantile regression.

Results: Sample consisted of 179 women, 53 in the EM group, 37 in the CM group and 89 in control group. Groups did not differ by demographics. WCP was reported by 35.8% of women with EM, 43.2% of those with CM and 16.8% of controls. Women with EM and WCP were older than those with EM without WCP [$p<0.01$; 95%CI (3.33; 17.84)]. Mean scores of SF-36 were 53.6 [standard deviation (SD) = 23.5] for EM, 44.2 (SD = 18.5) for CM and 61.8 (SD = 21.5) for controls. In multivariate analysis, SF-36 scores were predicted by CM status [$p = 0.02$; 95% CI (-18.52; -1.58). The influence of WCP in the SF-36 scores approached significance ($P = .08$; -0.78 [95% CI -1.64; 0.88]). Age did not contribute to the model. In women with EM WCP was significantly associated with lowest scores, overall [$p<0.01$; 95%CI (10.1; 30.15)] and also in role-emotional [$p=0.01$; 95%CI (11.78; 63.43), physical functioning [$p=0.01$; 95% CI (4.64; 32,73)] and role-physical [$p<0.01$; 95%CI (10.72; 56.54)].

Conclusions: Women with migraine are at an increased chance of WCP, and the chance increases as a function of headache frequency. In women with EM, WCP independently influences HRQoL.

P233

Relation of Migraine and Female Sexual Dsyfunction

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Objectives: In this study, we aimed to investigate whether sexual dysfunction was correlated with the frequency of migraine attacks and migraine-related disability. The second aim of the study was to find out whether depression and anxiety levels affected sexual function in female patients with migraine.

Background: Migraine is a chronic condition that is mainly seen in women and negatively affects the quality of life. There are only a few studies examining the relationship between migraine frequency, severity and sexual function. Depression and anxiety are two phenomenona that affect both headache and sexual functions. It is also reported that depression and anxiety levels in migraine sufferers are high.

Methods: Fifty female migraine patients (31.9 ± 6.5) were recruited to study. Patients fullfilled in sociodermographics form, Migraine disability assesment scale (MIDAS), Female sexual function index (FSFI), Beck depression inventory (BDI) and Beck anxiety inventory (BAI). FSFI is a brief, self-report measure of female sexual function. It consists of 19 questions on 6-domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain.

Results: Ninety per cent of the participants were married, with a mean (SD) duration of 8.1 ± 6.3 years, and 50% of them had at least one child. Most patients (90%) had a diagnosis of migraine without aura with a mean duration of 7.2 ± 4.8 years. Mean MIDAS score was 19.3 ± 12.8 and disability was severe in 40 % of the patients. The mean FSFI score was 20.9 ± 5.9 out of a maximum of 36. Based on total FSFI score, 45 women had scores less than the cutoff point of 26.55, which is accepted as low sexual function. Mean BDI score was 13.6 ± 7.9, 60 % of the patients had mild, moderate or severe depression and mean BAI score was 16.3 ± 10.8.

There was no significant correlation between FSFI total scores or any FSFI domain and age, education level, occupational status (whether the subject was actively working or not), duration of marriage, and having children or not. Also there was no significant correlation between FSFI and MIDAS scores, migraine duration, migraine attack frequency, and migraine severity. BDI scores were negatively correlated with total FSFI score ($r=-0.486$, $P<0.001$). FSFI domain scores for desire, arousal, lubrication, orgasm and satisfaction showed significant negative correlation with BDI score ($r=-0.406$, $P=0.004$; $r=-0.510$, $P<0.001$; $r=-0.454$, $P=0.001$; $r=-0.470$, $P=0.001$; $r=-0.558$, $P<0.001$, respectively). No significant correlation was detected in relation to FSFI and BAI scores.

Conclusions: In this small clinical sample of female patients with migraine, sexual dysfunction was very common. It was not associated with migraine related disability, frequency of attacks and migraine severity or anxiety. The most important factor predicting sexual dsyfunction in this group was depression.

P234

Prevalence of Menstrual Migraine in the General Population

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Objectives: To estimate the prevalence of menstrual migraine in the general population.

Background: The female preponderance of migraine has been hypothesized to be secondary to female hormones, since the prevalence is similar in boys and girls prior to menarche (1). ICHD II provides Appendix criteria for menstrual migraine and calls for more research before it eventually can be included in the main body of the classification (2). This is a population based epidemiological survey of menstrual migraine.

Methods: Five thousand women aged 30-34 years received a posted screening questionnaire about menstrual migraine. Those with self-reported migraine in at least half of their menstrual cycles were invited to participate in a semi-structured interview conducted by a neurologist. Those with $\geq$180 days/year were excluded. The ICHD II criteria were used.

Results: The response rate of the questionnaire was 73%. Three hundred and sixty women met the inclusion criteria. A total of 237 women were interviewed, 76 were not eligible and 47 did not want to participate. The prevalence of menstrual migraine was 6.1 % in the general population and 17.6% among migraineurs. Corresponding figures were 0.8% and 2.2% for pure menstrual migraine and 5.3% and 15.4% for menstrually-related migraine.

Conclusions: One out of sixteen women in this population had menstrual migraine. Pure menstrual migraine was rare.

P235

Evaluation of Cerebral Hemodynamics of Patients with Menstrual Migraine

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Objectives: Migraine is a neurovascular disorder characterized by autonomic nervous system dysfunction and severe headache attacks. 11% women with migraine have onset of migraine at menarche and are more likely to experience menstrual migraine. Only 14% of women with migraine have migraine only in association with their menstrual periods. Approximately 60% have migraine with menses and at other times during the menstrual cycle. Migraine is a neurovascular disorder. Change in the diameter of intracranial arteries is thought to be an important underlying mechanism in migraine pathophysiology. Transcranial-Doppler-Ultrasound (TCD) is a non-invasive method to evaluate intracranial vascular system. The Breath Holding Index (BHI) is a non-invasive method for evaluation of cerebrovascular reactivity.

Background: This study aimed to evaluate basal cerebral blood flow velocity and vasomotor reactivity (VMR) in patients with menstrual migraine on the third day of mensturation and on the tenth day of mensturation by using TCD.

Methods: Our study included 23 patients with menstrual migraine and 20 normal people. Mean blood flow velocity, BHI and PI were measured in the third and the tenth days of menses of the patients and any day of the control group in MCA and PCA bilaterally We compared the third and tenth days' and the control group's values.

Results: BHI was significantly decreased in MCA and PCA in migraine group ($p<0.001$). Differences Pulsatility index and Mean blood flow were insignificant in all groups. BHI was significantly increased in PCA in the tenth day compared to the third day (p :0,005). Differences in BHI in MCA, Pulsatility index and Mean blood flow velocity in both arteries were insignificant in those days.

Conclusions: Migraine is a neurovasculer disorder. There are no studies assessing cerebral hemodynamics in patients with menstural migraine. In our study, we have detected unaffected cerebral blood flow velocities in menstural migraine patients and reduced vasomotor reactivity in both MCA and PCA. These datas show that vasomotor reactivity of cerebrovascularstructures reduces in menstrual migraine periods and improves partially after the menstruation.

P236

Estrogen-Sensitive Migraine: An Exploratory Study of Its Relation to Menstrual-Cycle and Menstruation Disorders

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Objectives: The purpose of the study was to determine whether women with estrogen-sensitive migraine are more likely to have menstrual-cycle and menstruation disorders. The presence of such disorders may indicate an abnormal hormonal cycle and given migraine's hormonal sensitivity, it may be associated with a worse migraine condition. Hence, we also determined whether women with chronic migraine are more likely to have menstrual-cycle and menstruation disorders than those with episodic migraine.

Background: Migraine is a chronic condition of recurring moderate-to-severe headaches that affects an estimated 6% of men and 18% of women, with the highest prevalence in those 18 to 49 years of age, generally when women menstruate. In the majority of menstruating women with migraine, the headaches consistently occur or consistently worsen with menstruation, here referred to as estrogen-sensitive migraine.

Methods: We conducted a cross-sectional 42-point questionnaire study of 96 women, 18 to 45 years old, diagnosed with episodic or chronic migraine, to determine estrogen sensitivity of the headaches as defined above and the occurrence of the *menstrual-cycle disorders*, oligomenorrhea, polymenorrhea, and irregular cycle, and the *menstruation disorders*, dysmenorrhea and menorrhagia.

Results: Statistically significant findings included increased frequency of nausea with migraine (88.8% *versus* 68.8%; $p = 0.05$) and moderate or severe menstrual flow (75.0% *versus* 56.3%; $p = 0.01$) in the women with estrogen-sensitive as compared to non-estrogen-sensitive migraine, and increased frequency of menstrual-cycle disorders in general (41.2% *versus* 22.2%; $p = 0.05$) and dysmenorrhea (51.0% *versus* 28.9%; $p = 0.04$) in the women with chronic as compared to episodic migraine.

Conclusions: The worst migraine conditions, that are, estrogen-sensitive migraine and chronic migraine, are more likely to be associated with menstrual-cycle and/or menstruation disorders, which may be due to an amplified estrogen cycle in those women, negatively affecting headache intensity and frequency.

P237

Headache Feature, Comorbidity of Anxiety and Depression, Cognitive Impairment of Menstrual Migraine

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Objectives: To explore the headache feature, comorbidity of anxiety and depression, cognitive impairment of menstrual migraine.

Background: Migraine is a severe debilitating disease, of which headache seriously impact on the quality of life of patients, especially the female. Most female migraineurs have headache attacks associated with anxiety and depression, but the cognitive impairment of migraine has not yet been to conclusion.

Methods: Consecutive female patients who suffered from migraine without aura visited headache clinic of Hebei General Hospital between January 2010 and October 2011 were analyzed. Headache assessment included headache frequency, duration of attack, headache level ratings. The Hamilton Anxiety and Depression Scale were used to assess anxiety and depression associated with migraine, and Montreal Cognitive Assessment Scale to evaluate cognitive function of migraine patients.

Results: 256 patients were included in the study, and then were divided into three group: 57 cases of pure menstrual migraine without aura (PMMO) group, 97 cases of menstrually-related migraine without aura (MRMO) group and 102 cases of non-menstrually migraine without aura (NMMO) group. Migraine headache frequency score of the PMMO group was (0.95 ± 0.13), significantly lower than that of MRMO group (4.78 ± 2.28) and NMMO group (3.56 ± 1.98) ($P<0.01$). The score of headache severity and duration of headache attacks were higher in PMMO group and MRMO group than that of NMMO group ($P<0.05$), but no significant difference was detected between the two former. Migraine patients had higher anxiety or depression incidence that 45.7% of patients with anxiety and depression. The MRMO group have highest incidence ($P<0.05$); Inter-group chi-square test showed that the menstrual related migraine with anxiety and depression were significantly higher than non-menstrual migraine($\chi^2=6.89$, $P<0.01$). 256 female migraine patients without aura were accessed by MoCA Scale; as a result, migraine patients have a total score 26 points or more and showed no cognitive decline. Menstrual migraine patients with total score of 26.67 ± 0.56, non-menstrual migraine patients with cognitive function score 26.81 ± 0.24, t-test

showed no statistically significant difference (t=1.849, *P*=0.066).

Conclusions: Pure menstrual migraine and menstrual-related migraine headache patients have longer duration of attacks compared with the non-menstrual migraine, the extent of their headache is more intense than non-menstrual migraine. The phenomena may be the result of the sudden drop or fluctuation of estrogen levels. Pure menstrual migraine, which has lower frequency of attacks, its attacks can be predicted, and has less interference by other factors, maybe the best choice for studies of estrogen and migraine relationship. 45.7% of women migraine patients without aura have anxiety and depression, of which menstrual migraine have highest incidences. Female migraine patients have no obvious decline in cognitive function.

P238

Acute Migraine Treatment in Pregnancy: A Retrospective Pilot Study

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Objectives: To describe therapies employed and subsequent birth outcomes in pregnant patients presenting with acute severe migraine to a hospital setting.

Background: Teratogenic concerns and a lack of clinical studies and guidelines render acute migraine treatment in pregnancy challenging. There is similarly little information on birth outcomes in these patients who require hospital care for acute headache, although the baseline risk of preterm delivery stands at 11.4% nationally.

Methods: Consecutive inpatient neurology consultations for acute severe headache in pregnant women at an urban, tertiary hospital setting were captured in an interim analysis from 7/1/09 through 1/31/12 in a retrospective chart review.

Results: We identified 29 pregnant women with acute migraine free of secondary headache, including preeclampsia. The mean patient age was 29..2.2 years and gestational age was 27.5 weeks, with most patients presenting in the 3rd trimester (55.2%). Patients were mostly Hispanic (44.8%) or African American (37.9%), and multiparous, with a mean of 4.3 total pregnancies leading to an average of 1.5 viable births. Patients had migraine without aura (62.1%) and with aura (37.9%); 13.8% of patients had chronic migraine and 31.0% presented in status migrainosus. Most patients were considered high risk (72.4%), and 75.9% had at least 10 prenatal care visits during the entire pregnancy. Treatments included oral (86.2%), intravenous (IV) (65.5%), and both oral and IV medications (62.1%). The most common agent used was oral acetaminophen (79.3%), followed by IV metoclopramide (58.6%), the combination of oral acetaminophen and IV metoclopramide (55.2%), an oral or IV opiate (34.5%), oral acetaminophen/butalbital/caffeine (24.1%), and IV magnesium sulfate (6.9%). In addition, 10.3% of patients sustained insufficient relief from these agents and received peripheral nerve blocks (PNBs). No patients presented on migraine prophylaxis, and one patient was started on prophylactic treatment. The majority of patients delivered full-term infants (75.9%), 17.2% had pre-term deliveries, and 6.9% were lost to follow-up.

Conclusions: Pregnant patients presenting with acute migraine at our hospital were treated with a combination of oral and IV medications, most commonly acetaminophen and IV metoclopramide, but other agents, including opiates and PNBs, were also employed. The majority of patients experienced full-term vaginal deliveries, although rates of pre-term deliveries were slightly higher than in the general population. Prospective studies are indicated to help elucidate the relationships between acute headache presentations, therapies, and birth outcomes.

P239

Causes of Discontinuation of Naratriptan Treatment Against Menstrually-Related Migraine

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Objectives: The aim of the present study is to investigate the adherence to naratriptan treatment and causes of its discontinuation at an outpatient pain clinic in Japan.

Background: Menstrually-related migraine (MRM) is the commonest type of migraine affecting about 40–70% of females suffering from migraine. Several studies reported the efficacy of oral naratriptan in the treatment of MRM. The aim of the present study is to investigate the adherence to naratriptan treatment and causes of its discontinuation at an outpatient pain clinic in Japan.

Methods: We performed a single hospital-based retrospective study. We enrolled MRM patients who fulfilled the International Classification of Headache Disorders second edition (ICHD-II) criteria for MRM. We analyzed the efficacy, adherence, and causes of discontinuation in MRM patients who treated with 2.5mg of naratriptan between June 2008 and January 2010 using medical records. The efficacy of naratriptan was evaluated at 2h after medication.

Results: We analyzed 16 patients with MRM. The rate of efficacy was 14/16 (87.5%). No patients experienced adverse effects. However, two patients could not continue naratriptan treatment. Causes of discontinuation included (1) difficulty in oral administration of naratriptan due to nausea and vomiting (two patients), (2) slower-acting of naratriptan than other triptan (one patient), and (3) difficulty in determining the timing of oral administration of naratriptan (one patient). Although we instructed the timing of oral administration, they were not improved by naratriptan. Instead, subcutaneous sumatriptan self-injection improved their migraine.

Conclusions: Although naratiptan treatment is effective and well-tolerated for MRM, some patients might not continue the treatment because of nausea, its slow-acting, and difficulty in determining the timing of oral administration. In such cases, subcutaneous sumatriptan self-injection may be effective.

P240

Pain and Stress Profile of Women Who Work in Food and Drug Industries: Findings from the Survey of New York USA of America

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Objectives: New York is a state in the northeastern region of the USA of America. New York is the 27th-most extensive, the 3rd-most populous, and the 7th-most densely populated of the 50 USA of America. The aim of survey was to investigate the role of positive affect in the relationship between stress and pain, and negative affect in women with chronic pain, and possible implications of positive affect as an important psychological resource that a woman may use for coping efforts during periods of pain.

Background: Scientists in the field of positive and negative affect have shown mixed results. While some have argued that positive and negative affects are two ends of a single construct, others suggested that these two concepts are independent from each other.

Methods: 105 women who work in food and drug industries suffering from osteoarthritis and fibromyalgia were participated in the survey and completed the initial assessments for demographic data and personality characteristics. They subsequently completed 15 to 18 weekly interviews regarding pain, stress, negative and positive affect. After completion of the survey using cross sectional method, data were analyzed via hierarchical multilevel modeling.

Results: Outcomes showed that weekly increases in pain and stress could predict negative affect elevations. Higher weekly positive affect as well as higher average positive affect, weather directly and indirectly in interaction with pain and stress, resulted in lower levels of negative affect. In addition, increases in weekly negative affect and higher average negative affect, related to greater levels of pain in subsequent weeks. In contrast, higher levels of overall positive affect predicted lower levels of pain in subsequent weeks.

Conclusions: The survey emphasized that when individuals encounter pain or stress, positive and negative affects are not independent and therefore showed important role of positive affect in reducing negative affect related to pain and stress, which could be helpful for women to bear pain and reducing the resulted tension.

P241

Cranial Autonomic Symptoms Are Common in Pediatric Migraine Patients

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Objectives: To determine the prevalence of cranial autonomic symptoms in children and adolescents with migraine.

Background: Cranial autonomic symptoms, traditionally associated with the trigeminal autonomic cephalalgias, are also frequently seen in adult migraine. Many adult and pediatric migraineurs are initially misdiagnosed as having "sinus headaches", and the presence of cranial autonomic symptoms may contribute to this diagnostic confusion. Here we study the prevalence of cranial autonomic symptoms in pediatric/adolescent migraine patients, as such knowledge may help avoid misdiagnosis in these children.

Methods: We conducted a cross-sectional study measuring the prevalence of cranial autonomic symptoms in all pediatric and adolescent migraine patients evaluated by a single investigator at four different clinical sites over the course of the study period.

Results: Of 125 pediatric migraineurs, 67% had at least one cranial autonomic symptom based on current ICHD-II criteria; 70% had at least one symptom based on proposed ICHD-III criteria. The majority had more than one cranial autonomic symptom and the symptoms were most often bilateral. Age, gender, laterality of headache, presence of aura, and whether migraine was episodic versus chronic did not influence the likelihood of having cranial autonomic symptoms.

Conclusions: In pediatric migraine in patients seeking care, cranial autonomic symptoms appear to be the rule rather than the exception. Clinicians should consider migraine when evaluating a child with recurrent headaches and associated ocular or nasal symptoms to avoid misdiagnosis of migraine as "sinus headache".

P242

Outcomes of Greater Occipital Nerve Injections in Pediatric Patients with Chronic Primary Headache Disorders

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Objectives: To report the efficacy of greater occipital nerve injections in pediatric patients with chronic primary headache disorders.

Background: Chronic primary headache disorders are relatively common in pediatric patients, and often highly debilitating. Preventive medications generally take weeks to months to take effect, thus these children may end up hospitalized. Outpatient treatments with a shorter latency to benefit are needed.

Methods: The study population consisted of patients <18 years seen at a tertiary Headache Center for a chronic primary headache disorder (chronic migraine(CM), New Daily Persistent Headache (NDPH), or chronic trigeminal autonomic cephalalgias (TAC)) who were treated with a 1st-time greater occipital nerve (GON) injection. Headache classifications met ICHD-II criteria, although medication overuse could be present, and for those with NDPH more than one migrainous feature could be present. The proposed ICHD-III criteria for undifferentiated TAC were used. Injections were performed unilaterally and consisted of a mixture of Depo-medrol and lidocaine. Data were collected retrospectively from charts using a standardized abstraction form. Definitions for "benefit" and "significant benefit" were determined *a priori*.

Results: Forty-six patients were treated with GON injections. Thirty-five (76%) had chronic migraine, 9 (20%) had NDPH, and 2 (4%) had a chronic undifferentiated TAC. Medication overuse was present in 26%. Age ranged from 7-17 years, mean 14.7 (SD 2.5 years). Sixty-five percent were female. Follow-up information was available on 40 (87%). Overall, 53% benefitted from the injection. Of these, 52% had significant benefit. Timing of benefit onset ranged from 0-14 days after the injection, mean 4.7 (SD 4.3) days. Duration of benefit ranged from <1 week to 16 weeks, mean 5.4 (4.9) weeks. Among those with chronic migraine, 62% benefitted, 56% benefitted significantly. Of those with NDPH, 33% benefitted; only 1 significantly. Neither of the two children with a chronic TAC benefitted. Those with medication overuse were not less likely to benefit (55% vs. 52%, $p=0.87$). Age and sex did not predict outcome. One-third of patients noted transient tingling/numbness in the distribution of the injected nerve. Seventeen percent noted <10 minutes of light-headedness immediately following the injection, 10% had <3 days of local soreness at the site and one patient had prolonged soreness. There were no instances of significant bleeding or local alopecia.

Conclusions: GON injections appeared useful in over half of pediatric patients with chronic primary headache disorders. Given the benign and transient nature of the side effects, a trial of a GON injection seems worthwhile prior to admitting a child with a chronic primary headache disorder to the hospital. As this study was not blinded and involved subjective outcomes, a randomized double-blind placebo-controlled trial is needed to definitively determine the efficacy of GON injections in this population.

P243

Interpersonal Victimization, Psychological Distress, and Recurrent Headaches in Adolescents – The HUNT Study

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Objectives: To examine the relationship between recurrent headache disorders and interpersonal victimization, possibly mediated through psychological distress, in adolescents.

Background: Recurrent headache, is a main source of functional impairment in youth and cooccurs commonly with psychological distress, especially if trajectories are chronic and disabling. Traumatic events could represent important precursors.

Methods: A cohort of 10 464 adolescents, aged 12-20 years from the midst of Norway, were from 2006 through 2008 invited to participate in a cross-sectional study, encompassing a general health questionnaire, including questions on exposure to traumatic events, psychological distress, and a validated interview on headache (the Young-HUNT3 study). Data from the headache interview served as outcome. Recurrent headache was defined as headache recurring at least monthly during the past year and was further subclassified into monthly, weekly, and daily complaints. Subtypes were classified as tension-type, migraine, and/or 'other' headache.

Results: The response rate was 73% (7 620). Multiple logistic regression analysis, adjusted for sociodemographics, showed a steady trend of increasing odds for recurrent headache with increasing exposure to PTIEs, which was highly significant in both sexes. The same pattern was reproduced for all frequencies and subtypes of complaints. The direct effect of exposure to PTIEs decreased after the hypothesized mediator, psychological distress, was entered into the regression equation. This attenuation was observed for all recurrent complaints, regardless of the frequency or subtype of headache, suggesting consistent mediation by psychological distress. Also, the strength of mediation through psychological distress increased with increasing exposure to PTIEs and increasing frequency of complaints.

Conclusions: The empirical evidence of a strong, cumulative relationship between exposure to traumatic events and recurrent headache, possibly mediated by psychological distress, has implications for the prevention, assessment, and treatment of headache and requires a broader biopsychosocial approach that integrates the somatic and psychological health needs of adolescents. More specifically, regarding the upcoming revisions for the 3rd edition of the International Classification of Headache Disorders, our findings suggest an expansion of a recent proposal to map both psychological distress and adverse childhood experiences as part of the general assessment of chronic pediatric headache, to apply to all recurrent headache complaints. Prospective studies are needed.

P244

Health Related Quality of Life in Children with Migraine. A Controlled Study

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Objectives: To measure the impact of migraine on the HRQoL of children, by applying the Brazilian version of the *SF-36* in children with migraine and in controls.

Background: Headaches are prevalent in the pediatric population. Migraine significantly impacts the health-related quality of life (HRQoL) of sufferers.

Methods: In this cross-sectional study, HRQoL was measured with the SF-36, and scores for the 8 domains of the test were contrasted comparing children (5 to 14 years) with and without migraine.

Results: Sample consisted of 66 children (30 with migraine and 36 controls). Mean age was 10.9 years for migraine (Standard Deviation - SD = 3 years) and 10.4 for controls (SD = 3.1 years). Proportion of children with low HRQoL scores was significantly higher in the migraine group, relative to controls, for the 8 domains of the test:- vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health.

Conclusions: Children with migraine are significantly impacted in their HRQoL, relative to children without migraine.

	Control		MIGRAINE			p
SF 36 Scale	**N**	**%**	**N**	**%**	**Chi^2/F**	**value**
Functional Capacity						
000-060	0	0	10	33.3	-	<0.001
061-100	36	100	20	66.7		
Physical Functioning						
000-060	1	2.8	20	66.7	30.79	<0.001
061-100	35	97.2	10	33.3		
Pain						
000-060	1	2.8	16	53.3	21.88	<0.001
061-100	35	97.2	14	46.7		
General Health						
000-060	2	5.6	11	36.7	10.01	0.002
061-100	34	94.4	19	63.3		

(continued)

Continued

SF 36 Scale	Control N	%	MIGRAINE N	%	Chi^2/F	p value
Vitality						
000-060	2	5.6	13	43.3	13.29	<0.001
061-100	34	94.4	17	56.7		
Social Aspects						
000-060	1	2.8	11	36.7	12.63	<0.001
061-100	35	97.2	19	63.3		
Emotional Aspects						
000-060	4	11.1	13	43.3	8.88	0.003
061-100	32	88.9	17	56.7		
Mental Health						
000-060	1	2.8	13	43.3	16.10	<0.001
061-100	35	97.2	17	56.7		

P245

Burden of Headache in Children and Adolescents – Developing a Questionnaire for a Global Study

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Objectives: To develop a questionnaire for a global estimation of the burden of headache in children and adolescents, to assess its feasibility, to validate the diagnostic questions and to present preliminary data on quality of life (QoL).

Background: Burden of headache has been assessed in adults worldwide, but data in children and adolescents are sparse.

Methods: We developed a structured questionnaire for mediated-group self-administration by pupils in school, including demographic enquiry, questions on headache prevalence, 12 questions required for diagnosing migraine, tension-type headache (TTH) and probable medication-overuse headache according to ICHD-II, 13 questions on impact of headache and 12 on QoL. In a pilot study, we offered the questionnaire to pupils aged 11-17 years in Vienna and Istanbul and performed face-to-face interviews in randomly selected pupils in Vienna.

Results: We analyzed 711 completed questionnaires: 362 from Vienna and 349 from Istanbul (51% girls; mean age 13.7±1.5 yr). Participation rate was 75% in Istanbul, 65% in Vienna. The lifetime prevalence of headache was 96.5%; 1-year prevalence was 89.4%. Occurrence of headache and use of headache medication on all or most days were reported by 14.5% and 13.2%. Headache lasted hours to all day in 52% and was moderate in 40.2%, severe in 8.5%. Nausea, vomiting, photophobia and phonophobia were reported by 25.8%, 9.8%, 44.8% and 82.3%. Agreement between the questionnaire and 52 face-to-face interviews was <50% for headache on all or most days, frequent use of headache medication and quality of headache. Mean agreement for other diagnostic questions was 78.1% (range 70.6-100%). Excluding subjects with headache on all or most days, 47.8% had migraine (definite or probable) and 52.2% had TTH (definite or probable). Regarding impact of headache, 84% were unable to concentrate, 49% could not do things they wanted to, 42% were sad and 24% missed school because of headache on ≥1 day in the previous month. Regarding QoL, overall, 86% felt tired, 72% felt ill and 35% felt alone. Increasing headache duration, severity and number of fulfilled ICHD-II migraine criteria correlated with increasing impact of headache in most impact questions, and with decreasing QoL in 7, 4, and 10 respectively of the 12 QoL questions.

Conclusions: This pilot study revealed a marked selection bias towards subjects with headache. To the questionnaire, pupils over-reported headache and medication use on all or most days. Otherwise there was fair agreement between questionnaire and interview in the diagnostic questions. As a consequence of this pilot study the questionnaire will be adapted and re-evaluated. Meanwhile, these preliminary findings on impact of headache and QoL suggest considerable burden of headache.

P246

The Wocach Project. A Innovative Web-Based System for the Study of Headache in Children and Adolescents. A Preliminary Study of Methodological Issues

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Objectives: Our aim is to take account of the methodological opportunities offered by a web-based model for of the study of epidemiology features of headache in a large population of children and adolescents from multiple countries

all over the world, taking into account the co-occurring comorbid conditions and the correlations with disability.

Background: In children and adolescents, headache is one of the most common pain experiences (Ghandour *et al*., 2004) that has a high risk of development of physical and psychiatric morbidities and to persist into adulthood as a chronic condition. In adolescents, headache is one of the most common health problems, with a range of 5 to 25% of children and adolescents reporting severe or frequent headache (Anttila 2006). Perquin *et al*., (2000) found that 4.6% of 12-16 year old adolescents suffer from chronic headache. In addition, headaches have been shown comorbid with a range of physical and mental health problems including asthma (Lateef et al., 2009), allergies (Lateef et al., 2009), sleep disorders (Miller et al., 2003), suicidal ideation (Wang et al., 2009), emotional and behavioral problems (Strine et al., 2006), anxiety and depression (Guidetti et al., 1998).

Methods: The research is organised in a pyramidal way, in different geographical areas of the world.

Tests adopted will refer to the following comorbidities: Psychiatry-related; ADHD field; Epilepsy categories; Sleep disorders; Atopic disorders; Other areas investigated: Cognitive; Quality of life.

Data retrieval, with specific attention to security and encrypting, will be managed by "Sapienza" University of Rome. An Electronic Patient Record has been implemented with automatic protocols for data analysis.

Statistical models adopted:

1) Starting of the study: analysis of comorbidities; identification of differences between groups (area, age, sex,etc);

2) After 1 year: the same analysis of step 1 will be repeated to control for time variable (maturation, stability of phenomena observed);

3) Regression analysis and factorial analysis with data recorded for the identification of factor as predictive of selected pathologies;

4) Analysis of the different clinical approaches adopted; compared with results of steps 1-3 for the identification of the different power of therapeutic approaches adopted.

Results: By now, we are collecting data coming from 70 universities and clinical centers all over the world.

Conclusions: The web-based system, allowing the participants to follow on-line the developing of the data analysis process, could be a base for the creation of guidelines for deeper knowledge in headache, comorbidity and predictive factors.

P247

Metabolic and Imaging Abnormalities in the Evaluation of Children with Cyclic Vomiting Syndrome

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Objectives: To determine the need for imaging in patients with CVS. To evaluate the role of metabolic testing in this disorder.

Background: Cyclic vomiting syndrome (CVS) is a diagnosis made by exclusion of other organic diseases. It is considered a migraine variant. It has been suggested that patients with CVS may have mitochondrial dysfunction. The aim of the study was to evaluate our CVS patients to determine whether they had associated, undiagnosed metabolic abnormalities.

Methods: The study included 106 consecutive patients less than 21 years of age at diagnosis. Information regarding medical history, laboratory and imaging studies was collected. Metabolic studies in serum and urine were obtained when patients were well and when patients were in a vomiting cycle, which included serum amino acids, urine organic acids, and acylcarnitine profile.

Results: The mean age at diagnosis was 8.9 $\pm$ 5.0 years. The patient population was 57% male and 77% Caucasian. Patients reported cycles with median duration of 24 hours, 18 vomiting episodes per cycle and a peak of 5 emeses per hour at 4-week intervals. Most patients (88%) reported complete symptom resolution between episodes. 10% of episodes required IV fluids. Warning symptoms occurred in 63%, typically abdominal pain and nausea (37%). Episode triggers were identified in 66%, intercurrent illness (35%) seen most often, motion sickness in 16%. Autonomic symptoms were seen in 25%, with fever (13 patients) and hypertension (9 patients). For prophylactic treatment, amitriptyline was effective in 23 of 40 patients (58%) and cyproheptadine was effective in 30 of 61 (49%). High dose oral ondansetron improved or resolved acute symptoms in 56 of 85 (66%). There was a family history of migraines in 71% of patients, epilepsy in 10%. Personal migraine history was noted in 26%. Neuroimaging showed previously unknown intra-cranial abnormalities in less than 10% of patients, none

of which explained the vomiting symptoms. Abdominal ultrasounds (US) showed abnormalities in 15% of patients during an acute episode and 7% of patients when well. The most common finding was renal abnormalities. 61 patients had an upper gastrointestinal series (UGI) done, all of which were normal. 34% of patients completed metabolic testing when well, of which 28% had findings suggestive of mitochondrial dysfunction. 37% of patients completed metabolic testing with an acute episode, of which 20% had findings suggestive of mitochondrial dysfunction. The most common finding was increased alanine.

Conclusions: The initial work-up of these patients could potentially be more individualized in regards to neuroimaging, abdominal US, and UGI. Almost one-third of our patients had abnormalities in blood and urine suggesting mitochondrial dysfunction. Additional, and more detailed metabolic analysis of this population is being planned at our institution.

P248

Monthly Variation of US Emergency Department Visits for Headaches in School-Aged Children

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Objectives: To determine the monthly variation of acute US emergency department (ED) headache visits for school-age children.

Background: Headache disorders are prevalent in children and lead to significant disability and health-care utilization. School-related stress is a commonly reported headache trigger for school-aged children. However, studies have not explored month to month variation of headache exacerbations in children. We hypothesize that school-aged children will have increased ED visits related to headaches in the months associated with onset of school.

Methods: From a nationally representative sample of ED visits in the National Hospital Ambulatory Medical Care Survey from 1997 to 2009, we estimated number of ED visits associated with ICD-9 diagnosis codes related to headache, migraine, status migrainosus, or tension-type headache in any of the three diagnosis code fields. Age stratified multivariate models are presented for month of ED visit (July set as reference month) and adjusting for gender, race/ethnicity, region, urban setting, and admission.

Results: There was a national estimate of 320,000 (95% CI 296,000, 344,000) ED visits related to headache diagnosis (1.84 % of total ED visits) in individuals 5 to 18 years old from 1997 to 2009. Of these, 66.7% were female; 62.2% were non-Hispanic whites, 22.6% non-Hispanic blacks, 12.0% Hispanic; 79.2% lived in urban settings; and 3.51% were admitted to hospital from ED. In 5-11 year olds, there was significant lower ED visits in April (OR 0.38, 95% CI 0.20, 0.73). In 12-18 year olds, there was significant increase in ED visits in January (OR 1.77, 95% CI 1.12, 2.70) and September (OR 1.74, 95% CI 1.18, 2.64).

Conclusions: In adolescents aged 12 to 18 we found increased emergency department utilization for headache in January and September, in congruence with school onset. Alternatively, there were no increased utilization in these months for younger children or young adults. This monthly variation of ED utilization should be explored further for possible explanations including school related stress, sleep pattern disturbance, head trauma, and possibly viral etiologies.

P249

Lifestyle Changes for Headache Prevention among School Children in South Korea

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Objectives: We examined lifestyle among school children in South Korea and analyzed the relationship of lifestyle and headache.

Background: Despite the high prevalence of headaches among school children, lifestyle of school children with headache has not been well examined.

Methods: We conducted a cross-sectional school based study of a randomized and proportional sample of 5360 boys and girls. The mean age is 14.02±3.03 (range 7-19 years). The questionnaires collected demographic data in addition to specific a questions about headache according to the international classification of Headache Disorder criteria, 2nd Edition. And we analyzed according to exercise, regular eating, sleep time, fluid intake, and caffeine intake.

Results: School children to exercise have less headache ($p=0.02$). School children with eating regularly have less severe headache ($p<0.0001$, odds ratio=0.5). School children to sleep more have less headache ($p<0.0001$). School children taking more fluid have less headache ($p=0.0002$). School children taking more caffeine have more headache ($p<0.001$).

Conclusions: This is the study of relationship between headaches and lifestyle of school children in South Korea. We suggest that behavioral the lifestyle changes should be considered to prevent headaches among school children.

P250

Olfactory Hallucination in Childhood Primary Headaches: Case Series

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Objectives: To examine the frequency and characteristics of olfactory hallucination in children and adolescents with primary headaches.

Background: Olfactory hallucination (OH) refers to perceived smell in the absence of odorant stimulation. Reports of OH in the paediatric population are rare. Olfactory aura is yet to be recognised by the International Classification of Headache Disorders (ICHD-2).

Methods: 838 patients (494 females; 344 males) were eligible for the assessment of OH. Headache diagnoses on the basis of ICHD- 2 included migraine (n=536), tension type headaches (n=117) and other primary headache types (n=47). The remaining 138 patients had not yet specified headaches. The migraine category included 230 migraine with aura (MA) and 306 migraines without aura (MWA).The study was a retrospective analysis of prospectively collected data at the paediatric headache clinic at Queen's University Hospital between August 2009 and July 2012.

Results: Of the eligible 838 patients, 18 (ages ranging from 6.9 to 15.9 years) had OH during headache attacks. OH included smells such as rotten cheese, burned plastic and fish tanks.

OH shortly followed the onset of headaches and lasted from 15 to 50 minutes. Use of painkillers was not helpful to minimise or terminate OH and OH disappeared or considerably improved among 6 out of 18 patients following sleep. Headache attacks were never triggered by smell and OH was not present in between headache attacks. The smells were not experienced by others at the time.

Using the ICHD-2, all patients with OH had migraine (14 MA, 4 MWA). Of those with MA, nine patients had visual aura; two had somatosensory aura; one had motor aura and two had a combination of visual and somatosensory aura. In these patients, both OH and aura occurred in the same headache attacks.

Conclusions: Migraine was the only associated headache type among the 18 patients with OH and migraine with aura was the major linked headache. We found a prevalence of OH to be approximately 3.4% among migraineurs (6.1% among those with MA). OH was associated with the onset of migraine headache, occurred in at least two separate headache attacks, and correlated with other associated symptoms such as nausea, vomiting, photophobia and phonophobia. In these patients, OH lasted for more than five minutes and less than an hour, and was then followed by gradual spontaneous full recovery. The most reasonable hypothesis to explain our findings is to consider OH as a form of migraine aura. Prior to this study, to the best of our knowledge, there are 40 reported cases of OH in patients with primary headaches. Therefore, the entire cohort of patients, including our cases, comprises a total of 58 cases highlighting that OH occurs, although uncommonly, in patients with migraine.

P251

Attachment, Depression and Anxiety in Children and Adolescents with Migraine

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Objectives: Investigate the connection between dependence, depression and anxiety in children with primary headache syndroms.

Background: Few studies on the role of emotional dependence related to comorbidity. According to them, a significant correlation exists between depression, anxiety and low-safety perception in connection with attachment figures in children with migraine.

Methods: The experimental group was made of 100 subjects, 48 m. and 52 f., aged 8 to 14 y.o., with primary headache. Exclusion criteria: subjects with a diagnosis of secondary headache and p. older than 14 years. The monitoring group was composed of 100 s. without headache, 49 f. and 51 m., aged between 8 and 14 y.o. The experimental group presented Migraine Without Aura (60), Migraine With Aura (10), Tension-Type Headache (15), CDH (10) and BenignParoxysmalVertigo (5).Both groups were analized with a Security Scale [1] and SAFA scale A and D versions [2]. Security Scale is a self-administrated scale for ch. and adol. exploring the perception of safety with the mother (PSM) with the father (PSP) and with both parents (PSC). SAFA is a self-assessment scale for children and adolescents to assess anxiety (A) and depression (D). Total Anxiety (ANXTOT), Generalized Anxiety (GA), Social Anxiety (SA), Separation Anxiety (ASP) and School Anxiety (A_SCU). Total Depression (DEPTOT), Depressed mood (UD), Anhedonia and Apathy (AD), Irritable Mood (UI), Sense of Inadequacy (SI), Insecurity (I), Feeling of Guilt (SC) and Despair (DISP) were analized.

Results: t Student statistical analysis revealed a statistically significant difference between the control g. and the experimental one on PSC ($p < .001$) ANX TOT ($p < .001$), DEP TOT ($p = .007$). In the variable Anxiety: AG ($p < .001$), AS ($p < .001$), ASP ($p < .001$), A_SCU ($p < .001$). The variable Depression has reported the following values: UD (ns), AD (ns), IU ($p < .001$), SI (ns), I ($p < .001$), SC (ns), DISP (ns). The variable Perception of Safety reported the following values: PSM ($p < .001$), PSP ($p < .001$). In order to assess significant differences within the group of the variable headache, divided according to the pathology observed, an Analysis of Variance method (ANOVA) was employed. The results of Anxiety's subscales were statistically not significant ($p > .05$). Depression scale's data are not statistically significant ($p > .05$) except UD subscale in subgroups Migraine with Aura and Chronic Daily Headache ($p = .024$) and UI one,-between Tension-Type Headache and Chronic Daily Headache ($p = .02$). The variable Perception of Safety, don't show statistically significant values ($p > .05$).

Conclusions: High statistical significance of variables such as A, D, and Perception of Safety confirming our hypothesis and stressing the importance of a multifactorial assessment in a clinical studies, in order to provide full support with an integrated approach, with the aim to obtain a better understanding of the disorder in question.

P252

Factors Influencing Migraine Recurrence after Acute Inpatient Treatment in Children and Adolescents

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Objectives: To evaluate factors that influence the migraine recurrence rate after infusion and inpatient treatment for intractable migraine.

Background: Recurrence of migraine after acute treatment in an infusion and inpatient setting is not well documented in children and adolescents. Given the multifactorial pathogenesis of migraines, multiple factors may influence migraine recurrence after discharge. It has been reported that treatment with steroids may reduce the risk of migraine recurrence. The efficacy of steroids as a therapeutic adjunct has not been established. Studies in the adult population have yielded conflicting results.

Methods: This study is a retrospective chart review of patients presenting for treatment of an intractable migraine to the infusion unit or inpatient unit at Cincinnati Children's Hospital Medical Center. Data collected included: age, gender, location of treatment (infusion unit, inpatient unit), migraine duration, diagnosis, severity, the addition of steroids to treatment protocols, and recurrence of migraine 48 and 72 hours after discharge. Data was analyzed using Fisher's exact tests, logistic regression with backward elimination, and least squares mean slicing.

Results: Charts from 207 pediatric patients were analyzed. Using logistic regression analysis: location, gender, diagnosis, and age were all found to be significant predictors of migraine recurrence ($P<0.05$). Patients treated in the infusion unit were more likely to experience recurrence compared to inpatient admissions ($P=0.00024$). Male patients with chronic migraine were significantly more likely to experience recurrence than male patients with episodic migraine ($P=0.0074$). Episodic migraine patients were less likely to experience migraine recurrence with increased age, while chronic migraine patients more likely to experience migraine recurrence ($P=0.0008$). The inclusion of steroids in this study

population showed no significant reduction in migraine recurrence.

Conclusions: Recurrence is an important parameter when treating intractable migraines. Age, gender, diagnosis, and location of treatment correlate with migraine recurrence, but the inclusion of steroids does not. Considering these factors in the management of migraines may improve the outcome of these patients and reduce the risk of recurrence.

P253

Temperament and Character Traits in Pediatric Episodic and Chronic Migraine

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Objectives: (a) To compare temperament and character personality traits in children with migraine to normative data; (b) To compare temperament and character personality traits in children with episodic migraine to chronic migraine.

Background: Children with headaches are described as having lower level of vigor, intensified fear, higher emotionality, and being overly ambitious. Personality traits are associated with medication overuse headache, medication compliance, and cutaneous allodynia. Our aim was to understand personality traits in children with migraine and compare traits in those with episodic versus chronic migraine.

Methods: We conducted an IRB approved cross-sectional study of children aged 8-17 years old with migraine defined by International Classification of Headache Disorders – IIR seen by at a tertiary headache clinic. Demographics, headache type (episodic or chronic), and juvenile temperament character inventory (JTCI) was collected. For children less than 13, parent report JTCI was used. JTCI defines four temperament traits—novelty seeking, harm avoidance, reward dependence, and persistence—and three character traits—self-directedness, cooperativeness, and self-transcendence. Analysis included one-sample t-test to compare sample to normative data and two-sample t-test to compare personality traits between episodic and chronic migraine subgroups.

Results: Forty-nine children with migraine were enrolled with a mean age of 14.0 years (SD 0.37) and 65.3% female; 20 (40.8%) children with episodic migraine and 29 (59.2%) children with chronic migraine. Compared to normative data, children with migraine have higher novelty seeking ($p=0.05$), higher harm avoidance ($p=0.09$), higher self-directedness ($p<0.001$), and higher self-transcendence (spirituality domain; $p<0.05$). Compared to episodic migraine, children with chronic migraines have higher cooperativeness ($p<0.05$).

Conclusions: Children with migraine have distinctive personality traits; however there is no difference in those children with episodic versus chronic migraine except for cooperativeness trait.

P254

The Psychosocial Impact of Migraine in Adolescents

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Objectives: To assess the impact of migraine on psychological and social functioning in adolescents presenting to a tertiary headache center.

Background: Chronic pain affects 11 to 38% of children and adolescents, with migraine being one of the most prevalent chronic illness conditions. Chronic pain is associated with disruptions in domains of normal life, such as school attendance, school performance, and social functioning, and can result in lower quality of life.

Methods: The study sample consisted of 115 adolescents 11 to 18 years old evaluated in a multidisciplinary headache center for treatment of headache pain and met ICHD-II criteria for migraine with or without aura. Participants completed psychosocial questionnaires at the initiation of treatment and again 6-months later. Measures of psychosocial functioning included the Bath Adolescent Pain Questionnaire (BAPQ), the Social Consequences of Children's Pain questionnaire (SCP), the Pain Catastrophizing Scale for Children (PCS), the Pediatric Quality of Life Inventory (Parent- and self-report, PedsQL), and the Behavior Assessment Scale for Children (Parent- and self-report; BASC-II).

Results: At baseline, both parent and self-reported quality of life ratings had a mean of 70.Average parent and self-report symptom scores were not significantly elevated

with the exception of parent reported internalizing symptoms on the BASC-II (M = 60.86; at-risk range; $p<0.0001$). Across all subscales, 56% of parent reported symptoms fell within the at-risk or clinical range at baseline; this decreased to 31% at the six-month follow-up. Parent-reported internalizing symptoms significantly decreased from baseline to the six month visit ($p<0.001$). In addition, parent reported pain-related catastrophizing behaviors decreased significantly from baseline to six months ($p<0.05$).

Conclusions: On average, adolescents with migraine do not report significantly elevated symptoms of impairment. At baseline, average parent-reported internalizing symptoms fell in the at-risk range but were in the normal range at the 6-month follow-up. There is a subset of patients with migraine who did have clinically elevated symptoms reported which, in turn, can impact treatment management. Inclusion of psychosocial measures can aid in creating comprehensive treatment regimens for migraine.

P255

Pain Direction Subtends Different Pathophysiological Mechanisms in Children with Migraine

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Objectives: To investigate whether migraine adolescents with pain directed inside (imploding pain) and outside (exploding pain) the head have different mechanisms underlying their migraineous syndrome.

Background: In adult migraineurs, pain direction (exploding or imploding) has been associated with a different response to botulinum toxin treatment (Jakubowski et al., 2006). Thus far, there has been no objective evidence in favour of the hypothesis that pain direction depends on different pathophysiological mechanisms.

Methods: In the first study, concerning the somatosensory system excitability, 18 migraine children were recruited. Ten patients (mean age 14.5±1.4 years, 3 girls, 7 boys) had exploding pain (EP), while 10 patients (mean age 14.1±2.2 years, 4 girls, 6 boys) complained of imploding pain (IP). The recovery cycle of the short-latency somatosensory evoked potentials (SEPs) was measured and compared between both patients'groups. Twenty migraine children, 9 with EP (mean age 11.5±1.5 years) and 11 with IP (mean age 11.3±1.7 years) participated to the second study, investigating the pshychophysiological mechanisms of spatial attention. The amplitude of the N140 SEP component was measured in a neutral condition (NC), in which

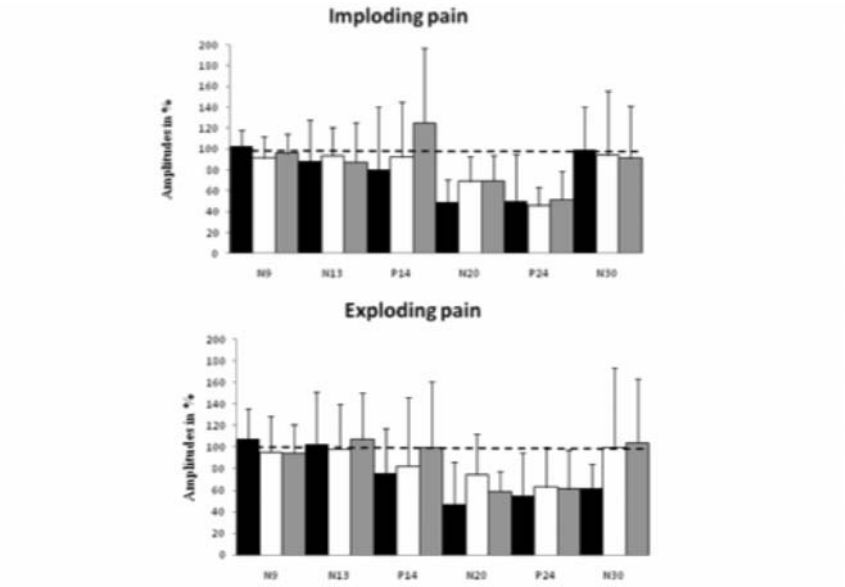


Figure 1. Mean SEP amplitudes at different interstimulus intervals (ISIs) in IP (upper) and EP (lower) patients. Black, white, and grey bars correspond to 5 ms, 20 ms, and 40 ms ISIs, respectively. The SEP amplitudes in the double stimulus conditions are expressed as percentage of the corresponding baseline amplitudes, considered as 100%. Notice that the N30 amplitude recovery cycle is faster in IP than in EP patients.

patients were asked to disregard the electrical stimulation, and in a spatial attention condition (SAC), in which patients had to count silently brief mechanical targets, made manually by a gauze ball on the tip of the first and the second finger of the hand ipsilateral to electrical stimulation. The N140 amplitude variations between NC and SAC were compared between both patients'groups.

Results: As for the somatosensory system excitability, the frontal N30 amplitude recovery cycle was shorter in IP than in EP patients, thus suggesting higher brain excitability in those patients complaining imploding pain. In the study about spatial attention mechanisms, the N140 amplitude increase during SAC, as compared to the baseline, was higher in IP than in EP patients. This suggests that, as compared with the EP migraineurs, the IP patients had to use a higher amount of attentional resources to accomplish the task.

Conclusions: The present study is the first to have shown neurophysiological differences, concerning somatosensory system excitability and spatial attention, between migraine children with either imploding or exploding pain. These results suggest that in pediatric migraine pain direction is associated with different pathophysiological mechanisms.

P256

Headache and Migraine Equivalents: Analysis of 1,134 Children and Adolescents Referring to a Pediatric Headache Centre

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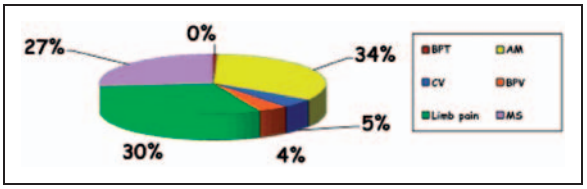
Objectives: To investigate the prevalence of migraine equivalents (MEs) in a large population of children referred to a pediatric headache centre.

Background: Migraine equivalents of infancy, childhood and adolescence, (also called "childhood periodic syndromes") are common clinical conditions without headache component, occurring as repeated attacks with complete remission between episodes. These signs may precede the development of migraine headache by several years and show a later evolution to more typical migraines. Studies investigating migraine and migraine equivalents (MEs) have shown data that support their association, which is not a pure coincidence. The International Classification of Headache Disorders, 2nd edition (ICHD-II, 2004) includes three MEs, named as "childhood periodic syndromes": abdominal migraine (AM, 1.3.2.), cyclical vomiting (CV, 1.3.1.), and benign paroxysmal vertigo (BPV, 1.3.3.). A fourth equivalent, benign paroxysmal torticollis (BPT, A 1.3.5.), is presented in the Appendix. Beyond the childhood periodic syndromes described by ICHD-II, other clinical entities, such as motion sickness (MS) and limb pain (sometimes referred to as "growing pain"), are not yet universally accepted and data are still lacking.

Methods: Patients were identified through systematic review of clinical charts of patients referred to our Headache Centre from June 2007 to April 2011. Secondary headache, cluster headache or patients who suffered from any other neurological or internal disease were excluded from our study. The final diagnoses of headache were made according to International Classification of Headache Disorders, 2nd edition (ICHD-II).

Results: A total of 1,134 of children/adolescents (52.3% boys and 47.7 girls; mean age 9.8 $\pm$ 3.0 years) were included in our study. Migraine was diagnosed in 73.2% of patients. The remaining patients had tension-type headache (TTH).MEs were reported in 70.3% of patients. Lower limb pain, motion sickness and abdominal migraine were the most common MEs. Many patients complained more than one ME (30.6% of the sample). No statistically significant effect was found between headache diagnosis and the presence of MEs (χ^2=33.2; P=0.27). We found that high frequency of headache was negatively correlated with the absence of MEs (p = 0.038; CI: -0.856 – -0.024; OR: 0.644). As regard as the intensity of attacks, we did not find any significant correlation with MEs.

Conclusions: The main results of the present study were: (1) MEs are a very common clinical condition in our pediatric headache population; (2) the presence of MEs shows a significant relationship with the frequency of attacks, but not with their intensity.



P257

The Multidimensional Impact of Migraine in Adolescents Presenting to Care

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Objectives: To examine the broad based impact of migraine in adolescents presenting to care.

Background: Pediatric migraine is one of the five most prevalent childhood disorders in the U.S., affecting up to 10% of children and up to 28% of adolescents. The functional consequences of adolescent migraine can be widespread and have a negative effect on many domains of normal daily life. The use of an integrated framework from a systems-based, contextual perspective can aid in examining the dynamic relationships between migraine pain and its functional consequences and help practitioners identify those patients whose pain has a widespread negative impact.

Methods: A longitudinal, multi-method and multifaceted assessment of migraine in a sample of adolescents presenting to a pediatric headache center was conducted to identify 1) the baseline impact of migraine across several domains, including physical and school functioning (e.g., PedMIDAS, school attendance, functional disability) as well as sleep quality and 2) changes in functioning at 6-months after initiating biobehavioral treatment in a specialty care center.

Results: 115 adolescents participated in the six-month study to examine baseline and 6-month follow-up functioning after initiating biobehavioral treatment. Descriptive statistics of functioning across these domains will be presented and also highlight components of the multidimensional assessment that are most sensitive to changes in migraine parameters. Briefly, baseline physical functioning as measured by the Functional Disability Inventory (range 0-60) had a mean of 9.98 (SD = 8.40). There was a significant improvement in physical functioning at 6-months (M = 7.55, SD = 6.82, $p = .02$). Mean PedMIDAS scores at baseline suggested moderate disability (M = 44.04, SD = 42.81), which significantly improved by the 6-month visit (M = 19.18, SD = 24.11, $p < .001$).

Conclusions: Increased attention and research into understanding the broad impact migraine can have can aid in the development and implementation of effective and sustainable interventions for adolescents presenting to specialty care.

P258

GLUT-1 Deficiency Presenting with Hemiplegic Migraine

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Objectives: To describe a case of GLUT-1 deficiency manifesting with hemiplegic migraine and absence seizures with good response to the Modified Atkin's diet.

Background: Glucose transporter-1 deficiency syndrome (GLUT1-DS) is a treatable epileptic encephalopathy caused by mutations in the SLC2A1 gene resulting in impaired glucose transport into the brain. Patients with GLUT-1 deficiency typically present with seizures resistant to conventional antiepileptic drug treatment. Paroxysmal dyskinesiaand movement disorders have recently been described as part of the phenotype. The only effective treatment is the ketogenic diet. Mutations in SLC2A1 have been reported in children with alternating hemiplegia of childhood. A case report has documented migraine headaches and GLUT1-DS in two related children, whose symptoms improved on the ketogenic diet[1]. Another case report documented paroxysmal episodic dyskinesia, absence epilepsy and hemiplegic migraines in a previously undiagnosed 25 years old woman[2].

Methods: Case Study.

Results: We report the case of an 8 years old boy with a working diagnosis of ataxic cerebral palsy who had a 3 year history of weekly headaches with hemiplegia. These episodes lasted 20-30 mins at a time and were associated with photopsia, pallor, nausea, phonophobia and photophobia. His mother, maternal uncle, two maternal aunts and maternal grandmother had similar headaches, sometimes associated with hemiparesis. He also had a history of blank episodes consistent with absence seizures. He had upper motor neuron signs in the legs, ataxic gait, scanning speech and an intention tremor. Previous investigations included two normal brain MRIs, negative testing for mitochondrial point mutations and normal serum lactate. CSF tested with the second MRI at 8 years of age showed a glucose of 2.0 mmol/L with a paired plasma glucose of 5.6 mmol/L (CSF: plasma ratio 0.36). A provisional diagnosis of GLUT-1 transporter deficiency was later confirmed by a missense mutation in the SLC2A1 gene. He was started on the Modified Atkins Diet restricting his carbohydrate intake to 25g/day but liberal fat intake. After three months on the diet his headaches had resolved; his neurological signs - gait and tremor as well as his cognition had improved. His headaches recurred when there were lapses in his diet.

Conclusions: The spectrum of GLUT-1 DS is expanding. We draw attention to an uncommon presenting symptom of hemiplegic migraine which resolved on treatment but recurred with lapse in treatment.

P259

Juvenile Migraine and the Role of Autonomic Nervous System: A Clinical Study

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Objectives: Cranial Autonomic Symptoms (CAS) are frequently reported in adult migraineurs, but the prevalence of CAS in children affected by primary headaches is unknown. Recent studies suggest a role of nervous autonomic system in the migraine by the involvement of trigemino autonomic reflex.

Background: We want to evaluate the prevalence of CAS during attacks in a juvenile population with primary headaches and to study the correlation between CAS and the main symptoms of migraine.

Methods: A total of 230 children suffering from headache (M 46 F64, aged 4–17) were enrolled in two years period. A short questionnaire investigating the presence of CAS was administered to all children. The following CAS were included in our study: conjunctival injection, tearing, palpebral oedema, nasal congestion, rhinorrhoea, red ear, facial flushing, miosis, ptosis, forehead or facial sweating. A second short questionnaire about presence of General Autonomic Symptoms (GAS), including orthostatic hypotension, vasomotors, cutaneous and secretomotors symptoms, gastrointestinal and digestive disorders, was administerd to 50 children migraineurs CAS+ and 50 CAS-.

Results: 230 children (105 m, 125 f, aged 4–17 years [age10.7 $\pm$ 3.1] were enrolled. In total, 198 children (86%) (94 m, 104 f) were found to be affected by migraine with/without aura (Migraine without aura: 173 subjects (75.21%), mean age 10.8 $\pm$ 3.1M89 (51.4) F 84 (48.6%); Migraine with aura: 25 subjects (24.79%), average age 11.7 $\pm$ 2.8 M 5(20%) F20 (80%), and 32 (14%) by Other Primary Headaches (primary stabbing headache, episodic and chronic tension-type headache). The prevalence of CAS in headaches was: general population, 116/230 (50.4%);Other headache 9/32 (28.1%);Migraine 107/198 (54.04%) Migraine without aura 89/173 (51.4%); Migraine with aura 18/25 (72%). CAS occurring more frequently in migraine than in the other primary headaches (107/198 versus 9/32) $p = 0.008$). The most common signs were facial flushing, red ear and conjunctival injection. Two or more CAS were present in 68.2 % of patients. At the univariate analysis CAS were significantly associated to the frequency of attacks ($P<0.02$) and aura ($P<0.05$). GAS were more common in CAS+ group than CAS- group (76%>46% - X^2 8.33 $p<0.01$).

Conclusions: These findings indicate that CAS are rather common in the course of pediatric migraine and prevalence is more significant than others headache. The presence of signs associated to local vasodilatation, showes an important activation of parasympathetic control on cranial vascular tone in this sub group. The significative association of CAS with frequency of attacks and aura suggests that activation of parasympathetic system has a role about of severity of disease in pediatric migraine, supporting the role of the trigemino-autonomic reflex in the pathophysiology of migraine. The frequency of GAS in CAS+ migraineurs may mean a more significant general activation of autonomic system.

P260

Frequency of Magnetic Resonance Imaging for Pediatric Migraine Management in a Tertiary Care Center

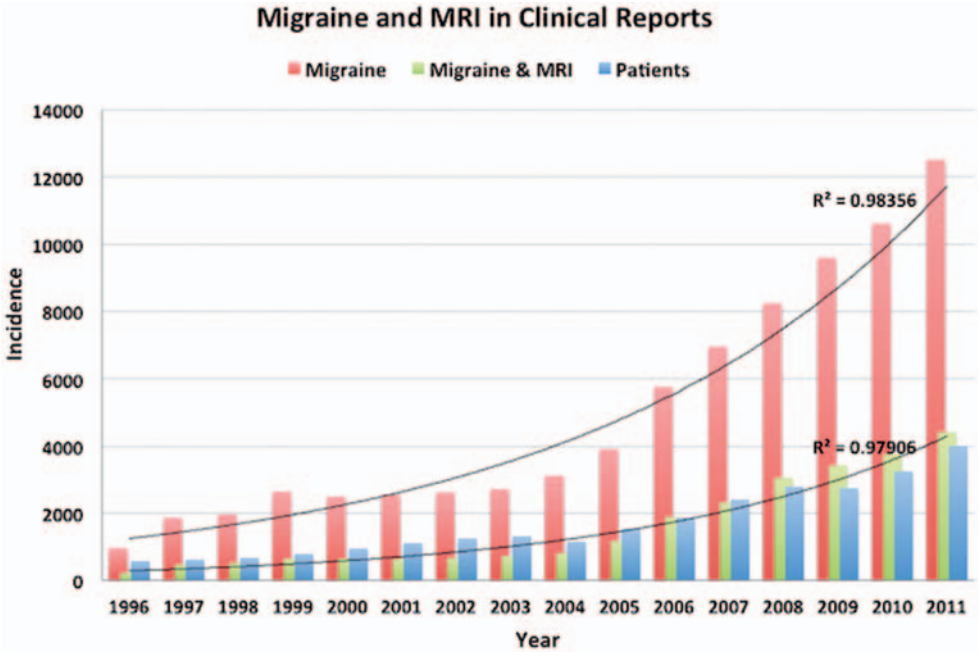
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Objectives: This study presents data on changes in the trend of using magnetic resonance imaging in pediatric migraine management.

Background: Migraine is a common neurological disorder, which frequently begins in childhood and extends into adulthood, affecting almost 8% of children and adolescents. However, pediatric migraine has features unlike that of adult episodic or chronic migraine as it may present without predominant head pain, occurring bilaterally for shorter durations, as a variant of migraine, or as a "childhood periodic syndrome" such as cyclic vomiting syndrome or confusional migraine. Moreover, pediatric migraine is often under-diagnosed as young children may have difficulty describing diagnostic characteristics of migraine, and diagnosis relies on inference from observed behaviors. Often, there is concern of structural changes or tumors in potential migraine patients, leading to a referral from primary care to neurology and, as such, magnetic resonance imaging is suggested.

Methods: After obtaining approval from the Institutional Review Board, we searched the electronic clinical charts of



patients from 1996 to 2011. Using search terms "migraine" and "migraine and MRI," we employed the search query and analysis tools on the institution's electronic charts to determine the number and trends for both of these search terms.

Results: The results show an exponential increase for both "migraine" ($R^2 = 0.98356$) and "migraine + MRI" ($R^2 = 0.97906$). Additionally, the number of patients diagnosed as a "migraineur" has dramatically increased since 1996 ($R^2 = 0.8932$). Counts for "migraine and MRI" were normalized to the counts for "migraine" in each year, and that number was used to calculate the percentage. These percentages suggest that MRI has been incorporated more often in recent years. The incidence is around 25% to begin with in 1996, and increases to above 30% in 2005-2007 and from 2007 to 2011 the incidence remains around 35%, about 10% higher than the beginning in 1996 to 2005.

Conclusions: The number of migraine diagnoses and children seen at this institution steadily increased since 1996. This increase is concurrent with the increased use of structural MRI of the brain. There was a 10% increase of MRI with pediatric migraine, despite increased scrutiny of health care expenses, insurance regulations and clinical guidelines for use of imaging in evaluating migraine. Presently, approximately a third of migraine patients seen at this institution receive a MRI as part of their disease management, as compared to a fourth between 1996 and 2004.

P261

Alexithymia in Tension-Type Headache and Migraine in Children and Adolescents: A Controlled Study with Celiac Disorder

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Objectives: Main aim of the study is comparing migraine, CTTH and Celiac disorder (CD) patients vs healthy controls in order to understand the role of alexithymia in primary and secondary disorders. We have compared an organic disease, such as celiac disorder, with migraine, since both diseases are chronic, and can influence the personality in our little patients.

Background: Alexithymia is a term used to describe a disorder where patients have difficulty in expressing their own feelings in words. It was initially used to denote an adaptive style creating a tendency to develop psychosomatic symptoms. However, a specific correlation between alexithymia and somatization could not be satisfactorily established. Alexithymia is poorly studied in headache disorders, but alexithymic traits have been evidenced both in migraine (1,2) and tension-type headache (CTTH) (3). Alexithymia has been stated as both a primary and stable personality construct and a secondary state that is created as a reaction to medical illnesses.

Methods: They are 432 children, 165 males and 267 females, aged 8-16 years. Four groups have been enrolled: 50 migraine patients (30f,20m); and 82 CTTH (65f,17m); according to ICHD-II; 100 CD (68f/32m); 200 healthy controls (104f,96m). The Toronto Alexithymic Scale (TAS-20) has been self-compiled. Data analysis have been performed considering the three factors of TAS (Factor 1: Difficulties in identifying feelings; Factor 2: Difficulties in describing feelings; Factor 3: Outside oriented thought;) plus the total scores. Data have been analysed by Student t test for independent data calculated among the parameter values assessed in all groups of patients. The p values £0.05 are considered significant.

Results: Migraine patients are statistically different by normal controls for each of TAS factors, but they show higher scores than CD only in Factor 3. We did not found differences between migraine and CTTH.

Conclusions: Both Migraine and CTTH patients showed significant alexithymic traits, but with a lower level than CD. The well-known organic basis of CD opens intriguing questions on the differences with headache and the possibility that alexithymia be a psychological reaction to chronic CD. Of interest, the role of Factor 3 in headache patients that may suggest a primary personality characteristics: the tendency to be more prone toward external stimuli than internal ones. Alexithymia seems an important psychological factor involved in Migraine and CTTH.

P262

Redefining Migraine without Aura in Children - A 7 Year Study Based on ICHD2 Diagnostic Criteria

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Objectives: To document short duration activity affected headaches in children without migraine diagnostic associated features and thus to redefine migraine without aura in children.

Background: Studies show that migraine in children are of shorter duration and when they present with recurrent activity affected headaches without out associated features like nausea, vomiting, phonophobia or photophobia, diagnosis can be a real challenge/ group 14.2 is applied (headache unspecified). This study is to document such recurrent short duration activity affected throbbing /non throbbing headaches in children without diagnostic associated features.

Methods: 7 year prospective cohort study. 1042 children, 5 to 15 years old. Inclusion criteria- 1) recurrent short duration throbbing/non throbbing headaches (unilateral/ bilateral / unilateral spreading bilateral), 2) activity affected (motionless/lie down/sleep off), 3) no nausea, vomiting, phonophobia or photophobia, 4) common migraine triggers in this region of India precipitating them, 5) one family member suffering from ICHD2 1.1/1.2/1.6. 6) history, physical, neurological and neuroocular examinations normal.

Results: Duration of headpain - 5 minutes to 45 minutes. Common regional triggers - sun exposure, bus travelling, missing meals, strenuous physical exercises and sleep disturbances. Family history - 83% mothers, 11% fathers and 6% siblings suffering from ICHD2, 1.1/1.2/1.6.

Conclusions: A new definition of pediatric migraine based on above findings will be extremely helpful for any clinician in a busy practice. Recurrent activity affected headaches precipitated by known or regional migraine triggers and with at least one family member suffering from migraine origin pain (1.1,1.2,1.6) in the absence of another disorder, should lead one to consider the diagnosis of migraine without aura in children.

P263

Sleep Disorders of Childhood and Adolescents Migraine and Episodic TTH

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Objectives: In order to evaluate cross-relationship between primary headache disorders and sleep disorders, we performed this tertiary clinical based prospective study. We also aimed search the effect of psychiatric comorbidities including attention deficit hyperactivity disorders (ADHD).

Background: There are some supportive data about the close relationship between sleep disorders and primary headache disorders, especially migraine and episodic-TTH.

Methods: This study performed in Mersin and Maltepe Universities Childhood and Adolescent Headache Outpatient Department. All patients evaluated by the Headache Specialist and ICHD-II headache diagnosis have been made. Also after face-to-face psychiatric evaluation, if

they had, DSM-IV diagnosis has been made. All of the parents of patients filled Turkish translation of Pediatric Sleep Questionnaire (PSQ)-the extended and Turkish validated version.

Results: Totally 102 patients with migraine (74.5%) or TTH (25.5%) evaluated. Totally 68.6% of the children reported important sleep disturbances over the cut-point of PSQ, not only migraine but also ETTH sufferers. Most important subtype of sleep disturbances was breath problems like snoring, followed by parasomnias and other sleep disturbances. Only 17.4% of the parent's had been reported some supportive data about ADHD over the test scores. There are close relationship between migraine and sleep disturbances and ADHD, correlated with headache frequency and severity.

Conclusions: Sleep disturbances are important problems both of children and adolescents with migraine and ETTH. Sleep problems and headache disturbances interacts each other's. Both of them have important effect on life quality of the kids. This comorbidity has to take into consideration both of management and coping strategies.

P264

Atypical Presentations of Paroxysmal Hemicrania (PH) Are Common in Children and Adolescents (C/A)

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Objectives: To increase recognition of the various presentations of this uncommon headache in C/A.

Background: PH was described in 1974, the diagnostic criteria were published in 1988. It is one of the trigeminal autonomic cephalalgias (TAC). PH is an Indomethacin responsive headache. PH is characterized by repeated attacks of strictly unilateral, severe, short-lasting pain (2-30 min) occurring with autonomic features and responds to indomethacin. Data concerning PH in children is scarce. We investigated the clinical spectrum of PH in C/A to aid in earlier recognition and treatment, thus preventing both exposure to multiple medications that are unlikely to work and avoid prolonged suffering.

Methods: A retrospective chart review. IRB approval was obtained. Subjects had multiple severe HA per day, unilateral location, again under 18. Anthropometrics, medical history, HA location, pattern, course of treatment and response were noted.

Results: Fifteen cases of possible PH were identified. We combined these cases with 20 found in the literature. Female/male ratio was 1:1. Age of onset 7.4 years; the age of diagnosis 9.6 years. In these studies there were 10 typical and 25 atypical cases. We defined cases being "atypical" if they did not show complete response to indomethacin or were responsive to other medications, had a stuttering course, variably lacked autonomic symptoms or had a spontaneous remission. Seven did not get relief on indomethacin. In four of the patients, the duration was more than 30 minutes. In three, the frequency was less than the usual average of 5 attacks per day. In four patients, the pain was bilateral. In six patients, there were no autonomic features. Typical and atypical cases will be presented.

Conclusions: There is a predominance of "atypical" presentations both in our cases and those previously reported. PH may have a stuttering course with fewer attacks, periods of remission, variable response to indomethacin and variable lack of autonomic features. Our hypothesis is that there is an evolution to this disorder. The clinical phenotype may not be fully expressed in C/A and only years later manifests as the stereotypical picture seen in adults. This may relate to the immaturity of the central nervous system in C/A, just as migraine varies with age in terms of frequency, duration and symptoms. It is important to suspect PH in any child that presents with multiple discrete short lasting headaches occurring in a single day even if autonomic features are lacking. If no etiology is found or there is no response to the usual symptomatic and preventive medications a trial of indomethacin should be considered.

P265

Post Concussion Headache (PCHA) in Children and Adolescents (C&A)

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Objectives: To determine the features of PCHA in C/A.

Background: Concussions are common in C/A. PCHA in C/A have received scant attention. There are an estimated 1.6 – 3.8 million concussions annually in the U.S. Many have PCHA. Details concerning types of HA, duration of symptoms, imaging data, treatment and prognosis are needed.

Methods: (1) A literature review was performed. (2) We reviewed 67 cases of PCHA seen 2010-2012. Data regarding age, sex, previous concussion, family history of HA, and concussion were collected. In all the Glasgow coma scale was >13.

Results: Only three relevant studies were found these included 101 patients. Details were not adequately profiled. Our 67 patients were taken from a total of 675 New HA patients seen during the same time. 39 were males, sports were football, hockey, lacrosse and falls. In 28/64 the HA was immediate, in the others it started after days or weeks. Types of HA include: episodic TTH and chronic daily headache with superimposed migraine. Pure episodic migraine was rare. Imaging was negative in all cases, save 3 who showed congenital abnormalities unrelated to the HA or injury. Concussion symptoms include but are not limited to headache, dizziness, irritability, anxiety, depression, photophobia, susceptibility to the effects of alcohol, stubbornness, and memory and concentration impairment. Children and adolescents are significantly more vulnerable to concussion injury because their bodies, more importantly their brain and skull, are still developing.

Conclusions: This OPD sample demonstrates that HA following head injuries are common. That even mild concussions result in prolonged HA which interfere with school function. Data regarding management in the first 6 weeks is lacking. If the HA has been present for >6 weeks, education, judicious use of rescue medication, preventive medication, psychosocial support and lifestyle approaches are useful. The prognosis is guarded and many HA last > 1 yr.

Additional prospective date regarding PCHA in C/A is needed. Agreement regarding approach to these patients is lacking in the absence of such data.

P266

Treatment of Acute Pediatric Headache in an Outpatient Infusion Center: Evaluation and Outcomes

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Objectives: 1. Identify pediatric patients with severe headaches and their respective headache types per ICHD-II criteria whose headaches are refractory to outpatient treatment. 2. Describe various IV medications and combinations used for treatment of acute headache in children at Texas Children's Hospital Outpatient Infusion Center. 3. Describe adverse events reported. 4. Evaluate efficacy of IV medications and/or combinations in treatment of pediatric acute headache 5. Identify variables that may confound outcomes of use of IV medication management of pediatric headache.

Background: Few treatments have been studied for use in treatment of pediatric migraine or acute headaches in children.

Methods: Retrospective chart review of the electronic medical record of patients seen and treated in the Headache Clinic at Texas Children's Hospital. Our success rate was defined as encounters where a 50% reduction in headache was seen. Of these encounters, the most frequently used treatment combination determined which of these treatments were most successful. Magnesium levels were not drawn pre or post-infusion of magnesium. EKG was obtained pre and post-infusion of Droperidol. Prior to any infusion in females of child-bearing age, urine HCG was obtained.

Results: There were 55 encounters, 46 which were unique patients. Of these 46 patients, 14 were males, 32 were females. There were 28 encounters where pain was reduced by 50% or greater. The most successful medication combinations used in these encounters were: 0.9% normal saline bolus with valproate and Ketorolac, and 0.9% normal saline bolus with diphenhydramine, metoclopramide and valproate. Of the most successful combinations, valproate was used most often. There was one significant adverse event, trembling, assumed to be a side effect of Droperidol infusion. 16 encounters were admitted to the hospital immediately after their infusion center visit, due to no or inadequate response to treatment. The average time of stay was 3 hours and 50 minutes. The longest stay was 6 hours and 46 minutes. The shortest stay was 55 minutes. In this cohort (of 46 patients), 31 were on a daily preventative. 27 had a diagnosis of chronic daily headache; 20 had symptoms of dysautonomia.

Conclusions: 51% of patient encounters saw a 50% or greater reduction in headache. This suggests an alternative method for treatment of acute pediatric headache other than the emergency room. Our clinic is in close proximity to the infusion center, making this alternative treatment for our patients feasible. 29% were admitted to the hospital. The average time of stay was 3 hours and 50 minutes. This may be shorter in comparison to a typical ER wait and visit. The morbidity was low, with only one significant adverse event recorded. Patients receiving infusion had other variables that may have contributed to their outcome (e.g. frequency of headaches, dysautonomia). Further research is needed to evaluate options in the acute treatment of pediatric headache.

P267

A Mobile Application To Track Headache Events and Symptoms in Adolescents

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Objectives: To examine the efficacy of an electronic diary to assess headache frequency and associated symptoms in adolescents presenting to a tertiary headache center.

Background: Headache diaries are typically used in both research and clinical care to track headache frequency, duration, and associated symptoms. Electronic headache diaries have increasingly been utilized as acceptable for reporting daily pain and also limit the potential for recall bias associated with retrospective ratings of pain parameters.

Methods: A mobile application (iMigraine) was developed in collaboration by a team of researchers, clinicians, and technology experts to enable adolescents to electronically enter and wirelessly transmit data about headache events and associated symptoms. As part of a larger longitudinal study, subjects were prompted to complete momentary assessments of pain occurrence headache events and associated symptoms up to 3 times a day (morning, afternoon, and evening with a one hour window to respond) for 45 consecutive days. Participants were incentivized per completed prompt.

Results: A random sample of 40 adolescents (11-18 years old) meeting ICHD-II criteria for migraine with aura or migraine without aura were enrolled. On average, 39 out of 40 subjects completed at least one prompt per day. Subjects were equally as likely to complete each of the three prompts during the day and adherence to completing daily prompts was about 66%. Participants reported having a headache on 49% of days they completed at least one prompt. On average, each participant reported having 23 headaches during the 45 day period. Objective data on the 40 participants to be presented will include: 1) Descriptive analyses on each of the headache measures summarized using daily means, variances and frequency distributions; 2) Non-parametric survival curves for headache events to illustrate the percentage of patients that report experiencing a headache on a given day for 45 days since the initiation of treatment; and 3) Demonstration of how data can be presented in a statistical control chart to statistically evaluate clinical processes in a prospective fashion.

Conclusions: Technology has the potential to transform treatments provided to youth and their families by giving youth an attractive way to actively participate in their own health care by recording health symptoms remotely. This can allow for health symptoms to be assessed remotely and in "real-time" fashion. This, in turn, can allow for increased patient-provider communication around response to care, potential factors exacerbating or relieving pain, need to modify treatment regimens, and/or feedback on symptom management that may significantly impact individualized clinical care for pediatric headache.

P268

Variability in Adolescent Migraine Symptoms and Correlates of Individual Symptom Variability

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Objectives: To systematically investigate daily variability in adolescent migraine symptoms and its impact on clinical outcomes.

Background: Research and clinical practice on pediatric migraine has typically used patient recall measures to describe symptoms. These reports can be useful in reporting typical symptoms and their overall impact, but do not identify clinically-relevant variability. Electronic momentary assessment measures hold the potential to capture day-to-day and even within-day variability, facilitating examination of the potential clinical impact. Research suggests that variability in pain symptoms may be associated with pain-related impairment. We propose to systematically investigate this with regard to pediatric migraine.

Methods: A mobile application (iMigraine) was developed by a team comprised of researchers, clinicians, and technology experts that allowed adolescents to wirelessly track momentary assessments of pain, stress, affect, functioning, and energy level (fatigue) using the commercially available Apple iPod Touch™ device.This longitudinal design was used to examine the temporal sequencing of pain and its associated impact as well as cross-lagged and causal modeling of these important constructs.

Results: A random subsample of 40 adolescents ages 11-18 presented to a specialty care clinic completed ongoing and momentary assessments of migraine pain and mood for 45 days. On average, 39 out of 40 subjects completed at least one prompt per day. Subjects were equally as likely to complete each of the three prompts during the day and adherence to completing daily prompts was about 66%. The results will a) describe the day-to-day and within-day variability of key migraine symptoms; b) examine the association between selected demographic variables (e.g., gender, age) and symptom variability; and c) explore the association between individual variability and migraine-related disability.

Conclusions: Findings from the current study will help elucidate the temporal, dynamic relationships and potential lagged effects between migraine pain, behavior, and various psychological states. This study will further our understanding of how adolescent migraine symptoms are experienced on a day-to-day level and how fluctuations in those symptoms might impact clinical outcomes.

P269

A Review of Medications Prescribed to Pediatric Migraine Patients at Boston Children's Hospital

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Objectives: The primary aim of this study was to determine the most common medications prescribed to pediatric migraine patients at Boston Children's Hospital.

Background: Migraine is a common disorder in children, present as early as preschool and affecting up to an estimated 23% of high school age patients. Many are treated with over-the-counter medications such as acetaminophen or ibuprofen, but prescription medication can be beneficial to pediatric patients. However, the medications approved for treatment of pediatric migraine differ from those approved for adult migraine, and a determination of the patterns of prescription to pediatric patients has yet to be made.

Methods: Using the Boston Children's Hospital Informatics for Integrating Biology and the Bedside (i2b2) tool, searches were performed to determine the most frequently prescribed medications for patients also diagnosed with migraine, ages 2-17. The migraine diagnoses used were classical migraine, common migraine, or unspecified migraine.

Once commonly prescribed medications were determined, searches were performed to determine the number of patients prescribed various types of medication: tricyclic antidepressants (amitriptyline and nortriptyline), anticonvulsants (gabapentin and topiramate), triptans (sumatriptan, zolmitriptan, rizatriptan, and eletriptan), cyproheptadine, butalbital with caffeine and APAP, and anti-nausea drugs (prochlorperazine, ondansetron, metoclopramide, trimethobenzamide hydrochloride, and promethazine). Results were categorized by age and gender of patients.

Results: Tricyclic antidepressants were the most frequently prescribed medications (prescribed to 8.18% of migraine patients), followed by triptans (7.21%), anticonvulsants (5.23%), cyproheptadine (2.83%), and butalbital with APAP and caffeine (2.19%). Additionally, pediatric migraine patients were prescribed anti-nausea medication with greater frequency than preventative or abortive treatments (9.40%). Amitriptyline was the most commonly prescribed tricyclic antidepressant (5.06%), and sumatriptan was the most commonly prescribed triptan (4.72%).

It was found that for all medications but cyproheptadine, the highest rate of prescription was in the oldest population, 17 years old. However, the highest rate of cyproheptadine prescription was in the 4 year old population, at 8.54%. Cyproheptadine also had the highest rate of prescription in a given age group and gender, with 14.44% of 5 year old female migraineurs receiving the prescription.

Conclusions: Findings from this study indicate that pediatric migraineurs are prescribed mostly tricyclic antidepressants and cyproheptadine as prophylactic medication, and that sumatriptan is the most prescribed triptan for pediatric migraine patients.

Unfortunately, the limitations of i2b2 only allow for comparison between medications. Many patients in the system have data regarding their diagnoses but not their medications, and so it is impossible to determine true rates of prescription using the tool as we have here.

P270

Headache Caused by Cerebral Venous Dysfunction in Children

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Objectives: To define the role of cerebral venous disturbances in children with different types of headaches.

Background: 1340 patients aged from 3 to 17 years who complained of headache have been examined.

Methods: Transcranial Doppler ("BIOSS", "SPECTROMED"), Transcranial Color Coded Duplex ("Logic P-5"), Magnetic resonance imaging (MRI).

Results: All children with headaches were separated into several groups according to the clinical and ultrasound findings: migraine headache (30%), tension type of headache (26%), headache with increase or reduction of arterial pressure (17%), headache caused by cerebral venous dysfunction (27%). Also there are cerebral venous hemodynamic disturbances in each of these groups with different intensity - 35, 40 and 35 percents, respectively. The most evident disturbances of cerebral hemodynamics were observed in children with structural cerebral abnormalities, such as Chiari I abnormality, hypoplasia of the cerebral venous sinuses. Clinically cerebral venous hemodynamic disturbances in children was characterized by headaches (100%), nasal bleeding (60%), sickness and vomiting (40%), noise in ears (35%), dizziness (30%), vegetative dysfunction, 1% of children had relative deafness, and 8% of children had tics (mostly of face muscles). All examined children complained of headaches localized in the occipital and parietal regions, that arised during or after night or a day sleeping. Increase of headaches occured after physical exercises, and lessons at school. 60% of children had typical nasal bleeding, mostly abundant and spontaneous as a "fountain". Evident disturbances of cerebral hemodynamics in straight sinus, great cerebral vein of Galen, cavernous sinus, vertebral veins, basilar and vertebral arteries were observed. We worked out a new approach of transcranial duplex scanning to visualize the cavernous sinus, with determination of structures and features of venous blood flow. This approach provides a good overview of forms and peculiarities of the hemodynamics of the cavernous sinus. Venous outflow in deep brain veins (cavernous sinus, straight sinus, great cerebral vein of Galen) was registered by ultrasonic Doppler and duplex methods and were "markers" of disturbances in cerebral venous hemodynamics. A correlation between TCD, TCCD and MRI data was found. The therapy has been prescribed in accordance with the data of TDC and duplex scanning. Positive effects were noticed after a prescription of the therapy at 85% of children.

Conclusions: Thus a venous outflow is stimulated and makes influence on intracranial venous circulation. These estimation of cerebral venous hemodynamic are of great importance in clinical manifestations, especially in children. Disturbances of the cerebral hemodynamics, revealed by ultrasonic methods, determine the tactics of advising patients (i.e. diagnosis and therapy) with different types of headaches.

P271

Vestibular Complaints in Children and Adolescents Who Have Episodic Tension Type Headache and Migraine

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Objectives: In order to determine and evaluate the frequency of vestibular symptoms-vertigo, dizziness and motion sickness in patients with migraine and episodic TTH in children, prospective cross-sectional tertiary center based study were planned. Since Episodic TTH is a bridge diagnosis in this age group, commonly converted or confused to migraine, both groups were studied.

Background: Headache and vertigo are two common, distressing and potentially interrelated neurological complaints. The association of migraine and vertigo is well recognized in adults. On the hand, vertigo is a frequent but under evaluated complaint in clinical practice even in childhood and adolescence.

Methods: Children and adolescents who were admitted to Neurology and Child-Adolescent Psychiatry departments with a complaint of headache were evaluated. Patients, who were diagnosed as Migraine or Episodic TTH (ETTH) according to ICHD-II, were given a questionnaire including questions about vertigo, dizziness and motion sickness.

Results: There were 128 patients with migraine or ETTH without any other medical problem, 87.5% of the patients were migraine and 12.5% were ETTH. Most of the migraine and ETTH patients had vertigo (71.9%) and dizziness (40.6%) during their headache attacks and 40.6% of the vertigo and dizziness complaints correlated with head position and 37.5% did not. Vertigo and dizziness were triggered by fasting, sleep disorders, computers game. Motion sickness was reported by 43.8% of the primary headache patients and migraine and ETTH were highly correlated. There was not any significant difference between migraine and ETTH patients in vertigo, dizziness

and motion sickness complaints. In other words, they were identical in gender and age and in vestibular complaints.

Conclusions: Our results showed that vertigo and dizziness and motion sickness were common in migraine and ETTH patients. Since there was not any significant difference between migraine and ETTH, ETTH might be a prodromal ongoing phase of the migraine, especially accompanied by vestibular complaints.

P272

Neck-Tongue Syndrome Manifesting in Childhood: A Case Report and Review of the Literature

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Objectives: To discuss a case of Neck-tongue Syndrome (NTS) affecting a child, review literature summarizing the historical aspect, anatomy, pathogenesis and treatment.

Background: The Neck-Tongue syndrome is an uncommon headache syndrome characterized by brief stabbing pain in the neck (one side in the upper neck or occipital region) accompanied by altered sensation (paraesthesia and numbness) in the ipsilateral half of tongue aggravated by sudden neck movement. There are three categories of NTS: idiopathic, traumatic or secondary (inflammatory or degenerative). We have reported the idiopathic or uncomplicated NTS. There is no anatomic connection between upper cervical spine and the tongue. However, a review of anatomy helps in understanding the links between two which will be discussed. The postulated theories for the mechanism are subluxation/compression and muscle spasm. Inflammatory disease, myelopathy or degenerative disorder are to be excluded. The treatment is generally conservative with limitation of motion and avoidance of trauma, coupled with NSAIDs and judicious use of agents for neuropathic pain. Use of cervical collar or postural training exercises in conjunction with patient education may be beneficial in cases of idiopathic NTS.

Methods: Case study.

Results: A 13-year old boy who presented with symptoms of neck pain and tongue numbness was seen in the clinic. Further history from parents revealed that he had been experiencing symptoms since he was 4 years old. When he turned his head to one side he used to feel "sharp" pain on left side of neck. The spells were recurrent and the frequency varied with his activity level. For the last 3 years, in addition to neck pain, he had been experiencing numbness on the left side of his tongue. It lasted for a few seconds. Parents had also noticed that sometimes he felt so numb in his tongue that there was alteration in his voice. There was no loss of awareness during the spell. The neck and tongue symptoms were consistent from one episode to next. There was no history of trauma or any cervical instability. He denied any visual or vestibular complains. There was no history of headache, joint pain or swallowing difficulties. Unenhanced and enhanced MRI of the brain and cervical spine were normal. Normal cervical alignment was seen in the MRI without any disc pathology. No abnormalities were visualized in cervical and upper spinal thoracic cord. Patient was given a trial with cervical collar and exercise. There is report of some improvement of his symptoms.

In the discussion, we reviewed the literature including the historical data and then summarized the pathogenesis and treatment.

Conclusions: This case report illustrates the clinical presentation of an uncommon condition in children. Clinicians should be made aware of this rare condition as early recognition is essential for appropriate management and prevention of unnecessary investigations.

P273

Significance of Continuous Performance Test in Children with Headaches

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Objectives: The study examines the continuous performance test (CPT) in children with headaches. Headaches in children have known to be associated with the difficulty in concentration or school performance. But limited data are available for the measurement of attention deficit or changes of attention after treatment in relation with pediatric headaches or CPT.

Background: The computer-based CPT was useful method for scoring the degree of impaied attention in the children with attention deficit hyperactive disorder. Children with reccurent headaches often reported impaired school performance. So it was meaningful to apply the CPT for checking impact of functional impairment of cognition or attention etc during or after headache attacks.

Methods: We enrolled 14 children and adolescents at Kangnam Sacred Heart Hospital during March to August in 2012, suffering from primary headaches according to diagnostic criteria of the international classification of headache disorders (ICHD-II). The control group was 14 patients with ADHD and no history of recurrent headaches.

All of them were assessed using advanced test of attention (ATA), one of CPT in Korea, during the headache attacks and after medication for treatment.

Results: The auditory ADHD indexes (AI) of headache patients were as high as that of control ADHD group. The visual and auditory AI of the headache patients in some parts were improved after treatment.

Conclusions: During the headache attacks, attention of children with headaches was as disable as ADHD patientsin the CPT. The patients showed statistically improvement of clinical symptoms and AI aftertreatment. The CPT was efficient test to assess the degree ofdisability and improvement after treatment in attention of pediatric headaches.

P274

Metacognition and Migraine: A Monitored Research on Psychiatric Comorbidity in Developmental Age

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Objectives: The purpose of this research is to evaluate the exhibition of deficits in metacognitive processes in children with migraine.

Background: Metacognition in infants and adolescents with migraine is scarcely studied.

In addition, scientific literature emphasizes the influence of metacognitive processes over a specific number of psychiatric diseases such as anxiety and depression.

Methods: EG 147 S., (100 Mwo; 35 TTH; 12 Mwa; m.a. 10.8) All the S. respected the ICHD 2 criteria. CG (130 non-clinical S. m.a11.3y.o.), recruited in schools. Recruiting citeria for CG:absence of migraine and psychic diseases, and of previous psychotherapy.

Metacognitions Questionnaire for Children (MCQ-C) [2], adapted for infants in ages between 8 and 13, in order to evaluate the positive and negative convictions, the cognitive monitoring, anxiety and intrusive thoughts and the Self-Administration Scale for Infants and Adolescents (SAFA) (3) in two versione: A (Anxiety) ans D (Depression).

Results: Significant difference emerges between the monitoring and the experimental group, regarding metacognition features. The results of SAFA test show an important relation between migraine, anxiery and depression.

Anxiety features, related to Generalized Anxiety (GA), Social Anxiety (SA), Separation and Loss-related Anxiety (ASP), School Anxiety (A_SCU), present a high statistical signifiance ($p < 0.001$), while depression features showed a satistical importance only in connection with Irritable Humour (HI) and Insicurity (I) ($p < 0.001$), depression, Anhedonia and Apathy, Unsuitableness sensation (US), Guilt feelings and Desperation (DISP) are not significant ($p \geq 0.05$).

The intra-group variance analisys (ANOVA), doesn't show any important element connected to anxiety features; whereas in regard to depression onlu the UD feature presents important differences between migraine without aura and tension migraine ($p < 0.035$). The factors connected to metacognition, analyzed using the variance analysis method, don't show any statistical difference in regard to other migrain subgroups (MWA, MWO, TTH) ($p < 0.05$).

Conclusions: Minor consciousness of its thoughts and a more evident appearance of anxiety and depression in the EG. Cognitive and metacognitive factors in the comprehension of psychiatric comorbidity in children with migraine are relevant. Determining the meaning that a child confers to his intrusive thoughts, which can compromise the quality of his life during the entire developmental periodis higly usefull. We have compared an organic disease, such as celiac disorder, with migraine, since both diseases are chronic, and can influence the personality in our little patients.

P275

Unusual Primary Headaches of Children and Adolescents: Practical Tips for Physicians

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Objectives: In this presentation eight rare known primary headache disorders of children and adolescents have been given with practical clues for physicians.

Background: Childhood and adolescent headaches somehow looks like adulthood headaches but not known as its.

Methods: All of the cases have been selected from the archives of Mersin University School of Medicine Childhood and Adolescent Headache Outpatient Department database and discussed with literature.

This presentation cases diagnosed as retinal migraine, migraine with complex visual aura, primary stabbing headache, abdominal migraine, vestibular migraine, hypnic headache, hemicrania continua, benign exertional headaches.

Results: Tip 1. Unilateral unexplained reversibl visual field disturbance can be a sign of retinal migraine especially in subject with migraine equivalent or positive family history of migraine.

Tip 2: Unexplained complicated visual hallucination can be a sign of migraine with aura after exclusion of epileptic syndromes and intracranial abnormality.

Tip 3: Unilateral short-lasting stabbing headache attacks without autonomic features can be a sign of primary stabbing headache after exclusion of secondary causes.

Tip 4: Unexplained abdominal pain attacks of childhood and adolescents, even adults, can be a sign of migraine, even abdominal migraine after exclusion of secondary causes.

Tip 5. Headache associated vertigo attacks can be a sign of Vestibular Migraine, especially in girls with a positive past history of migraine or family history of migraine.

Tip 6: Sleep related short duration headache attacks can be a sign of Hypnic headache after exclusion of secondary causes.

Tip 7. Unilateral sustained headaches at the same side of the head, associated with cranial autonomic features, can be a sign of Hemicrania Continua after exclusion of secondary causes.

Tip 8. Headache attacks with triggered by any specific activity such as excercise, cough, sexual activity etc. can be a sign of Benign Exertional Headaches after exclusion of secondary causes.

Conclusions: The differential diagnosis of unusual headaches in children requires a systematic approach. All of the cases with atypical headache syndrome requires excluding secondary causes of headache.

P276

Headache (HA) in Children and Adolescents (C/A) with Fibrous Dysplasia (FD) of the Skull

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Objectives: To determine the frequency of HA in C/A with FD of the skull. To determine if the relationship is causal or incidental.

Background: FD is a disorder in which abnormal fibrous tissue gradually replaces normal bone. It begins in children and adolescents, and may progress into adulthood. It may be symptomatic or asymptomatic. It can lead to bone distortion, expansion, and compression of nervous and vascular structures. The presentation is dependent on the site of involvement and extent of expansion. Cranial monostotic FD involves any bone(s) of the cranium, polyostotic FD involves at least one additional area of the skeleton.

Methods: Data was collected by two methods. (1) A literature review of C/A with FD of the skull. (2) A retrospective chart review of patients $\leq$18 years of age at the Cleveland Clinic Foundation from January 2006 to June 2011 identified with FD of the skull. Data was collected on clinical features, demographics, neuroimaging, treatment, and outcome.

Results: Literature on C/A with FD of the skull is limited. A study of 28 children and adolescents with FD with a mean age of 11.4 at presentation was reviewed. There were 17 boys and 11 girls. FD most often involved the orbital region and the floor of the anterior cranial fossa as a continuous lesion. The frontal bone (82%), sphenoid (71%) and ethmoid bone (68%) were involved most commonly. Cosmetic complaints were present in 23 (82%). Symptoms were headache (25%), visual loss (7%), proptosis (47%), or other cranial asymmetries (39%). All underwent surgery. Resection of less then 90% of the FD was a significant predictor of disease recurrence. Six cases had stenosis on the optic foramen, 4 of which had normal vision. Of these 4, 3 with optic nerve compression underwent a prophylactic unroofing of the optic canal. Two presented with impaired vision. One underwent staged bilateral optic nerve decompressions and is stable. The second had significant unilateral reduction in visual acuity and profound unilateral optic disk pallor. 10 cases of monostotic FD were identified. Mean age was 12.8 at diagnosis, with a 1:1 male to female ratio. Primary reasons for imaging were headache (60%), vision abnormalilies (20%),

nasal abnormalities (10%) and jaw expansion (10%). The primary bones of involvement were the sphenoid (5), maxilla (3), ethmoids (1), and occipital (1). Contiguous bone involvement was seen in 7 cases. Optic nerve compression was present in 4 cases, all of which underwent surgery. None presented with headache. 6 cases without associated symptoms underwent imaging for HA and were incidentally diagnosed with FD. It could not be established that the FD caused the HA in these patients.

Conclusions: We report 10 cases of monostotic FD in C/A. Diagnosis of cranial FD is often incidental and discovered during imaging for HA. FD does not cause headache, unless accompanied by associated symptoms such as nerve compression or bony expansion and deformity. Patients presenting with headache as their only symptoms should undergo conservative treatment with regular follow-ups. The use of pamidronate is an option.

P277

Does Internet (I) and Mobile (M) Abuse Interfere with Headache and Somatic Complaints (SC) in Adolescence (A)?

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Objectives: Aim of our study is to verify if the abuse of that is associated with more Headache and other SC.

Background: It is well known that A. use I and M for many h.x day.

Methods: The sample is composed by 764 students (M 396; F 368) (10-16 yo; m.a. 12,39; ds 1.01) of a borough near by Rome.

All the S. received a cluster of self reported questionnaire:

The sample was divided in Internet N-Abusers (<4 h x d.) and Abusers (> 4 h x d); Mobile N-Abusers (<12 h x d with mobile switched on) and Abusers (>10 h x d with mobile switched on) according to the Self reported Q.

Chi square Test and Anova was applied.

Results: Headache General (293S.): 145 S, 20,1% (70M; 75 F) referred at least one attack of M (M. Mwa, Probable M) in the last year, 148 S. 20,3% (78M; 70 F) of TTH.

Questionnaire back were 723 (drop out 41, 5,4%):

IMQ results:

NA: INTERNET: 620/723 (88%); MOBILE: 444/723 (60%)

A: INTERNET: 92/ 723 (12%); MOBILE: 304/723 (40%)

ABUSERS WITH HEADACHE /MIGRAINE: INTERNET 72/92 8 ($p<0,001$); MOBILE 247/304 ($p<0,001$)

No statistical difference between M and TTH, neither in Gender.

MPAS Results:

Inside the Abuser group M present more nausea ($p<0.05$) and Vertigo ($p<0.01$). F more Daytime Sleepiness ($P<0.05$), Difficulties in falling asleep ($p<0.05$), Night Awakeings ($p<0.05$), Stomachache ($p<0.05$), Lack of Appetite ($p<0.05$), Food Intollerance ($p<0.01$).

Among headache suffers, females reported higher scores than males on the Addiction Mobile Scale of SPQ (F: M= 21,80 – DS=10,35 vs M: M=20,70 – DS=9,83). Conversely gender differences is not observed in the scores regarding Internet Addiction scale of **SPQ**. (F: M= 22,59 – DS=10,78 vs M: M=23,33 – DS=10,36).

A positive and statistically significant correlation is highlighted between *Internet addiction* (**SPQ**) and somatic complaints (**CSI**) (r=,202 $p<0.01$), in particular with neurological (r=,179; $p<0.01$), cardiovascular (r=,221; $p<0.01$), and gastrointestinal cluster symptoms (r=,102; $p<0.05$), but not with those symptoms related to pain (r=,078; $p>0.05$). Conversely, with regard to *Mobile addiction* a positive and statistically significant correlation with somatic complaints is observed (r=,088; $p<0.05$), especially with the symptoms related to pain (r=,126; $p<0.01$).

Adolescents with M and TTH have highest level of somatic complaints in CSI versus non sufferers (M:1,18; $p<0.01$) independently of sex but dependently on excessive use of I and M.

Conclusions: I and M abuse deeply influenced Headache and Migraine in Adolescence.Internet and M Checking Q. (IMQ, Cerutti 2005) M Abuse S (MPAS, Cerutti 2005). Both of them analyze use/ abuse of I and MShorter Promize Q. (SPQ, Christo 2003). All the varieties of Addiction risks.Children Somatization Inventory (CSI, Walker 1992) focused on Somatic Complaints (SC). Headache Clinical Record. Based on ICHD-2, 2004.

P278

Medical Messages about Headaches in the Traditional Media. A History of Glorification of High-Tech Therapeutic Approaches and Miseducation. Media Observatory Alleanza Cefalalgici. How Media Tell Things

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Objectives: Alleanza Cefalalgici, (Al-Ce.), an Italian organization for headache sufferers working for increasing awareness on headache, has creates a Media Observatory (MO), a multidisciplinary team including headache specialists, patients and journalists with the aim to study and analyze the information about headache released by traditional media.

Background: 31% of EU citizens consider medicine as the most interesting issue on news and 64% of the Italians declare to be interested in being informed on scientific research. Traditional media are the most popular means for medical information (61% of EU citizens watch regularly or occasionally TV programs about health and science – Eurobarometer 2007). Media reports about medical issues may influence general public, policy makers and health professionals. No study has ever investigated how the traditional media inform about headaches.

Methods: MO monitored the 4 main Italian newspapers and the 6 national traditional TVs, looking for information regarding headaches. In addition all Al.Ce. members were invited to inform MO about headaches info/news released by other sources. For every piece of information, MO evaluated: a) the form of presentation b) the topic of the news and their c) relevance/usefulness, d) reliability/accuracy, e) correctness/objectivity, f) comprehensibility. The study lasted six months and was completed on November 2010.

Results: Forty pieces of information were identified in the study period (80% from journals and 20% from television). 72.5% of the info were presented as short news and 20% as in-depth news. 40% of the pieces analyzed were released by journalists, 27.5% were integrated by specialists' interview and 23% consisted only in specialists' interview. The majorities of the media information was about "new therapies"(50%), followed by "general information" (13%), "basic research data" (13%) and "patographies" (13%). The relevance, accuracy and correctness of media information about headaches was rated as poor/very poor in 35%, 43% and 55% of the pieces, respectively. The comprehensibility was almost always considered as good.

Conclusions: The traditional media information about headache is essentially limited to a sensationalistic and poorly objective glorification of high-tech therapies creating unrealistic expectations in headache sufferers. Traditional media dedicate space to popular medical topic such as the headaches but they seem to do so without an educational project, rather following what the media experts call a "fast thinking" or "fast coping" strategy.

P279

Hiccups as a Migraine Aura

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Objectives: To report a case of hiccup as a migraine aura.

Background: The most common migraine aura symptoms are visual and sensory. Prolonged or intractable hiccups have been well described in the literature, and may be gastrointestinal, systemic or drug induced. Central nervous system disorders are associated with intractable hiccups include brain stem lesions such as vascular malformations, ischemia, or plaques of multiple sclerosis or neuromyelitis optica[1]. There has been one case report of intractable hiccups associated with migraine [2], however the patient had prolonged hiccups which did not clearly precede his migraine attack.

Methods: A 24-year-old woman had episodic migraine without aura starting at age 15. Her headaches worsened at age 17. She developed mild dysphagia and tongue deviation was found on neurologic exam. MRI revealed a Chiari malformation. She underwent posterior fossa decompression surgery with resolution of her neurological deficits but she continued to have episodic migraines. A year later, she developed hiccups which preceded her migraine attacks 90% of the time. Her hiccups lasted 30-60 minutes, and were followed by her typical migraine 30 minutes later. The rate of hiccups remained constant during their duration. Her headaches were left-sided and met ICHD-2 criteria for migraine. Her severe migraines lasted 2 hours and occurred about 3 times a week.

Results: Intractable hiccups have been associated with various central nervous system causes. Hiccups as a migraine aura has not been described. The pathophysiology of hiccups is not well understood, but includes afferent, efferent

and central mediators [3]. Many of these structures are also involved in pathogenesis of migraine. The afferent limb includes the sympathetic chain, phrenic and vagus nerves. The efferent limb (phrenic nerve) includes the complex interaction between the brainstem and midbrain areas, including respiratory center, phrenic nerve nuclei, medullary reticular formation, and hypothalamus[1,3]. The central connection between afferent and efferent limbs seems to be a nonspecific anatomic location between the cervical spine (C3 - C5) and the brainstem. Hiccups have also been linked to phasic autonomic efferent activity[4] and migraineurs are prone to autonomic dysfunction[5]. GABAergic effects may be involved. Cortical spreading depression, the likely pathophysiology of aura is modulated by GABA receptors, and GABA agonists are frequently used as hiccups treatment. Our patient satisfied the ICHD-2 criteria for migraine although hiccup is not a stated aura symptom in the ICHD-2 classification. Her Chiari malformation was unlikely related to her headaches, as her hiccups started after successful decompression surgery.

Conclusions: Hiccups can present as a primary aura symptom in patients with migraine.

P280

Effect of Anodal Transcranial Direct Current Stimulation Over the Visual Cortex on Thermosensitivity Assessed by Quantitive Sensory Testing and Contact Heat Evoked Potentials

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Objectives: To explore the effect of anodal tDCS over the visual cortex on thermal Quantitative Sensory Testing (QST) and Contact Heat Evoked Potentials (CHEPs) in episodic migraine patients interictally and in healthy volunteers.

Background: We have shown that the visual cortex is hyperresponsive in migraine between attacks because of a habituation deficit likely due to a decreased preactivation level (1). Moreover, reciprocal interrelations were recently demonstrated between the visual cortex and the trigeminal pain system (2, 3). Anodal transcranial Direct Current Stimulation (tDCS) can increase the activity level of the underlying cortex and thus, is able to increase VEP 1st block amplitude and habituation (4).

Methods: We recorded 13 patients (EM, 22.1 $\pm$3.7 yrs; 4M) suffering from episodic migraine in interictal phase and 13 healthy volunteers (HV, 22.8 $\pm$ 2.9 yrs; 6M). Migraine preventive drugs were not allowed. Thermal QST was performed with an ATS thermode (Medoc Ltd, USA). We determined cold and heat detection (CS, WS) and pain thresholds (CP, HP) on the volar wrist and the forehead. For CHEPs we delivered 20 heat stimuli to the right wrist and forehead (53°C, ISI 10-25 s). CHEP N2-P2 component was recorded from Cz-Fz EEG activity and averaged in 5 successive blocks. Both QST and CHEPS were recorded before and after a 15-min session of anodal tDCS performed (anode over Oz, cathode on the chin at an intensity of 1 mA).

Results: Anodal tDCS of the visual cortex did not modify QST values in neither group of subjects.

In HV tDCS significantly increased the percentage of habituation between 1st and 5th block of the CHEP N2-P2 component obtained after stimulation of the forehead ($p<0.05$) and tended to increase the habituation slope over the 5 blocks of averaging ($p=0.08$). Anodal tDCS had no effect on the initial CHEP 1st block amplitude.

In EM, anodal tDCS did not induce any CHEP modification.

Conclusions: Anodal (excitatory) tDCS over visual cortex is able to increase the habituation of forehead i.e. trigeminal Contact Heat Evoked Potentials in HV. This suggests that the activation of visual areas is able to decrease responsiveness of cortical generators of the thermonociceptive response and confirms the functional link between vision and trigeminal pain processing. Such an effect may not be demonstrable in migraineurs because the preactivation level of the visual cortex is lower.

P281

Therapeutic Response to Cranial Peripheral Nerve Stimulation in Patients with Chronic Refractory Primary Headaches

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Objectives: To determine the efficay, safety and outcomes of simultanous supraorbital and occipital nerve

stimulation in patients with chronic primary refractory headaches.

Background: Chronic migraine (CM) and New Daily Persistent Headache (NPH) are chronic primary headaches (CPH) frequently related to treatment refractoriness and low quality of life. In the last years it has been proposed simultaneous supraorbital nerve (SON) and occipital nerves (ON) stimulation (NS) posses higher efficacy than ON stimulation alone. Currently there is few experience in Colombia and Latin America with the use of this therapeutic approach.

Methods: Observational study of a cohort of patients with chronic primary refractory headaches (CPRH) that were subjected to SON and/or ON NS between May 2010 and July 2012. We included all patients with at least six months of follow-up after implantation who responded to a first month phase trial. Patients must have been considered to be chronic, refractory according to AHS 2008, disabled by the headache, and without uncontrolled neuropsychiatric disease. The surgical procedure was done after a headache staff meeting. The results are presented with a comparison of means and proportions for paired samples using non-parametric statistics.

Results: 15 Patients were subjected to NS in the study period; 14 met the inclusion criteria. The average age was 41 years (SD: 8.8); 57.1 % were women. The 85.7 % of the patients had chronic refractory migraine (CRM) and 14.3 % NDPH. The average evolution time was 16 years (SD: 11.1); before the procedure the average abortive treatments used was 21 (SD: 3.4) and 19 preventive medications (SD: 4.4); only one patient had no criterion of analgesics overuse. Half of the patients had associated anxiety or depression. 78.6 % of the patients showed global improvement, wich was clinically and statistically significant. Before surgery, except one patient none of the subjects had headache (HA) free days or HA free hours per month; after NS, half of the patients reached at least three hours HA free/day (on average 6+3 hours) and at least five days HA free/month (on average 9+4 days). Before surgery, all patients had moderate to severe HA (VSA $>$ 8, 71.4 % severe HA); after NS, the 85.7 % of the patients significantly decreased HA intensity to 6 or less; the average percentage of improvement according to VAS was 51% (SD: 20.2 %). Similarly, the average percentage of subjective improvement was 55% (SD: 23.2 %).

Conclusions: Simultaneuos SON and ON NS can be an effective and safe therapy for CPRH patients. Optimal selection of candidates and the successful of NS therapy it is related always to an interdisciplinary team work. There is a need to identify the profile of patients that can respond to this treatment.

P282

Hypoxic Preconditioning with Cobalt Chloride Attenuates the Orofacial Pain

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Objectives: The aim of the study was to investigate the effects of one dose versus 3 weeks CoCl2 preconditiong on orofacial pain test (OFT) in mice.

Background: Cortical spreading depolarization waves (CSD), massive temporary neuronal depolarizations that slowly propagate through cerebral cortex from brain injured tissue could cause hypoxia (1). Hypoxic injuries can be prevented by preconditioning with cobalt chloride (CoCl2), a hypoxia mimetic, that stabilizes HIF-1 (degraded in normoxic conditions) (2,3), possible through enhancing the antioxidant status by the reduction of ROS/NO and by lowering NFkappaB DNA binding activity and its regulated pro-inflammatory mediators (4).

Methods: Thirty-two BALB/c male mice were divided into 4 groups: 2 of the groups received CoCl2 12.5 mg/Kg b.w. intraperitoneally – group CoCl2 acute (single dose 1 hour before formalin injection), group CoCl2 chronic (multiple doses daily for 3 weeks). 2 groups served as control (group S-acute & group S-chronic), mice treated with saline in a dose /time manner similar with CoCl2 groups. The time mice spent grooming and rubbing the injected area was reported separately for the two phases of the OFT. One-way ANOVA followed by Bonferroni's post-hoc comparisons tests were performed in statistical analyses.

Results: A single CoCl2 dose decreased the first phase of OFT ($p = 0.004$) with no effect on the second phase as compared with control group. Hypoxic preconditioning with CoCl2 for 3w attenuates the pain on the second phase of the OFT ($p = 0.041$), but have no effect on the first phase when compared with control group. In the first phase of OFT there was a significant difference ($p = 0.001$) between one dose analgesic effect (36.98%) vs. repeated dose of CoCl2 effect (1.28%). Although in the first 3 hours after single CoCl2 injection, the motor activity (activity cage and Rota rod tests) was significantly disturbed; in the preconditioning experiment the motor activity recovered starting with the 14th day.

Conclusions: Our results demonstrate that CoCl2 exposure modulates orofacial pain. Although a single dose of CoCl2 has no significant effect on the inflammatory orofacial pain, the antinociceptive effect observed in the first phase must be interpreted with caution as long as the motor coordination and activity were disturbed. 3 weeks of CoCl preconditiong significantly increased the nociceptive threshold for the orofacial inflammatory pain.Taken together our data shows that hypoxia precondition in BALB/c mice has an analgesic effect on the inflammatory phase of the OFT.

P283

Placebo tDCS Induces Acute Changes in the Endogenous mu-Opioid System

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Objectives: We aimed to investigate the immediate effects of placebo transcranial Direct Current Stimulation tDCS in the human endogenous mu-opioid system.

Background: TDCS is widely used method of non-invasive brain stimulation that has been proved to be safe and effective in patients with chronic pain disorders, such as: central pain after traumatic spinal cord injury, fibromyalgia, orofacial pain, and also in chronic migraine. Nevertheless, its mechanisms involved in pain control as wells as its placebo components are not fully elucidated. Although different neuroimaging techniques, using magnetic resonance imaging (MRI) have been applied to investigate tDCS effects, positron emission tomography (PET) is considered a more sensitive method to detect molecular changes in the central nervous system function driven by non-invasive brain stimulation.

Methods: A total of nine healthy volunteers were recruited to this study. All were right-handed, ages between 18 and 65 years old, with no history of chronic pain (e.g. fibromyalgia or migraine) or systemic disorders (e.g. diabetes or multiple sclerosis). The protocol included two PET scans for each subject, using a radiotracer with specific affinity for μ-opioid receptors, [^{11}C]carfentanil. The first PET provided a baseline evaluation of the regional mu-opioid receptor (MOR) availability *in vivo* (non-displaceable binding potential BP_{ND}). Placebo tDCS was only applied during the early phase of the second PET exam, using the primary motor cortex and frontal cortex, the most common montage adopted for pain control.

Results: Placebo tDCS was associated with a decrease of $MORBP_{ND,}$ indicating a release of endogenous opioids, in the periaqueductal grey matter (PAG), left thalamus and posterior cingulate cortex.

Conclusions: Although still preliminary, our results suggest that clinical outcomes observed with tDCS can be, at least in part, related to placebo tDCS-induced activation of the endogenous mu-opioid system.

P284

Thin Film Spectacle Coatings for the Treatment of Photophobia and Migraine

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Objectives: To determine if thin film spectacle coatings may be used to reduce photophobia, migraine frequency and migraine severity.

Background: Nearly all migraine patients report photophobia (light sensitivity) during a migraine and many migraineurs report that light may trigger an attack. Some patients are chronically light sensitive (1). The pathway that mediates photophobia appears to involve intrinsically photosensitive retinal ganglion cells (IPRGCs) and trigeminal afferents (2,3). These retinal ganglion cells do not require input from photoreceptors to be activated by light and have been shown to be responsible for circadian rhythm entrainment and the pupillary light reflex. As such, these cells constitute a pathway separate from the visual pathway (4). IPRGCs contain the chromophore melanopsin. Melnopsin has an action spectrum that peaks at 480 nm, in the blue-green region of the visible spectrum.

We used thin film technology to design a lens coating that when applied to standard spectacles would function as an optical notch filter, blocking out the light that activates IPRGCs. We hypothesized that wearing spectacles that integrated this filter, subjects would experience less light sensitivity, fewer migraines, and a decrease in headache severity.

Methods: This research was approved by the IRB and informed consent was obtained prior to enrollment. We recruited 50 subjects who met IHS criteria for migraine with or without aura and chronic migraine. We utilized two sets of glasses: Our interventional glasses blocked light at 480 nm and our sham glasses blocked light at 620 nm. Subjects were randomized to wear one set of spectacles for two weeks. After a two-week washout period, subjects crossed over to wear the other glasses for two weeks. Both the investigators and the subjects were masked as to which glasses were being worn throughout the trial. Photophobia, migraine frequency and migraine severity were measured using headache diaries, a photophobia questionnaire, and the Headache Impact Test (HIT-6™). Analysis was performed on an intention-to-treat basis. Primary outcome was change in HIT-6 induced by the two pairs of glasses compared to baseline. Secondary outcome was improvement in headache frequency and severity as measured by the diaries and questionnaires.

Results: Two patients have been treated with prototype filters and both experienced dramatic improvements in light sensitivity, headache frequency and headache severity. Because of this anecdotal success, we have initiated a prospective, randomized, double-masked crossover study. This clinical trial is not yet complete, but will be completed prior to the Annual Meeting. Results will be presented at the Annual Meeting.

Conclusions: We hope to demonstrate that modulation of light at 480 nm can be used prophylactically in the treatment of migraine and chronic daily headache.

P285

Cutaneous Allodynia Influences the Analgesic Effect of Transcutaneous Electrical Nerve Stimulation Therapy in Headache Sufferers

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Objectives: To test if cutaneous allodynia influences the response to treatment with TENS in headache sufferers.

Background: Transcutaneous electrical nerve stimulation (TENS) therapy has been reported to be effective in the management of headache symptoms. It has been suggested that the presence of cutaneous allodynia decreases the response to treatment with triptans in migraine.

Methods: One hundred and forty –five consecutive headache sufferers were randomized to be treated either with real or sham TENS therapy. Cutaneous allodynia and pain were assessed using 12 item allodynia symptom checklist (ASC-12) and 10 cm –visual analogue scale (VAS), before the treatment and during the follow-up. Patients were grouped in 2 groups according to cutaneous allodynia total score: Group 1 consisted of 59 patients with a score from 0 to 5 (non-allodynic patients), and Group 2 consisted of 86 patients with a score above 6 (allodynic patients). TENS therapy was administered at the back of the head bilaterally for 30 minutes, three times a day for two consecutive weeks. During the follow-up, all patients were examined at 15, 30 and 60 days in order to evaluate the analgesic effect of TENS therapy. Primary end-point was change in number of headache free-days (>50%).

Results: A significant change in number of headache free-days above 50% was observed in 53 (49%) out of 108 patients treated with real TENS. Of these patients thirty-seven respondents (82%) were non allodynic. While 47 (75%) out of the 63 non respondents were allodynic patients. Only 2 (5%) out of the 37 patients were responsive to sham TENS therapy. Of note, we observed that the analgesic effect of TENS therapy lasted about 60 days in these patients.

Conclusions: Cutaneous allodynia influences the analgesic effect of transcutaneous electrical nerve stimulation therapy in headache sufferers, suggesting that TENS therapy may be useful in the short management of headache sufferers without severe cutaneous allodynia.

P286

Combined Occipital and Supraorbital Neurostimulation for Chronic Migraine Headaches: A Multicenter Retrospective Analysis of 171 Consecutive Patients

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Objectives: To present the results of a retrospective analysis of 171 consecutive patients with chronic migraine treated by combined occipital nerve and supraorbital nerve stimulation (ON-SONS).

Background: In 1999 we introduced occipital nerve stimulation (ONS) as a novel treatment for occipital neuralgia. Others extended the methodology to migraine headaches with the results suggesting a lower response rate than that for occipital head pain. Hypothesizing that the addition of supraorbital stimulation may improve the results for chronic migraine, we developed the associated procedure and in 2009 reported positive results in a series of patients treated by combined ON-SONS. Thereafter, we further perfected the methodology and to date have implanted combined systems in over 300 patients. Here we report the results of a retrospective analysis of 171 consecutive patients from 5 implanting specialists across 3 different centers.

Methods: Between May 1, 2009 and April 18, 2012 our group implanted combined ON-SONS systems in 171 patients. Following a review of the medical record, each patient received a survey request. Included were scores for the Migraine Disability Assessment (MIDAS) and a set of clinical parameters, including headache frequency and severity, medication usage, and overall patient satisfaction.

Results: 162 patients (126 female; 34 male) responded to the survey. 24 were adolescents, ages 14 to 19. All suffered from chronic migraine that had failed to respond to conservative management. The average time since permanent implant was 14 mo. 85% of patients reported over 50% improvement in HA frequency (HA days/mo) and/or severity (VAS 0-10). The average HA days/mo decreased by 73% (27 to 7), and the average severity of the headaches, when they occurred, improved by 59% (9 to 4). 50% saw virtually complete resolution of headaches (0-1/mo). 71% of patients decreased medication usage by over 50%, and 38% were able to completely discontinue all routine headache medications. The MIDAS score improved by 76% (avg 208 to 50). 87% felt the treatment to have been successful, and 93% would recommend it to others. 93% of patients preferred the combined ON-SONS mode, as opposed to a mode that stimulated only the ONs.

Conclusions: Combined ON-SONS provides effective therapy for some patients with intractable chronic migraine headaches. The degree of responsiveness reported here was markedly improved over that reported by most studies evaluating ONS alone, including the large multicenter (Medtronic, St. Jude) study groups. The data strongly supports the addition of SONS to ONS (alone) when evaluating these patients for PNS therapy.

P287

Combined Occipital and Supraorbital Neurostimulation for Chronic Migraine Headaches in Adolescents (Ages 14-19): A Retrospective Analysis of 23 Consecutive Patients

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Objectives: To present the results of a retrospective survey of adolescent patients with severe, intractable chronic migraine treated with combined occipital-supraorbital neurostimulation (ON-SONS).

Background: In 1999 we introduced occipital nerve stimulation as a novel treatment for occipital neuralgia. Hypothesizing that the addition of supraorbital stimulation may improve the results for chronic migraine, we developed the associated procedure and in 2009 reported positive results in a series of patients treated by combined occipital nerve-supraorbital nerve stimulation. Thereafter, we further perfected the treatment methodology, and to date have implanted the combined system in over 300 patients, including a growing series of adolescents.

Methods: Between December 14, 2009 and May 3, 2012 our group implanted combined ON-SON stimulation systems in 23 adolescent patients. Following a review of the medical record, each patient received a survey request. Included were scores for the Migraine Disability Assessment (MIDAS) and a set of clinical parameters, including headache frequency and severity, medication usage, overall patient satisfaction, and patient preference for either the combined or single modality therapy (ON-SONS vs. ONS).

Results: All 23 patients (14 female; 9 male) responded to the survey. Their ages ranged from 14-19 (mean 16). All suffered from chronic migraine that had failed to respond to conservative management. The average time since permanent implant was 12 mo. 87% of patients reported over 50% improvement in HA frequency (HA days/mo) and/or severity (VAS 0-10). The average HA days/mo decreased by 79% (29 to 6), and the average severity of the headaches, when they occurred, improved by 80% (9 to 2). 76% saw virtually complete resolution of headaches (0-1/mo). 86% of patients decreased medication usage by over 50%, and 57% were able to completely discontinue all routine headache medications. The MIDAS score improved by 68% (avg 243 to 77). 87% overall felt the treatment to have been successful and all would recommend it to others. All patients could have their stimulators programmed to

stimulate only the ONs or the combined ON-SONs. Almost all (95%) used both frontal and occipital stimulation modes exclusively.

Conclusions: Combined ON-SONS provides effective therapy for some patients with intractable chronic migraine headaches. The degree of responsiveness reported here was markedly improved over that reported by most studies evaluating ONS alone, including the large multicenter (Medtronic, St. Jude) study groups. The data strongly supports the addition of SONS to ONS (alone) when evaluating these patients for PNS therapy.

P288

Neuromodulation: Model-Based Control of Cortical Excitability in Early and Late Aura Phase

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Objectives: We investigated statistical properties in a computational model to gain a dynamical understanding of spontaneous episodes of spreading depression (SD) and we suggest a novel neuromodulation approach by model-based control that prevents these episodes.

Background: SD is the key to the subtype of migraine with aura (MA). Computational, mathematical, and animal models of SD have been extensively investigated by many research groups. SD is a transient pattern forming cortical state. During the course of SD, the ion homoeostasis is massively perturbed in the cortex by initially seizure-like discharges, followed by a nearly complete depletion of ion gradients across cell membranes. The recovery last several minutes.

Methods: We analyze spontaneous episodes of SD in computer simulations of localized SD wave fragments formed in the gyrified human cortex obtained by fMRI.

Results: The results supports the controversial idea that SD can have a causal relationship with the headache phase in migraine. In particular three predictions are discussed: (i) that the cascade initiating the pain phase depends on a sufficiently large area instantaneously affected by SD, (ii) that SD in migraine without aura (MO) is neither lasting long nor propagating far enough to cause noticeably aura symptoms because the initial perturbation covers a large area, and (iii) that only from a smaller ictogenic focus SD can break away and propagate as a localized wave. This would also explain, why, on average, the headache is reported to be less severe in MA than in MO.

Conclusions: Neuromodulation techniques that target SD waves must stimulate in the early and late phase of SD with different protocols to individually attack pathways of aura and pain formation.

P289

Safety and Efficiency of Supraorbital Transcutaneous Neurostimulation with the Cefaly® Device for Headache Treatment: Outcome of a Prospective Registry on 2,313 Patients

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Objectives: The objective of this short survey was to assess the satisfaction of patients using the supraorbital transcutaneous neurostimulator Cefaly® for headache prophylaxis and to record their self-reported adverse events.

Background: Supraorbital transcutaneous neurostimulation (STN) has recently demonstrated its efficacy over sham stimulation in episodic migraine prevention (1) but its safety and performance in larger cohorts of "all coming" headache sufferers are unknown.

Methods: The adverse events (AEs) and willingness to continue STN therapy were prospectively monitored in patients renting the Cefaly® device (STX-Med, Belgium) to treat their headaches. The evaluation was performed at the end of the rental period (40 or 80 days). Patients were coming from Belgium and France which are countries where the Cefaly® device is available as OTC for rent and sale.

Results: From September 2009 to June 2012, 2313 headache patients (1641 females, 672 males, aged 14-87 years) accepted to provide a follow-up after STN treatment (by phone call and/or email). Basically, all of them had been contacted as they had mentioned a regular triptan use prior to STN therapy; a majority was therefore likely to suffer from migraine. Among the 2313 users, 53.4% were satisfied with STN treatment and were willing to buy the Cefaly® device, while the other 46.6% stopped the therapy. Ninety-nine patients (ie 4.3%) reported one or more AEs but none of them were serious. A large majority (91%) could be anticipated and was likely to be related to the stimulation, and for 9% the relationship with STN was questionable (for example palpitations or panic attack during the night following a session of STN). The most

frequent AEs were local pain/intolerance to paresthesia (47 patients, ie 46%), sleep disorders (mostly sleepiness/fatigue, sometimes insomnia, 19 patients, ie 18.6%), headache occurrence after stimulation (12 patients, ie 11.7%) and local reactions related to STN (7 patients, ie 6.7%).

Conclusions: This registry of more than 2000 patients confirms that STN is a safe and well-tolerated technique. More than 50% of patients wanted to buy the device after the rental period, which emphasizes its probable effectiveness in a majority of them.

P290

There Is No Venostenotic Idiopathic Intracranial Hypertension without Papilledema in Headache Sufferers. Clinical Findings and CSF Pressure Measurements

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Objectives: To determine the frequency and the clinical findings of non-venostenotic idiopathic intracranial hypertension (IIH) without papilledema (IIHWOP) in headache sufferers.

Background: Bilateral transverse sinus stenosis (BTSS) is common in patients with IIH with papilledema. However, it is less clear whether BTSS is always present in patients with IIHWOP.

Methods: In a prospective study from July 2010 to December 2012, 60 headache sufferers (51 men and 9 women, mean age 42 years, SD 13; mean BMI = 32, SD= 5) who fulfilled the diagnostic criteria for IIHWOP underwent 3D-PC MR venography of the brain the day before lumbar CSF pressure measurement. All patients underwent lumbar puncture (LP) in order to measure lumbar CSF opening pressure and to monitor CSF pressure for 1 h through a lumbar needle.

Results: Cerebral MR venography displayed BTSS in 37 (62%) out of 60 patients with established IIHWOP. While, 23 (38%) patients had normal appearances of both transverse sinuses. Comparing those patients with non-venostenotic IIHWOP vs venostenotic IIHWOP, there was difference in CSF opening pressure and mean CSF pressure. Moreover, chronic tension-type headache and tinnitus were more common in non-venostenotic patients.

Conclusions: Our findings highlight that non-venostenotic IIHWOP may occur in headache sufferers, suggesting that BTSS is only one of the contributing factors in IIHWOP.

P291

Vertigo: Think Migraine

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Objectives: This study aims to identify the clinical predictors of the diagnosis of migraine associated vertigo(MAV) amongst a group of patients who were referred for Electronystagmography.

Background: Vestibular cause is often suspected when vertigo is the presenting symptom. Bedside testing and ENG (Electronystagmography) are commonly used to diagnose vestibular causes of vertigo. When a vestibular cause is not found, clinicians often navigate the maze of non-vestibular causes of vertigo. In this scenario, one of the diagnostic possibilities that is worthy of consideration is MAV. In the past decade, MAV has drawn research interest to establish its validity as a clinical entity. This paper seeks to understand the clinical predictors of MAV amongst patients with vertigo.

Methods: The study was a retrospective chart study at a tertiary health center with electronic medical records. IRB approval was obtained. Data was requested from a computerized data base of people who have had an ENG performed between the time period of January 1, 2005 to December 30, 2010.

Of these, patient who were 18 yrs. or older with the presenting complaint of vertigo were included in the study. 128 patients met the inclusion criteria. Clinical diagnosis of MAV was gathered before ENG (stage 1), after ENG (stage 2) and at follow up visit (stage 3). Those who were diagnosed with MAV at stage 2 were managed with standard treatments for migraine, including abortive and/ or prophylactic treatments. The clinical predictors evaluated were age, gender, duration of vertigo, otic, neurologic and migraine associated symptoms at stage 1, ENG results, audiometry and neuroimaging results (when available). In addition, Pre ENG and Post ENG diagnosis of Migraine associated vertigo were studied as clinical predictors, to determine if ENG results influenced the final clinical diagnosis of MAV.

A decision tree analysis was performed to identify predictors of diagnosis of MAV at stage 3.

The follow up (stage 3) diagnosis was organized in two categories: MAV and other. Using a technique known as Classification and Regression Trees (CART), an analysis was conducted to predict the dichotomized follow up diagnosis from the fifteen demographic and clinical variables mentioned above. The worth of the method is determined by the degree of classification accuracy. Only two of the fifteen predictors made it into the tree. 10-fold cross validation was done. The overall classification accuracy was 85%.

Results: Diagnosis of MAV at stage 2 was the best predictor of diagnosis of MAV at stage 3.

Age over 44 yrs. was the next best predictor of MAV.

Neither Migraine associated symptoms at stage 1 nor ENG results by themselves were strong predictors of MAV.

Conclusions: When bed side testing yields unclear results and ENG is performed in patients, it can be valuable in excluding peripheral vestibular cause and reliably diagnose MAV. When peripheral vestibular cause is excluded by ENG, vertigo by itself may be the only symptom of MAV.

P292

A Record of Retinal Artery Vasospasm with Transient Monocular Visual Loss with Subsequent Headache

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Objectives: In order to clarify the mechanism of development in this case, we conducted this study.

Background: Transient monocular visual impairment with subsequent migraine headache is known as retinal migraine. However, the characteristics of the headache sometimes do not satisfy the criteria of migraine. It is also difficult to confirm the dynamic vasospasm. We report here a case of headache observed with retinal artery spasm.

Methods: A 29-year-old women who came to our hospital because of transient monocular right visual loss. She had histories of typical aura with non-migraine headache as well as typical aura without headache several times a year for these 9 years. She had taken medication for pituitary microadenoma for 5 years. One the day she came to our hospital, she felt blurry vision in her right eye subsequent visual field constriction. The symptoms resolved completely after 5 minutes and then mild headache appeared. After the second episode of visual symptoms, she visited our hospital. During the attacks her visual acuity was under light perception. Her general medical and other neurologic examinations were normal. Magnetic resonance brain imaging and angiography were normal.

Results: We recorded her fundus through a slit-lamp microscope and a non-contact concave lens during the episode of visual loss. During the attack the record showed narrowing of the retinal arteries and veins and disc pallor, and relative afferent pupillary defect (RAPD) was observed. In the late phase of the attacks, we confirmed the reperfusion of the retinal circulation. After the episode resolved, the retinal vessels, especially the veins, were dilated and the disc was hyperemic.

Conclusions: RAPD indicates possible existence of mild optic neuropathy. Therefore, her visual symptoms may be due to not only retinal ischemia but also optic nerve ischemia.

Her visual dysfunction was monocular and completely resolved followed by headache. We surmised, therefore, that this case is diagnosed as retinal migraine, but failure to accompany the headache does not satisfy the criteria of retinal migraine.

P293

Reduced Circulating Endothelial Progenitor Cells in Reversible Cerebral Vasoconstriction Syndrome

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Objectives: To investigate the numbers of circulating endothelial progenitor cells (EPCs) in patients with reversible cerebral vasoconstriction syndromes (RCVS).

Background: The pathophysiology of RCVS remains elusive. Endothelial dysfunction might play a role, but direct evidences are lacking. We hypothesized that patients with RCVS might have a reduced capacity of circulating EPCs to repair the dysfunctional endothelial vasomotor control.

Methods: We prospectively recruited RCVS patients (within 2 weeks of disease onset) and healthy controls. Flow cytometry was used to quantify the numbers of circulating EPCs defined as KDR^+CD133^+, $CD34^+CD133^+$, $CD34^+KDR^+$ double-positive mononuclear cells. The mean flow velocities of middle cerebral arteries and Lindegaard index (LI) in patients with RCVS were recorded via transcranial color-coded sonography on the same day of blood drawing.

Results: This study recruited 23 patients with RCVS and 17 healthy controls (age: 49.1±8.0 vs. 41.6±14.5 yrs, p=0.072; M/F: 4/19 vs. 4/13, p=0.702). Patients with RCVS had reduced numbers of $CD34^+KDR^+$ (0.009±0.006% vs. 0.017±0.011%, p=0.026) and KDR^+CD133^+ cells (0.031±0.015% vs. 0.043±0.022%, p=0.041), but not $CD34^+CD133^+$ EPCs (0.046±0.028% vs. 0.054±0.034%, p=0.395), in comparison with controls. After controlling for age, the adjusted P values were 0.010 for $CD34^+KDR^+$, 0.052 for KDR^+CD133^+, and 0.384 for $CD34^+CD133^+$ EPCs. The numbers of $CD34^+KDR^+$ cells were negatively correlated with the LI (r=-0.489, p=0.034).

Conclusions: Patients with RCVS had reduced circulating EPCs, which was correlated with the severity of vasoconstrictions. Endothelial dysfunction might contribute to the pathogenesis of RCVS.

P294

Head and Neck Cancer Masquerading as Trigeminal Neuralgia

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Objectives: To describe 2 patients with head and neck cancer presenting as Trigeminal Neuralgia (TGN) and to review literature of similar cases.

Background: Trigeminal Neuralgia is idiopathic in nature, the commonest cause being arterial compression. There are no case reports of either tongue or nasopharyngeal cancer presenting as TGN in literature.

Methods: This is a case report and review of literature.

Results: Case 1: A 54-year-old Caucasian man presented with 2 types of severe right sided face pain for 2 years; a constant 3/10 pain with frequent exacerbations radiating to the jaw, ear, right side of tongue and throat and a second type of short –lasting sharp, stabbing pain on his face and jaw described as 10/10 triggered by chewing or talking. Neurological examination, routine laboratory workup and MRI of brain were unremarkable. He was diagnosed with TGN and glossopharyngeal neuralgia. Repeat brain MRI showed a loop of the PICA artery draped across cranial nerve (CN) IX and the superior cerebellar artery draped across the distal portion of right trigeminal nerve, before entering the Meckel cave. Patient was referred to neurosurgery and had posterior fossa microvascular decompression of CN V and IX. After surgery, he was pain free for a few weeks, but gradually the pain recurred and escalated to severe intractable similar to the previous pattern and distribution. Repeat brain MRI was unremarkable. Patient failed standard oral therapy; he was unable to open his mouth due to pain. Ultimately, lesions in oral cavity were detected by speech therapy; confirmed as carcinomas by biopsy. There were no metastases on head and neck imaging. Patient was treated with chemotherapy and surgery.

Case 2: A 77 year-old retired Chinese man presented with right sided face pain and sensitivity while brushing teeth and eating especially in the morning for a year. Past medical history was significant for double vision diagnosed as possible stroke 1 year ago and left foot drop diagnosed 4 months ago. Neurologic examination showed hypersensitivity and allodynia on the right trigeminal nerve area in V1, V2 distribution along with a right 6th nerve palsy and left lower extremity motor weakness especially on dorsiflexion. Babinski was positive on left side. Electro diagnostic studies showed severe left sided peroneal neuropathy and a possible L5-S1 radiculopathy bilaterally. MRI of the brain was unremarkable except for multiple periventricular white matter changes. He was treated with multiple medications including gabapentin. Repeat brain MRI after several months due to continuous pain, showed right posterior nasopharyngeal mass with extension to the cavernous sinus, oral fossa, and parapharyngeal space. Biopsy of the mass confirmed nasopharyngeal squamous cell carcinoma with invasion to the cavernous sinus. Patient was treated with radiation.

Conclusions: Two cases are described in which carcinoma was masquerading as trigeminal neuralgia. These cases have some atypical features and were not responsive to any of the treatment given. Brain imaging for trigeminal neuralgia should emphasize the oropharynx and nasopharynx.

P295

Potential Reduction in Headache Rate and Cost of Care Following Lumbar Puncture at a Single Tertiary Care Hospital

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Objectives: To determine the rate of post-lumbar puncture headache at a tertiary care hospital using standard 20-gauge Quinke needles and the potential cost-savings of switching to a Sprotte needle.

Background: AAN guidelines recommend the use of Sprotte needles because of lower rates of headache following lumbar puncture in randomized trials.

Methods: We retrospectively reviewed the charts of all patients who had a lumbar puncture in the outpatient neurology clinic at Henry Ford Hospital in Detroit, Michigan between January 2004 and December 2005. Baseline data collected included demographic features, medical history, weight, and antithrombotic use. Outcome data included occurrence of headache, back pain or epidural hematomas within two weeks of the procedure. Rates of headache, back pain, and epidural hematomas were calculated. Costs associated with the use of the current system were compared with the projected costs of switching to a Sprotte needle system. Historical literature for headache rates was used for the Sprotte needle system.

Results: 274 patients underwent lumbar puncture (62% women, mean age 55). Of these, 38 (14%) had a post-lumbar puncture headache; 12 patients were admitted for a total of 21 hospital days. There were three days of hospitalization for back pain. No patients had an epidural hematoma. The rate of headache associated with the Sprotte needle according to published literature is 4%. The total cost associated with the use of the Quinke needle (including kit and care of the patient with headache) was $64,327. The projected cost of using a Sprotte needle is $22,919. The estimated cost-savings would be approximately $20,000 per year.

Conclusions: Our analysis indicates that in our institution use of a Sprotte needle would potentially be associated with less adverse events and less cost.

P296

Magnetic Resonance Angiographic Screening of Aneurysms in Migraine

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Objectives: The present study screens aneurysms in migraineurs using magnetic angiographic (MRA) images to differentiate aneurismal migraine from general migraine patients and to delineate fundamental characteristics.

Background: As brain neuroimaging technology has advanced, decreasing morbidity from cerebral aneurysm to subarachnoid hemorrhage (SAH) has been observed.It is still difficult to detect and properly deal with suspicious aneurysm in migraineurs. These patients are asymptomatic prior to aneurisms growing to a certain size, or they are hard to distinguish from general migraine patients.

Current aneurysm research is now trending towards describing unruptured aneurisms' natural history and epidemiology. Headache including migraine in the case of unruptured cerebral aneurysms may be caused by small hemorrhages involving the nerve, destruction of the aneurismal sac, direct pressure on nerves or pain structures or pressure on the adjacent free edge of the tentorium. Known risk factors include age, female gender, smoking, hypertension, excessive use of alcohol, having one or more affected relatives with SAH and autosomal dominant polycystic kidney disease.

Given the uncertainty in the literature, we propose defining fundamental characteristics of migraineurs who have had aneurysms that can discriminate them from general migraine patients. The present study screens for aneurysms in migraineurs using magnetic angiographic images. This allowed comparison and estimation of detection rate, aneurismal features and outcome demographics between the aneurismal migraineurs and non aneurismal migraineurs.

Methods: All 4,416 study subjects were interviewed and completed self-reported questionnaires on headache. Of that group 1,773 were screened for aneurysm by MRA. Detection rates of aneurysm, size, number, morphology and locations were evaluated. Based upon MRA findings, subjects were grouped into aneurismal migraineurs and those without aneurysm.

Results: The incidental aneurysm rate was 3.6% (63/1773). The mean age was 56.0 years, with a higher proportion of women (p=0.005). The average size of aneurysms was is 3.5 $\pm$ 2.13 mm, and none were ruptured. There was proportionally more of anterior circulation than posterior. During follow-up all patients were in good condition. Of the risk factors surveyed smokers were 37.5% of males, 0% of female, while drinking was 12.5% of the males and 3.6% of the females. Symptoms differing by aneurismal migraineurs include 'pain location' (p=.025), 'double vision' (p=.026), 'aggravation by hormone therapy' (p=.039) and 'had a history of migraine in youth' (p= .021).

Conclusions: This study surveyed found that characteristics of aneurismal migraineurs followed literatures descriptions of aneurysm sufferers rather than migraine. The natural history of aneurysm can suggestive of influences from the social environment and population based on gender. The findings of different clinical characteristics warrant further study to be of predictive value for screening incidental aneurysms in migraineurs.

P297

Non-Neuropathic Non-Stabbing Peripheral Face Pain: Masseter Myalgia

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Objectives: The purpose of the study was to describe the presentation of face pain secondary to masseter myalgia and to review the studies related to its treatment. The presentation is described on the basis of patients seen personally by the second author. For review of the studies related to its treatment, an extensive literature search was conducted.

Background: When peripheral in location, non-neuropathic non-stabbing face pain is muscular in nature, originating from the muscles of mastication, particularly the masseter muscles. The cause is a dysfunction of those muscles, resulting in myalgia, leading to masseter tension or spasm, described in the literature under a variety of terms.

Methods: For review of the treatment of masseter myalgia, we searched the literature using PubMed® utilizing the following terms: orofacial muscle pain, facial pain with masticatory hyperactivity, localized myalgia of the masticatory system, masseter muscle pain and spasm, masticatory muscle pain, masticatory myofascial pain, myofascial pain of the jaw muscles, myofascial pain of the masticatory muscles, myofascial temporomandibular disorder, myogenous facial pain, myogenous craniomandibular disorder, myogenous pain of the masticatory muscles, myogenous temporomandibular disorder, temporomandibular disorder of myogenous origin, and tendomyopathy of the masticatory musculature.

Results: Among the patients seen by the second author since 2009, we identified 34 with master myalgia. The majority of them were women (88.2%) and their average age at presentation was 44.6 ± 12.6 (S.D.) years. The median pain suffering was 6.0 years (range: 0.2-34 years). In 85.3% the pain occurred daily and in 52.9% it was bilateral. Chewing or eating made it worse in 50.0% and talking in 29.4%. On examination, tightness of the masseter muscle(s) was present in 58.8% and tenderness also in 58.8%. Studies related to the following treatments were found: self care, physical therapy, laser therapy, dry needling, acupuncture, appliance therapy, and pharmacotherapy, including botulinum toxin.

Conclusions: Non-neuropathic non-stabbing peripheral face pain mostly affects women, generally occurs daily, and is equally often unilateral and bilateral. Chewing, eating, and talking are the most common aggravating factors and tightness or tenderness of the masseter muscle(s) is often found on examination. The majority of the studies related to its treatment involve a relative small number of patients involved and are not placebo- or sham-controlled.

P298

Coexistence of "Headache Attributed to Airplane Travel" and "Free/Scuba Diving Headache"

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Objectives: The term "Airplane headache" (AH) refers to a recently described form, whose attacks are strictly related to airplane travel, mostly to the landing phase.

Background: We studied AH features in a large series of patients (1).

Methods: Through a detailed questionnaire we identified, in a series of 85 AH cases, 9 patients suffering from headache attacks also occurring during free or scuba diving.

Results: These patients (5 females, 4 males, mean age 37 years ± 12), who complained of AH attacks during landing in more than 50% of their flights, referred the occasional onset of jabbing, severe, unilateral headaches in the frontotemporal region during free or scuba diving. They described this headache as presenting with the same features, as compared with that experienced during landing. Equally, no accompanying symptoms were reported. Three patients free-dove, attaining the maximum depth of 5-8 meters and six patients scuba-dove, reaching an average depth of approximately 20 meters; the pain started shortly after the ascent, reaching its peak in a few minutes. No

concomitant airways disturbance was reported during diving. In 8 cases the pain occurred in >30% of the dives; one patient complained of the headache occasionally. Brain MRI, Angio-MRI, and cranial CT-scan for sinuses were normal.

Conclusions: The coexistence of headache with peculiar, overlapping features triggered by these different situations, landing and ascending after diving, supports the hypothesis of a shared pathophysiological mechanism, i.e. the rapid change of external pressure, which occurs in both conditions, not paralleled with an adequate compensation inside the cranial sinuses.

P299

Periorbital Neuralgias - A 7 Year Study

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Objectives: To document cranial neuralgias manifesting in the orbito-periorbital region.

Background: Cranial neuralgias manifesting in the orbito-periorbital region are not well studied. They can be confused with many other local ocular/orbital disorders and diagnoses can often be missed and expensive investigations ordered.

Methods: 7 year prospective study done in two South indian coastal clinics. ICHD2 diagnostic criteria (group 13) applied in all. 32400 headache patients were screened during this period. Age group 10 to 70 years.

Results: Head or facial pain attributed to acute Herpez zoster (8), optic neuritis (7), ocular diabetic neuropathy (7), External compression headaches (5), Central post stroke pain (5), Other terminal branch neuralgias (5), post herpetic neuralgias (4), Headache attributed to ingestion or inhalation of a cold stimulus (4), Cold stimulus headache (3), V1 trigeminal neuralgia (3), Persistent idiopathic facial pain (3), Supraorbital neuralgias (2), nasociliary neuralgias (2), Probable ophthalmoplegic migraine (2), Tolosa hunt syndrome (2), persistent idiopathic facial pain (2), Nummular headache (2), Facial pain attributed to Multiple sclerosis (1). Acute orbito-periorbital pain lasting from 3 days to 15 days, before the appearance of diagnostic signs, was the initial manifestation in five of the above neuralgias (herpez, optic neuritis, diabetic neuropathy, ophthalmoplegic migraine and Tolosa hunt syndrome). External compression precipitated migraine with out aura headaches in 2.

Conclusions: Cranial neuralgias manifesting in the periorbital region are rare. Five ominous periorbital neuralgias may initially manifest only with moderate to severe pain and diagnostic signs appeared later. Diagnosing them by applying ICHD2 criteria will definitely help in successful treatment and to avoid unnecessary expensive investigations.

P300

New Onset Hemicrania Continua after Acoustic Neuroma Resection

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Objectives: To describe a case of new onset hemicrania continua after an acoustic neuroma resection.

Background: Hemicrania continua is by definition a unilateral, continuous headache of moderate intensity with superimposed exacerbations of severe pain accompanied, by at least one of the following ipsilateral to the pain: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis or miosis. A complete response to Indomethacin is required for the diagnosis. The majority of cases of hemicrania continua arise without an identifiable trigger. However, secondary etiologies such as internal carotid artery dissection, brainstem stroke, pineal cyst, head trauma, pituitary tumor, ipsilateral tumor of clinoid process at base of skull, HIV infection, and lung adenocarcinoma have been reported.

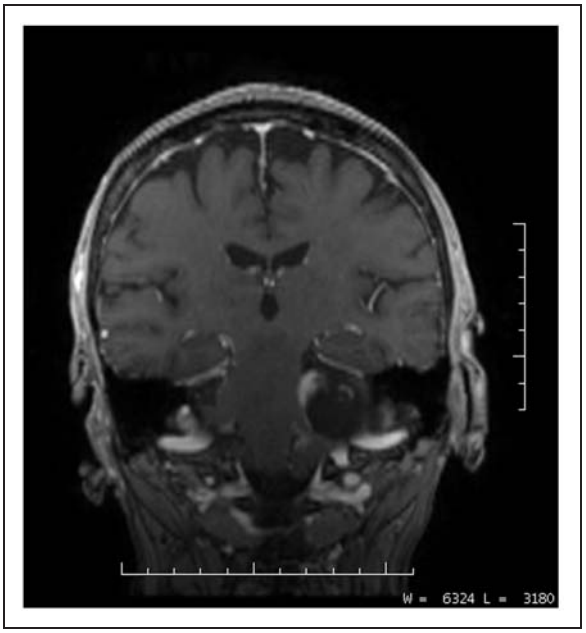
Methods: Case report.

Results: Case:

A 73 year old woman with a history of hypertension presented with symptoms of dizziness, difficulty with balance, numbness and weakness to the left hand and hearing loss. MRI imaging revealed a large left sided acoustic neuroma which compressed the left pons, cerebellar punduncle and cerebellar hemisphere requiring surgical intervention. Two days post resection she developed a left sided headache. She described a continuous headache in the left temporal and frontal region with intermittent escalations of pain associated with left sided lacrimation and rhinorrhea. Escalations of her pain with associated autonomic symptoms occurred 3 to 4 times per day, with some escalations lasting as long as 40 minutes. After 2 weeks of treatment with oral Indomethacin 50mg twice daily, she reported resolution of her headache and associated autonomic symptoms.

Discussion: In patients with hemicrania continua, functional imaging studies have demonstrated activation of the contralateral posterior hypothalamus, the ipsilateral dorsal pons and ventrolateral midbrain. The headache described in this case presentation was likely precipitated by surgical intervention and residual post-surgical changes involving the left pons. This case report demonstrates anatomoclinical evidence of the involvement of brainstem structures in the pathophysiology of hemicrania continua.

Conclusions: This study provides an example of new onset hemicrania continua secondary to a structural pathology in the brainstem.



P301

Orofacial Pain Following Invasive Dental Procedures: A Dozen Cases

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Objectives: The purpose of the study was to describe the presentation of orofacial pain following invasive dental procedures as well as the putative mechanisms involved.

Background: Orofacial pain following invasive dental procedures, such as tooth extraction, root-canal treatment, or occlusion alteration, is not uncommon. Postoperative symptoms ensuing from such procedures, such as pain, sensitivity to hot or cold, or numbness, generally resolve within a few hours or days. However, sometimes pain persists at the site of the procedure or develops at another site and may result in consultation of specialists other than dentists, particularly neurologists.

Methods: Ten of the twelve patients presented here were seen by the authors at the Craniofacial Pain Center of Tufts University School of Dental Medicine. The remaining two cases were obtained from the literature; they were the only cases generated by an extensive literature review.

Results: The patients in the cases presented range in age from 36 to 66 years; ten of them are women. The offending dental procedure was a tooth extraction in six, endodontic treatment in two, anesthetic injection in two, prosthetic-tooth placement in one, surgical adjustment of teeth in one, and professional dental hygiene in one (one patient had two procedures: surgical adjustment of the teeth and tooth extraction). The resulting orofacial pain was ipsilateral to the side of the procedure and located on the left in eight and on the right in four. It involved the cheek in seven patients, the jaw in four, the teeth/gum in three, the upper lip in two, the anterior neck in two, and the ear, pre-auricular area, retro-auricular area, temple, and side of the nose each in one. Examination revealed signs suggestive of *quantitatively*-altered nerve function in four (*hypoesthesia* or *hyperesthesia*) and of *qualitatively*-altered nerve function in three (*allodynia, dysesthesia,* or *paresthesia*).

Conclusions: Review of the cases suggests that orofacial pain following invasive dental procedures, unless caused by local pathology, is either musculoskeletal or neuropathic, resulting from muscle and nerve injury, respectively. The muscle injury seems to be caused by the force applied during tooth extraction and/or the wide and prolonged opening of the mouth or from an altered occlusion causing strain on the muscles of mastication. The nerve injury seems to mostly result from anesthetic injection and/or endodontic treatment. With neuropathic pain, the pain tends to be limited in location and not necessarily lancinating or burning in nature, while with pain of musculoskeletal origin, it tends to be more widespread.

P302

Allergic Migraine and Migrainous Allergy

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Objectives: To document allergic inflammations triggering migraine without aura attacks and vice versa.

Background: It is documented that mast cell degranulation can promote a state of excitation of trigeminal nociceptors and can activate a pain pathway undelying migraine headache. It is also tempting to hypothesise that excitation of trigeminal neurons can cause mast cells to degranulate.

Methods: Prospective cohort study spanning 8 years. 260 patients. age group 10 to 50 years. ICHD2 migraine without aura diagnostic criteria applied. Allergic disorders were diagnosed from symptoms, local signs and referral to concerned specialists.

Results: Nasal allergy (allergic rhinitis) precipitated migraine without aura (1.1) in 98 patients and probable migraines (1.6) in 33. 18 reported brief migraine like attacks missing two criteria. Ocular allergy, both(seasonal and perennial) triggered migraine without aura in 33 and probable migraine in 19.Scalp allergy and bronchial allergy were reported by 8 and 7 respectively. Headache started either immediately after allergic manifestations or just the subsidence of allergic symptoms. 44 patients reported various allergic manifestations during the course of their migraine episodes (migrainous allergy).

Conclusions: This study should yield better insight into the pathophysiology of both diseases and an opportunity to treat both with a single drug. This documentation of allergic migraine and migrainous allergy shows that allergic inflammations increased the risk for migraine and vice versa. This bidirectional association helps the clinician to explain the causative molecular mechanisms and genetic origin of these two disorders in the most simple way to their patients.

P303

CSF Leakage Might Be a Cause of Postrural Tachycardia Syndrome (PoTS)

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Objectives: To examine CSF leakage might cause postural tachycardia syndrome (PoTS) or not.

Background: It is well-known that both CSF leak and postrural orthostatic tachycardia syndrome (PoTS) causes postural headache. Both of them cause postural headache that means they feel severe headache when they take upright position. We experienced 3 CSF leak patients and one post-lumbar headache patient from June 2011 to June 2012. We checked whether they are complicated with PoTS or not.

Methods: We had 3 CSF leak patients and one post-lumbar headache patient in our hospital from June 2011 to June 2012. We did Schellong test or head-up tilt test to all of them in order to confirm to be complicated with PoTS or not before starting the treatment of CSF leakage or post-lumbar headache. And after the symptom disappeared we checked Schellong test or head-up tilt test again.

Three CSF leak patients were made a diagnosis with MRI or RI cisternography. And one CSF leak patient is complicated delayed orthostatic hypotension (OH). All of them were treated with bed rest and peripheral intravenous infusion of the isotonic fluid. And they were completely recovered.

All of them were examined whether PoTS was complicated with or not by Schellong test or head-up tilt test twice, before and after the treatment.

Results: One CSF leak patient was complicated with delayed OH. And another 3 cases were complicated with PoTS. Delayed OH or PoTS were recovered after the symptom disappeared.

Conclusions: CSF leakage might cause postural headache complicated with PoTS.

P304

Headache Attributed to Refractive Errors and Refractive Migraines

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Objectives: To document refractive errors precipitating migraine without aura attacks.

Background: Headache attributed to refractive errors (ICHD2, 11.3.2) are mild, frontal and in the eyes and associated with uncorrected / miscorrected refractive errors. These errors can also trigger migraine attacks (1.1/1.6) in migraineurs if visual task is prolonged.

Methods: 7 year prospective cohort study. 478 patients. age group 10 to 50 years. ICHD2 diagnostic criteria applied (1.1/1.6/11.3.2).

Results: Headache attributed to refractive errors were documented in 341 patients. Refractive migraines without

aura were diagnosed in 137 patients. The causative refractive errors were presbyopia (78), hyperopia (31), astigmatism (22). Miscorrected errors triggered migraines in 6 patients. All of them were getting migraine without aura attacks either at presentation or in the past when exposed to the common migraine triggers in this region. All were given proper refractive correction and 72, who came for follow up reported significant relief of their migraines, both refractive and non refractive.

Conclusions: This study shows that uncorrected and mis corrected refractive errors can cause mild frontal headaches in susceptible persons and can trigger migraine without aura (1.1/1.6) attacks in known migraineurs.

P305

Primary Headaches Interfere with the Efficacy of Temporomandibular Disorders Management

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Objectives: The aim of this cross-sectional study is to evaluate the influence of Primary Headache (PH) on efficacy of a Temporomandibular Disorder (TMD) conservative therapy.

Background: PH has an excitatory effect in myofascial and jaw pain conditions and individuals with headache may experience more severe and frequent symptoms of TMD and vice versa. However the relationship between these two entities is not well established in literature yet. Some studies have shown that TMD therapy reduces the complaint of headache in both intensity and frequency when treating articular and muscular pain related to TMD, nevertheless, to the best our knowledge, the impact of PH on TMD therapy efficacy has not been published yet.

Methods: This study performed 1200 evaluations in medical records from an orofacial pain clinic in University of São Paulo, Brazil. The sample was composed of 400 medical records divided into 4 groups: I) Muscular TMD through AAOP criteria (n=64); II) Muscular TMD + PH based on International Headache Society (IHS) fulfilling the criteria for migraine and/or tension-type headache (n=48); III) Muscular TMD + Articular TMD through AAOP criteria (n=173); and IV) Muscular TMD + Articular TMD + PH (n=115). All groups had undergone a conservative TMD therapy for three months with a rigid acrylic upper full coverage stabilisation appliance and counselling for habits and behavioural changes. No specific headache management was done. Current pain intensity was investigated according to self-reported pain on Visual Analogue Scale (VAS) at baseline and after three months of TMD therapy. The results were analyzed with repeated measures ANOVA with a significance level of 5%.

Results: A conservative therapy with stabilisation appliance and counselling for habits and behavioural changes were effective in the TMD pain relief in all groups ($p<0.05$). Significant results revealed a better pain improvement for group I (70.74%) compared to group II (46.32%) and for group III (66.44%) compared to group IV (42.56%) ($p<0.05$).

Conclusions: This study could elucidate the important effect that headache may have in the TMD management, and the approach of both pain conditions together may promote a better pain improvement for patients.

P306

The Effect of Trigeminal Neurectomy on Cortical Spreading Depression in Migraine Model Rat

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Objectives: The objective of this study is to investigate both the acute and the chronic effect of trigeminal neurectomy (TN) on cortical spreading depression (CSD), and to elucidate trigeminovascular system function upon cortical excitability.

Background: Migraine is a recurrent neurological disorder characterized by throbbing headache associated with nausea, vomiting, photophobia and phonophobia. The pathogenesis of migraine is still unclear, but many evidences indicate that the migraine may depend on the activation and sensitization of the trigeminovascular pain pathway. Also cortical spreading depression has important role in pathophysiology of migraine with aura. Recent study suggested that CSD activate peripheral and central trigeminovascular neurons. Another PET study of migraine shown that photophobia is linked with visual cortex hyperexcitability. But interaction of cortical excitability and trigeminovascular system is not fully understood.

Methods: (For acute TN model) 6 rats were used. Male Sprague-Dawley rats, weighing 350-600g, were anesthetized with isoflurane and ventilated mechanically with 30% O_2. The nasociliary nerve (NCN), a cerebrovascular branch of the trigeminal nerve in the rat, was approached from the left orbit. Parietal cortical blood flow (CoBF) was

continuously monitored with the laser-Doppler flowmeter. A hydrogen electrode was placed in the other parietal open cranial window to measure direct current potential (DCP). CSDs were induced with application of 1M KCl solution with the volume of 3μl on parietal lobe surface through another open cranial window. DCP and CoBF were measured for 60min after application of KCl to compare induced CSDs before and after the NCN neurectomy.

(For chronic TN model) 5 male rats were used for this experiment. They were anesthetized and also underwent NCN neurectomy by the same mathod. CSDs were triggered and measured in the same way one week after NCN neurectomy.

The CSD data were analyzed by paired-T test in acute TN model and unpaired-T test in chronic TN model.

Results: In acute TN model, the number of CSD was decreased from 9.0 to 5.8, significantly ($P < 0.05$). In chronic TN model, number of CSD is significantly less than sham operation, 9.0 vs. 1.0, ($P < 0.01$).

Conclusions: Both acute and chronic cerebral vascular branch of trigeminal nerve neurectomy suppressed generation of CSD. This result suggests that the trigeminovascular interaction may modulate cortical excitability in migraine with aura.

P307

Modulation of Trigeminovascular Activity by Leptin: A Novel Antinociceptive Mechanism?

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Objectives: To study the effect of acute administration of leptin on neuronal firing in the trigeminocervical complex (TCC) in response to dural electrical stimulation of the middle meningeal artery (MMA).

Background: Fasting, by skipping meals for example, is a recognized trigger of headache in susceptible individuals. Leptin is a peptide hormone encoded by the mouse obese gene (*ob*) and is mainly secreted by white adipocytes. Plasma levels of leptin are regulated to reflect body energy stores: levels of leptin fall in response to fasting and are increased in several models of murine obesity. Leptin signaling decreases feeding and increases energy expenditure by activating the long form of its receptor (Ob-Rb) in areas of the brain including the brainstem, midbrain, hypothalamus, thalamus, and cortex. Interestingly, circulating leptin concentration is important in regulating its receptor gene expression. Furthermore, previous data indicates that migraine patients have lower serum leptin levels in headache-free periods, compared to healthy individuals.

Methods: Adult male Sprague-Dawley rats were anesthetized with pentobarbitone (60 $mg.kg^{-1}$) and cannulated for measurement of blood pressure and intravenous administration of supplementary anesthesia with propofol (15-20 $mg.kg^{-1}.hr^{-1}$). The parietal bone was removed over the MMA for electrical stimulation of the dura mater and electrophysiological recording of second order neurons in the TCC was made using a tungsten electrode. Rats received either rat recombinant leptin in a dosage of 1 $mg.kg^{-1}$ or 3 $mg.kg^{-1}$ (i.v.) dissolved in sterile water, or sterile water alone as the control group. The effects of leptin on TCC neuronal activity in response to MMA stimulation were recorded.

Results: Leptin 1 $mg.kg^{-1}$ significantly reduced cell firing in response to trigeminovascular activation within the TCC ($p < 0.05$). This effect reached a maximum inhibition of nearly 13% at 45 minutes post-infusion of leptin. Infusion of leptin 3 $mg.kg^{-1}$ and sterile water alone had no significant effect on MMA stimulation-evoked firing.

Conclusions: The data show leptin at 1 $mg.kg^{-1}$ inhibits stimulus-evoked trigeminal activity, which might explain, in part, why fasting, a condition characterized by low levels of circulating leptin, may have a role in headache. The lack of effect of the higher leptin dose (3 $mg.kg^{-1}$) may represent the effect of an inverted U-shaped dose response. Studying the effects of lower doses of leptin may dissect the dose-response effect of leptin in the trigeminovascular system. Exploring the interaction between feeding physiology and trigeminovascular nociceptive mechanisms may contribute to our understanding of this very common trigger.

P308

Effective Connectivity in EEG alpha and Beta Bands during Visual Stimulation in Migraine with and without Aura

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Objectives: A still unclear point in migraine pathophysiology regards the origin of aura symptoms perception. The aim of this study was to evaluate effective connectivity and information flow in high density ongoing EEG together with Functional Magnetic Resonace Imaging under visual stimulation in the interictal phase of migraine patients with and without aura compared to non migraine controls.

Background: The results of functional and effective connectivity represent a significant added value to neuroscience, since they allow to pinpoint the temporal pattern of activation and information transfer between cortical areas (1). Preliminary evaluation enabled to observe a different pattern of effective connectivity in fast EEG rhythm in migraine with and without aura, employing an ustructured visual stimulus and few recording electrodes (2).

Methods: EEG was recorded by 65 scalp electrodes from 20 migraine without aura patients (MO), 20 migraine with aura patients (MA) and 10 healthy subjects (control group (N)). Visual stimulus consisted in black and white checkerboard gratings with two spatial frequencies (0.5 and 2.0 cpd) at 5 and 10Hz (10 and 20 reversal/s). The same stimulus was employed to obtain FMRI in 10 migraine with aura, 10 without aura patients and 6 controls. Non linear Granger causality and transfer entropy were evaluated filetring the EEG in alpha and beta bands.

Results: The intensity of directed interactions in beta band, revealed by Granger causality, increased in MA compared to both MO patients and controls, with an information flow from the occipital to the frontal cortex. The FMRI showed a larger recruitment of posterior cortical areas during visual stimulation, including parietal and posterior temporal zones.

Conclusions: There were clear differences in ongoing EEG and FMRI under visual stimulation, which emerged between the two forms of migraine, probably subtended by increased cortical activation in migraine with aura, and compensatory phenomena of reduced connectivity and functional networks segregation, occurring in patients not experiencing aura symptoms. Clinical manifestation of aura symptoms may be subtended by a peculiar neuronal connectivity pattern.

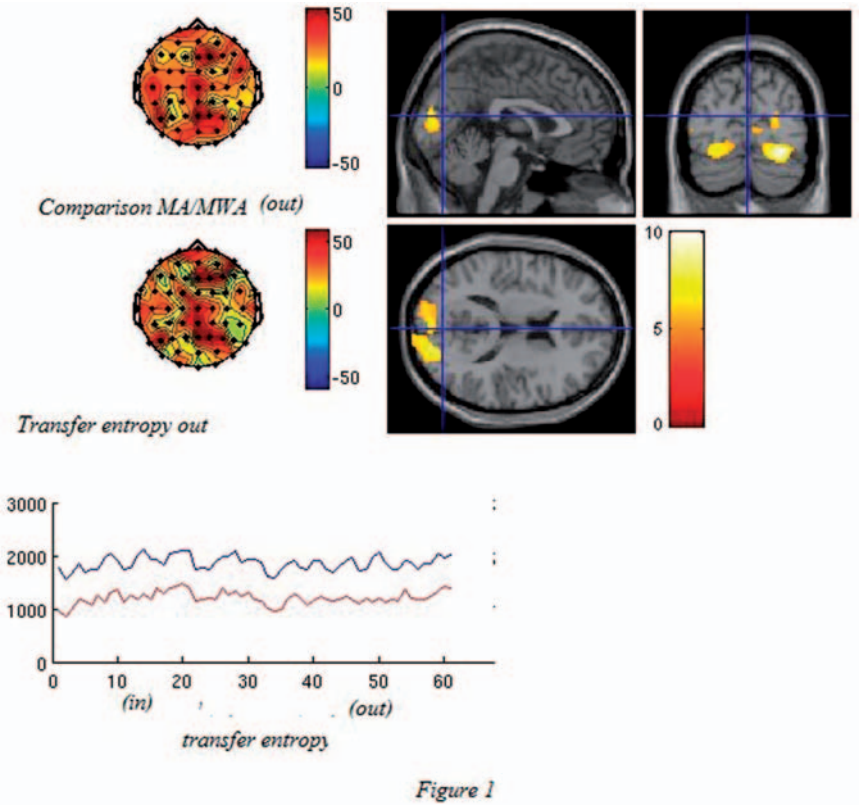


Figure 1

P309

Trigeminal Pain Is Increased by High-Fat Diet Induced Obesity in Mice

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Objectives: To assess trigeminal pain in obese mice using two objective and quantitative behavioral assays.

Background: Obesity has been associated with multiple pain disorders, including migraine. However, most animal models used to study mechanisms of head pain have limitations and don't assess the affective component of pain. We have recently found that diet-induced obesity increases neuronal activation in the trigeminal nucleus caudalis evoked by a low dose of capsaicin (Rossi et al., 2012). This suggests that obesity may prime the trigeminal pathway making it responsive to normally innocuous stimuli. To translate these findings to animal behavior, we used an operant facial pain assay and conditioned place aversion to determine whether obese mice are responsive to subthreshold doses of capsaicin.

Methods: We used C57BL/6J mice fed high-fat or regular diet. In the operant facial pain assay, water-deprived mice have to place their face against a thermal painful stimulus in order to access water. We measured the number of licks at the water bottle. Mice were tested before and after facial application of capsaicin cream (0.025%). The conditioned place aversion test consists of two connected compartments with different tactile cues. During the two preconditioning sessions, mice were allowed to freely explore the apparatus. Conditioning occurred on the next two consecutive days. In the morning, mice received bilateral saline eye drops and were confined to one of the compartments. In the afternoon, mice received bilateral capsaicin eye drops (0.1% or 0.01%) and were confined to the other compartment. On day 5, they were tested in the apparatus with free access to both sides, without corneal stimulus. We determined the time they spent on the side paired with the painful stimulus relative to the pre-conditioning baseline.

Results: In the operant facial pain assay, all mice exhibited normal response to increasing temperatures, but capsaicin only had an effect on obese mice. The number of licks after capsaicin cream application was less than half in obese than control mice ($p=0.01$). Mice on regular diet did not respond to this dose of capsaicin. In the conditioned place aversion test, all animals displayed aversion for the side paired with 0.1% capsaicin. However, 0.01% capsaicin only induced aversion in the obese mice, which spent 60% less time on the capsaicin-paired side ($p=0.01$).

Conclusions: Taken together, our results suggest that diet-induced obesity in mice causes increased sensitivity of the trigeminal pain pathway. Furthermore, these studies investigate higher pain processing. This is an advantage over models based on reflex responses to pain and will facilitate future translational research.

P310

A Translational Approach to Studying Triptan-Induced Reversal of Established Central Sensitization of Trigeminovascular Neurons

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Objectives: To study the effects of the migraine trigger, glyceryl trinitrate (GTN), on the responses of noxious and innocuous dural and cutaneous inputs on trigeminovascular neurons, and determine the effects of a triptan, 5-$HT_{1B/1D}$ receptor agonist, on these responses after established GTN-induced trigeminovascular sensitization.

Background: Migraine is thought to involve activation and sensitization of trigeminovascular neurons that engages nociceptive pathways resulting in head pain. Existing animal models of prolonged central trigeminovascular sensitization use dural inflammatory mediators, which is difficult to translate to patients. GTN is a trigger of migraine in patients, causing a delayed attack after several hours, and has been demonstrated to activate background firing of trigeminovascular neurons. Its prolonged effects on trigeminovascular neurons and the subsequent effects on dural and cutaneous inputs are unknown.

Methods: Rats were anesthetized with pentobarbitone (80 $mgkg^{-1}$) and cannulated for measurement of blood pressure and intravenous administration of supplementary anesthesia with propofol (15-20 $mgkg^{-1}hr^{-1}$-i.v. infusion). An established model of trigeminovascular nociception was employed, which uses noxious and innocuous dural and cutaneous stimulation, to activate the ophthalmic division of the trigeminal nerve. These neuronal responses were measured at intervals, after a low (1.0 mg/kg, sc) or high (10 mg/kg, sc) dose of GTN and followed for 3 hours. In some experiments naratriptan (10 mg/kg, iv) was given after 2 hours.

Results: GTN caused sensitization of central trigeminovascular neurons for up to at least 3 hours. Dural-evoked ($F_{2.9,31.8} = 4.6$, $P < 0.01$) and spontaneous background ($F_{4.3,47.8} = 5.2$, $P < 0.005$) neuronal firing in the trigeminocervical complex was significantly increased after GTN (10 mg/kg), but there were no changes after lower dose

GTN (1.0 mg/kg). Neuronal responses to cutaneous noxious ($F_{4,32} = 41.3$, $P < 0.001$) and innocuous ($F_{4,32} = 3.3$, $P < 0.05$) stimulation of the ophthalmic dermatome were also significantly increased by only 10 mg/kg GTN. When naratriptan (10 mg/kg, iv) was given after 2 hours, these responses were significantly reversed back to baseline.

Conclusions: These data demonstrate that only the higher dose of GTN is able to activate and sensitize central trigeminovascular neurons over a prolonged period, for up to 3 hours, similar to the time interval of delayed migraine in patients. GTN causes hypersensitivity to both noxious and innocuous dural and cutaneous inputs. These responses to established central trigeminovascular sensitization are all reversed by the migraine treatment, 5-$HT_{1B/1D}$ receptor agonist, similar to migraine relief demonstrated in the clinic of GTN-induced migraine. GTN-induced sensitization of trigeminovascular neurons represents a translational model of the pathophysiological neuronal changes occurring during migraine, and reflects the migraineurs response to triptan treatment.

P311

Mitochondrial Dysfunction in a Rat Model of Chronic Migraine

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Objectives: To investigate if mitochondrial dysfunction contributes to the development of chronic trigeminal pain.

Background: Impairment of mitochondria in migraine patients has been observed. Clinical studies show that coenzyme Q10 (CoQ10) and riboflavin, both thought to increase activity of the electron transport chain (ETC), are effective in reducing migraine frequency. In light of these clinical observations, we tested a rat model of chronic migraine for deficiencies in mitochondrial respiration. We then used acetate, a mitochondria substrate known to induce headache in this rat model and not in naive rats, to see if the observed deficiencies impacted acetate utilization by the mitochondria. This model uses repeated infusion of an inflammatory soup (IS) on the dura of awake rats to induce long-lasting sensitization of the trigeminal system that outlasts the last infusion by >8 weeks.

Methods: To assess behavioral sensitization, periorbital pressure thresholds were determined by applying a range of von Frey monofilaments. Rats that had transitioned to chronic periorbital sensitivity had thresholds of $\leq$ 2.0g, whereas naive rats have a threshold of 8-10g. To determine the effects of mitochondrial respiration on the development of sensitivity, CoQ10 (200mg/kg) was administered daily during the infusion period and acetate (20 mg/kg i.p) was administered after the rats had transitioned. We used a qPCR gene chip to compare mitochondrial gene expression in rats who received IS infusions vs. rats who received saline infusions. Mitochondrial respiration was measured in brain slices of the trigeminal nucleus caudalis (TNC), spinal cord, and cortex using the Seahorse XF analyzer.

Results: Concurrent administration of CoQ10 was sufficient to prevent the transition to chronically low periorbital thresholds. Administration of acetate increased periorbital sensitivity by 50%. mRNA expression in the TNC, showed significant changes in mitochondria related genes. Specifically, transcription of ETC complex III and IV components were decreased and fatty acid metabolism enzymes were increased. Transitioned rats had threefold less spare respiratory capacity than naïve rats. Also, transitioned rats did not utilize acetate as a substrate as efficiently as naïve rats. The addition of 1mM acetate increased respiration to only 105$\pm$6% of baseline OCR (Oxygen Consumption Rate) in transitioned rats, whereas in naïve, acetate increased respiration to 124$\pm$7% of baseline OCR.

Conclusions: These data indicate decreased mitochondrial function in rats with chronically low trigeminal thresholds within the TNC. Behaviorally, administration of acetate as a substrate for mitochondria to transitioned rats increased periorbital sensitivity while supplementing mitochondrial function with CoQ10 throughout the infusion period prevented low periorbital sensitivity. Respiratory analysis indicates a decreased spare respiratory capacity in transitioned animals and a lesser ability to utilize acetate as a substrate. Analysis of mRNA expression suggests that the decreased mitochondrial respiration may be due to a malfunctioning of complex III and IV in the ETC.

P312

Neuropeptide Y Inhibits Neuronal Activation in the Trigeminocervical Complex: Implications in Pain Processing in Migraine Pathophysiology

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Objectives: To determine the effect of systemic administration of NPY on neuronal activity in the trigeminocervical complex (TCC) in response to dural electrical stimulation of the middle meningeal artery (MMA).

Background: Neuropeptide Y (NPY) is a neuropeptide abundant in the central and peripheral nervous systems, acting on six G-protein coupled receptor subtypes ($Y_{1\text{-}6}$). It is involved in regulation of the cardiovascular system, pain modulation, appetite control and circadian rhythm synchronization. NPY is abundantly synthesized by neurons of the hypothalamic arcuate nucleus, a key brain area of energy homeostasis regulation, and is one of the most potent orexigenic peptides whose expression is upregulated by fasting. NPY Y_1 and Y_2 receptors are present in human and rat trigeminal ganglia and NPY is known to inhibit neurogenic dural vasodilation and plasma protein extravasation via NPY Y_1 and NPY Y_2 receptors, respectively. Moreover, migraine symptomatology can include changes in appetite. It is, therefore, important to elucidate the role of NPY system in modulating trigeminovascular neurons to help in our understanding of its potential role in migraine pathophysiology.

Methods: Adult male Sprague-Dawley 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). The parietal bone was removed over the MMA for electrical stimulation of the dura mater and electrophysiological recording of second order neurons in the TCC was made using a tungsten electrode. Rats received either human NPY in a dosage of 10 μg/kg, 30 μg/kg or 100 μg/kg (i.v.) dissolved in sterile water, or sterile water alone as the control group. The effects of NPY on TCC neuronal activity in response to MMA stimulation were recorded.

Results: NPY (30 μg/kg) significantly reduced cell firing in response to trigeminovascular activation within the TCC ($p < 0.001$, $n=9$). This effect reached a maximum inhibition of nearly 16% at 25 minutes post-infusion. Injection of NPY 100 μg/kg significantly reduced cell firing ($p < 0.05$, $n=7$) showing 18% of inhibition at 45 minutes. Infusion of NPY 10 μg/kg or sterile water alone had no significant effect on MMA stimulation-evoked firing.

Conclusions: This study demonstrates that NPY dose-dependently inhibits stimulus-evoked trigeminal activity. It is possible that disruption of the NPY system through its role in the regulation of appetite might explain fasting as a potential headache trigger in susceptible individuals. Understanding how energy homeostasis is regulated in migraine, through the NPY system, and how this might influence the modulation of the trigeminovascular activity will improve our understanding of the pathophysiology of migraine.

P313

Dural Fibroblasts Play an Active Role in Headache Pathophysiology

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Objectives: Determine whether dural fibroblasts release factors that promote nociceptive signaling from the meninges using preclinical models.

Background: Afferent nociceptive signaling from the meninges is proposed to be a necessary event in the pathophysiology of many forms of headache. However, the events within the meninges that drive afferent activity in meningeal nociceptors are not clear. Fibroblasts are a major cell type in the dura but these cells have traditionally been thought of as producing the extracellular matrix proteins that constitute the dura and not as active participants in headache pathophysiology. The purpose of these studies was to determine whether dural fibroblasts release factors that activate/sensitize dural afferents and produce headache-like behavior in preclinical models.

Methods: Dura mater was removed from male Sprague-Dawley rats and dural fibroblasts were cultured for 3 days until confluent. Confluent fibroblast cultures were then stimulated for 1 hour with vehicle or 5μg/mL lipopolysaccharide (LPS), an activator of toll-like receptor 4 (TLR4). Cultures were washed to remove LPS and conditioned media was collected for 5 hours. Fibroblast media conditioned with either vehicle or LPS stimulation was applied to rat trigeminal ganglion neurons in vitro that had been retrogradely labeled from the dura 7 days earlier. Patch-clamp electrophysiology was performed to determine whether conditioned media increased the excitability of identified dural afferents. A preclinical behavioral model was also used where conditioned media was applied directly to the rat dura to determine the presence of cutaneous facial and hindpaw allodynia.

Results: Application of fibroblast media conditioned with LPS to identified dural afferents in vitro produced a significant increase in the number of action potentials evoked by depolarizing ramp current injections, indicating the presence of sensitizing agents in the media following LPS stimulation. Media collected from fibroblast cultures stimulated with vehicle did not produce any effect on action potential firing. Similarly, LPS-fibroblast media applied to the dura of awake rats caused the development

of cutaneous facial and hindpaw allodynia that peaked at 2 hours and returned to baseline by 5 hours. Vehicle conditioned media did not produce allodynia.

Conclusions: Fibroblasts stimulated with LPS release factors capable of sensitizing and/or activating dural afferents indicating that they can play an active role in the pathophysiology of headache. The identity of these factors is not yet known but is currently being investigated. Although the current findings using LPS as a stimulus are most applicable to bacterial infections of the meninges, stimuli relevant to other forms of headache may also promote the release of activating/sensitizing factors from fibroblasts. Knowledge of the role fibroblasts play in headache pathophysiology may provide an avenue for novel therapeutic targets for the treatment of headache.

P314

Abnormal Synaptic Morphology and Neuronal Ca^{2+}-Homeostasis in Migraine Mutant Mice

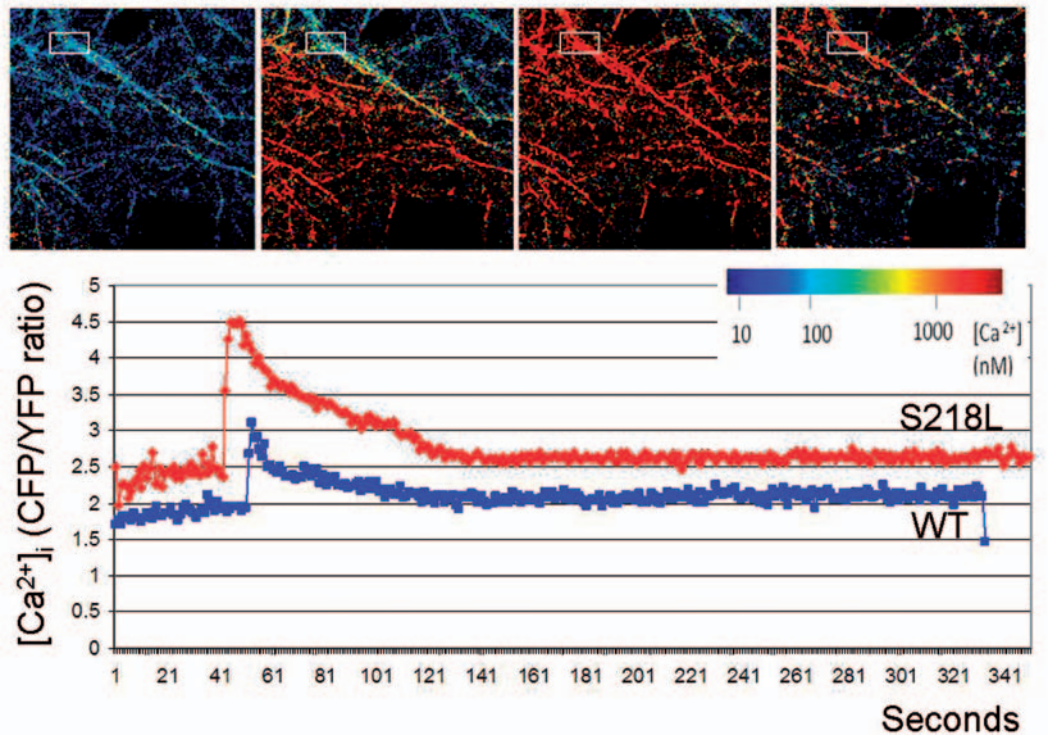
K. Eikermann-Haerter[1], M. Arbel-Ornath[2], K. Kuchibhotla[2], E.S. Yu[1], C. Lattarullo[2], D. Thyssen[2], N. Yalcin[1], I. Rosen[1], A. Arreguin[1], M. Climov[1], F. Keles[1], A. Belcher[2], B. Sengul[1], A. Negro[1], E. Hudry[2], M.D. Ferrari[3], A.M. van den Maagdenberg[3], B. Bacskai[2], C. Ayata[1]

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Objectives: To assess neuronal structure and intracellular Ca^{2+}-levels ($[Ca^{2+}]_i$) at baseline, during and after CSD in transgenic mice for familial hemiplegic migraine.

Background: Familial hemiplegic migraine (FHM) is caused by gain-of-function mutations (e.g., S218L) of $Ca_v2.1$. Excitatory neurotransmission may be enhanced, and, *in vivo*, FHM1 mice show enhanced susceptibility to cortical spreading depression (CSD). CSD, the electrophysiologic event underlying migraine, is a transient disruption of membrane ionic gradients that propagates across cortex.

Methods: *In vivo* 2-photon microscopy images of cortical layers were obtained 5 weeks after intracortical injection of the genetically encoded Ca^{2+}-indicator Yellow Cameleon (AAV2-YC3.6), in female wild type (WT) and S218L transgenic mice. YFP/CFP ratios were measured, and exact $[Ca^{2+}]_i$ can be determined because YC3.6 is a FRET based indicator. SD was evoked by KCl (300 mM). *Before* and *after* CSD, we assessed a cortical volume of



(A)

Time course		$[Ca^{2+}]_i$		Dendritic beading		
		Axon	Dendrite	Density (/μm)	Diameter (μm)	Duration (sec)
WT	Baseline	1.79±0.52	0.78±0.04	0.20±0.05	1.54±0.22	149±62
	Slope	0.82±0.39	0.73±0.21			
	Peak	3.11±0.15	1.93±0.42			
	Plateau	2.1±0.39	1.44±0.30			
SL	Baseline	2.06±0.37^	0.88±0.08^	0.19±0.02	1.61±0.11	156±61
	Slope	1.73±0.39^	1.39±0.30^			
	Peak	4.30±0.50^	2.97±0.58^			
	Plateau	3.0 ± 0.44^	2.23±0.41^			

(B)

Z-stack		Structure						
		Axon varicosity		Dendritic spine				
		Density (/μm)	Area (μm²)	Head diameter (μm)	Neck diameter (μm)	Density (/μm)	Mushroom (%)	Stubby (%)
WT	Baseline	0.22 ±0.05	1.09 ± 0.25	0.36 ± 0.03	0.08 ± 0.03	0.36 ± 0.1	24 ± 14	46 ± 6
	Post CSD	0.29 ± 0.04*	0.79 ± 0.21*	0.36 ± 0.03	0.10 ± 0.08	0.37 ± 0.07	34 ± 16	31 ± 15
SL	Baseline	0.21 ± 0.04	1.42 ± 0.31^	0.35 ± 0.03	0.07 ± 0.04	0.39 ± 0.1	24 ± 6	48 ± 2
	Post CSD	0.28 ± 0.06*	0.95 ± 0.13*	0.39 ± 0.03*	0.09 ± 0.04	0.35 ± 0.09	32 ± 7*	41 ± 13

600x600x100μm depth. *During* CSD, we performed single-plane timecourse movies 30-40 μm deep (Fig. 1).

Results: At baseline, $[Ca^{2+}]_i$ was higher in S218L. During CSD, $[Ca^{2+}]_i$ abruptly increased by ~3-fold, and then declined to a plateau. The onset of calcium increase, peak and plateau $[Ca^{2+}]_i$ were higher in S218L, in both axons and dendrites. Acute and transient structural changes of neurons during CSD (e.g. density, diameter, or duration of dendritic beading) did not differ (Fig. 1, 2A).

We found structural differences in neuropil, at baseline and after CSD. At baseline, the average area of an axonal varicosity was larger in S218L (A). Ten minutes after CSD, the density of axonal varicosities increased, and their area decreased. The percentage of mushroom type spines increased. In S218L, the diameter of dendritic spine head increased (Fig. 2B).

Conclusions: FHM1 mutations increase $[Ca^{2+}]_i$ at baseline and during CSD, and alter axonal morphology as well as lasting structural changes after CSD.

P315

Sleep Deprivation Enhances Susceptibility to Cortical Spreading Depression

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Objectives: To investigate the effect of sleep deprivation, a well-known migraine trigger, on cortical spreading depression (CSD) susceptibility.

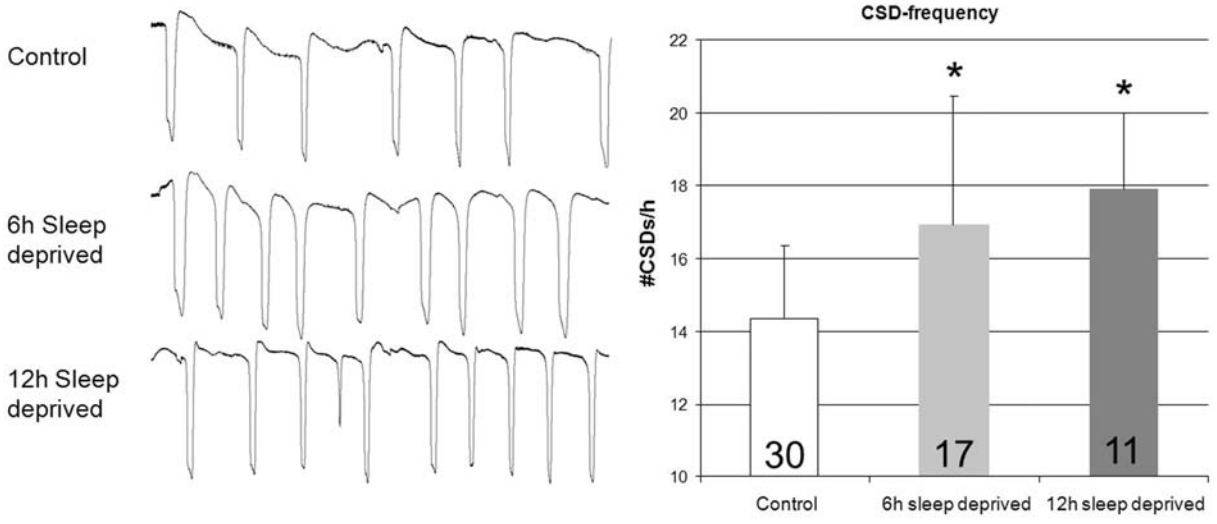
Background: Many factors that modulate migraine (e.g. sex hormones, migraine prophylactic drugs) have been shown to also modulate in the same direction susceptibility to CSD, the electrophysiologic event underlying migraine. Changes in sleep rhythm and sleep deprivation are well-known migraine triggers. Sleep deprivation modulates neocortical excitability both in humans and in animal

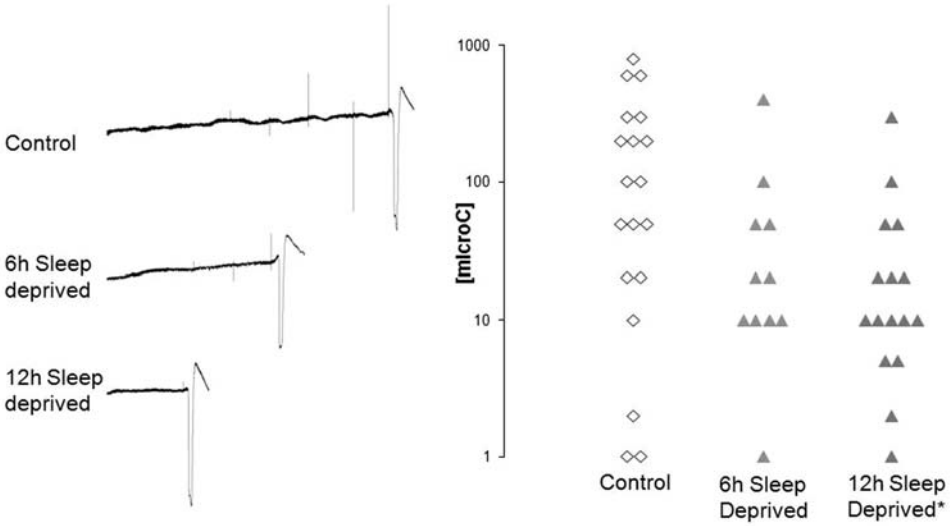
models. Sleep deprivation can facilitate the migraine chronification and trigger attacks.

Methods: Acute sleep deprivation was induced for 6h or 12h starting with daylight, using the "gentle handling method" (Eur J Neurosci 2002; 16: 1163-7) in male Sprague-Dawley rats (340±40g). Control group was kept in the same environment but undisturbed to allow sleep. Following sleep deprivation, rats were anesthetized, and femoral artery cannulated to monitor arterial blood gas and blood pressure. Rats were intubated and ventilated to maintain a normal systemic physiologic state. CSD susceptibility was assessed by measuring the frequency of CSDs evoked by topical KCl (1M), or using the direct cathodal stimulation intensity threshold (bipolar electrode, 1-800mC). Amplitude, propagation speed, and duration of CSD were also recorded. All experiments were done blinded. Data are mean ± standard deviation.

Results: Sleep deprivation increased the frequency of CSDs [Figure 1; (p=0.01 and 0.007, 6h and 12h sleep deprivation, resp.)] and decreased the electrical CSD threshold [Figure 2; (p=0.095 and 0.037, 6h and 12h sleep deprivation, resp.)] in a duration-dependent manner compared to controls. Other CSD parameters and systemic physiology did not differ between groups.

Conclusions: In keeping with other migraine modulators, sleep deprivation enhances CSD susceptibility to explain its mechanism as a migraine trigger. Our data underscore the importance of CSD as a migraine substrate that can be targeted therapeutically.





P316

Interhemispheric Differences of fMRI Responses in Migraine with Unilateral Aura

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Objectives: To examine the cerebral responsivity of cortical visual areas to visual stimulation in patients with migraine with unilateral visual aura.

Background: Migraine sufferers with aura often report visual discomfort outside of attacks and many consider bright or flickering light an attack-precipitating factor.

The nature of this brain hypersensitivity and its relation to the underlying pathophysiology of the migraine aura is unknown. Using fMRI measurements during visual stimulation we examined the visual cortical responsivity of patients with migraine with aura. We applied a highly sensitive within-patient design by assessing functional interhemispheric differences in patients consistently experiencing visual aura in the same visual hemifield.

Methods: We recruited 20 patients with frequent fixed-side visual aura attacks (>= 90% of auras occurring in the same visual hemifield) and 20 age and sex matched healthy controls and compared the fMRI blood oxygenation level dependent (BOLD) responses to visual stimulation between symptomatic and asymptomatic hemispheres during the interictal phase and between migraine patients and controls.

Results: BOLD responses were selectively increased in the in the symptomatic hemispheres. This was found in the inferior parietal lobule (P=0.002), the inferior frontal gyrus (P=0.003) and the superior parietal lobule (P=0.017). The affected cortical areas comprise a visually driven functional network involved in oculomotor control, guidance of movement, motion perception, visual attention, and visual spatial memory. The patients also had significantly increased response in the same cortical areas when compared to controls (P<0.05).

Conclusions: We discovered a very specific and lateralized alteration of a visually driven functional network, which may explain the commonly reported visual discomfort and dysfunction in migraine with aura.

P317

Altered Resting-State Connectivity of the Visual Network in Migraine

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Objectives: To identify if the intrinsic brain connectivity of the visual cortex is altered in migraine.

Background: Visual cortex excitability is abnormal in migraine. During interictal periods of migraine, there is lack of habituation in visual evoked potentials or magnetic fields. Moreover, the phosphene threshold is reduced in transcranial magnetic stimulation studies. The mechanism of visual cortex excitability changes remains uncertain, whereas an alteration of the functional connectivity between visual cortex and other cortical regions may be the culprit.

Methods: Resting-state functional magnetic resonance imaging data from 18 patients with migraine without aura during interictal state and 18 age- and sex-matched healthy control subjects were analyzed using dual-regression independent components analysis, which is a data-driven approach for the identification of multiple independent brain networks. Resting-state connectivity was evaluated in the medial visual network (MVN, bilateral primary visual cortex) to identify regions of interest with different connectivity between groups (migraine vs. control). The connectivity in the default mode network (DMN) was also assessed to serve as a non-visual control.

Results: Patients with migraine showed reduced connectivity between MVN and the left prefrontal cortex (superior frontal gyrus, SFG), a region with prominent role in cortical inhibition (corrected $P<0.05$ vs. controls). In migraine patients, the strength of connectivity between MVN and the left SFG was not correlated with headache parameters (headache frequency and history length). The connectivity in DMN did not differ between migraine patients and controls.

Conclusions: These findings extend the role of visual cortex in migraine pathophysiology, featured by a connectivity change which may disrupt cortical inhibition.

P318

Photophobia in Obese Mice: Implications for Migraine

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Objectives: To assess the effects of obesity on photophobia using a mouse model of trigeminal pain.

Background: Neuroinflammation driven by overnutrition may represent one of the underlying mechanisms in the association between obesity and migraine. We hypothesize that obesity may prime pain pathways, rendering them more sensitive to otherwise innocuous stimuli. We have recently shown that diet-induced obesity in mice enhances nociceptive activation in the trigeminal nucleus caudalis (TNC) in response to a very low dose of capsaicin (Rossi *et al.*, 2012). The trigeminal system is implicated in photophobia, an important migraine symptom. To translate our findings to animal behavior, we have modified the light-dark test to assess photophobia in mice.

Methods: We assessed light avoidance in C57BL/6J mice fed high-fat or regular diet. We used the light aversion test, an assay based on the natural conflict between exploration and light avoidance. Mice were tested individually in a chamber with two identical covered compartments, one of them dark and the other one lit (1000 lux, equivalent to an overcast day). We measured the percentage of time spent in each compartment. To control for anxiety, we tested the effects of diazepam (0.2, 1, and 2 mg/kg IP) and measured serum corticosterone. We also assessed the effect of systemic sumatriptan (0.4, 4, and 40 mg/kg IP). To determine whether photophobic behavior correlates with the neuronal changes observed in the TNC, we tested light aversion after treatment with a low dose of subcutaneous capsaicin (0.01%) in the face.

Results: Control mice spent about the same amount of time in the light and dark sides of the modified light-dark box. Obese mice spent about 10% less time in light than controls ($p<0.005$). This light avoidance was not reversed by diazepam or systemic sumatriptan. Furthermore, corticosterone levels were similar in both diet groups. After capsaicin treatment, obese mice spent more than 75% of the time in the dark while control mice did not respond to this dose of capsaicin.

Conclusions: Our results suggest that activation of the trigeminal system with capsaicin induces light avoidance, a surrogate of photophobia, in obese mice but not in lean mice. The lack of effect of diazepam and similar levels of corticosterone in both diet groups support the concept that light avoidance in this test represents photophobia and not anxiety. Ongoing studies will address central effects of sumatriptan and its role in blocking evoked photophobia.

P319

Intracranial Pathology and Headache – A Population Based Imaging Study (MRI HUNT)

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Objectives: Examine the relationship between headache and MRI findings.

Background: While some intracranial pathology is known to cause headache, it is disputed whether other pathology like intracranial cysts can. Previous studies on this have mostly included selected clinical populations. We present the intracranial pathology among self-reported headache sufferers and headache free in an unselected cohort drawn from a large epidemiological study (the HUNT 3 study, 2006-08).

Methods: Among participants in HUNT 3, those who had answered the headache questionnaire and who had also participated in the population-based imaging study of the head among persons between 50 and 65 years (MRI-HUNT, 2007-09) were included in this study ($n=864$). The neuroradiologists reviewing the images were blinded for personal data, but additional medical information was gathered after the review to diagnose with certainty multiple sclerosis, progressive supranuclear paralysis and to differentiate between silent and clinical infarctions. Based on the headache status in HUNT 3, the participants were categorized as headache sufferers or non-sufferers, and the number of individuals with intracranial pathology was compared between the groups. Pearson chi-square was used for all analyses except for conditions in which n was expected to be <5 (meningiomas, microhemorrhages and cerebral contusions) where Fisher's Exact Test was used. Demographic characteristics between MRI-study participants and MRI-study invited non-participants were quite similar (1).

Results: Macropathology as a whole were quite common in both groups, but it was not associated with headache

($p = 0.37$). Examining sub-groups with various pathologies, headache was significantly ($p = 0.04$) more common among individuals with rare pathology, i.e. each occurring in <1% (occlusion of carotis interna, arteria cerebri media stenosis, carotid siphon stenosis, venous angioma, cavernous hemangioma, arteriovenous malformation, postoperative alterations, hypophyseal expansion, Chiari malformation, calcification of the parenchyma, grey matter heterotopia, multiple sclerosis, progressive supranuclear paralysis, vestibular schwannoma, malignant neoplasm and mega cisterna magna).

Conclusions: In this MRI-examination of an unselected cohort, there was no difference in intracranial macropathology among headache sufferers and non-sufferers. Interestingly, however, headache was more likely among those with rare pathology.

	Total	Non sufferers		Headache sufferers		
Pathology	N	N	%	N	%	p
Included	864	552	100	312	100	
No pathology	714	461	83.5	253	81.1	0.37
Macropathology	150	91	16.5	59	18.9	0.37
Total Infarction	39	29	5.3	10	3.2	0.16
Silent infarction	25	18	3.3	7	2.2	0.39
Clinical infarction	14	11	2.0	3	1.0	0.25
Cyst	50	31	5.6	19	6.1	0.78
Non-arachnoidal	17	11	2.0	6	1.9	0.94
Arachnoidal	33	20	3.6	13	4.2	0.69
Aneurysm	15	10	1.8	5	1.6	0.82
Meningioma	9	5	0.9	4	1.3	0.73
Microhemorrhage	12	7	1.3	5	1.6	0.77
Cerebral contusion	9	3	0.5	6	1.9	0.08
Rare pathology	32	15	2.7	17	5.4	0.04

P320

Distribution of Glutamate and Glutamate Transporters in the Trigeminovascular System; Their Relationship to CGRP and CGRP Receptor Components

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Objectives: To study the distribution of glutamate, the vesicular glutamate transporter 1 and 2 (VGLUT1 and VGLUT2) in dura mater, trigeminal ganglion (TG) and the spinal trigeminal nucleus (STN).Their relation to CGRP and its receptor components- calcitonin receptor-like receptor (CLR) and receptor activity modifying protein 1 (RAMP1).

Background: Glutamate is suggested to play a significant role in migraine pathophysiology. The role of glutamate in migraine is implicated by data from animal and human studies. These studies suggest that there is a link between migraine pathology and the glutamate system, putatively in two ways. (i) The second order neurons in the brainstem contain glutamate as a main signaling molecule. (ii) Some of the trigeminal neurons contain glutamate as a co-transmitter. The neuropeptide calcitonin gene related peptide (CGRP) is suggested to play an important role in migraine and CGRP receptor antagonists have antimigraine efficacy.

Methods: Immunofluorescence was used to study the distribution of glutamate, VGLUT1 and VGLUT2 in dura mater, TG and the STN.Their relation to CGRP and its receptor components, CLR and RAMP1 was studied.

Results: Glutamate immunoreactivity was found in thin fibers, while VGLUT1 was expressed in thicker fibers in dura mater. Glutamate and the glutamate transporters expression was found in neurons of the TG and around fiber bundles in the superficial laminae of STN.Glutamate positive neurons were found in STN. In TG, some satellite glial cells displayed glutamate and VGLUT2 immunoreactivity. Glutamate positive neurons rarely co-expressed CGRP in TG, only few smaller cells expressed both markers. Double-staining of VGLUT1 or VLUT 2 and CGRP showed no co-expression in any of the areas. Double-staining of VGLUT1 and CLR showed co-expression in the thick fibers of dura mater. Double-staining of VLGUT1 and CLR showed that they could be expressed in the same cells, mainly in larger TG neurons. Not all VGLUT1 positive neurons were positive for CLR. No co-expression was found between VLUT2 and the CGRP receptor components.

Conclusions: Glutamate expression was found in thin fibers in dura mater, medium-sized trigeminal neurons and at the level of STN. VGLUT1 was instead expressed in thicker fibers and larger neurons. In addition, some satellite glial cells displayed glutamate and VGLUT2 immunoreactivity. Interestingly, we found co-expression of VLUT 1 and the CGRP receptor components. These results suggest that there may be an interaction between the glutamatergic system and CGRP receptors.

P321

Attentional Control Abnormalities in Migraineurs in between Headache Attack

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Objectives: The goal of this study was is to examine attentional control in migraineurs in between headache attacks.

Background: Previous research indicates that people with migraine, as compared to controls, have increased excitability in visual cortex in between headache attacks. For example, migraineurs' visual cortical response to repetitive innocuous visual stimuli such as a checkerboard reversal does not show normal habituation effects. Specifically, while the amplitude of visual-evoked potentials to repeated stimuli normally diminish over time, migraineurs show no evidence of this sensory attenuation. Given that visual cortical excitability can be modulated by attention, we predicted that abnormal attentional control may be playing at least some role in the visual cortical abnormalities found in migraine.

Methods: We compared responses of migraineurs (with and without aura) to non-migraine control subjects in canonical visual spatial cuing tasks. Using three separate experiments, we assessed responses in: behavioral reaction times, event-related-potentials (ERPs), and functional magnetic resonance imaging (fMRI).

Results: We have three key findings when comparing migraineurs to the non-migraine controls. First, the reaction time results suggests that migraineurs have increased reflexive orienting responses to sudden-onset stimuli in the visual periphery. Second, the ERP results suggest migraineurs have increased cortical responses to unattended or "to-be-ignored" visual events. Finally, the fMRI results suggest that migraineurs have altered functioning in the frontal-parietal attentional control network.

Conclusions: Together, this evidence suggests that migraineurs have interictal abnormalities in attentional control that specifically relate to the detection of and reaction to objects that are normally outside the focus of attention. Given that the key role of attention is the allocation of processing resources, these attentional abnormalities could be contributing to interictal visual cortical excitability in migraine.

P322

Impact of a Spontaneous Migraine Attack in the Endogenous μ-Opioid System *In Vivo*

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Objectives: We reported for the first time the impact of a spontaneous migraine attack in the μ-opioid system of a patient's brain in vivo using Positron Emission Tomography and a novel 3D-Immersive & Interactive Neuronavigation (3D-IIN).

Background: MRI-based studies show that migraine appears to result, and possibly to endure, from the alteration of specific neural processes in the central nervous system. However, information is lacking on the molecular impact of those changes, especially over the endogenous opioid system during migraine attacks.

Methods: We aimed to investigate, using a novel 3D immersive and interactive neuronavigation (3D-IIN) approach, the endogenous μ-opioid transmission in the brain during a migraine attack *in vivo*.

A 36-year-old female, who has been suffering with migraine for ten years, was scanned in the typical spontaneous headache (ictal) and non-headache (interictal) migraine phases using Positron Emission Tomography (PET) with the selective radiotracer [^{11}C]carfentanil, produced in cycloton in the vicinity, which measures *in vivo* the μ-opioid receptor availability in the brain (non-displaceable binding potential - $\mu ORBP_{ND}$). Both PET scans, (potentially) interictal or ictal, were scheduled during separated mid-late follicular phases. During ictal PET session her spontaneous headache attack reached severe intensity levels; progressing to nausea, and vomiting at the end of the scan session.

Results: There were significant reductions in $\mu ORBP_{ND}$ in pain-modulatory regions during the ictal phase, including

cingulate cortex, nucleus accumbens, thalamus and periaqueductal gray matter (PAG); indicating that μORs are preoccupied by endogenous μ-opioids released in response to the ongoing pain.

Conclusions: To our knowledge, this is the first time that changes in $\mu ORBP_{ND}$ during a migraine attack are reported, and also explored using a novel 3D neuronavigation approach, allowing for advanced investigation of the actual data in a full virtual reality. Either by the changes in occupancy or number of μ-opioid receptors available, these findings could explain why opioids are controversial as a prophylactic treatment for patients with migraine, since prolonged opioid therapy has been linked with its endurance and worsening.

P323

Heavily T2-Weighted Magnetic Resonance Myelography in Post-Lumbar Puncture Headache

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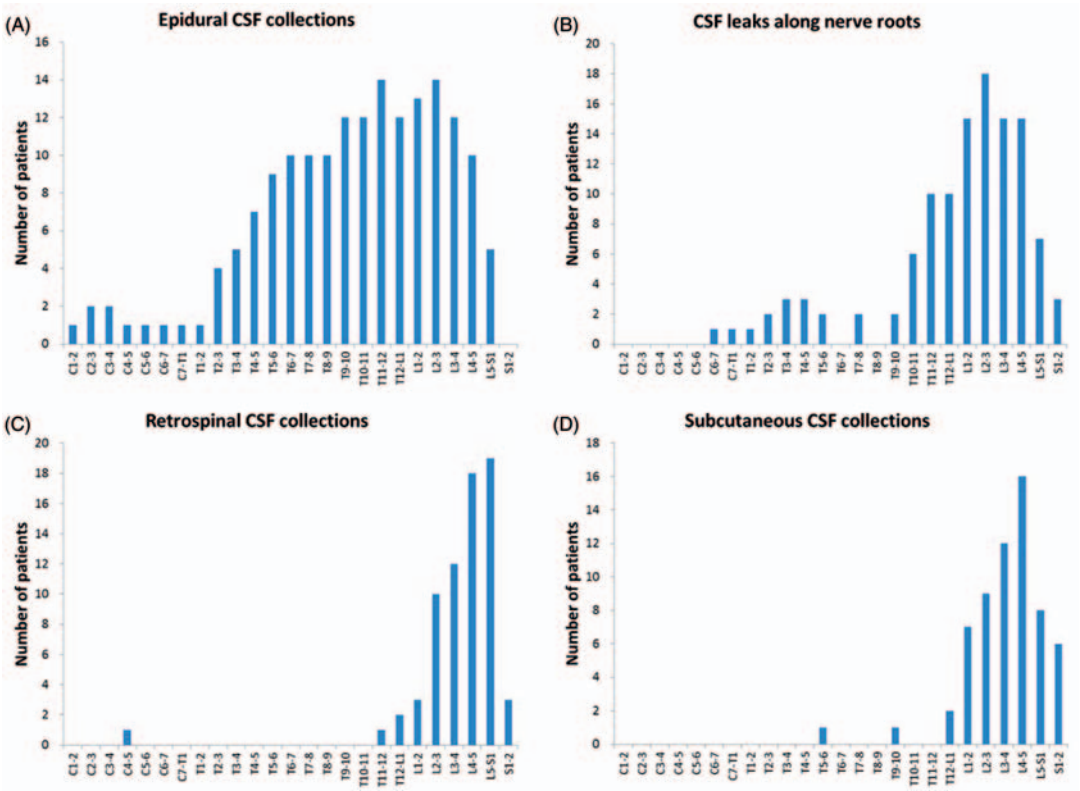
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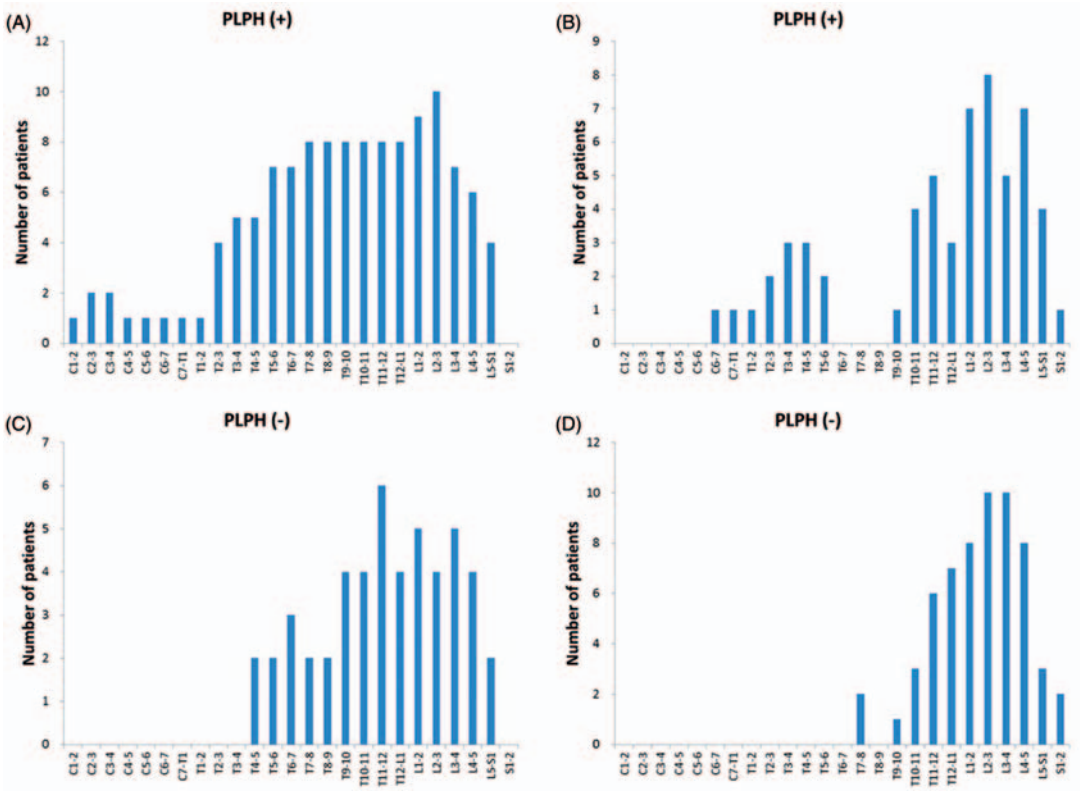
Objectives: (1) To characterize post-lumbar puncture (LP) CSF leakage with heavily T2-weighted magnetic resonance myelography (HT2W MRM), (2) to explore the radiological correlates of post-LP headache (PLPH).

Background: About one third of patients undergoing diagnostic LPs develops PLPH, and its correlation with the characteristics of CSF leakage remains unknown.

Methods: Patients indicated for diagnostic LPs were enrolled prospectively. HT2W MRM was carried out after LP. CSF leakage on HT2W MRM was assessed with four measures: CSF leaks along the nerve roots, epidural CSF collections, retrospinal CSF collections, and subcutaneous CSF collections. Images were interpreted by a blinded neuroradiologist. Comparisons were made focusing on PLPH.

Results: In total, 79 patients (50F/29M, age 48.0±14.6 years, range 18-83) completed the study, and 24 (30.4%) had PLPH. There was evidence of post-LP CSF leakage in 61 patients (77.2%): epidural CSF collections in 29 (36.7%), CSF leaks along the nerve roots in 44 (55.7%), retrospinal CSF collections in 33 (41.8%), and subcutaneous CSF collections in 27 (34.2%). CSF leakage beyond L3-4 was seen





in 57 (72.2%). Epidural CSF collections were mostly seen between mid-T to upper L regions, and CSF leaks along the nerve roots centered around upper L and upper T regions. Retrospinal and subcutaneous CSF collections were seen at the L-S regions. Patients with PLPH had higher percentages and more segments of CSF leaks along the nerve roots (91.7% vs 40.0%, $p<0.001$) (2.4±2.2 vs 1.1±1.9 segments, $p=0.010$) and epidural CSF collections (66.7% vs 23.6%, $p<0.001$) (5.0±5.8 vs 0.9±2.3 segments, $p=0.003$) than those without, and the distributions were more cephalad. Multivariate logistic regression analysis identified two factors associated with PLPH: the presence of CSF leaks along the nerve roots (odds raio [OR] = 18.2, 95% CI=3.0-112.1, $p=0.002$) and the length of epidural CSF collections (OR=1.3 per segment, 95% CI=1.1-1.5, $p=0.002$).

Conclusions: PLPH is associated with a greater amount and a more cephalad distribution of CSF leakages following LPs. Visualization of CSF leakages on HT2W MRM after diagnostic LP is common, and extravasation beyond the level of LP is frequently observed.

P324

Modulation of Migraine-Related Cortical Excitability by Adenosine and Its Receptors

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Objectives: This study explores the potential role of different types of adenosine receptors in basic mechanisms of migraine, with the goal of identifying new treatments that target these receptors.

Background: Migraine is a complex brain disorder that involves signaling by multiple neurotransmitters. The modulation of migraine by caffeine, a nonselective adenosine receptor antagonist, suggests that adenosine and its receptors (ARs) play significant roles in the disorder. There are four types of ARs: A1, A2a, A2b and A3. These are expressed in neurons, glia and vessels at different levels. A1R and A2aR are the two subtypes most highly expressed in CNS. New therapies targeting adenosine receptors are currently in development for a variety of disorders.

Methods: Confocal videomicroscopy was used to quantify the effects of adenosine receptor agonists and antagonists on the activity of cortical neurons and astrocytes in culture. Optical intrinsic signal imaging and field potential

recordings in anesthetized mice were used to investigate the effects of adenosine receptor agonists and antagonists on cortical spreading depression evoked by KCl.

Results: Adenosine (100 nM to 1 μM) rapidly and reversibly inhibited spontaneous calcium transients caused by action potential firing in cortical neurons. CCPA, a selective A1R agonist mimicked the adenosine effects. Two non-selective AR antagonists, Caffeine and CGS15943, activated calcium transients in cortical neurons indicating inhibition of ongoing tonic adenosine receptor activation. This effect was reproduced by an A1 selective receptor antagonist, DPCPX, pointing to a role for the A1R in adenosine-medicated neuronal effects. Adenosine was also able to inhibit glutamate-induced neuronal activation suggesting important neuromodulatory properties for ARs. Each of the AR compounds tested (non-selective AR antagonists, Caffeine and CGS15943; A1R selective antagonist, DPCPX; A1R selective agonist, CCPA; A2R selective antagonist, SCH 58261, and A2R selective agonist, CGS21680) had specific effects on cortical bursting activity, intracranial vascular tone, and on individual phases of cortical spreading depression.

Conclusions: Adenosine receptors are involved in multiple basic mechanisms of migraine. Adenosine and its receptors represent an attractive target for acute and preventive migraine therapies.

P325

Influence of Caffeine on Nociceptive Responses of the Trigeminocervical Complex after Orofacial Formalin Model

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Objectives: We investigated the influence of the caffeine on pain pathways involving trigeminocervical complexes (TCC) using a orofacial formalin injection model.

Background: Medication overuse has been known to be one of major contributing factors to worsening of headache. Caffeine is a kind of medication that usually overused in clinical field, but the exact mechanism of caffeine on nociceptive pathway is unclear.

Methods: In Spraque Dawley rats, we divided into subgroups depending on the caffeine administration: acute treatment group (50mg/kg, intraperitoneal injection), chronic treatment groups (1g/L or 2g/L, in combination in the drinking water per oral for 4 weeks), chronic treatment and withdrawal group (2g/L, in combination in the drinking water per oral for 4 weeks, then withdrawal for 1 week). After caffeine treatment or withdrawal, formalin was delivered into the left periorbital area and nocicepetive pain behavior was measured by monitoring the time spent rubbing the injected area during 60 min after formalin injection. The sensory threshold for mechanical stimulation, assessed by the von Frey monofilament threshold (VFMF) was also measured after treatment.

Results: In acute treatment of caffeine groups, formalin induced pain behavior was not different to vehicle treatment. Chronic treatment of caffeine significantly attenuated formalin-induced pain behavior ($P < 0.05$). After withdrawal caffeine, formalin-induced pain behavior was significantly increased compared to chronic caffeine treatment group ($P < 0.01$). Sensory thresholds for VFMF did not changed in acute and chronic treatment of caffeine compared to vehicle. After withdrawal of caffeine, threshold for VFMF was significantly decreased ($P < 0.01$) from baseline.

Conclusions: Chronic treatment of caffeine showed the inhibitory effect on nociceptive pathways from trigeminal nerve endings to the TCC and withdrawal of caffeine after chronic treatment decreased sensory threshold to mechanical stimuli.

P326

The Role of the Orexin-2 Receptor in the Nucleus Raphe Magnus on Trigeminovascular Nociceptive Transmission

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Objectives: To examine the effects of local orexin 2 receptor (OX_2) modulation in the NRM on trigeminocervical complex (TCC) neurons in response to nociceptive activation of trigeminal afferents innervating the craniovascular dura mater.

Background: The orexins are hypothalamic neuropeptides whose neurons project to the brainstem nuclei and spinal cord and are involved in the processing of

nociceptive transmission. The nucleus raphe magnus (NRM), in the brainstem, is also involved in spinal and trigeminal nociceptive processing, yet the role of the orexins in the NRM is unknown.

Methods: Adult male Sprague-Dawley rats were anesthetized with pentobarbitone sodium (60 $mgkg^{-1}$). We examined the effects of microinjecting orexin A and orexin B into the NRM, on the trigeminal neuronal activity, in response to electrical stimulation of trigeminal afferents that innervate the middle meningeal artery, its branches, and periarterial dura mater (MMA). The responses were challenged with a specific OX_2 receptor antagonist.

Results: Microinjection of orexin A or orexin B 100 μM into the NRM facilitated TCC neuron firing ($p < 0.05$). Pretreatment with an OX_2 receptor antagonist intravenously 5 min before orexin A or orexin B microinjection into the NRM blocked the facilitation of TCC neuron firing ($p < 0.05$). In addition, intravenous OX_2 receptor antagonist administration had no effect on TCC neuron firing ($p > 0.05$).

Conclusions: The present study demonstrates thatorexin microinjection into the NRM has facilitated trigeminovascular nociceptive transmission. High concentration of orexin A and orexin B have pronociceptive effects on trigeminovascular nociception that are mediated by OX_2 receptors. This implicates OX_2 receptors in NRM descending control of pain modulation in response to electrical stimulation of the MMA. Understanding the role of orexinergic control of trigeminal nociceptive transmission in the NRM may improve our knowledge of the pathophysiology of migraine and other primary headache disorders.

P327

Influences of Smoking and Caffeine Consumption on Trigeminal Pain Processing

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Objectives: To investigate whether smoking or caffeine consumption influences trigeminal pain processing.

Background: The influence of caffeine and smoking on pain processing is well described in literature. Various analgesic as well as nociceptive properties of both conditions have been reported, previously. Smoking and caffeine consumption are quite common in the general population, and even more pronounced in some patient populations (e.g. smoking in cluster headache). Caffeine itself can induce or exacerbate some pain entities (e.g. migraine, caffeine-withdrawal headache). Smokers are more prone to develop back pain and other pain conditions. Additionally, higher pain intensity scores have been reported in smokers.

Methods: Sixty healthy subjects were investigated using simultaneous recordings of the nociceptive blink reflex (nBR) and pain related evoked potentials (PREP) following nociceptive electrical stimulation on both sides of the forehead (V1). Thirty subjects were investigated before and after smoking a cigarette, thirty subjects before and after taking a tablet of 300mg of caffeine.

Results: After smoking PREP showed decreased N2 (182.15 ms vs. 176.89 ms; $p<0.005$) and P2 latencies (131.35 ms vs. 128.32 ms; $p<0.05$) indicating central facilitation at supraspinal (thalamic or cortical) level. NBR showed a decreased area under the curve (AUC) (110.52 (x10-3) (μV xms) vs. 97.09 (x10-3) (μV xms); $p<0.05$) indicating central desensibilisation at brainstem level. After caffeine intake no significant changes were observed comparing nBR and PREP results before and after consumption.

Conclusions: Smoking influences trigeminal pain processing on supraspinal and brainstem level. This observation might contribute to the further understanding of the pathophysiology of pain disorders that are associated with excessive smoking habits such as cluster headache. Additionally, it adds infomation how smoking itself influences pain processing and might alter pain perception. In contrast, caffeine consumption does not alter trigeminal pain processing significantly. Therefore, previous smoking has to be taken in account when performing electrophysiological studies to avoid bias of study results.

P328

Implication of TRPM8 in the TRPV1-Mediated Trigeminal Nociception

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Objectives: We aimed to explore the distribution of TRPM8 in the trigeminal ganglion and brainstem and the functional interaction between TRPM8 (transient receptor protein melastatin subfamily, member 8) and TRPV1

(transient receptor potential vanilloid subfamily, member 1) using a cell-based assay.

Background: Recent genome-wide association studies have identified TRPM8 as an important gene that determines the susceptibility to migraine.

Methods: Immunostaining for TRPM8 and TRPV1 in the trigeminal ganglion and brainstem was performed using Sprague-Dawley rats.

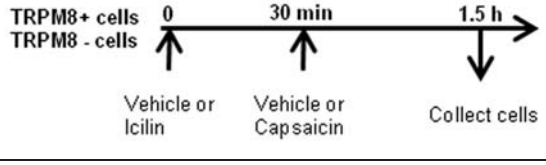
We transfected a plasmid vector bearing the full-length *TRPM8* cDNA expression cassette into PC12 cells stably expressing an EGFP-TRPV1 fusion protein. Using these cells, we examined the effect of pharmacological TRPM8 activation on capsaicin-induced JNK phosphorylation. The experimental protocol is shown in Figure.

Results: In the trigeminal ganglion, TRPM8 immunoreactivity was found in small neurons (diameter 21.2 $\pm$ 3.4μm, n $=$120), a portion of which was also positive for TRPV1 (4.3 $\pm$ 1.6%, n $=$1044). In the brainstem, TRPM8 immunoreactivity was observed in neurons of the medullary reticular nucleus, a region closely related to pain processing. Consistently, we observed the up-regulation of c-Fos expression in glutamine synthase-positive astrocytes in the medullary reticular formation following TRPV1 stimulation with capsaicin in the trigeminal area.

Capsaicin induced dose-dependent JNK phosphorylation in PC12 cells stably expressing an EGFP-TRPV1 fusion protein. Pre-treatment with icilin, a specific TRPM8 agonist, attenuated such capsaicin-induced JNK phosphorylation, implying that TRPM8 has an antagonistic action against TRPV1 with regard to JNK phosphorylation.

Conclusions: From the above data, there seem to be functional interactions between TRPM8 and TRPV1 at least at the levels of the primary sensory neurons and brainstem in vivo. Notably, TRPM8 and TRPV1 can act antagonistic to each other in a cell autonomous manner. It is inferred that some derangement of the functional interactions between TRPM8 and TRPV1 may play a role in the pathophysiology of migraine.

Figure



P329

Cortical Modulation Affects Visual Evoked Potentials Differently in Migraineurs Compared to Healthy Controls

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Objectives: To investigate the effect of navigated high-frequency repetitive transcranial magnetic stimulation (rTMS) on visual evoked potentials (VEP) in interictal migraineurs, preictal migraineurs and in healthy controls.

Background: The effect of rTMS on VEP may provide insight in how cortical excitability is altered in migraine. The migraine cortex may have a reduced homeostatic plasticity and therefore a reduced ability to counteract increases in cortical excitability. If so, rTMS should affect VEP differently in migraineurs compared to healthy controls. Because visual subsystems may be differently affected in migraineurs, VEPs were performed with both small 8' and large 65' checks. In addition, if the cortical excitability in migraine changes in the period before a migraine attack, rTMS may have a different effect on VEP in preictal compared to interictal migraine.

Methods: Forty-three migraineurs and 34 healthy controls participated in the study. Thirty-two healthy controls, 25 interictal migraine and 7 preictal migraine ($<$ 48 hours prior to headache) remained after exclusions. Four subjects in the attack phase and one in the postictal period ($<$ 48 hours after headache) were excluded. Five migraineurs were excluded because of drowsiness. Two healthy controls and one interictal migraineur were excluded because of technical difficulties.

rTMS output was set to phosphene threshold or 110% of motor threshold if phosphene threshold was $>$75% of stimulator output or if no phosphene was observed. VEPs using 8' and 65' checks were averaged in six blocks of 100 before, directly after and $>$25 minutes after rTMS.

The investigators were blinded for diagnosis during rTMS and recordings of VEPs. During visual determination of VEP-peaks, the investigator was blinded for diagnosis and block number. The primary habituation measure, linear VEP amplitude change over the six blocks, were analysed with repeated measures ANOVA.

Results: VEP habituation was found in interictal and preictal migraine and healthy controls before rTMS. There

were no differences in VEP habituation between the groups before rTMS. With 65' checks, N70-P100 habituation was decreased in interictal migraine compared to healthy controls after rTMS ($p = 0.013$). With 8' checks, N70-P100 and P100-N145 habituation was decreased in preictal migraine compared to interictal migraine and healthy controls after rTMS ($p < 0.016$).

Conclusions: Migraineurs may have a vulnerability to develop attacks because of a reduced ability to counteract changes in cortical excitability. Differences between the healthy controls and interictal migraine was only found for 65' checks, therefore the magnocellular visual subsystem may be affected in the period between attacks. The effect of rTMS in preictal migraine was only different from the other groups with 8' checks, therefore the parvocellular visual subsystem may be affected in the period before a migraine attack.

P330

Optical Measurement of Craniofacial Autonomic Function: A Tool for Quantification of Autonomic Dysfunction in Headache

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Objectives: To develop a clinically feasible protocol for measurement of craniofacial autonomic function.

Background: Craniofacial autonomic outflow is altered in several headache disorders. While systemic sudomotor, adrenergic, and cardiovagal responses are widely tested, there is currently no routinely available, standardized method of measuring craniofacial autonomic phenomena.

Methods: Subjects were placed supine and imaged under green, red and blue light. A high sensitivity CCD camera was used to image the upper 2/3 of the face. A pulse oximetry probe was placed on the earlobe. A twin-bore tube was inserted into one nostril, and the contralateral nostril was occluded. Imaging and pulse oximetry were recorded before, during and after stimulation with ammonia vapor, which was directed into the nostril via vacuum pump. Additional testing in selected cases included correlation with Schirmer's test and slit-lamp evaluation, as well as pharmacological blockade.

Results: Data was collected in 11 subjects. At baseline, low frequency fluctuations in skin reflectance were noted, that were distinguishable from reflectance changes due to heartbeat. Between 1-3 seconds after ammonia stimulus, bilateral consensual pupillary dilation, followed by relative constriction, was observed. During and shortly following the pupillary constriction phase, reflectance over the forehead, nose and cheeks decreased bilaterally (most prominent ipsilaterally), concurrent with a reduction in spontaneous vascular fluctuations. Scleral/conjunctival reflectance also decreased bilaterally, and tearing increased ipsilaterally. Imaging at multiple wavelengths, as well as slit lamp exam with a similar paradigm, suggested that the mechanism of reflectance change is an increase in blood volume due to vasodilation.

Conclusions: Our optical, multi-modal measure of craniofacial trigeminovascular autonomic function fills a gap in current clinical measurement of autonomic function. This technique is clinically feasible and may enhance our ability to further characterize migraine and facial neuralgia-related autonomic changes.

P331

Distinctive Anatomical and Physiological Features of Migraine Aura Revealed by 20 Years of Patient Recording

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Objectives: To present detailed characterization of a large number of visual auras recorded in one patient over two decades.

Background: Descriptions of the migraine aura have been presented as prospective self-observations by physicians and other professionals who had migraine with aura or migraine aura without headache.

Methods: A patient documented and made detailed drawings of 1000 aura attacks over 20 years. Drawings were made in real time with documentation of the aura wavefront at 1 minute time intervals.

Results: Most aura attacks originated centrally (within 10 degrees eccentricity), but there were also other distinct sites of initiation in the visual field (figure 1).

Figure showing the complete visual field up to 26.5° eccentricity. The right visual field of the patient is from (0-180°) and the left visual field is from (180-360°). Consistent patterns of aura initiation, propagation, and termination were observed in both right and left visual fields. Auras preferentially propagated first through

lower nasal field (69-77 % of all auras) before travelling to upper and temporal fields, on both sides.

Some auras propagated from peripheral to central regions of the visual field – these typically followed the same path as those travelling in the opposite direction. The mean velocity of the perceived visual phenomenon did not differ between attacks starting peripherally (17.6 mm/min $\pm$ 1.06) and centrally (16.2 mm/min $\pm$ 0.59), ($P = 0.41$). Based on duration and imaging we estimated the speed of the underlying cortical event to be 2.1-3.1 mm/min.

Conclusions: These results indicate that there can be multiple distinct sites of aura initiation in a given individual, and that there are consistent patterns of aura propagation that indicate non-concentric patterns of spread. Structural and functional imaging studies are currently being performed to define the anatomical correlate of this individual's aura.

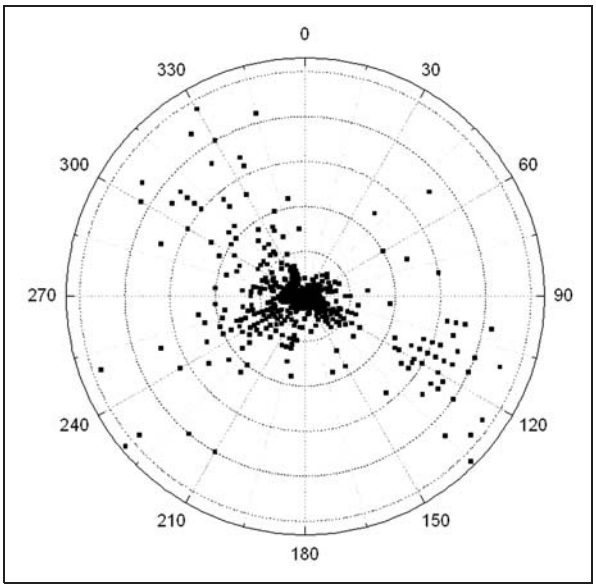


Figure 1. Points of aura origin, N=800.

P332

Lateral Inhibition in Somatosensory Cortex of Migraine without Aura Patients between Attacks

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Objectives: Our objective was to investigate lateral inhibition within the somatosensory cortex in a group of migraine without aura (MO) patients compared to healthy volunteers (HVs) by stimulating two peripheral nerves simultaneously, while recording somatosensory evoked potentials (SEPs).

Background: Cortical potentials evoked by various sensory stimuli are characterized interictally in migraine by lack of habituation. Both deficient intracortical inhibition and low cortical pre-activation levels have been claimed in explaining this phenomenon. However, they are not mutually exclusive, since the latter could induce the former via reduced lateral inhibition.

Methods: Somatosensory evoked potentials were elicited by electrical stimulation of the right median and ulnar nerve at the wrist separately and simultaneously (2Hz repetition rate, 1.2 motor threshold, 300 sweeps per condition), in 21 MO patients between attacks and in 17 healthy volunteers (HVs). We measured parietal N20-P25 amplitudes and we evaluated the ratio MU/(M+U)*100, where MU is the SSEP amplitude obtained simultaneously stimulating both median and ulnar nerves (MU), and M+U is the sum of amplitudes obtained by stimulating each nerve separately (M+U). Higher ratio of SSEP suppression means less inhibition. This ratio was considered an index of cortical lateral inhibition (ICLI) between afferent inputs from the two peripheral nerves. Habituation was calculated as the slope of the linear regression between the 1st and the 3rd block of 100 averaged sweeps.

Results: SSEP N20-P25 amplitudes decreased along the blocks in HV (-0.08%), whereas they significantly increased in MO patients (+0.22%, p=0.03). On grand-average, ICLI resulted similar between groups (60.5% and 60.9% respectively in HV and MO, p=0.94). The habituation slope was positively correlated with ICLI only when data of HV and MO patients were combined (r=0.331, p=0.04).

Conclusions: These results suggest that lateral inhibitory mechanisms within the somatosensory cortex may contribute to induce the interictal lack of habituation of N20-P25 SSEPs amplitude seen in migraine patients. This interpretation is supported by the positive correlation we observed between habituation and ICLI: in other words, the more marked the habituation deficit the less pronounced the lateral inhibition. However, since the correlation is significant only if the data from HV and MO patients are pooled, this suggest that it is a more general phenomenon related to the habituation mechanisms, not specific to migraine.

P333

Cerebellar Function in Migraine Patients and Its Relation with Cerebellar Ischemic Lesions

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Objectives: To asses cerebellar function in a large population-based case-control study, by evaluating the function with four validated tests, and correlate the outcomes with MRI imaging of the cerebellum.

Background: Previous studies showed cerebellar lesions in migraineurs, and diminished cerebellar function was reported in other studies. So far, direct comparison between lesions and functional cerebellar outcomes was lacking.

Methods: The population-based CAMERA study included 282 participants, 200 migraine patients (111 migraine with aura,) and 82 controls, with a mean age of 57 years (range 43-72), 72% were female. As a positive control group, we evaluated a small set (n=12) of patients with Familial Hemiplegic Migraine with a proven mutation in the *CACAN1A* gene (FHM1, 42 years (range 19-64, 67% female). The Purdue peg board task, the block design test from the Wechsler Adult Intelligence Scale (WAIS) III, the prism adaptation test and the eyeblink conditioning task were performed. All tests were done inter-ictally and investigators were blinded for all participant characteristics.

Results: Results: From the CAMERA cohort, migraineurs (independent of subtype) and controls all performed equally on all four cerebellar tests. MRI showed a cerebellar infarct-like lesion in 21 (7%) participants, 18 of them were migraineurs. Migraineurs with these lesions on MRI performed worse on the pegboard task, a specific test for fine motor skills, number of pegs with both hands was 9.5 compared with 10.8 in the non-infarcted migraineurs, $p<0.05$.

FHM1 patients, as a positive control group, showed deficits on all four tests; Peg assembly ($p=0.04$); block design mean scaled score ($p<0.001$); prism adaptation ($p<0.001$), timing of conditioned eyeblink responses ($p< 0.05$). No MRI images were obtained in the FHM group.

Conclusions: Migraine patients (independent of subtype) and controls have comparable inter-ictal cerebellar function. Importantly, migraineurs with one or more small cerebellar infarct-like lesion have diminished fine motor skills.

P334

Navigated High Frequency Transcranial Magnetic Stimulation in Interictal Migraineurs: Abnormal Modulation of Thermal Thresholds

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Objectives: To investigate how thermal detection and pain thresholds vary after navigated 10 Hz repetitive transcranial magnetic stimulation (n-rTMS) on the secondary sensory cortex (SII) in healthy controls (CO), interictal (MINT) and preictal (MPRE) migraineurs.

Background: High frequency rTMS on the motor cortex and various other sites has been shown to modulate experimental pain. The secondary sensitive cortex is largely involved in pain processing, but it has not been widely used as a target for pain modulation by rTMS (Mylius, Borckardt et al. 2012). However, one study suggested that n-rTMS on SII was most effective to increase heat pain thresholds in healthy subjects (Valmunen, Pertovaara et al. 2009). Our aim was accordingly to investigate this effect in interictal and preictal migraineurs.

Methods: Detection and pain thresholds for cold and heat were recorded before, after sham rTMS and after active n-rTMS on SII. Sham rTMS was performed with the coil tilted 90 degrees. Thirty-eight migraineurs and 31 healthy controls were analysed in this blinded study. Repeated measures ANOVA (with site and stimulus as within-subjects factors and diagnosis as between-subject factor) were applied.

Results: Cold pain thresholds (CPTd = 32°C-CPT) increased after rTMS compared to sham in CO, but decreased in MINT (ANOVA group x stimulus interaction $p=0.006$). RTMS had the same effect on heat pain thresholds (HPTd = HPT-32°C) with an increase in CO and a decrease in MINT ($p=0.030$). Thresholds after rTMS also differed from baseline for both CPTd ($p=0.041$) and HPTd ($p=0.030$). Heat detection thresholds (HDTd) decreased after rTMS in MPRE compared to CO ($p=0.035$).

Conclusions: Our results imply that cold and heat pain sensitivity is modulated differently by n-rTMS in CO and MINT as MINT patients become more sensitive while CO become less sensitive. The results suggest that a normal protective mechanism, preventing increased cortical excitability after SII activation, is altered in MINT. Our results also suggest that sensory detection of heat is modulated differently in MPRE and CO.

P335

A History of Migraine Accelerates Infarct Growth in Stroke Patients

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Objectives: To assess acute stroke evolution in patients with a documented migraine history.

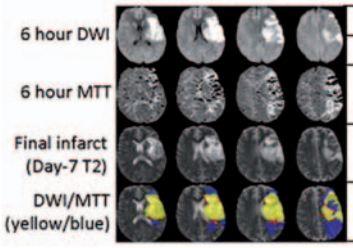
Background: Migraine is an independent stroke risk factor, particularly in otherwise healthy persons. A migraine history increases stroke risk, especially in young females suffering from migraine with aura (6-fold). Recent animal experiments suggest that migraine mutations increase brain vulnerability to ischemia via excitatory mechanisms (Circulation 2012; 125:335). Migraine mutant mice develop higher number of ischemic depolarizations and accelerated infarct growth during hyperacute stroke, with worse outcomes. Anti-excitatory treatment prevents this severe stroke phenotype.

Methods: We retrospectively analyzed lesion volumes on diffusion-weighted imaging (DWI), and the volume of perfusion defect on perfusion-weighted imaging (PWI) using mean transit time (MTT), from consecutive patients in Massachusetts General Hospital stroke database (years 2003-2012). Measurements were done blinded to migraine status.

Results: A total of 155 stroke patients had reliably documented presence or absence of a migraine history (Figure 1). Stroke patients with a migraine history were younger and more often female, compared to those without. Migraineurs less frequently had coronary artery disease or diabetes. The frequency of posterior circulation lesions was significantly higher in migraineurs. Otherwise, groups were comparable. In patients with PWI scans, DWI-PWI mismatch was calculated on spatially co-registered DWI and MTT maps, as a marker for viable tissue at risk for infarction. In migraineurs, a larger area of the perfusion defect showed DWI changes, resulting in smaller DWI/PWI mismatches. Indeed, a larger proportion of migraineurs showed no mismatch (i.e., DWI/PWI>0.9; Figure 2, *p=0.011, †p=0.002), indicating that the entire perfusion defect was already infarcted.

Conclusions: Our data show that a history of migraine, particularly with aura, is associated with accelerated acute infarct growth. A prospective case-control study is warranted to confirm and extend these data. With regard to stroke treatment, data suggest a shorter therapeutic window for acute stroke interventions in migraineurs, due to rapid loss of salvageable brain tissue.

	Migraine				No migraine
	Any type	with aura	without aura	unknown type	
n	111	35	19	57	44
Age, mean±SD	55±18	54±17	55±22	55±16	63±14
Age, median(IQR)	58(27)	57(30)	53(35)	59(26)	64(22)
Gender, male, n(%)	37(33)	8(23)	6(32)	23(40)	32(73)
DWI, availability	111(100)	35(100)	19(100)	57(100)	44(100)
PWI, availability	25(23)	9(26)	6(32)	10(18)	25(57)
Proximal occlusion	55(50)	19(54)	11(58)	25(44)	24(55)



	Migraine		No migraine
	Any	With aura	
Number of patients with DWI/PWI scans	25	9	25
DWI/PWI [median (range)]	0.8 (0.8)	1.0 (1.7)	0.5 (0.6)
Patients with DWI/PWI>0.9	9* (36%)	5† (56%)	1 (4%)

P336

Unilateral Cranial Autonomic Symptoms in Migraine: A Retrospective Case Series on 757 Patients

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Objectives: To extend our previous findings on frequency and characteristics of migraine with unilateral cranial autonomic symptoms (UAs) in a retrospective study on a large case series in an Headache Centre.

Background: UAs (i.e. lacrimation, conjunctival injection, eyelid oedema and nasal congestion), the hallmark of trigemino-autonomic cephalalgias, also occur in a proportion of migraine patients during the attack. In a previous study on 177 migraineurs attending an Headache Centre we reported UAs in 45.8% of patients.

Methods: We retrospectively investigated all consecutive migraine patients seen at our Headache and Pain Unit from 1st January 2010 to 31st December 2012. Demographic information and detailed clinical migraine features were gathered using a structured questionnaire with face-to-face interviews. We compared demographic and clinical characteristics of migraineurs with UAs with those of migraine patients without UAs.

Results: We studied 757 consecutive migraineurs (M/F = 153/604; age = 39.05 $\pm$ 12.7 yrs). Two hundred eighty-three patients (37.4%) reported the presence of at least one UAs homolateral to pain during the attack. Migraine patients with UAs showed longer disease duration (20.8 $\pm$ 13.1 *vs* 18.2 $\pm$ 13.3 yrs) ($p < 0.009$), higher pain severity ($p < 0.005$), more strictly unilateral pain (59% *vs* 41%) ($p < 0.001$), longer attack duration ($p < 0.001$) and more frequent allodynia (57% *vs* 29%) ($p < 0.001$) compared to migraineurs without UAs.

Conclusions: In a large retrospective study we report that UAs occur in almost 1 out of 3 migraineurs referred to headache centres. This proportion is slightly lower than that previously reported by our group on a smaller patient sample. The present study confirms that migraineurs with UAs have more severe and more strictly unilateral headache and adds new data revealing that they have longer disease duration and attack duration and more frequent allodynia during the attack. We suggest to carefully consider this migraine phenotype in epidemiological and pharmacological studies on migraine.

P337

A New Electronic Tool for Mapping Spatial and Temporal "Hotspots" in Migraine Pain

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Objectives: This study introduces a novel tool for electronically collecting data on the patterns of migraine headache onset and progression.

Background: Migraine pain is a common, yet not well understood headache pathology, which occurs in 11.7% of US households. Here, we present an electronic tool to quantitatively capture the pattern of migraine pain onset and distribution as the headache progresses in localized areas of the head and neck: a tool for understanding migraine pain distribution and locating migraine "hotspots."

Methods: This study was approved by IRB, and all subjects gave informed consent prior to using this tool. Study data were collected and managed using REDCap electronic data capture tools, a secure web-based application that supports research study data capture.

A total of 44 segments were defined on a schematic map of face, head and neck. The segmentation was based on previous reports of migraine pain, and by the distribution of the nerves in these regions as confirmed by *Gray's Anatomy,* Fig 784. The segments were color-coded and the subjects were advised to identify the origin of pain at headache onset and regions when the headache was full-blown. Next, patients were asked to identify all regions in which they typically experienced pain.

Results: Implementing this tool in our research study, 36 migraineurs successfully used this pain survey tool to capture "pain hotspots" and the changes and evolution of pain over the course of a migraine. Consistent with previous findings, 58.3% of migraineurs indicated that they experience throbbing pain in the right temple region, and 55.6% indicated throbbing pain in the left temple. A tertiary care study has previously described migraine pain prevalence at 58% for the temple region. Pain in the frontal region increased from 25% to 42% of migraine patients as a typical migraine progressed, while pain in the area behind the eyes decreased from 39% to 28% and then to 19% as a migraine progressed.

Conclusions: The pain map survey is a useful tool for understanding migraine pain and its underlying mechanisms. Using the data captured in the survey, this novel tool could be used to create maps of pain "hotspots" and serve as a quantitative measurement of the spreading of pain during migraine. Additionally, it could be useful for understanding complex headache cases, providing information to systematically include or exclude migraine headache based on the pain pattern presented and to verify if the trigeminal nerve network is closely linked to migraine headache attacks. Furthermore, this tool could be developed into a streamlined clinical application for personal use and documentation of each migraine headache by patients. Using this compiled information, physicians could have a comprehensive understanding of each patients' unique headache characteristics and patterns.

P338

Withdrawn by the author.

P339

Effect of Cortical Spreading Depression on the Phosphorylation of ERK in the Trigeminal Ganglion of Rat

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Objectives: In this study we examined the effect of CSD on the phosphorylation of ERK in the TG.

Background: In migraine pathophysiology, cortical spreading depression (CSD) and activation of the trigeminovascular system are known to contribute to aura and headache, respectively. However, the relation between CSD and activation of the trigeminal nerve is still obscure. Phosphorylation of extracellular signal-regulated kinase (ERK) in sensory neurons by noxious stimulation is considered to contribute to pain hypersensitivity, and we have already reported the occurrence of phosphorylation of ERK in the trigeminal ganglion (TG) after stimulation of dural TRPV1, which is a major nociceptive receptor.

Methods: Sprague-Dawley male rats were used for the experiment. D.C. electrodes were set on the bilateral exposed parietal cortex under anesthesia. We also installed a small open cranial window near the electrode to induce CSD using 1M KCl solution. In the first experiment, animals were divided into three groups. Bilateral TGs were dissected immediately (group-2; n =6) or at 30 minutes (group-3; n =6), after the first wave of CSD. As control (group-1; n =6), saline was applied on the open cranial window instead of 1M KCl solution.In another experiment, animals were divided into two groups. Capsazepine (50 nM), which is an antagonist of the TRPV1 receptor, was injected into the cisterna magna (group-5; n =6). For control, vehicle (20% DMSO in saline) was injected instead of capsazepine (group-4; n =6). In both groups, 1M KCl was applied on the cranial window to induce CSD, and 30 minutes later, bilateral TGs were dissected. In both experiments, the specimens were used for western blot analysis to observe the expression of pERK and total-ERK. The ratios of the intensity of pERK to total ERK were calculated using the image analysis software.

Results: The ratios of pERK/ total-ERK were 1.82 $\pm$ 0.48 for ERK1 and 2.97 $\pm$ 0.76 for ERK2 in group-3, 1.12 $\pm$0.45 for ERK1 and 1.24 $\pm$ 0.63 for ERK2 in group-2. The ratios of pERK/ total-ERK showed significantly higher levels in group-3 compared with group-1, however there was no significant difference between group-1 and group-2.

The ratios of pERK/ total-ERK were 0.23 $\pm$ 0.35 for ERK1 and 0.35 $\pm$ 0.43 for ERK2 in group-5. The ratios of pERK/ total-ERK showed significantly attenuated levels in group-5 compared with group-4. The frequencies of CSD occurrence during 30 minutes were 4.7 $\pm$ 0.5 times in group-4 and 4.7 $\pm$ 1.4 times in group 5, and there was no significant difference between group-4 and group-5.

Conclusions: Our data demonstrated that CSD caused the phosphorylation of ERK in TG, and these responses were inhibited by TRPV1 antagonist. From the above findings, it is inferred that CSD may cause the nociceptive response to TG via TRPV1, and activate trigeminovascular system.

P340

Gray Matter Changes in Vestibular Migraine

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Objectives: To determine structural gray matter differences in patients with vestibular migraine and healthy controls in comparison to reported brain changes in migraine with and without aura.

Background: Dizziness and vertigo are common complaints of patients with migraine either in form of aura preceding the migraine attack or in form of autonomic symptoms during the attack, similar to nausea and vomiting. The strong relation of vestibular symptoms with

migraine lead to the term vestibular migraine, but it remains uncertain as to whether it is a variant of migraine with or without aura, or whether it may represent a separate disorder.

Methods: 27 patients with vestibular migraine (mean age 42 years, 21 women) were compared to 27 age and gender matched healthy controls using voxel-based morphometry (VBM). The images of all subjects were acquired in a 1.5 T Siemens Avanto Scanner using a high resolution MPRAGE sequence with a voxelsize of 1x1x1 mm^3. For the analysis we used the "new segment" and the DARTEL algorythm of SPM8 (www.fil.ion.ucl.ac.uk/spm/).

Results: Patients with vestibular migraine showed a marked decrease of gray matter in the middle and superior temporal gyrus, cingulate gyrus, insula, inferior parietal, visual, as well as prefrontal cortex. No increase of gray matter was observed in this regard.

Conclusions: The brain regions with decrease in gray matter identified in vestibular migraine are quite similar to what was described previously in migraine with and without aura. These areas play a pivotal role in human somatosensory and nociceptive processing, but also are partly involved in multisensory vestibular control. The superior temporal, inferior parietal, as well as insula may point toward the pathophysiological origin of the common complaint of vertigo and dizziness in patients with migraine in general and vestibular migraine in particular. Further research is needed to directly compare migraine without aura, migraine with aura and vestibular migraine to further elucidate this interesting relation.

P341

Thermo-Sensitivity in Migraine between Attacks: A Study of Quantitive Thermo-Sensory Testing and Contact Heat Evoked Potentials

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Objectives: To study cephalic and extracephalic cutaneous thermal sensory and pain thresholds using Quantitative Sensory Testing (QST) and amplitude as well as habituation of Contact Heat Evoked cortical Potentials (CHEPs) in episodic migraine patients between attacks and, for comparison, in healthy volunteers.

Background: Cutaneous allodynie occurs during migraine attacks, chiefly in the trigeminal territory, and is also reported more prevalent than in healthy controls between attacks (1). Electrophysiologically, migraine is characterized between attacks by a habituation deficit of various evoked cortical responses. Including laser evoked potentials (2).

Methods: We enrolled 15 patients (mean age: 21.86 $\pm$3.6 yrs; 4M, 11F) suffering from episodic migraine without aura (ICHD-21.1) in the interictal phase and 15 healthy volunteers (22.6 $\pm$ 2.6 yrs; 6M, 9F). Patients had no preventive treatment and no analgesic drug intake during the 72 h preceding the recordings.

Thermal QST was performed with an ATS thermode (Medoc Ltd, USA). We determined cold and heat detection (CS, WS) and pain thresholds (CP, HP) on the volar wrist and on the forehead. All thresholds were randomly assessed 3 times and averaged off line.

For CHEPs we delivered 20 heat stimuli (53°C – baseline temperature: 42°C) with a CHEP stimulator (Medoc Ltd, USA) to the right volar wrist or forehead with a randomized inter-stimulus interval between 10 and 25 seconds. EEG activity was recorded from Cz-Fz and off-line averaged in 5 sequential blocks for N2-P2 amplitude and habituation (% and slope over the 5 blocks) measurements.

Results: Thermal QST was on average not different between migraine patients and healthy neither at the wrist nor at the frontal site.

In both patients and controls the CHEP N2-P2 amplitude was significantly larger when the forehead was stimulated compared to the wrist ($p<0.05$).

There was no difference in CHEP amplitude or habituation between migraine patients and healthy subjects, but in patients the habituation slope was steeper in the forehead than at the wrist ($p<0.05$).

Conclusions: Between attacks, thermal sensory perception and pain thresholds are on average normal in migraine without aura both in the trigeminal territory and the upper limb. The same holds true for contact heat evoked cortical potentials. By contrast with LEPs, habituation of CHEPs is increased rather than decreased in migraine patients.

Overall these results do not favor persistent central sensitization between attacks in migraine without aura.

P342

Changes in Calcitonin Gene-Related Peptide (CGRP) Receptor Component and Nitric Oxide Receptor (sGC) Immunoreactivity in Rat Trigeminal Ganglion Following Nitroglycerin Pretreatment

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Objectives: In the present study we examined changes in immunofluorescence of the CGRP receptor components (CLR and RAMP1) and soluble guanylyl cyclase (sGC), the intracellular receptor for NO, in rat trigeminal ganglia, after pretreatment with nitroglycerin (GTN).

Background: Nitric oxide (NO) is thought to play an important role in the pathophysiology of migraine. Infusion of the nitrovasodilator glyceroltrinitrate (GTN), which mobilizes NO in the organism, is an approved migraine model in humans; the underlying nociceptive processes can partly be examined in animal experiments. Calcitonin gene-related peptide (CGRP) is regarded as another key mediator in migraine. Increased plasma levels of CGRP have been found during spontaneous as well as nitrovasodilator-induced migraine attacks.

Methods: In the present study we performed GTN pretreatment and examined changes in immunofluorescence of CGRP receptor components and soluble guanylyl cyclase (sGC), the intracellular receptor for NO, in rat trigeminal ganglia.

Results: In vehicle-treated animals, 42% of the trigeminal ganglion neurons were immunopositive for RAMP1 and 41% for CLR. While CLR-immunopositivity was unchanged after GTN pretreatment, there was an increase in neurons immunopositive for RAMP1 to 46%. sGC-immunopositive neurons,were on average smaller than sGC-immunonegative neurons, and the percentage decreased from 51% in vehicle to 48% after GTN infusion.

Conclusions: Prolonged infusion of GTN resulted in decreased fractions of sGC- and increased fractions of RAMP1-immunopositive neurons in different divisions of the trigeminal ganglion. The observed alterations are likely immunophenotypic correlates of the pathophysiological processes underlying nitrovasodilator-induced and spontaneous migraine attacks.

P343

Interictal Alterations of Pain Processing Pathway in Migraine Patients with Cutaneous Allodynia

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Objectives: The present study aimed to find out the cerebral functional alterations related to the establishment of central sensitization in migraineurs, using blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI).

Background: Cutaneous allodynia (CA) is a characteristic of central sensitization, predicting migraine progression and poor response to therapy. Whether it attributes to persistent functional changes in the central nociceptive pathway is still unknown.

Methods: The experiment was performed in 15 migraineurs with CA (MWCA), 19 patients without CA (MWoCA) and 20 matched healthy controls. Demographic and headache characteristics were collected from all participants, and they all underwent MRI scanning in the absence of headache. Each subject was given transcutaneous electrical nerve stimulation (TENS) at the left forehead during fMRI scanning, achieving to a previously determined level of pain sensation (i.e. VAS $=$ 40).

Results: Demographic and headache characteristics were balanced between migraine groups. The contrast images of both migraine groups comparing to healthy controls exhibited decreased activation of various brain regions (e.g. cerebellum and insulae), which probably take part in the pathophysiological procedure of migraine. The direct comparison between the two migraine groups revealed that activation in the dorsal pons and contralateral (right) inferior parietal lobule of WMCA subjects were significantly lower than it in WMoCA ones.

Conclusions: The interictal dysfunction of pain processing pathway may be responsible for (at least relevant to) central sensitization in migraine patients, via abnormal modulations of nociceptive transmission.

P344

A Pilot fMRI Study of Patients with Tension-Type Headache

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Objectives: We conduct a pilot study using blood oxygen level Dependent Functional MRI (BOLD fMRI) to explore whether TTH patients have functional changes compared to healthy subjects.

Background: Tension-type headache (TTH) is the most common type of primary headache. Previous studies showed gray matter (GM) decreased in patients suffering chronic tension-type headache (CTTH) through magnetic resonance imaging (MRI) and voxel-based morphometry (VBM), suggesting the brain structure has small changes in CTTH. Considering structural network may affect functional connectivity via GM decrease in TTH patients, we wannan know whether TTH patients have functional changes compared to healthy subjects.

Methods: We included TTH patients assessed by ICHD-II and age-, gender- and education-matched healthy controls in our study. We firstly collected and compared their clinical characteristics, and then used a 3.0-T MRI system to obtain MRI data, and analyzed rest functional MRI (rfMRI) data by regional homogeneity (ReHo) method.

Results: Ten subjects with TTH and ten matched controls were included. There were no significant differences in demographic features and cognitive function between groups, but the scores reflecting the degrees of anxiety and depression of TTH group were significantly higher than those of the controls ($p<0.05$). Compared with healthy controls, TTH patients showed that ReHo value increased in bilateral lentiform nucleus and caudate, which may play an important part in pain processing.

Conclusions: Our study provided evidence to support the above brain regions may be abnormal in pain process in TTH patients.

P345

Capsaicin-Induced Nerve Fiber Degeneration in the Spinal Tract of the Trigeminal Nucleus

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Objectives: The aim of this study is to explore the effect of repetitive capsaicin trigeminal stimulation on the morphology of nerve fibers of the spinal tract of the trigeminal nucleus (TNS).

Background: TRPV1 (transient receptor potential vanilloid subfamily member 1) is expressed in sensory neurons and serves as a transducer of various noxious stimuli into pain signals, and it is implicated in the pathophysiology of migraine[1)]. TRPV1 agonists have been used for treating intractable pain conditions. Notably, capsaicin, a well-known TRPV1 agonist, is shown to be effective in aborting migraine attacks[2)]. Recent evidence shows that TRPV1 stimulation induces morphological changes of sensory neurons and nerve fibers[3)].

Methods: Male C57BL/6J mice ($n = 9$) were used. A patch containing 10 mM capsaicin was applied to the left V1 region of the face for 30 minutes. A vehicle-containing patch was applied to the same region on the contralateral side. The patch application was repeated daily and mice were sacrificed at Day 3, 5 and 7 ($n = 3$ each) after the initial patch application. The mice were transcardially perfused with 2.5% glutaraldehyde/0.1 M cacodylate-buffer and brainstem sections harboring TNS were prepared. Electron microscopic analysis of TNS nerve fibers was performed.

Results: Capsaicin induced a significant reduction in the proportion of myelinated nerve fibers with the diameter of $\leq$ 1.0 mm in the whole myelinated nerve fibers examined at Day 3 compared to the vehicle-treated side (13.3% $\pm$ 2.7 % [mean $\pm$ SD] vs. 36.7% $\pm$ 6.6%, $p = 0.005$, t-test). The proportion did not significantly differ at Day 5 (13.7% $\pm$ 6.0%), but exhibited a significant increase to 29.3% $\pm$ 5.8% at Day 7 ($p = 0.025$). At Day 7, there was a trend for the decreased proportion of nerve fibers with the diameter of $\leq$ 2.0 and $>$1.0 mm on the capsaicin-treated side compared to the vehicle-treated side (28.7% $\pm$ 10.9% vs. 39.7% $\pm$ 7.7%, $p = 0.228$). Capsaicin also caused a time-dependent decrease in the proportion of unmyelinated nerve fibers (11.7% $\pm$ 0.31% at Day 3, 6.4% $\pm$ 0.2% at Day 5, and 5.4% $\pm$ 4.8% at Day 7).

Conclusions: Repetitive capsaicin administration causes the degeneration of both myelinated and unmyelinated fibers in TNS. Myelinated fibers with the smaller diameter appear to be more vulnerable than those with the larger diameter, and the increase in the proportion of myelinated nerve fibers with the diameter of $\leq$ 1.0 mm between Day 5 and Day 7 was likely to be explained by concomitant degeneration of larger nerve fibers. Capsaicin-induced unmyelinated nerve fiber degeneration in TNS is a time-dependent process. Such degenerative changes may be relevant to the anti-nociceptive action of capsaicin.

P346

Inflammation Induced Activation of pERK1/2 and NF-κB Show Co-Localization with CGRP and Its Receptor Components in Rat Trigeminal Ganglion

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Objectives: Temporomandibular joint inflammation induced activation of mitogen-activated protein kinase pERK1/2 and transcription factor NF-κB is in connection with the sensory neurotransmitter CGRP and its receptor components in rat trigeminal ganglion.

Background: The trigeminal ganglion plays central role in cranial pain syndromes. It has been shown that calcitonin gene-related peptide (CGRP) has a wide biological function in the sensory system. In the trigeminal ganglion CGRP is expressed in small- and medium-sized neurons and fibers, while its receptor components (calcitonin receptor-like receptor - CLR - and the receptor activity modifying protein 1 - RAMP1 -) in large neurons and satellite glial cells. Previous studies have shown that acute inflammation induced by injection of complete Freund's adjuvant into the temporomandibular joint (TMJ) resulted in phosphorylation of the mitogen-activated protein kinase extracellular signal-regulated kinase 1/2 (pERK1/2) in satellite glial cells. Activation of pERK1/2 initiates induction of nuclear factor kappa B (NF-κB) which was present in the cytoplasm of small- and medium-sized neurons in the trigeminal ganglion.

Methods: We hypothesize that there is a connection between the activated protein kinase and CGRP receptor components and between the transcription factor and CGRP in rat trigeminal ganglion using immunohistochemistry.

Results: We observed co-localization between activated pERK1/2 and CLR/RAMP1 in the satellite glial cells after TMJ activation. In addition, double staining of small- and medium-sized neurons with NF-κB and CGRP revealed that some cells were only NF-κB positive, others only CGRP positive, and a number contained both markers (double-stained).

Conclusions: CGRP-containing small- and medium-sized neurons may release CGRP, acting on CLR/RAMP1-containing satellite glial cells and large neurons in the trigeminal ganglion. Our results indicate that following TMJ stimulation there is activation of satellite glial cells, activation of mitogen-activated protein kinase pERK1/2, an inflammatory transcription factor NF-κB, the sensory neurotransmitter CGRP and its receptor components. This suggests that TMJ induced inflammation can elicit a cascade of events in the trigeminal ganglion that may be involved in cranial pain developments.

P347

White Matter Abnormalities in Corpus Callosum in Episodic and Chronic Migraine Patients: A Tractography Study

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Objectives: We aimed to characterize and compare microstructural changes in corpus callosum in patients with episodic and chronic migraine. We analyzed indices derived from diffusion tensor magnetic resonance imaging (DT-MRI) study.

Background: DT-MRI can detect cerebral white matter abnormalities non displayed on conventional MRI sequences. Some studies have shown abnormal white matter properties in several brain regions in migraine patients, including corpus callosum, as well as a correlation between some of the indices studied and frequency of migraine attacks or comorbidity with depressive or anxious disorders. Chronic migraine is the most severe end of the broad spectrum of migraine; chronicity in migraine is not simply an increased quantity of headache days, but rather a qualitative shift, perhaps based on pathophysiological differences.

Methods: We selected 12 patients (1 male, 11 females) attended in a headache clinic in a tertiary hospital. Episodic migraine (Group A) was diagnosed accordingly to ICHD-II. For chronic migraine (Group B) we considered ICHD-II revised criteria. We administered six-item Headache Impact Test (HIT-6) and Hospital Anxiety and Depression Scale (HADS). A GE Signa 1.5 T MR scanner was used in this study. We analyzed genu, body, and splenium parts of

corpus callosum. Computation of the fiber tracts was made by means of a forth order Runge-Kutta algorithm to interpolate the vector field composed by the major eigenvector of the diffusion tensor at each voxel. Each of the image voxels belonging to the white matter were considered as a seed for fiber trajectory estimation. Once all the fiber tracts had been computed, the bundle of interest was selected using a set of regions of interests (ROIs). Indices considered were fractional anisotropy (FA), relative anisotropy (RA), mean diffusivity (MD), tract integrity, lineal, planar and spherical coefficients and eigenvalues (EV). Independent sample t-test was used to test the differences of indices means between Group A and B.

Results: Five patients (1 male, 4 females, 35.6 $\pm$ 5.2 years) were included in group A, and seven (all females, 34.5 $\pm$ 11.4) in Group B. We found no differences between groups A and B in HIT-6 score (60.6 $\pm$ 3.2 vs 64.4 $\pm$ 4), or HADS anxiety (4.6 $\pm$ 2 vs 3.7 $\pm$ 4) and depression (1.8 $\pm$ 2.1 vs 2.1 $\pm$ 4.4) scores. Chronic migraine patients showed significantly lower MD in ROIs of the body part of corpus callosum (0.099 $\pm$ 0.006 vs 0.117 $\pm$ 0.009, p:0.003). This difference between both groups was also consistently observed in the three EV of ROIs considered.

Conclusions: In spite of the short number of patients considered, compared with episodic migraine, chronic migraineurs showed significantly more white matter abnormalities in body part of corpus callosum.

P348

New Onset Migraine with Aura after Treatment Initiation with Ivabradine

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Objectives: We report on the case of a patient with new onset migraine with aura after treatment initiation with the novel ion channel blocker, ivabradine and explore the effect of this drug on the laboratory model of CSD.

Background: Migraine with aura is a complex neurological disorder modeled in animals by cortical spreading depression (CSD). It is less usual to find complete animal models for disease so any opportunity to test a human effect back at the bench is welcome.

Methods: The patient, a 24 year old woman who developed new onset episodic migraine with visual aura shortly after treatment initiation with ivabradine for frequency control in hypertrophic cardiomyopathy. Before starting ivabradine, she had infrequent and low intensity headache without typical migrainous features, and without migraine aura. With ivabradine treatment, she developed frequent attacks of migraine with aura attacks.

Adult male Sprague-Dawley rats were separated into two groups, control and ivabradine. In both groups CSD was induced by topical application of 3 mg KCl on the frontal cortex. After inducing one CSD and recording of the respective DC shift and cerebral blood flow (CBF), ivabradine (2 mg kg^{-1}, i.v.) or saline (control group) was administered, and DC shifts and CBF were recorded with a glass microelectrode and laser Doppler flow meter, respectively, for one hour.

Results: Six-teen rats received either ivabradine or saline and the number of DC shifts and CBF changes induced by CSD were measured in both groups. The number of DC shifts was 9$\pm$2, and 9$\pm$1 in the control and ivabradine treated groups, respectively. The average amplitude of the DC shifts was 19.7$\pm$3.2 and 21.4$\pm$3.8 mV and the duration of the DC shifts was 46.8$\pm$12.6 and 45.0$\pm$15.0 seconds in the control and ivabradine treated groups, respectively. The difference between groups was not statistically significant in any parameter of DC shifts as well as in terms of hyperemia as determined by CBF measurement ($p>0.05$).

Conclusions: The clinical case suggests that ivabradine may have facilitatory effects on the development of migraine aura. However, we were unable to prove that the drug influences the susceptibility of the brain to CSD. Further knowledge about the exact biological and clinical properties of ivabradine with its more widespread use may help to better understand the frequency of effects on migraine and aura as well as the potential mechanisms.

P349

Transcranial Doppler in the Objective Diagnosis of Primary Cephalgia

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Objectives: Determination of the usefulness of transcranial doppler in the objective diagnosis of primary cephalgia.

Determination of the utility of transcranial doppler in the objective diagnosis of primary cephalgia.

Background: Determination of the usefulness of transcranial doppler in the objective diagnosis of primary cephalgia, Patients with migraine primary headaches showed an increase of 30-35% in blood flow velocity (BFV).

Methods: Three groups of 25 patients each were studied: the first group consisting of patients with migraine primary headaches, the second group with tension-type headache, and the third group with symptomatic headaches of varying etiologies. Transcranial Doppler (TCD) was used.

Results: Patients with migraine primary headaches showed an increase of 30-35% in blood flow velocity (BFV). The measurable effects of vasoconstriction were observed in the cervical blood vessels, such as the interior and exterior carotid arteries, with a lower incidence on the common carotid artery. Intracranially the findings were less conspicuous, showing a higher degree of alteration in the middle cerebral artery and a lower degree in the ophthalmic arteries.

The cerebral artery normal BFV was measured as 30-60 meters per second (m/s), while the BFV of altered blood vessels was measured above 80 m/s.

Conclusions: Since TCD is a non-invasive technology with a relative ease of use by trained hands, which allows not only an objective measurement of the cervical and cerebral BFV, but also the determination of the pulsatility and resistance indexes. TCD, besides being one of a handful of methods for objectively evaluating the cerebral arteries, is an essential tool in the verification of primary cephalgia and cases that reach a migrainous state and a valuable aid in functional prognosis.

P350

Quadrigeminal Plate Lipoma Presenting with Migraine with Visual Aura

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Objectives: Migraine has been associated with a variety of structural brain lesion, including tumors and clinically silent infarct-like lesions in the posterior circulation territory and white matter hyperintensities.

Background: The association of midbrain lesions and migraine has been described in the literature, as has migraine associated with midbrain lesions. Intracranial lipomas located in the quadrigeminal plate and ambient cistern account for 13 % and 43 % and are less symptomatic. The most common symptoms in the quadrigeminal lipomas are epilepsy, behavioural abnormalities, increased intracranial pressure, mass effect, and hydrocephalus.

Methods: We report the case of a patient presenting migraine with visual aura located in the quadrigeminal area.

Results: A 36-year-old woman with daily attacks of migraine with visual aura is presented. The aura always occurred on the left and the migraine headache always on the left side of the head.

Conclusions: The case is discussed in the light of our present understanding of the pathogenesis of the migraine attack. The brainstem lesions could induce periaquaductal gray matter and trigeminothalamic pathway and cause migraine with aura.

P351

Visual Auras May Explain a Cause of Migraine

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Objectives: Pinpoint the origins of migraine in occipital cortex.

Background: It is commonly accepted that visual aura indicates Cortical Spreading Depression (CSD), or depolarization, which is a neuro-chemical disturbance leading to some migraines. The goal here was to identify repeating aura/CSD origins.

Methods: More than 1,000 visual auras were logged on one person over 15 years, with their progressions plotted in degrees of visual angle at 1-minute intervals, and then matched to MRI images and precise 3-D models of the same visual cortex.

Results: It appears that these aura (and CSD) paths correlate with the calcarine sulcus, where the origins of CSD consistently correlate with rare irregularities such as pits or kinks deep in the fundus, and progress as a traveling "spot" of about 5x10 mm, and not as a radially expanding front.

Conclusions: Natural spontaneous human CSD seems to be explainable as propagation of a transient local pressure increase, when the effect of normal cyclic swelling in neurons and astrocytes (due to ion flux), is amplified in the tight folding of outer cortical layers I and II. When constrained in sulci irregularities, it might create a traveling "spot" of extra-cellular compression, excreting potassium,

and preceding CSD. This suggests research into a new prophylaxis for migraine.

P352

Capturing the Aversive State of Headache Pain Preclinically

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Objectives: Preclinical evaluation of headache pain by assessment of reward from pain relief.

Background: One impediment in discovery of new therapies for migraine has been a lack of preclinical models of headache.

Pain is aversive at threshold and demands a behavioral response, i.e., relief. Relief of pain is a reward in humans and in animals. Human neuroimaging studies demonstrate that cerebral systems implicated in pain processing and reward are integrated with multiple overlapping brain areas including the anterior cingulate cortex (ACC). We have shown that relief of ongoing pain in rats with non-opioid treatments (e.g., peripheral nerve block) activates the mesolimbic dopaminergic reward circuit in a model of post-surgical pain.

We made the assumption that activation of dural nociceptors with a cocktail of inflammatory mediators (IM) would elicit headache pain in rat. Our previous studies show that activation of dural nociceptors engages pain facilitation mechanisms from the rostral ventromedial medulla (RVM). Inactivation of the RVM with local anesthetic is thus expected to produce relief of ongoing pain.

Methods: Rats received either IM or synthetic interstitial fluid (SIF) onto the dura mater via previously implanted cannulae to elicit headache pain. Three hr after the dural treatment, lidocaine was microinjected into the RVM. Behavior was assessed with conditioned place preference (CPP) where animals learn to associate a context with a rewarding treatment, in this case, "pain relief" from RVM lidocaine. Drugs were microinjected within the nucleus accumbens (NAc) or the rostral anterior cingulate cortex (rACC). Immunohistochemistry and microdialysis measurements were also performed.

Results: RVM lidocaine produced CPP selectively in rats receiving dural IM. Following RVM lidocaine, increased c-FOS expression and dopamine release were observed in the NAc selectively in IM rats and CPP was blocked by intra-NAc α-flupenthixol, a dopaminergic antagonist. Intravenous treatment with $CGRP_{(8-37)}$,3hr post dura-injection, produced CPP selectively in IM-treated rats. Elimination of pain-induced aversiveness by prior rACC lesion, or treatment with s.c. sumatriptan, or i.v. $CGRP_{(8-37)}$ abolished RVM lidocaine-induced CPP in IM-treated rats. S.c. sumatriptan (30 min post dura injection) prevented NAc dopamine release in IM treated rats receiving RVM lidocaine.

Conclusions: Treatments that are not intrinsically rewarding can become rewarding in the presence of pain. Headache pain was unmasked in rats by assessment of motivated behavior to seek relief captured through CPP. The relief of headache pain activates the dopaminergic reward pathway to produce negative reinforcement of behavior. Medications effective for treatment of migraine headache in humans abolish CPP from pain relief. These studies provide a platform for understanding migraine pathophysiology and for the discovery of new mechanisms that may translate to effective therapies for headache pain.

P353

Effect of 5-HT Receptor Antagonist on Cortical Spreading Depression in Rats

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Objectives: In this study, the effects of ASP1017FM, pizotifen malate and topiramate on KCl-induced cortical spreading depression (CSD) in rats were evaluated.

Background: It has been reported that CSD generated within brain is playing an important role in the pathophysiology of migraine.Among neurotransmitters, 5-hydroxytryptamine (5-HT; serotonin) has important roles in the pathophysiology of migraine. Almost all 5-HT receptor antagonists such as methysergide, pizotifen, cyproheptadine and amitryptyline which are used as migraine prophylactics display relatively high affinity to $5\text{-}HT_{2B}$ and $5\text{-}HT_7$ receptors and these affinities have been shown to correlate with pharmaceutically active doses of these agents.

Methods: Male Sprague-Dawley rats were treated with ASP1017FM, pizotifen malate and topiramate as single daily oral administrations for 6 weeks.On the last treatment day, animals were anaesthetized and operated. The direct current (DC)-potential changes were recorded with an electrometer. A cotton ball soaked with 1 mol/L KCl was placed on the pial surface and kept moist by placing 5μL

of KCl solution every 15 minutes. The number of KCl-induced CSD was counted for 2 hours. The number of KCl-induced CSD was counted for 2 hours.

Results: In control rats chronically administered vehicle, topical KCl application induced 15.4 $\pm$ 0.4 of CSD in 2 hours. Six weeks' treatment with each of the three test drugs decreased the number of the KCl-induced CSD in rats. Chronic treatment with ASP1017FM, pizotifen malate, and topiramate suppressed CSD, with the minimum effective doses of 0.1, 3, and 60 mg/kg po, respectively.

Conclusions: The effect of ASP1017FM, a new selective 5-HT_{2B} and 5-HT_7 dual receptor antagonist, on KCl-induced CSD in rats was evaluated. Additionally, the effects of the anti-migraine prophylactic drugs pizotifen malate and topiramate, on CSD were also evaluated. Results showed that six weeks treatment of ASP1017FM, pizotifen malate, and topiramate suppressed KCl-induced CSD in rats. These findings suggest that both 5-HT_{2B} and 5-HT_7 receptor may contribute to suppressing effect of serotonin-related agents on CSD and ASP1017FM may be effective as an anti-migraine prophylactic drug.

P354

Effect of CGRP Antagonism in Nitroglycerin-Induced Hyperalgesia

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Objectives: The aim of the present study was to test the analgesic effect of CGRP receptor antagonist MK885, in two animal models of pain: the tail flick test and the formalin test, following 'sensitization' by nitroglycerin.

Background: The release of calcitonin gene-related peptide (CGRP) from trigeminal nerves plays a central role in the pathophysiology of migraine. Clinical evidence shows an anti-migraine effect for CGRP antagonists. Systemic administration of nitroglycerin (NTG), a nitric oxide (NO) donor, consistently provokes spontaneous-like migraine attacks in migraine sufferers. In the rat, systemic NTG induces a condition of hyperalgesia, probably via the activation of cerebral/spinal structures involved in pain transmission.

Methods: Male Sprague-Dawley rats were treated systemically with nitroglycerin. Thei nocicpetive response to the tail flick test and to the formalin test were evaluated in baseline conditions and following co-administration of the CGRP antagonist M8825.

Results: MK8825 counteracts nitroglycerin-induced hyperalgesia in both nocicecptive tests. The results also show that M8825 reduces the nociceptive behavior when administered both simultaneously or prior (30-60 minutes before) to nitroglycerin.

Conclusions: These data suggest that MK8825 may represent a potential tool for the treatment of migraine by interacting with upstream mechanisms in the cascade of events that mediate the attack.

P355

Intravenous Administration of CGRP in Unanaesthetized Rats Causes Increase Expression of c-Fos in the Nucleus Tractus Solitarius and Caudal Ventrolateral Medulla, but Not in the Trigeminal Nucleus Caudalis

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Objectives: The human GTN infusion model has been translated to the rat. We hypothesize that CGRP infusion in unanaesthetized freely moving rats will induce migraine like pain reflected by increase in Fos expression in TNC, without intervening factors such as anaesthesia, acute surgery and severe hypotension.

Background: CGRP and glyceryl trinitrate (GTN) infusion in humans provokes headache resembling spontaneous migraine, and CGRP receptor antagonists are effective against acute migraine.What is still fiercely contested, is the site of action of CGRP and CGRP receptor antagonists.

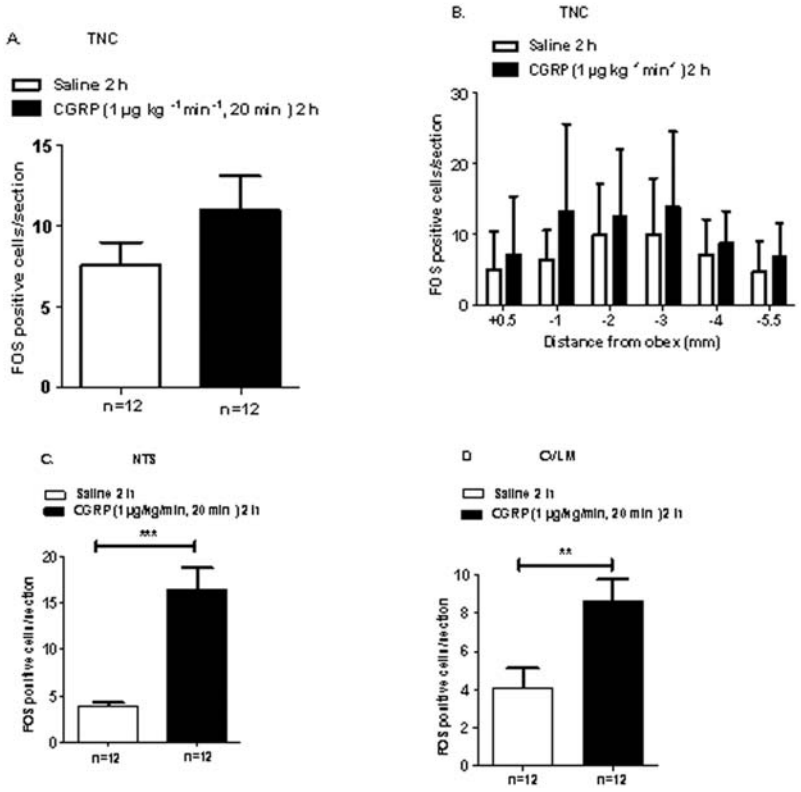
Methods: CGRP was infused in freely moving rats. The effect of infusion of CGRP (0.25 $\mu g\ kg^{-1}\ min^{-1}$ and 1.00 $\mu g\ kg^{-1}\ min^{-1}$, for 20 min) on diameter of middle meningeal artery (MMA) and on mean arterial blood pressure (MABP) in anaesthetized rats was recorded by using the genuine closed-cranial window (CCW) model. TNCs were isolated at different time points after infusion. The

level of Fos mRNA and protein expression in TNC were analyzed by qPCR and immunohistochemistry. FOS stained nuclei were also counted in the nucleus tractus solitaries (NTS) and caudal ventrolateral medulla (CVLM), integrative sites in the brain stem for processing cardiovascular signals. We also studied mRNA expression of CGRP and its receptor component in trigeminovascular and other pain processing structures in the brain.

Results: Intravenous (i.v.) infusion of CGRP (0.25 μg kg^{-1} min^{-1} and 1.00 μg kg^{-1} min^{-1}, for 20 min) caused a significant drop in MABP both in the unanaesthetized rats (-19 ± 4 % and -33 ± 6 %) and in the anaesthetized rats (-34 ± 3% and -41 ± 4 %), and the same doses caused significant increase in MMA diameter (154 ± 28 % and 162 ± 28 %) in the CCW model. No significant activation of c-Fos in TNC at mRNA and protein level was observed. A significant ($p<0.05$) increase in c-Fos protein was observed in NTS and CVLM in the brain stem. The mRNA expression profile showed that CGRP and its receptor components are widely distributed in trigeminovascular and other pain processing structures. The mRNA expression of CGRP and its receptor components in TNC was unaffected 2 h after CGRP infusion.

Conclusions: The mRNA expression of CGRP receptors in various central pain pathways suggests involvement of CGRP in migraine. Incontrast to our previous studies with GTN, i.v infusion of CGRP had no effect on expression of Fos in TNC. The CGRP infusion model in the naïve rat seems unsuitable for studying activation of second order trigeminal neurons.

Figure 1. Changes in Fos immunoreactive cell count after 2 h of CGRP (1 μg kg-1 min-1, 20 min) infusion in unanaesthetized rats, compared to the saline infused rats. A. Total FOS count in TNC; B. Rostrocaudal (distance from obex in mm) analysis of FOS count in TNC; C. FOS count in NTS, ***P<0.001 (unpaired t-test) and D. FOS count in CVLM, **P<0.05 (unpaired t-test).



P356

Expression, Localization and Neuro-Modulatory Properties of the IP Receptor in Migraine Relevant Tissues

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Objectives: To study the expression **and localization** of IP receptor and effect of its agonist on **KCl induced** CGRP release in migraine relevant tissues.

Background: Prostaglandins I_2 (PGI_2) and calcitonin gene-related peptide (CGRP) are able to induce headache in humans. PGI_2 acts via a G-protein coupled receptor 'IP'.

Methods: The mRNA and protein expression of the IP receptor was studied by real-time PCR and western blotting, respectively. Co-localization of the IP receptor and CGRP in the rat trigeminal ganglion (TG) and trigeminal nucleus caudalis (TNC) was studied by immunofluoresence. The effect of IP receptor agonists and antagonists on immunoreactive CGRP (iCGRP) release was investigated in freshly isolated rat dura mater, TG and TNC by ELISA.

Results: The IP receptor was significantly more expressed in the rat dura mater than in the cerebral arteries on both mRNA and protein levels. mRNA and protein for the IP receptor were significantly more expressed in TG than in TNC. We found that IP receptors and CGRP are co-localized in the neurons of TG and on the nerve fibres in TNC. In dura mater, the iloprost, an IP receptor agonist significantly decreased KCl induced iCGRP release from 61.5 ± 14.05 pg/ml to 41.4 ± 7.1 pg/ml and it was not reversed by the IP receptor antagonist, CAY10441 or the $EP_1 > EP_3$ receptor antagonist, SC51322. In TG iloprost had no effect on KCl induced iCGRP release. Per se iloprost had no effect on basal iCGRP release in dura mater and TG.

Conclusions: We found the IP receptor was expressed in migraine relevant tissues. In TG the IP receptors were co-localized with CGRP. Thus, the IP receptor might be a target for development of future anti-migraine drugs.

P357

The Feverfew Constituent, Parthenolide, Inhibits Transient Receptor Potential Ankyrin 1-Mediated Responses: Relevance for Migraine Treatment

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Objectives: We hypothesized that parthenolide inhibits TRPA1 on trigeminal nerves, thereby reducing nociception and sensory neuropeptide release.

Background: *Tanacetum parthenium* L. (feverfew) has long been known as a migraine remedy and, according to positive results of clinical trials, it is currently recommended for migraine prevention. However, the mechanism responsible for such protective action remains unknown. The sesquiterpene lactone, prthenolide, a major ingredient of feverfew, is a reactive molecule that can interact with nucleophilic sites of the transient receptor potential ankyrin 1 (TRPA1) channel. The role of TRPA1 in migraine pathophysiology has been suggested by the observation that both the reactive α,β-unsaturated aldehyde and TRPA1 agonist, acrolein, and one major volatile ingredient of the headache tree, umbellulone, target TRPA1 to produce a CGRP-dependent meningeal vasodilatation.

Methods: We used cultured cells, isolated rat tissues, rats and wild type and TRPA1 deleted mice. Electrophysiological and calcium imaging responses, neuropeptide release, smooth muscle motility were evaluated *in vitro*. Allodynic and nociceptive responses, and changes in meningeal blood flow were studied *in vivo*.

Results: Parthenolide selectively activates recombinant (transfected cells) or constitutive (rat/mouse trigeminal neurons) TRPA1, and by TRPA1 stimulation releases calcitonin gene-related peptide (CGRP) from trigeminal nerve endings. However, parthenolide behaves as a partial agonist at neuronal TRPA1 of rat urinary bladder, desensitizes the recombinant TRPA1, and, by channel targeting, renders TRPA1-expressing nerve terminals unresponsive to any stimulus. These effects result in inhibition of nociceptive responses selectively evoked by TRPA1 agonists, and of CGRP release from trigeminal neurons and CGRP-mediated meningeal vasodilatation evoked by different and unselective stimuli.

Conclusions: These three novel actions of parthenolide (TRPA1 partial agonism, selective channel desensitization, and unselective defunctionalization of

peptidergic TRPA1-expressing trigeminal neurons) may contribute to the protective effect of feverfew in migraine.

P358

VIP and PACAP in the Circulation after Sumatriptan

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Objectives: To examine the effect of sumatriptan on Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase-Activating Polypeptide (PACAP) levels *in vivo*, under conditions without trigeminovascular system activation.

Background: The triptans, 5-hydroxytryptamine (5-$HT_{1B/D}$receptor agonist), are effective and well tolerated in acute migraine management. Triptans may lead to a decreased release of neuropeptides such as calcitonin gene-related peptide (CGRP) but potentially also other neuropeptides, as VIP and PACAP.

Methods: In 16 healthy volunteers, we sampled blood from the internal and external jugular, the cubital veins and the radial artery before and after administration of subcutaneous sumatriptan.

Results: We found no difference in VIP and PACAP concentrations between the internal and external jugular, the cubital veins and the radial artery ($P > 0.05$), and the circulating levels of VIP and PACAP did not change over time ($P > 0.05$). VIP (squares) and PACAP (triangles) before and after 6 mg subcutaneous sumatriptan(median ± SEM).

Conclusions: Sumatriptan did not change the levels of circulating VIP and PACAP in the intra or extra cerebral circulation in healthy volunteers. Under baseline conditions, without trigeminovascular activation, sumatriptan does not affect the release of neuropeptides VIP and PACAP.

P359

The Effects of Acute Intrathecal and Intraperitoneal Glyceryl Trinitrate Administration on Orofacial Pain in Mice

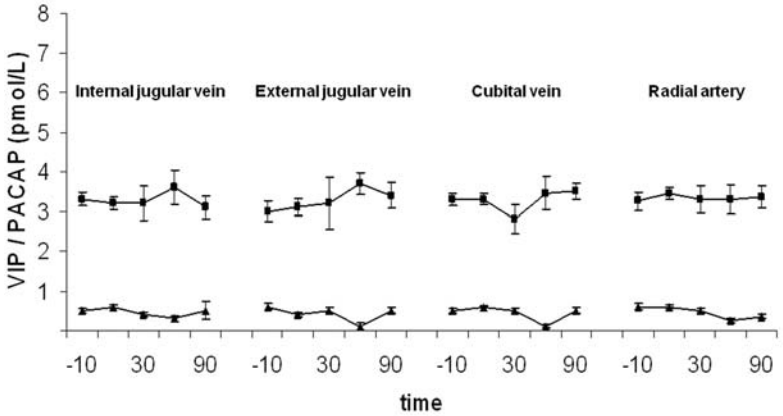
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Objectives: The aim of the study was to investigate the effects of acute intraperitoneal (i.p.) and intrathecal (i.t.) administration of glyceryl trinitrate (GTN) on orofacial pain in mice.

Background: GTN administration is considered a reliable experimental model of migraine, based on the GTN neuronal effects on the integrative-nociceptive structures. The underlying mechanisms are not known, but a central effect might be responsible for its effects, such as a change in neuronal excitability and synaptic transmission of various CNS areas involved in pain and behavior. The actions of glyceryl trinitrate (GTN) are the result of its bioconversion into nitric oxide (NO) that increases the intracellular concentration of cyclic guanosine monophosphate, which produces pain modulation in the central and peripheral nervous system.

Methods: Thirty-two BALB/c male mice were divided into 4 groups: two of the groups received GTN injections



- i.p. GTN 10 mg/Kg b.w. (group GTN i.p.) and i.t. GTN 0.01 mg/kg b.w. (group GTN i.t.) and the other two groups served as control and were administered i.p. or i.t. equivalent volumes of saline (group S-i.p. & group S- i.t.) and were treated in a dose/time manner similar with GTN groups. Two hours after the injection, the formalin orofacial test was performed. The time mice spent grooming and rubbing the injected area was reported separately for the first phase (5 minutes) and the second phase (20 minutes). The results were analyzed by means of ANOVA one-way testing (Bonferroni coefficient).

Results: Intrathecal GTN administration had a significant effect on both phases of the formalin induced orofacial pain (p=0,025 and 0=0,013) when compared with intrathecal administration of saline. Intraperitoneal administration of GTN had an analgesic tendency (p=0,054) on phase one and no statistically significant effect (p>0,05) on phase two when compared to control.

The analgesic effects of intrathecal administration was superior to that of intraperitoneal administration (p=0,002).

Conclusions: The effects of nitroglycerine on pain are controversial. Some studies report that GTN, by increasing NO concentration, can develop and maintain persistent hyperalgesia in rats. Other studies indicate the fact that increased NO concentration can have an antinociceptive effect and that GTN administration can lead to analgesia.

In our study, intrathecal GTN administration in mice exerted analgesic effects on both acute and inflammatory pain, proving to be superior to intraperitoneal administration. Taken together, our results demonstrate that the manner in which a substance is administered and metabolized influences greatly its effect on pain.

P360

The Relationship of Headache and Insomnia Reviewed and That of Insomnia and Migraine Studied with Eszopiclone

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Objectives: The purpose of the review was to summarize the literature and analyze it in light of the nature of the headache-insomnia relationship. The purpose of the study with eszopiclone was to determine whether improving insomnia in migraineurs improves headache.

Background: Headache, including migraine, and insomnia are very common and burdensome complaints worldwide. Globally, the percentage of the general population with headache is 47%, including 10% with migraine, and the prevalence of insomnia in general is 30% to 48% of the general population.

Methods: For the review, an extensive literature search was conducted using the terms, "headache", "migraine", "insomnia", "sleep", "sleep deprivation", and "sleep loss", on the search engines, PubMed®, ScienceDirect®, Medline®, and Google Scholar®. In the context of the study, we treated 79 subjects with ICHD-II migraine with or without aura and DSM-IV primary insomnia for 6 weeks with 3 mg eszopiclone or placebo at bedtime, using a randomized, double-blind design.

Results: The review suggested that headache or migraine is associated with insomnia, while only *severe* insomnia is associated with headache or migraine. In addition, it was found that insomnia is a risk factor for headache or migraine onset and for increased headache frequency, specifically for tension headache and migraine. Of the 79 subjects randomized in the study, 75 were evaluable, 35 in the eszopiclone group and 40 in the placebo group. The study showed that of the sleep variables, total sleep time, sleep latency, night-time awakenings, and sleep quality, only the number of night-time awakenings during the 6-week treatment period was significantly lower in the eszopiclone group than in the placebo group. Of the three sleep-related daytime variables, alertness, fatigue, and functioning, this was also the case for fatigue. The headache variables, frequency, duration, and intensity, however, did not show statistically significant differences from placebo during the 6-week treatment period.

Conclusions: As insomnia appears a risk factor for headache or migraine onset, patients with insomnia should probably be routinely evaluated for headache. As it also seems to be a risk factor for increased headache frequency, particularly in tension headache and migraine, patients with these disorders should probably be routinely treated for insomnia, if present, as part of their overall management. In the study, we attempted to test this approach for migraine using eszopiclone to treat insomnia but the medication did not sufficiently improve insomnia for the test to be valid.

P361

How Long Do I Have To Wait? Interval for the Effect of Different Triptans in Acute Migraine. A Study in Mexican Population

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Objectives: To determine the interval for the effect and its degree of different triptans in Mexican migranous patients during treatment of acute attacks.

Background: The interval for the onset of the effect of most triptans has not been studied properly. There are no studies in Mexican population on this issue.

Methods: Inclusion criteria were: adult patients, any gender, migraine w/wo aura according to IHS criteria and treatment of al least two attacks. Period of study: july 1, 2011 – november 30, 2012. Data were obtained retrospectively and prospectively. The patients were instructed to use the triptan indicated by his/her physician and to look at the onset of the anagesic effect, measured in minutes, the interval to achieve 50% release (T1) and > 80% (T2), as well as side effects. Pain intensity was measured with a visual analogue scale. To investigate interval difference, we used repeated measures ANOVA with within-subjects factors with 2 levels (T1 vs. T2) and between-subjects factors with 3 levels (ELT, RZT, ZMT). We also performed a post-hoc analysis using Bonferroni correction for multiple comparisons.

Results: 56 patients were studied, 47 female. 23 with eletriptan (ELT), 18 with zolmitriptan (ZMT) and 15 with rizatriptan (RZT). Mean age for the group was 34.8 (16 min - 52 max) with no differences between subgroups of triptans or gender. Migraine w/a were 49 and wo/a were 7. Mean (SD) T1/T2 for all the patients were 30 (±29)/62 (±58) min, and for the subgroups (ELT/RZT/ZMT): T1 24.45 (±15.56)/39.73 (±47.23)/28.89 (±17.95), and T2 47.04 (±32.83)/81.33 (±96.15)/64 (±35.22). The dispersion measured by the standard deviation was greater in the RZT than ELT and ZMT. As expected, we found a significant difference between Intervals (T1/T2: $F(1, 52) = 54.35$, $p < .001$). However, there was no significant interaction between Interval and triptans, nor we found an effect of the triptans. Overall, although the mean interval was greater in the RZT, the type of triptan did not affect the interval.

Conclusions: Our resuls show that the onset o triptan effect is shorter than reported in this sample of Mexican population. Although the sample size is small, all three triptans studied showed no difference in interval. Should this be corroborated, it could change the recomendations for their use.

P362

Headache Following Mild TBI in Children: What Are the Risks?

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Objectives: To determine the risk factors for headache 3 and 12 months after mild traumatic brain injury (mTBI) in children ages 5-17 years.

Background: Headache is the most common complaint following mild TBI. However, there are little data regarding risk factors for prolonged post-traumatic headache following concussion or mild TBI in children and adolescents.

Methods: This is a prospective cohort study of children with mTBI (n=402) or arm injury (n=122) in which we analyzed the prevalence of and risks factors for headache 3 and 12 months after injury. Parents completed surveys at the time of injury and 3 and 12 months thereafter. Headache was defined as any headache in the week prior to survey completion. Persistent headache was defined as having headache at both the 3- and 12- month follow-up surveys. We used multivariate logistic regression to determine which factors were associated with both 3 month and persistent headache risk.

Results: Three months after injury, 43% of those with mTBI and 26% of those with arm injury had headache [RR: 1.7 (95% CI:1.2-2.3)]. Persistent headache was more common after mTBI than arm injury (28% vs. 19%), but this difference was not statistically significant [RR: 1.2 (95% CI:0.9-1.5)]. Headache 3 months after mTBI was associated with female sex [OR:2.9 (95% CI:1.7-5.0)], family history of headache [OR: 1.8 (95% CI:1.1-2.9), pre-injury chronic pain [OR:6.7 (95% CI:1.4-32.6)], prior NSAID use [OR: 2.2 (95% CI:1.2-3.4)], lower pre-injury quality of life [OR: 0.96 (95% CI:0.94-0.98)], and loss of consciousness (LOC) with amnesia [OR: 2.6 (95% CI: 1.4-4.8)] at the time of injury. Presence of intracranial hemorrhage or skull fracture was not associated with headache risk.

Persistent headache was associated with female sex, family history of headache, chronic pain prior to injury, lower quality of life, prior NSAID use, and low income, but was not associated with injury characteristics.

Conclusions: Both pre-injury factors and injury characteristics are associated with headache 3 months after pediatric mTBI. Clinical indicators of injury severity such as LOC and amnesia were associated with headache risk but skull fracture and intracranial hemorrhage were not. The risk for persistent headache after mTBI was associated with pre-injury patient characteristics rather than injury severity. Although there are limited data on the optimal treatment of post-traumatic headache in pediatrics, given our findings, providers should consider early intervention for patients with multiple risk factors for prolonged headache following mTBI.

P363

Comparison of the Post-Concussion Syndrome (PCS) in OEF/OIF Veterans with Traumatic Brain Injury (TBI) Due to Blast Injury (BI) or Direct Head Trauma (DHT) Over Periods up to 8 Years

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Objectives: Compare symptoms of the PCS produced by pure blast injury with those produced by DHT within periods of 1-4 and 5-8 years post-injury.

Background: TBI is a major problem of the military OEF/OIF campaigns. An issue of importance is whether pure blast injury (BI) without Direct Head Trauma (DHT) produces brain injury similar to that with DHT. This study compares the Post-Concussion Syndrome (PCS) produced by these two mechanisms of TBI with follow-up over a period of up to 8 years after TBI.

Methods: Veterans of OEF/OIF Campaigns were screened for deployment-related TBI (D-TBI) as part of a general medical examination. Those with a possible D-TBI were referred for a TBI evaluation including a Beck Depression Inventory and a screen dealing with the TBI and the post-concussion syndrome (PCS). Screen symptoms were graded on a 5 point scale from none to very severe based on pain and interference with function. Items chosen to represent the PCS were: 1. Headache, 2. Dizziness, 3. Balance Problems, 4. Poor Coordination, 5. Difficulty with decisions, and 6. the BDI score. Patients were queried about duration of loss of consciousness and associated symptoms immediately after the TBI, and about symptoms present within the last 30 days. Blast injury was divided into categories of Primary, Secondary, Tertiary, and Quarternary. Only subjects with primary (blast wave only) or secondary (blast plus dust sand or small shrapnel) BI were used. DHT subjects had TBI related to falls, assaults or other circumstances with direct trauma to the head without any associated blast. TBI was graded as mild (dazed or loss of consciousness [LOC] of $<$30 minutes) or moderate-severe (LOC$>$ 30 minutes).

Subjects were divided by time between TBI and date of evaluation in the TBI Clinic into periods of 1-4 and 5-8 years. Comparisons were made with the Likelihood Ratio Chi Square test.

Results: The study deals with the first 500 subjects evaluated in the TBI Clinic. For1-4 years post-TBI, there were 56 blast and 63 DHT subjects. For 5-8 years post-TBI, there were 28 blast and 50 DHT subjects. In comparing the primary/secondary blast versus the DHT subjects, there was no difference in the occurrence of symptoms #1-5 above representing the PCS with the exception of poor coordination in subjects 5-8 years post-TBI in which *No difficulty* and *mild/moderate* difficulty with poor coordination occurred 3.3 and 1.7 times as often in DHT as opposed to blast subjects ($p=.008$). There was no difference between groups in the occurrence of Depression. The results will be presented in detail.

Conclusions: With the exception of poor coordination at 5-8 years after TBI, There is essentially no difference in the PCS produced by blast or direct head trauma over an 8 year follow-up.

P364

Medication Usage Patterns in Headache after Mild Traumatic Brain Injury

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Objectives: We sought to examine self-report of treatment for headache in the first year following mild traumatic brain injury.

Background: Mild traumatic brain injury (mTBI) and mTBI sequelae are commonly managed by non-specialists. Therefore, an understanding of post-injury problems, such as headache, and subsequent management is crucial for improving care and long-term outcomes. Recent studies

suggest that headaches after mTBI are common with multiple headache phenotypes. Outside of previous opinion papers, few studies have guided primary care treatment of these complicated headaches or examined the effectiveness of the interventions suggested.

Methods: 212 subjects admitted to a Level 1 trauma hospital with mTBI were prospectively enrolled and evaluated within 7 days of injury, and at 3, 6, and 12 months after injury.

Results: The sample was primarily male (76%), white (75%), injured in vehicle crashes (58%) and had completed high school (83%). Thirty seven percent of subjects lived within the county surrounding the hospital, 26% resided in neighboring counties, and an additional 37% were living in outlying areas or outside of the state. A high headache burden (never less than 58% of respondents at each period) was reported at 3, 6, and 12 months after injury, with headaches meeting ICHD-2 criteria for migraine, probable migraine, tension, cervicogenic, and unclassifiable headaches. Despite the diverse nature of headaches, more than 70% of those with headache at each time period used acetaminophen or a nonsteroidal anti-inflammatory drug (NSAID) for headache control. Few participants, 19% of those with migraine and 32% of those with unclassifiable headaches, endorsed complete relief (vs. partial or no relief) after medication use. The majority of individuals with unclassifiable headache reported never taking medication.

Conclusions: Headaches after mTBI are frequent and are not well managed. Results suggest that many individuals with mTBI may be self-treating their headaches by utilizing over-the-counter pain relief medications. These medications, however, are not providing effective treatment for this population. Further research must be conducted to guide treatment and educate providers.

P365

Retrospective Review of Efficacy and Safety of Acupuncture for Treatment of Active Duty Service Members with Headaches after Non-Penetrating Blast Exposure

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Objectives: Determine if acupuncture augmenting interdisciplinary care of Active Duty Service Members (ADSMs) with headaches after non-penetrating blast exposure is a safe and effective treatment.

Background: Traumatic Brain Injury (TBI) is defined as a force applied to the head that disrupts brain function. After a decade of combat with frequent blast exposure, some ADSMs may suffer from headaches, as well as changes in mood, memory, sleep and balance. These symptoms, often subtle in mild TBI (mTBI), can impair performance and negatively impact quality of life. Many ADSMs with a history of blast exposure suffer from post traumatic stress disorder as well as mTBI. Affected patients are typically started on several medications to address varying symptoms. The medications are not always effective, and frequently have adverse side effects.

A National Institutes of Health consensus statement concluded that acupuncture for headache was a treatment option but further research was indicated.[1] We report on the results of a retrospective study of acupuncture in conjunction with medications and rehabilitation in ADSMs with a diagnosis of headache following blast exposure being treated in an interdisciplinary clinic.

Methods: Medical records of ADSMs with a history of combat related non-penetrating blast exposure resulting in a diagnosis of mTBI with subsequent headaches that consented to treatment with acupuncture in the Marine and Sailor Concussion Recovery Center at Naval Hospital Camp Lejeune from January to June 2012 were reviewed after approval by our Research Review Committee and the Naval Medical Center Portsmouth Institutional Review Board. A search of the Department of Defense electronic medical record identified 21 ADSMs who met the inclusion criteria for this retrospective review.

Results: Battlefield Acupuncture (BFA), an auricular acupuncture consisting of acupuncture points Cingulate Gyrus, Thalamus, Omega 2, Point Zero Prime, and Shen Men was administered in 18/21 patients. Auricular Trauma Protocol consisting of acupuncture points Hypothalamus, Amygdala, Hippocampus, Master Cerebral, Point Zero, and Shen Men was administered in 2/21. Koffman cocktail protocol, consisting of acupuncture points Large Intestines 4 bilaterally, Liver 3 bilaterally, Governor Vessel 20, Yin Tang 2 was administered in 2/21 (one patient had both Koffman and BFA). Patients also received various acupuncture treatments based on their specific headache location and symptoms. Eighty-one percent (17/21) of patients reported improvement, 10% (2/21) reported no change and 10% (2/21) had no outcome documented.

Conclusions: Acupuncture is a safe, complementary therapy for treating headaches following non-penetrating blast exposure. Larger, prospective studies are indicated to compare acupuncture to standard therapy.

Views expressed are the authors' and do not reflect policy or positions of the Departments of the Navy or Defense, or US Government.

P366

Resolution of Sports Related Chronic Post Traumatic Headache and Prolonged Post-Concussion Syndrome after Onabotulinum Toxin Injection

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Objectives: Is onabotulinum toxin type A an effective treatment for chronic post traumatic headache related to sports concussion.

Background: Onabotulinum toxin type A BTX-A is the only FDA approved medication for Chronic Migraine.

Methods: Case Report of a 15 year old male with chronic post traumatic headache and prolonged post concussion syndrome.

Results: This is the first case report of its kind where onabotulinum toxin type A has been used to treat chronic post traumatic headache secondary to sports concussion. Our patient experienced a complete resolution of his headache and associated concussion symptoms shortly after injection with onabotulinum toxin type A and continued to experience complete resolution of his symptoms 6 months after initial injection. He was able to return to baseline physical function and his academic performance improved to baseline as well. The author discusses the mechanism and physiology of concussion in sports, mechanism of post traumatic migraine and its relationship to the cervical spine, and outlines possible anatomic and physiological connections. The author also discusses the current literature relating to sub concussive events and their relation to mild traumatic brain injury. He also outlines the underlying mechanism of greater, lesser, supraorbital and auriculotemporal nerve blocks and the underlying mechanism of BTX-A in the treatment of headache (including a review of the literature). Finally he poses the following question for discussion. In patients with prolonged post concussion symptoms where headache is the predominant symptom. Is the patient experiencing prolonged post concussion syndrome or are the symptoms attributable to chronic post traumatic migraine?

Conclusions: BTX-A may be an effective treatment in very select athletes with chronic post traumatic headache and prolonged post concussion syndrome.

P367

Safety, Pharmacokinetics, and Pharmacodynamics of LY2951742: A Monoclonal Antibody Targeting CGRP

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Objectives: The objective of this Phase 1 study is to determine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of LY2951742 (LY), a novel antibody that binds to calcitonin gene-related peptide (CGRP).

Background: LY is a potent, selective monoclonal antibody targeting calcitonin gene-related peptide (CGRP) and is being developed as a potential therapy for migraine prevention. CGRP induces vasodilation via the CGRP receptor and is implicated in neurogenic inflammation. As such, CGRP may play a pivotal role in migraine pathophysiology, and neutralization of the ligand may provide an alternative means for migraine prevention.

Methods: A Phase 1, first-in-human, double-blind, randomized, placebo-controlled trial was performed in healthy volunteers. Subjects received subcutaneous injections of either placebo, or 1, 5, 25, 75, 200, or 600 mg as a single dose, or four (4) repeat administrations of150 mg of LY every 14 days.

Results: LY was well tolerated. There was no relationship between dose and the type or number of adverse events, changes from pre-dose in vital signs or vascular tone as measured by pulse wave analyses, laboratory values, or ECG parameters. No clinically meaningful difference in adverse events vs. placebo was observed. PK was linear; peak serum concentration (Tmax) ranged from 7-14 days, and the terminal elimination half-life (T1/2) ranged from 25-30 days. PD was assessed using laser Doppler imaging (LDI) to determine inhibition of dermal blood flow induced by capsaicin. PD effects were robust and persisted 42 days following a single dose and 99 days following repeat administration.

Conclusions: LY was well tolerated after both single and repeat administrations. There was no dose dependent difference in either type or frequency of Adverse Events, and no clinically meaningful difference when compared to placebo. PK was linear and dose-proportional. PD effects using LDI were robust and durable after both single and repeat administrations. Based on these data, further exploration of LY2951742 as a potential therapy for migraine prevention is warranted.

P368

Role of Caffeine Cessation in Migraine Management

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Objectives: To evaluate the efficacy of caffeine cessation in migraine management.

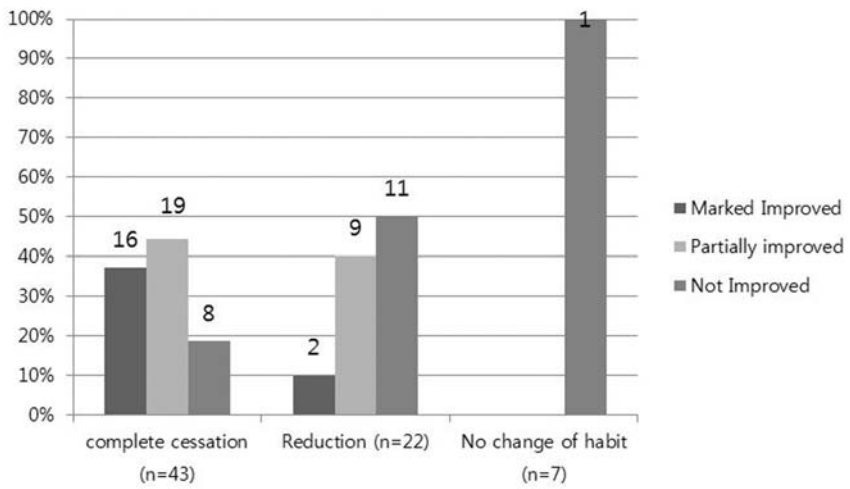
Background: Caffeine is a well known 'modifiable lifestyle factor' in migraine, however no clear relationship has been described between modifying caffeine habit and following migraine improvement. Therefore caffeine cessation has been neglected by most of the patients or physicians.

Methods: Subjects were the patients who were newly diagnosed as episodic migraine in Samsung Medical Center between March 2012 and July 2012. All patients were advised to eliminate caffeine thoroughly without tapering. Change of migraine pattern following caffeine elimination was assessed after 1 month. Patients were divided by patient who quit caffeine completely, reduced the intake amount 50% or more, or reduced less than 50% or not changed at all. Treatment efficacy was regarded as 'Partial improve' if the patient had half reduction in frequency or less disabling attacks. 'Marked Improve' is when the patient had more than half reduction in frequency with less disabling attacks. Patients with no improve of headache were categorized as 'No Improve'.

Results: Among 116 patients who are taking caffeine regularly, 21 patients were treated with prophylactic medication from the beginning. Other 95 patients were advised to quit caffeine completely for 1 month without any daily medication. A total of 72 patients were analyzed.

43 (59.7%) patients eliminated caffeine at once, 22 (30.6%) patient reduced and 7 (9.7%) patient did not change their intake at all. 16 patients (37.2%) out of 43 who eliminated caffeine at once reported marked improve of headache. On the other hand, only 9.9% of the patients who reduced caffeine and none of the patient who didn't change their caffeine habit, achieved remarkable headache improvement. Complete caffeine cessation was clearly related to headache improvement, than reducing or not changing the caffeine intake ($p<0.001$). Compared with the patients who quit caffeine completely, patients who continued caffeine, either reducing or not, headache improvement were definitely less achieved (OR 15.345, $p<0.001$).

Conclusions: According to our observation, migraine improvement can be achieved by only changing caffeine consumption habit, especially when its completely eliminated. Physicials should pay more attention to patient's life syle and caffeine cessation must be recommended as an effective baseline non-pharmacological therapeutic strategy before initiating pharmacological treatment or trying more invasive procedures.



	Headache improvement		
	No Change (n= 26)	Partial+Marked (n=46)	*p*
Female	21 (80.8%)	41 (89.1%)	
Age, y	43.2 ±11.1	43.2 ±11.9	0.99
Disease duration, y	10.5 ±10.4	11.3 ±10.3	0.69
Frequency, per month	4.9 ±3.6	4.3 ±4.3	0.53
Hypertension	2 (7.7%)	3 (6.5%)	1
Diabetes	0	1 (2.2%)	1
Hyperlipidemia	3 (11.5%)	8 (17.4%)	0.735
Smoking			0.704
Current-smoker	1 (3.9%)	1 (2.2%)	
Ex-smoker	3 (11.5%)	3 (6.5%)	
Insomnia	3 (11.5%)	0	0.044
Caffeine			<0.001
Complete cessation	8 (30.8%)	35 (76.1%)	
Continue intake (Reduce or no change)	18 (69.2%)	11 (23.9%)	

P369

A Screen of Prophylactic Anti-Migraine Medications in a Chronic Nitroglycerin Mouse Model

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Objectives: The objective of this study was to validate a novel mouse model of chronic migraine by testing known and potential prophylactic migraine therapies.

Background: Migraine is a highly debilitating disorder that affects a large portion of the population. Unfortunately, current therapies for chronic migraine are often ineffective or poorly tolerated. The development of novel migraine therapies has been slow due to the small number of clinically relevant animal models. We have recently developed a new model of chronic migraine using chronic intermittent nitroglycerin, a known migraine trigger in humans.

Methods: Nitroglycerin was administered IP to male and female mice every second day for 9 days. Basal and nitroglycerin-evoked mechanical hypersensitivity was evaluated using manual von Frey hair stimulation of the hindpaw.

Results: Acute nitroglycerin administration evoked mechanical hyperalgesia in a dose dependent manner. Chronic intermittent treatment with nitroglycerin induced a progressive and sustained basal hypersensitivity which was also dose dependent. The prophylactic migraine treatment, topiramate, effectively attenuated the basal hypersensitivity induced by chronic nitroglycerin. We also determined the effects of other known and novel anti-migraine medications - DL-propranolol, a beta blocker; amiloride, an acid sensing ion channel inhibitor; and memantine, a NMDA receptor antagonist.

Conclusions: Overall, these studies indicate that progressive hyperalgesia induced by chronic intermittent treatment with nitroglycerin in mice represents a new translational model for migraine progression. This model establishes a novel screening tool for testing potential anti-migraine therapies.

P370

Translational Pharmacodynamics of CGRP Monoclonal Antibody LY2951742 in Capsaicin-Induced Dermal Blood Flow Model

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Objectives: The objective of the study is to evaluate the effects of LY2951742 (LY) on dermal blood flow (DBF) in an experimental model of capsaicin induced vasodilation in both preclinical animal models and clinical studies.

Background: LY is a potent, selective monoclonal antibody that neutralizes CGRP, and is being developed as a potential therapy for migraine prevention. CGRP induces potent vasodilation, is implicated in neurogenic inflammation, and may play a pivotal role in migraine pathophysiology.

In previously conducted pharmacodynamic (PD) studies, small molecule CGRP receptor antagonists inhibited DBF induced by capsaicin as measured by laser Doppler perfusion imaging (LDI). Small molecule CGRP receptor antagonists that exhibited potent pathway inhibition in this model went on to show clinical efficacy in the treatment of acute migraine.

Methods: The PD effects of LY were evaluated by assessing capsaicin induced vasodilation via LDI. Preclinical studies were conducted in rats, and cynomolgus monkeys, using subcutaneous (SC) and intravenous (IV) administration of LY, respectively. Subjects in a Phase 1 trial of LY received single SC doses ranging from 5mg to 600mg, or four (4) repeat administrations of 150 mg every 14 days.

Results: Doses of 4 mg/kg SC (rats) and 5 mg/kg IV (monkeys) demonstrated robust inhibition of capsaicin induced DBF. In monkeys significant inhibition of capsaicin induced DBF persisted for $>$29 days. In humans, the inhibitory effect on DBF was dose-dependent, starting at 5mg between Days 28-42. At doses of 75mg and higher inhibition was significant on Day 3 and remained almost maximal until Day 42.

Conclusions: PD assessment using LDI provided a useful biomarker for assessing the durability and magnitude of effect on DBF after administration of LY2951742. Results were scalable and predictable across species. Utilization of this PD model provides a means for understanding a PK and PD relationship that may assist in the clinical development of LY2951742 for migraine prevention, and in the translational research of other CGRP pathway inhibitors.

P371

RN307, a Humanized CGRP Function-Blocking Antibody with Potential as a Treatment for Migraine Prophylaxis

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Objectives: The purpose of this study was to characterize the in vitro and in vivo properties of RN307, a humanized CGRP function-blocking antibody with potential use in migraine.

Background: CGRP is a 37 amino acid neuropeptide with two isoforms, alpha and beta. The sequence of both isoforms is identical between human and cynomolgus monkey. CGRP has a well established role in migraine and there is abundant clinical evidence for the therapeutic effect of CGRP signaling blockade. RN307 is a humanized antibody of the IgG2Δa isotype that binds to human CGRP and blocks its binding to and activation of the CGRP receptor.

Methods: The binding affinities of RN307 towards human CGRP were determined in solution at 25°C using the kinetic exclusion assay (KinExA).

The structure of the CGRP:RN307 complex was determined by standard X-ray crystallography techniques utilizing molecular replacement method.

Surface plasmon resonance (SPR) binding assays were used to map the epitope of RN307 by screening a panel of CGRP variants that incorporated an Alanine scan, point mutations, fragments, and acid/amide modifications. SPR was also used to determine the specificity of RN307 to CGRP via solution competition with other CGRP family members; adrenomedullin, calcitonin and amylin.

To better understand the activity of RN307 in vivo, the antibody was tested in a cynomolgus monkey capsaicin flare model.

Results: RN307 bound human alpha and human beta CGRP with equilibrium dissociation constant (KD) values of 9.5 and 4.0 respectively, which were indistinguishable within the 95% confidence limit of each global fit.

The crystal structure of the RN307 Fab in complex with the CGRP peptide revealed that RN307 has a deep pocket that binds to CGRP residues 29-37. Nearly 70% of the surface area of residues 29-37 are solvent inaccessible with the amidated Phe37 being located deepest in the

binding pocket. Consistent with the structure of RN307:CGRP complex, the screening of CGRP variants showed that RN307 binding is most sensitive to substitutions of CGRP residues Gly33 and Phe37 and that amidation of the extreme N-terminal residue (Phe37) is required for high affinity binding.

To determine the specificity of RN307, it was premixed with a large molar excess of either amylin, calcitonin or adrenomedullin (CGRP family members). Results were comparable to the control response (RN307 plus buffer) demonstrating that RN307 did not form a detectable complex with these peptides and therefore is specific to CGRP alone.

Treatment of cynomolgus monkeys with a single dose of RN307 resulted in a potent, dose dependent, and long lasting inhibition of capsaicin induced flare with an ED50 of 5.8mg/kg at two weeks and 15.9mg/kg at 8 weeks post dose.

Conclusions: These results demonstrate that RN307 is a high affinity, highly specific, potent and long lasting CGRP function blocking antibody which makes it a promising therapeutic for migraine prophylaxis.

P372

Gabapentin for the Prophylaxis of Migraine in Adults. Update of a Cochrane Review

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Objectives: To assess the evidence on efficacy and tolerability of gabapentin for preventing attacks in adults with episodic migraine.

Background: Some antiepileptic drugs are marketed for migraine prophylaxis. In evidence-based treatment guidelines, the European Federation of Neurological Societies lists gabapentin as a drug of third choice (only probable efficacy) and the American Academy of Neurology and American Headache Society list it as Level U (inadequate or conflicting data to support or refute medication use). This review updates an existing Cochrane review[1] and will be published in *The Cochrane Library.*

Methods: We searched PubMed/MEDLINE (1966 to 2013), EMBASE (1974 to 2013) and the Cochrane Central Register of Controlled Trials, and handsearched *Headache* and *Cephalalgia* to January 2013. Two independent reviewers selected studies and extracted data. For migraine frequency, mean differences (MDs) from placebo were calculated for each study and across all studies. For dichotomous data on responders (≥50% reduction in migraine frequency), odds ratios (ORs) were similarly calculated. Safety data from single-dose studies were summarized and numbers-needed-to-harm (NNHs) calculated.

Results: Five trials of gabapentin and one of its prodrug gabapentin enacarbil met the inclusion criteria (1009 total patients). For attack frequency, three trials of gabapentin 900 mg, 1200 mg and 1800 mg daily respectively found no significant reduction whereas one of gabapentin titrated to 2400 mg daily found a small but significant reduction (MD -0.80; 95% CI -1.55 to -0.05). Pooled results across these four studies (n=352; MD -0.44; 95% CI -1.43 to 0.56) were negative. One trial of gabapentin enacarbil (n=523) was also negative. For responders, one trial of gabapentin titrated to 1800 mg daily found no difference between active and placebo and one of gabapentin titrated to 2400 mg daily found a small but significant superiority of gabapentin (OR 2.79; 95% CI 1.09 to 7.17). Pooled results (n=235; OR 1.59; 95% CI 0.57 to 4.46) were negative. On this measure, the trial of gabapentin enacarbil (n=523) was also negative. Adverse events from gabapentin were common.

Conclusions: The evidence derived from all published trials of gabapentin and its prodrug gabapentin enacarbil suggest that it is not efficacious for the prophylaxis of episodic migraine in adults.

P373

Effect of Acupuncture Stimulation on Cerebral Blood Flow Using Arterial Spin Labeling MRI in Patients with Migraine

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Objectives: To clarify the mechanism of action of acupuncture in patients with migraine, we compared the effects of acupuncture stimulation on cerebral blood flow in patients

with migraine and healthy controls, by using arterial spin labeling (ASL) of MRI without contrast material.

Background: Although the acupuncture therapy for migraine is as effective as standard preventive medicine, its specific effects have been doubted since its precise mechanism is not scientifically clear.

Methods: The subjects were 10 patients with migraine who met the diagnostic criteria of the International Classification of Headache Disorders; 2nd Edition [3 males and 7 females, mean age: 39.2 ± 11.2 years (mean ± S.D.)] and 10 healthy controls (6 males and 4 females, mean age: 32.3 ± 9.2 years). The sites of acupuncture stimulation included ST8 located slightly superior to the bulge of the temporalis muscle, ST6 located anterior and superior to the angle of the jaw at the prominence of the masseter muscle, GB21 located in the upper trapezius muscle, and GB12 located in the splenius muscle. Acupuncture was performed using nonmagnetic silver needles (diameter: 0.2 mm, length: 50 mm) for 10 minutes. The method for measuring cerebral blood flow was as follows: 3TMRI (Siemens' MAGNETOM Verio) was used and the pulsed ASL method was employed. The patients were allowed to rest for 30 minutes or more and then cerebral blood flow was measured between attacks 6 times, for 4 minutes each time; namely, before stimulation, 5 minutes after the start of stimulation, 10 minutes after start of stimulation, immediately after its completion, and 15 and 30 minutes after its completion. The cerebral blood flow images obtained were statistically analyzed by Statistical Parametric Mapping to compare the images at rest and thereafter. The images at rest in patients and controls were also evaluated.

Results: Both in patients and controls, blood flow in the pars opercularis or cingulate gyrus, islet and thalamus/hypothalamus increased 5 and 10 minutes after the start of stimulation. However, the increase was more prominent in patients. Furthermore, the increase of blood flow at the same sites persisted longer immediately after, and 15 and 30 minutes after stimulation in patients than in controls. In addition, cerebral blood flow specifically increased in the anterior part of the parietal lobe of patients.

Conclusions: These results of this study suggested a difference in responsiveness to acupuncture stimulation in migraine patients and healthy controls.

P374

Migraine Prophylactic Drugs Suppress Peri-Infarct Depolarizations and Improve Stroke Outcomes

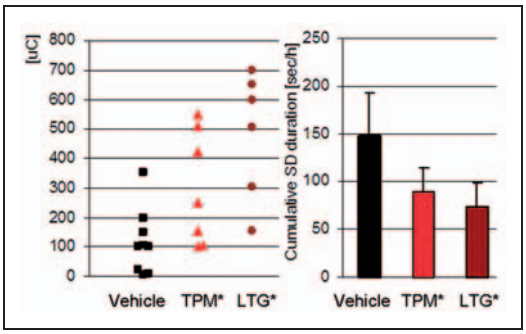
J.H. Lee[1], K. Eikermann-Haerter[2], A. Daneshmand[2], E.S. Yu[2], Y. Zheng[2], B. Sengul[2], A. Can[2], N. Yalcin[2], C. Ayata[2]

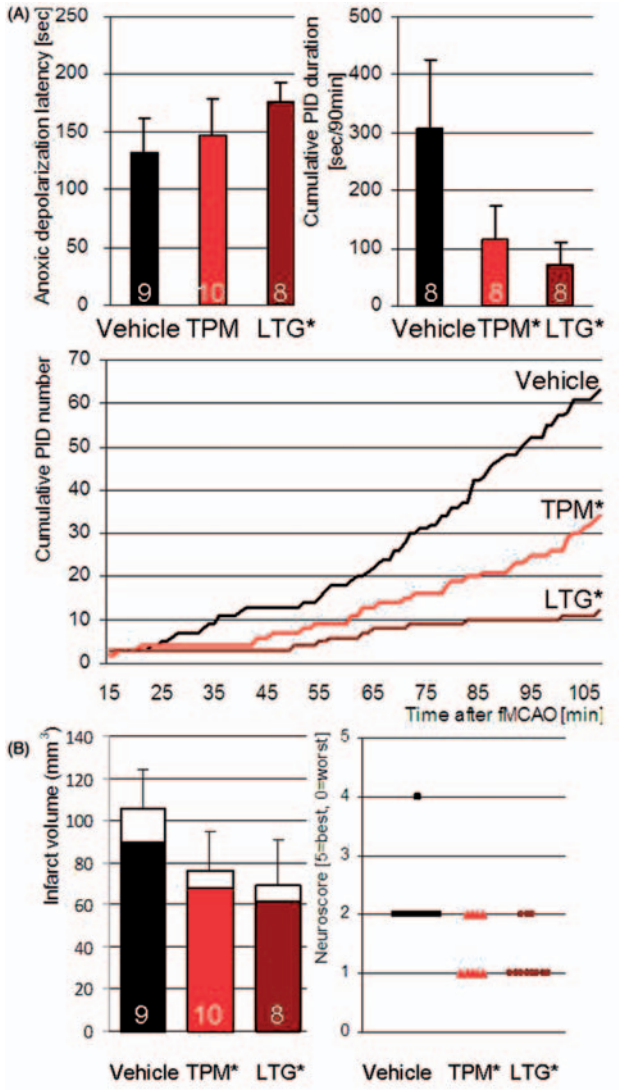
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Objectives: To test whether migraine prophylactic drugs that suppress spreading depolarization protect against ischemic stroke.

Background: Migraine is an independent stroke risk factor. Excitatory mechanisms have been implicated in pathogenesis of both migraine and stroke. It has recently been shown that migraine mutations increase brain vulnerability to ischemia via excitatory mechanisms (*Circulation* 2012;125: 803-812). Migraine mutant mice developed a higher number of peri-infarct depolarizations (PIDs) upon experimental stroke, associated with accelerated infarct growth and worsened outcomes. PIDs are related to spreading depression (SD), the electrophysiologic event underlying migraine aura, and enlarge infarcts by worsening the metabolic mismatch.

Methods: Mice (C57BL6/J) were treated for 6 weeks with the migraine prophylactic and antiepileptic drugs lamotrigine (LTG, 30mg/kg/d, p.o.), topiramate (TPM, 80mg/kg/d, p.o.), or vehicle. We measured: i) SD susceptibility by topical KCl or direct cathodal stimulation, ii) anoxic depolarization latency and PID frequency during filament occlusion of the middle cerebral artery (fMCAO), and iii) infarct volumes and neurological deficits 24h after stroke onset. In electrophysiological studies, mice were ventilated, and blood pressure and blood gas monitored and maintained





within normal range. Data are mean ± standard deviation. *p<0.05 vs. vehicle.

Results: Chronic treatment with LTG or TPM suppressed SD susceptibility in mice. A stronger electrical stimulus was necessary to induce SD, and the cumulative SD duration upon topical KCl was reduced. Both drugs also delayed the onset of anoxic depolarization upon fMCAO, and suppressed the frequency and cumulative duration of PIDs during 105min of fMCAO (A). Consequently, both drugs improve stroke outcomes, by reducing infarct size (infarct and ischemic swelling volumes; colored and white bars, respectively) and improving neurological function 24h after 1h fMCAO (B).

Conclusions: These data further support the notion that increased stroke risk in migraineurs is related to enhanced susceptibility to ischemic depolarizations, and suggest that migraine prophylaxis may improve stroke outcomes.

P375

Does Medication Overuse Matter? Response to Botulinum Toxin Type A in Chronic Migraine in Patients with or without Medication Overuse

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Objectives: To identify differences in responder rates between analgesics misusers and non misusers with chronic migraines treated with botulinum toxin type A (Botox).

Background: Chronic Migraine (CM) represents the most disabling form of the headache disorder. 50-80% of CM sufferers overuse painkillers as defined by the International Headache Society (IHS) criteria for medication overuse. It remains uncertain whether analgesic overuse is a cause or complication of CM. For effective management of CM, analgesic overuse must be addressed, although there is lack of consensus on whether preventive treatment is introduced before or after detoxification. The only controlled trial evidence comes from a small study of topirmate in CM (1) in which patients with medication overuse responded equally to those without overuse.

Data from Hull prospective study of Botulinum Toxin types A (Botox) in CM was analysed to compare response rate among patients with or without analgesic overuse.

Methods: Adults with CM were offered BOTOX after discussion of treatment options. Patients were injected intramuscularly as per PREEMPT (2), and maintained a headache diary for 30 days before/after treatment. Medication overuse was defined as use of simple analgesics on $\geq$ 15 days a month or $\geq$ 10 days a month for triptans, opioids or combined analgesics

Data were collected for the number of headache; migraine and crystal clear (headache free) days. A responder was defined as $\geq$50% reductions in headache, migraine days, or an increment in crystal clear days twice that of the baseline in a 30-day period and the results were compared for the two groups. We also compared the 50% & 75% responder rate between groups.

Results: Full data were available on 139 patients; results are illustrated in table 1. Table 2 illustrates the responder rate between the 2 groups of patients. Patients with medication overuse were slightly older and had more headache, migraine days and less crystal clear days before treatment. The median changes of all three parameters after treatment were similar in the two groups; 50% and 75% responder rates showed no difference.

Conclusions: Patients with medication overuse responds equally well to preventive treatment with Botulinum Toxin with significant reduction in the number of painkiller days.

Table 1.

		Non misusers	Misusers
Number		74	65
Median age (range)		42.5 (19-69)	48 (19-91)
Male: female		15: 59	10: 55
Headache days (median)	Before	24	28
	after	15.5	20
	Med. change	-8.5	-8
Migraine days (median)	Before	12	17
	After	6	10
	Med. Change	-6	-7
Crystal clear days (median)	Before	6	2
	After	15	10
	Med. Change	+9	+8
Simple analgesics days (median)	Before	8	20
	After	5	12
	Med. change	-3	-8
HIT-6 (median)	Before	69.5	68
	After	58	62
	Med. Change	-11.5	-6

Table 2.

	Non misusers (74)	Misusers (65)	P value
50% responders	53 (71.6%)	46 (70.7%)	Ns
75% responders	34 (45.9%)	35 (53.8%)	Ns

P376

Hull Prospective Analysis of Botulinum Toxin Type A (Botox) Use in the Treatment of Chronic Migraine

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Objectives: To identify the change in frequency of chronic migraine symptoms before and after treatment with BOTOX in real-life settings.

Background: Botulinum toxin type A (BOTOX) is licensed for the prophylaxis of headaches in adults with chronic migraine (CM)[1]. A prospective study was performed to examine the change in frequency of CM symptoms before and after treatment with BOTOX in real-life settings.

Methods: Adults with CM were offered BOTOX after discussion of treatment options. Patients were injected intramuscularly as per PREEMPT[1], and maintained a headache diary for 30 days before/after BOTOX treatment. Data were collected for the number of headache; migraine and crystal clear (headache free) days. A responder was defined as $\geq$50% reductions in headache, migraine days, or an increment in crystal clear days twice that of the baseline in a 30-day period.

Results: Full data were available on 162 patients (32 males (mean age 47.3 years; range 26-76 years); 130 females (mean age 42.9 years, range 19-70 years) who received BOTOX. 129/162 (79.6%) tried 3 preventive treatments and 70/150 (46.7%) were overusing analgesics as defined of International Headache Society[2]. The median number of headache days reduced from 26 before BOTOX to 18 after BOTOX ($p<0.001$); the median number of migraine days reduced from 13 before to 8 after ($p<0.001$); the median number of crystal clear days increased from 4 before to 12 after ($p<0.001$). Of the cohort, 30% reported $\geq$50% reduction in headache days, 51% a $\geq$50% reduction in migraine days and 58% a $\geq$50% increase in crystal clear days. Triptan days reduced from 6 before BOTOX to 3 after ($p<0.001$). Data on days off work was available for 56/162 patients; in these, the median number of days off work per month reduced from 3.5 before to 2 after BOTOX ($p < .01$). The quality of life and well being was measured using HIT-6 questionnaire that changed from 69 to 60 ($p<.001$) after treatment 18/162(11.1%) reported adverse events; 10 with pain at injection sites, 1 with worsening headache, 3 with partial ptosis,3 could not frown and 1 fainted during Rx.

Conclusions: BOTOX is a valuable addition to preventive treatment options in patients with CM. It significantly reduces the number of headache and migraine days, and significantly increases the number of crystal clear days in a real-life settings.

Table 1. Patient response to BOTOX treatment

Outcome	$\geq$50% reduction n (%)	$\geq$75% reduction n (%)
Headache days	49/162 (30%)	27/162 (16%)
Migraine days	83/162 (51%)	37/162 (22%)

(continued)

Table 1. Continued

Outcome	≥50% reduction n (%)	≥75% reduction n (%)
Crystal clear days	≥ 2-fold increase n (%)	≥ 3-fold increase n (%)
	94/162 (58%)	67/162 (41%)
Any of the above categories responders	116/162 (71%)	82/162 (50%)
All of the above categories responders	40/162 (24%)	13/162 (8%)

P377

Placebo Spectacles - An Excellent Non Pharmacological Treatment for Pediatric Migraine

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Objectives: to document excellent placebo spectacle response in children with migraine without aura (1.1/1.6).

Background: Studies show high placebo response in pediatric migraine. Clinical trials and other non pharmacological interventions record placebo headpain relief of upto 50% in children.

Methods: Prospective cohort study spanning 7 years. 2422 children. Age group 5 to 15 years. ICHD2 migraine without aura diagnostic criteria applied in all. Inclusion criteria – 1) children with a diagnosis of ICHD 2 migraine without aura (1.1/1.2/1.6), 2) history of abortive / prophylactic treatment failure, 3) fed up with different drug regimens, 4) dislike to scientific drugs, 5) subsiding with drug treatment but recurring, 6) past history of some one in the family got better with spectacle wear, 7) adverse effect of current/past drugs, 8) minimal improvement/ no blurring of vision with +/_ 0.25 SPH /CYL (placebo spectacles), 9) no eye strain symptoms other than migraine pain occasionally involving the periorbital region.

Exclusion criteria - all with documented refractive errors and typical eye strain symptoms.

Results: All were advised avoidance of all possible triggers (known and regional) and 2days / week of abortive medications as a treatment option initially. 1792 (74%) reported more than 50% improvement within a week of wearing spectacles. Improvement lasted from 3 months to one year. 574 (32%) of these children reported complete relief of their recurrent migraine pain during a follow up period of 2 years.

Conclusions: This study proves that constant(day time) wearing of placebo spectacles along with trigger avoidance will be an excellent non pharmacological way of treating migraine in children.

P378

The Influence of Migraine Prophylactic Drug on Hyperleptinemia as a Risk of Chronic Migraine

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Objectives: It is known that obesity is one of the risks of migraine chronification. Furthermore, it is speculated that obese person's hyperleptinemia have some kinds of association with migraine. In this time, we examined the effect of migraine prophylactic drugs on Zucker fatty rat cortical spreading depression (CSD) model to clarify the relation between hyperleptinemia and migraine.

Background: There are some reports about increased body weight and abdominal obesity are concerned with pathogenesis of migraine. Although migraine prevalence does not vary with BMI, the risk of transformation of episodic migraine attacks to chronic form has been found to be high in obese migraineurs. It is speculated that several adipocytokines such as Leptin which plays an integral role in feeding and obesity have some kinds of association with migraine. We have examined the effect of Leptin on the rat CSD model to clarify the relations between Leptin and migraine. Our recent data suggest that Leptin modulates the pathological mechanisms of migraine, and episodic migraine may be transformed into chronic migraine by chronic hyperleptinemia.

Methods: Thirty male Zucker fatty rats were used. Migraine prophylactic drugs (amitriptyline 20mg/kg, DL-propranolol 20mg/kg, valproate 200mg/kg, topiramate 80mg/kg) or saline (as vehicle) was administered intraperitoneally once a day for 28 days (respectively n=6). After that, under anesthetizing condition by administering α-chloralose and urethane intraperitoneally, a tracheostomy was performed for controlled ventilation. To investigate physiological parameter and blood gas, right femoral artery was catheterized. A laser-Doppler probe was placed on the cerebral cortex through the left bone

fenestration for measuring cerebral blood flow (CBF). The two other bone fenestrations were opened for measuring direct current (DC) potential of CSD, and for dropping KCl solution. After 1.0 mol KCl solution was dropped through the bone fenestration to induce CSD, we measured the CBF, DC potential, the number of CSD, the duration of CSD.

Results: The number of CSD was significantly decreased by all migraine prophylactic drugs (amitriptyline: 6.3±1.0, DL-propranolol: 7.7±1.0, valproate: 7.7±1.0, topiramate: 6.5±1.3) compared with vehicle rats (15.8±1.8). The duration of CSD were significantly decreased by all migraine prophylactic drugs (amitriptyline: 33.7±8.5, DL-propranolol: 66.0±5.0, valproate: 61.7±8.2) except for topiramate compared with vehicle rats (60.7±6.0). There was no significant difference with between administration of all migraine prophylactic drugs and vehicle in % change of CBF and DC potential.

Conclusions: Inflammatory cytokines and CGRP which have some relationship with pathogenesis of migraine are increased by leptin. These results suggest that migraine prophylactic drugs can inhibit transformation of episodic migraine into chronic due to hyperleptinemia.

P379

The Effects of Single Versus Subchronic Administration of Riboflavin on Orofacial Formalin-Induced Pain and Nociception

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Objectives: To identify whether vitamin B2 subchronic administration has an influence on orofacial formalin-induced pain (OFP) in mice.

Background: Riboflavin supplementation has been recommended widely as a safe and effective prophylactic therapy for migraine. Brain energy metabolism in migraine has been found to be abnormal in all types of migraine, making the migrainous brain hyper-responsive to many stimuli [1]. The theory of migraine as a deficit of mitochondrial energy metabolism seems to have abundant support [2]. Riboflavin is the central component of the cofactors FAD (which is reduced to $FADH_2$ in complex II of the mitochondrial electron transport chain) and FMN (which is reduced to $FMNH_2$ in complex I).

Methods: Thirty-four adult BALB/c male mice were divided into 4 groups. Groups I (n=8) and II (n=9) received a single i.p. injection of 50 mg/kg b.w. riboflavin and saline, respectively. Groups III (n=8) and IV (n=9) received daily i.p. injection of 50 mg/kg b.w. riboflavin and saline, respectively, for 30 days. One hour after the last injection, the mice were injected with 20 μL of 5% formalin into the whisker pad and the intensity of the orofacial pain was assessed. The data was analyzed by one-way ANOVA followed by Bonferroni's post hoc test. The thermal nociceptive response of the mice was also recorded at two days intervals using the hot plate and tail flick tests.

Results: A single riboflavin dose induces a decrease of 31.13% on the first phase of OFP test (not statistically significant), and a 45.3% decrease on the second phase ($p=0.014$) as compared with the saline group. For the subchronic group, there was no statistically significant difference, although for the second phase there was a 30.36% decrease ($p=0.09$) in the grooming behavior of the mice. In the first phase of OFP, the difference between one dose and repeated doses of riboflavin was close to reaching significance ($p=0.07$), but no difference was observed in the second phase. There were no modifications in the hot plate test along the recorded 30 days. In the tail flick test, the response latencies significantly increased for the first 10 days ($p<0.05$), then slowly returned to the baseline values.

Conclusions: Our results suggest that vitamin B2 acute injection has an analgesic effect on OFP and on the tail flick test for the first 10 days of administration (probably the time needed for the reserves of riboflavin to be replenished). Thirty days administration of riboflavin didn't modify neither nociception nor inflammatory pain, although the second phase of the OFP test was diminished by a p value of 0.09.

P380

Preventive Effect of Cyproheptadine Hydrochloride in Patients with Frequent Migraine

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Objectives: In this study, we investigated the preventive effect of cyproheptadine hydrochloride in whom no other conventional preventive treatments had been previously effective.

Background: Cyproheptadine hydrochloride is rarely used in adults because of medication of sleepiness. For this reason, no reports of this drug have been reported in patients with migraine in Japan.

Methods: The migraine preventive effect of cyproheptadine hydrochloride was investigated in 12 of 132 migraine patients treated at our hospital. These 12 subjects had received all of the unsuccessful migraine prophylaxis with lomerizine,valproic acid and topiramate, or had discontinued such treatments due to adverse reactions.

Initial drug of cyproheptadine hydrochloride was 4mg before sleep. In those who experienced no clinically significant sleepiness following the treatment, the drug was orally administered 4mg after breakfast as well. Drug efficacy was evaluated by examining the frequency of migraine one month and three months after the treatment was initiated.

Results: The frequency of migraine was dramatically reduced in all patients by 7 to 10 days after starting treatment. Almost no migraine attacks were observed in 9 of the 12 patients for 1 month. In the other two patients, the frequency of monthly migraine was reduced to about 1 time. The average frequency of migraine during the three-month period was an average of 2.6 times. These results demonstrate that cyproheptadine hydrochloride had significant effect in preventing migraine.

Conclusions: Currently, antidepressants, beta-blockers, antiepileptic agents, or calcium antagonists are in Japan available to prevent frequent, intractable migraine in adults. The results of this study demonstrate that cyproheptadine hydrochloride is effective as a migraine preventive treatment for Japanese patients in whom such conventional drugs have shown no efficacy or for those who have difficulty in using them due to side effects.

P381

Efficacy of Botulinum Toxin Type A Botox® for Chronic Migraine, Results from a Headache Center in Medellin- Colombia

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Objectives: Longitudinal study of a cohort to evaluate the effectiveness and safety of preventive treatment with botulinum toxin type A Botox ® (BTA-A) in patients with chronic migraine (CM) and medication overuse (MOH).

Background: CM is the main cause of chronic primary headaches, patients frequently are a challenge. Few medications have demonstrated efficacy as pharmacological option for CM. BTX-A is considered one of the most important treatments; nevertheless, there is still little experience in Colombia and Latin America with it use.

Methods: It was made a descriptive analysis of all demographic variables to describe population characteristics. To determine the effectiveness of BTX-A treatment in CM and MOH, several variables were measured in different moments for furhter comparison. All of these variables were calculated in different moments of the treatment; statistical tests used were Friedman test, ANOVA and Tests of multiple ranges with percentages of minimum significant differences of Fisher to determine if the opposing differences were statistically significant.

Results: 190 patients were evaluated in a two year period follow up. The age average was of 45.2 years (with a 9 year-old minimum age and a 93 year-old maxim). On average, migraine turned chronic at 26.26 years (with a 3 year-old minimum age and 72 year-old maxim). Most of the patients had on average 24 days of abortive overuse. After treatment patients referred subjective improvement on average 7.48 (first cycle), 6.47 (second cycle) and 6.24 (last cycle); friedman test between each cycle p = 0-000. The number of headache (HA) days/month before and after each treatment cycle was divided in three categories: 1. Mild (less than 4 days with HA a month) 2. Moderate (Between 5 and 7 days) and 3. Severe (more than 8 days). Before BTX-A, just one patient was in category 1 (0.52%) while 96.84% were in category 3; after treatment it was noticed an increase in number of patients in the mild category (23, 12.1%) and reduction of patients in category 3 (76, 40%). The F reason is similar to 52,1919 and P value of F test smaller than 0,05, a statistically significant difference exists among the variables with a level of confidence of 95,0%. It can be appreciated that the number of HA free days after each cycle increased; on average 2.6 (first cycle), 3.4 (second cycle) and 3.7 (last cycle). The F reason in this case is similar to 15,9159 and P value of F test smaller than 0,05, a statistically significant difference exist among the variables with a level of confidence of 95,0%. There was not statistically significant differences in the percentage of improvement after each treatment. Globally it was achieved improvement of 64.34 (first cycle), 67.44 (second cycle), 68.37 (last cycle).

Conclusions: CM it is a difficult to treat disorder, with few efective medications available. Prevention with BTX-A demonstrated to be an efective pharmacological option for CM.

P382

Long Term Safety of Methysergide

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Objectives: Methysergide (Deseril; Sansert) was introduced as a headache prophylactic drug by Sicuteri in 1959. It soon became clear that a small minority of patients (perhaps 1:5000) developed fibrotic complications, especially retroperitoneally, though this risk can be reduced by using no more than 6mg daily for no more than six consecutive months.

Background: Over the years many other proven agents have been preferred, but nevertheless it remains very useful in specialised clinics seeing patients unresponsive to more familiar drugs. While many patients are able to stop for 4 weeks, in some the recurrence is so severe that it seems kinder to allow them to take it continuously.

Methods: I have reviewed the records of 38 patients, 27 with migraine and 11 cluster headache.

Results: Six with migraine and 8 with cluster headache had successful short courses, 5 with migraine had side-effects and 9 (6 with migraine) did not respond. There were 10 long-term migraine patients - 4 for over 10 years and 6 for over 5 years; most took 6mg daily, though one used 8mg, and another was happy on 1mg. They all had regular echocardiograms and renal tract ultrasound screening, and none have developed any significant fibrosis.

Conclusions: The short-term tolerability of methysergide seems comparable to many other agents, and it seems safe in the longer term, so long as the dose is below 6mg, and regular checks are made. We would not expect complications with these small numbers; in such difficult circumstances the likely benefit needs to be weighed against the very small risk.

P383

Official Treatment Guidelines in Migraine Treatment Should Be like Caesar's Wife. A Critical Review of the Content and Practical Consequences of 3 Recent Guidelines for Migraine Prevention

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Objectives: Treatment guidelines by distinguished society like AAN and AHS, European Federation of Neurological Society and Canadian Neurological Society should be and are evidence-based. In addition, " common sense" should be used when the evidence is judged.

These 3 societies have published guidelines for preventive of migraine and the content and possible resulting consequences for the practical use of these drugs will be reviewed.

Background: Only AAN has extensive formal rules for constructing guidelines with graded treatment recommendations from evidence (randomized, controlled trials). The major inherent problem for the AAN/AHS guidelines from 2012 is that the recommendations are based solely on efficacy and tolerability is not taken into account. Thus topiramate is recommended as an effective drug (and it was superior to placebo in a large trial program) without the clinically very useful information that 24% (93/384) of patients treated with topiramate 100 mg in 3 pivotal RCTs discontinued the trials because of adverse events. In addition, in several cases of recommendation of drugs as possible effective in the AAN/AHS guidelines the judgment of the evidence must be considered dubious.

Methods: In the European guidelines from 2009 gabapentin is recommended as a third choice drug despite the fact that a Cochrane review from 2008 recommended that the drug needed further evaluation, Venlafaxine with one placebo-controlled RCT (and two open studies) was recommended as a second choice drug, whereas lisinopril and candesartan with one similar placebo-controlled RCT each were recommended only as third choice drugs.

In the Canadian guidelines verapamil is given a weak recommendation (low quality of evidence) and one can question whether the drug should be recommended at all since it has only been compared with placebo in 2 extremely small RCTs ($n = 12$ and 14). Magnesium is given a strong recommendation (low quality of evidence) with one positive and 2 negative placebo-controlled RCTs. It is stated that " there is some evidence for benefit and side effects are minimal".

Results: In none of these 3 treatment guidelines is the problem of comparative preventive RCTs in migraine without placebo-control taken into account. The placebo-response in preventive RCTs in migraine varies from 20 to 70% and the inclusion of placebo is therefore mandatory in comparative RCTs in order to "test the reactivity of the patient sample", as has been recommended by the IHS and EMEA.

Conclusions: As illustrated above migraine treatment guidelines should not, despite being developed by leading headache and methodological experts, be regarded as sacrosanct documents and should be open for discussion.

P384

Botulinum Toxin A as a Treatment for Hemiplegic Migraine: 3 Cases

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Objectives: To report 3 cases of hemiplegic migraine (HM) that responded well to onabotulinumtoxinA (BTX), 150 units given every 3 months.

Background: Compared to patients with typical migraine with aura, patients with HM tend to have more prolonged aura symptoms. In some cases, reversible unilateral weakness may last days to weeks. There are no randomized trials on prophylactic therapy for HM, but there is anecdotal evidence supporting the use of verapamil, acetazolamide, and lamotrigine.

Methods: Three case reports.

Results:

Case 1: 18 year-old F with severe daily migraines associated with visual, sensory, and motor aura (true weakness) lasting about 20 minutes each. She had some improvement on divalproex sodium and amitriptyline, decreasing severe migraine with aura to only 2 days/week. Since starting trimestral BTX (after 3 sessions) she has had only mild headaches without sensory/motor aura.

Case 2: 47 year-old F with migrainous headaches following right posterior frontal stroke. She had 25 days/month of headache with 15-17 days of severe migraine with aura. Aura involved numbness/paresthesias in the left lower face spreading to left hand/arm (15 min) then left leg (25 min). Ten minutes after numbness onset, she would develop left facial droop followed by gradual arm then leg weakness. Some headaches would have associated visual aura as well, lasting hours. Numbness would last the duration of the headache (1 to 6 days). Weakness would not resolve entirely until 12 hours after the end of the headache. Verapamil helped headaches, but was associated with arrhythmia. Patient failed multiple other preventative agents. She has had 3 sets of BTX injections and reports averaging 10-12 headache days/month with mild aura 2 days/week and severe aura with weakness every 6 weeks. Effect starts one week after injections and wears off after 10 weeks on average.

Case 3: 44 year-old F with migraine with aura described as right facial numbness/paresthesias that spread gradually to right arm, associated with right arm weakness. While weak, she is unable to hold a glass in her hand, and has to lean down to brush her teeth as she is too weak to bring her hand to her face. Frequently, migraine will have visual aura as well. Sensorimotor aura may last 0.5-1 day, up to 3-4 days. She had daily headaches with typical migraines with aura 15 days/month. Verapamil helped some but was associated with constipation. She failed other preventatives due to side effects. She has now had four sets of BTX injections and reports 10 days/month of migraine headache, with only 3-4 days/month of aura. The aura is less severe, with mild numbness and no weakness.

Note: Case 3 had a daughter with motor aura (no genetic testing) but other cases had no family history of aura.

Conclusions: To the authors' knowledge, there is only one other case report describing the successful treatment of HM with botulinum toxin.[1] Combined with the current cases, there is suggestion that BTX may be another treatment option for the prophylaxis of HM.

P385

The Effectiveness of Cymbalta in the Treatment of Cervicogenic Migraine (CM)

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Objectives: The objective of the study is to evaluate the effectiveness of Cymbalta in the treatment of Cervicogenic Migraine (CM).

Background: The treatment of CM is considered a challenge for most clinicians, as symptoms can be similar, due to its anatomic and pathophysiologic complexities. Successful treatment usually requires multi-disciplinary approach.

Methods: 80 patients were evaluated according to IHS classification of secondary headaches at the Pain & Headache Center, IMC, KSA. Patients were randomly allocated to either Cymbalta alone or in combination with Tizanidine for 6 months. Both groups were allowed to have an average of 10 sessions of physical therapy. First group (N=38) received Cymbalta 60mg

once daily and Tizanidine 2mg at bed time, while the second group (N=42) received Tizanidine 2mg only. Inclusive criteria: 36 males, 44 females; ages between 25-65 years, with a mean of 45. Exclusive criteria: pediatrics, patients older than 55, with uncontrolled diabetes and blood pressure, and other neurological deficits.

Results: Average improvement of 76% and 59% were seen in patients who were treated with the combination therapy (Cymbalta and Tizanidine), and Tizanidine alone, respectively.

Conclusions: Patients receiving the combination therapy of Cymbalta and Tizanidine showed more significant improvement compared to those receiving Tizanidine alone.

P386

Reversible Sensory Ataxia Induced by Memantine Therapy for Chronic Migraine

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Objectives: To describe the unique association of a dose-related sensory ataxia in the treatment of chronic migraine (CM) with memantine.

Background: Memantine, a low- to moderate-affinity noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) type of glutamate receptor, is widely approved for the treatment Alzheimer's disease at a maximum dosage of 10 mg twice daily. However, higher doses have been administered off-label for chronic headache prophylaxis. Known adverse effects include neurological symptoms but not sensory ataxia, defined as the loss of coordination secondary to disrupted sensory input into the central nervous system.

Methods: Case report from a tertiary medical center.

Results: After numerous treatment failures with other agents, a 39-year-old woman with refractory CM was initiated on memantine for headache prophylaxis, increasing weekly by 5 mg/day increments until she reached a dose of 15 mg in the morning and 20 mg at night. At a dose of 25 mg daily, she noted spatial perception difficulties, distal extremity paresthesias, and mental clouding, which progressed with further increases to 35 mg daily. Neurological examination revealed marked impairment of proprioception and vibratory sensation in the hands and feet, pseudoathetosis of the fingers, and a postural tremor. A Romberg sign was floridly positive. There was no dysmetria or dysdiadochokinesia but her gait was cautious, slow, and wide-based. Memantine was gradually tapered off over a 5-week period, and her neurological symptoms and examination normalized over several months. Diagnostic testing including MRI, serologic, cerebrospinal fluid, and nerve conduction studies revealed no other cause of the sensory ataxia.

Conclusions: The temporal contiguity between memantine initiation and the onset of sensory ataxia, as well as the dramatic improvement upon cessation of memantine, suggests a causal relationship. High doses of memantine may be associated with a reversible sensory ataxia, perhaps by overblockade of specific NMDA receptor subtypes which are found in high concentrations on afferent A-fibers. Patients with diffuse peripheral and central sensory sensitization, including individuals with CM, may be more susceptible to such adverse effects.

P387

Efficacy of Osteopathic Manipulative Treatment in the Prophylaxis of Migraine without Aura

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Objectives: Our objective was to evaluate the efficacy of osteopathic manipulative treatment (OMT) in the prophylaxis of migraine without aura in patients that were not taking preventive therapies.

Background: Complementary and alternative treatment (CAM) is used more often among adults with migraines or severe headaches. However, there are few report using OMT to specifically treat migraines or severe headaches and research data on OMT use for headache disorders remain poorly documented.

Methods: All patients included in the study had to compile an Headache Diary during the study and the MIDAS questionnaire at the beginning and the end of the study. Total duration of follow-up was six months, during this period the patients may take only symptomatic medications for their headache. During the first quarter the patients had to record frequency, intensity and duration of the attacks. In the second quarter they had 5 OMT: 3 OMT weekly, the 4th following 2 weeks, and the 5th following 1 month. All data recorded during the first

and the second quarter were comapred. Dysfunctional anatomical segments were also assessed.

Results: Twenty-two patients, respectively 19 women and 3 men were included. At the end of the study the mean of migraine days per month was decreased with respect to the beginning (20.73 vs. 15.36, Δ 5.37, p=0.018). The mean of days of consumption of medications was decreased at the end of the study with respect to the beginning (14.82 vs. 8.68, Δ 6.14, p=0.001). The mean level of pain intensity was decreased at the end of the study with respect to the beginning (6.05 vs. 4.64, Δ 1.41, p=0.0005). The mean score of MIDAS was 20.1±19.3 before OMT and 12.4±10.2 at the end of the study period (p=0.0862). 5.7% of anatomical segments was disordered. Sygma and spheno-basilar synchondrosis were the anatomical segments more frequently affected.

Conclusions: The results of this study indicate that OMT is an efficacious treatment for the prophylaxis of migraine without aura.

Considering that these therapies often carry a very low risk of serious side effects and frequently are much less expensive than pharmacologic therapies, there is a need for further rigorous research employing mixed method designs and utilizing large national samples to understand the effectiveness and mechanisms of CAM treatments in adults with migraines or severe headaches.

P388

Clozapine as Add on Therapy for Difficult Migraine Patients

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Objectives: The aim of this study is to evaluate whether the atypical neuroleptic clozapine, which acts on serotoninergic, dopaminergic and noradrenergic systems, may help improve the treatment response in migraineurs who did not present headache frequency reduction of higher than 50%, despite the previous use of numerous drugs.

Background: Difficult-to-treat migraineurs are frequently seen in tertiary centers. Although these patients pose a challenge to physicians, personnel and even other patients, underlying mechanisms and effective treatments are still uncertain. Neuroleptics such as quetiapine, chlorpromazine and others have been used although with poor evidence of its efficacy.

Methods: It was an open study carried out in two headache clinics during the period of 2009-2012. Every migraineur, according to the IHS-II classification, who did not respond to at least 5 pharmacological preventive agents used alone or in combination, in addition to complain of sleep problems, was prospectively studied. Clozapine was added to patients already in use of other agents in a single daily dose at bedtime, starting with 12,5mg and was titrated every 14 days to 25mg and 37,5mg. The dosages of the other pharmacological agents in use were not adjusted during the previous two months. A detailed headache calendar had to be filled by all patients.

Results: Eighteen patients (12 women, 6 men, ages 27-62 years, mean 45) were included and 15 completed the use of the drug. After 2 months (one month with 37,5mg) the patients were evaluated regarding the decreasing of headache frequency of higher than 50%. The average headache frequency before the use of clozapine was 10 days/month and after was of 9,4 days/month. Adverse effects were reported by 12 (80%) and gaining weight, somnolence and drowsiness were the most reported events. Fever was presented by 3 patients. Two patients among the 15 did not reach 37,5mg and remained with 25mg/day due to fear of side effects.

Conclusions: It is not known why some headache sufferers do well with the use of neuroleptics. Psychiatric comorbidities don't seem to explain it since the dosages used are much lower than that for psychiatry. However, the modulatory effect of these drugs on various neurotransmitter systems may play a role. Despite the open methodology, clozapine does not seem to be useful for the prevention of migraine even as add on therapy. Controlled studies with higher doses are necessary to confirm these observations.

P389

Once Daily Gastroretentive Gabapentin Formulation for Episodic Migraine Prophylaxis: The First Case Report

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Objectives: To report the use of a once daily gastroretentive gabapentin (G-GR) formulation for the prophylaxis of episodic migraine.

Background: Gabapentin is a calcium channel $\alpha 2\delta$ ligand that increases γ-aminobutyric acid (GABA) concentrations in the brain; it has been hypothesized to play a role in migraine prophylaxis. However, according to the 2012 updated evidence-based guideline report of the Quality

Standards Subcommittee of the American Academy of Neurology and American Headache Society, the evidence is conflicting or inadequate to support or refute the use of gabapentin for migraine prevention (Level U recommendation). There are known side effects and limitations to the use of immediate release gabapentin (G-IR), and the conflicting data may be due to the difficulty in patients attaining and sustaining optimal dosages (due to side effects and frequency of administration). Gralise® is a once daily G-GR formulation approved by the U.S. Food and Drug Administration (FDA) for the management of postherpetic neuralgia (PHN); PHN patients seem to respond to G-GR without the same burden of side effects that limit dose titration of G-IR. We hypothesized that G-GR may play a beneficial role in the prophylaxis of episodic migraine.

Methods: Case report.

Results: A 36-year-old woman with a 15-year history of episodic migraines without aura (frequency 7 migraines/month, intensity 4-6/10) presented to a headache specialist; her body-mass index (BMI) was 27 kg/m^2. In the past, she had attempted topiramate (up to a dose of 200 mg/day), which was discontinued secondary to cognitive side effects and propranolol 80 mg three times a day, which was discontinued due to hypotension. She refused to attempt antidepressants for migraine prophylaxis due to her concerns regarding the potential for neuropsychiatric side effects. G-GR was initiated at 300 mg with her evening meal, and it was titrated up over 2 weeks to 1800 mg with her evening meal. The patient denied any side effects and within the first month of treatment, her migraine frequency reduced to 3 migraines/month (average intensity 3/10). By the third month of treatment, her migraine frequency had reduced to 1–2 migraines/month (average intensity 2-3/10). 6 months after initiation of G-GR, her migraine frequency remains at 1 migraine/month (average intensity 2/10). The patient denies any treatment-emergent side effects and is satisfied with her migraine prophylaxis.

Conclusions: This case report suggests that G-GR should be further studied in case series, prospective open-label studies and, eventually, randomized double-blind placebo controlled trials for the prophylaxis of episodic migraines. Our patient may respond even further with escalating doses of G-GR beyond 1800 mg a day, and perhaps with administration with the morning, rather than evening, meal or even twice a day (with breakfast and dinner) dosing. However, dosing deviations from that approved for PHN may have the disadvantage of increased side effects. Dose finding trials, including serial measurement of serum gabapentin, will be invaluable in helping to elucidate the potential role of G-GR in the prophylaxis of episodic migraines.

P390

Efficacy and Tolerability of Acetazolamide in Migraine Prophylaxis and Klinefelter Syndrome: A Case Report

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Objectives: We describe an interesting case of migraine headaches with aura in a 47, XXY male Klinefelter Syndrome (KS) intreatment with Acetazolamide and resolutionof symptoms.

Background: A 16-year-old boy presented to the outpatient clinic migraine headaches throbbing, onset evening that lasts for a week and is presented once a month with aura, associated with nausea and vomiting.

Methods: The boy is a preterm at 28 WG for gestosis, the birth weight was 800 gr. He presented psychomotor retardation, and flat feet, and scoliosis. On neurological examination cranial nerves were intact. Detailed testing of motor strength, sensory exam, gait and coordination was also normal, as were his reflexes. Plantar responses were flexor bilaterally. The EEG was normal. He presented tall stature, abdominal adiposity and small testicles. The karyotype 47, XXY showed the presence of KS. The final diagnosis was new onset migraine headache with aura in patient with KS. Due to the frequency of his headaches and the disability associated he was treated with a prophylactic medication, before with Levetiracetam and then Topiramate and then Flunarizine without resolution of symptoms.

Results: Afterintroduction prophilaxis with acetazolamidein an oral dose of 500 mg dailysymptoms haveresolved. Patients with KS have reduced testosterone and increased circulating estradiol. Migraine is suspected to be intimately connected with increased circulating levels of estradiol. In our patient the 17-B- extradiolo at the same timeof migraine attackswas high. After introduction prophylaxis with acetazolamide for a period of six mounth thepatient experienceda reduction inmigraine attacks.

Conclusions: Our case report supports the importance of hormonal influences in migraine headaches, while alerting physicians to consider unusual causes of hormonal dysregulation, such as KS in male patients presenting with new-onset headaches.

P391

Relationship between Migraine-Related Disability and Somatosensory Amplification

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Objectives: The aim of this study was to evaluate the associations between migraine related disability and somatosensory amplification, depression, anxiety, and stress.

Background: Somatosensory Amplification Scale (SSAS) evaluates the extent to which individuals are sensitive to their bodies[1]. Previous studies have shown that the SSAS was also significantly correlated with depression and anxiety [2,3]. Although the above psychiatric conditions are well known to be comorbid with migraine, less is known about the relationship of migraine and the experience of somatic sensation.

Methods: Fifty-five migraine patients (31.9±7.2;42 female, 13 male) and 28 control subjects without migraine (31.8±5.8;19 female, 9 male) were recruited for the study. Sociodemographic form, Migraine Disability Assessment Scale (MIDAS), the Pittsburgh Sleep Quality Index (PSQI), Depression-anxiety-stress Scale (DASS), and SSAS were administered to the subjects.

Results: The mean duration of migraine was 8.7±6.8 years. The mean MIDAS score was 23.5± 34.4 and disability in 61.1 % of the patients was moderate or severe. According to the PSQI score, 43.6 % of the migraine patients had more than the cutoff point of 5, which was accepted as sleep disturbance. According to the DASS score, 38.2 % of the migraine patients had mild, moderate or severe depression; 61.8 % of the migraine patients had mild, moderate or severe anxiety; and 52.7 % of the migraine patients had mild, moderate or severe stress levels.

The mean PSQI, Depression Anxiety Stress Scale, and SASS scores in the migraine patients were significantly higher than in the control subjects: PSQI (5.5±2.8 vs 4.5±2.7, p=0.05); depression (10.0±8.7 vs 7.0±8.7, p=0.03); anxiety (10.2±7.3 vs 7.8±8.3, p=0.03); stress (16.5±8.2 vs 12.6±8.8, p=0.02), SSAS (29.9±6.6 vs 26.1±7.1, p=0.03) respectively.

In the migraine patients, MIDAS was significantly correlated with the SASS (r=0,287, p=0,001), PSQI (r=0,332, p=0,002) and depression levels (r=0,271, p=0,005).

Conclusions: This study showed that migraine-related disability was more prevalent in patients with higher levels of depression, sleep disturbances and high somatosensory amplification. The relationship between migraine and depression and sleep problems is well known. However, the association between migraine and somatic amplification has only recently been established. People who have a tendency to experience somatic sensations as intense and disturbing can evidently suffer more from painful symptoms and their social and occupational functioning may be affected more severely. Therefore, it is suggested that patients with migraine may also be evaluated not only for depression and anxiety but also for somatic amplification.

P392

Effect of Pharmacological Prophylaxis Treatment or Combination of Pharmacological and Psychological Management on Outcome of Migraine Patients

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Objectives: To evaluate the effect of pharmacological treatment or combination of pharmacological and psychological management on outcome among migraine patients.

Background: Longitudinal data demonstrate a complex bidirectional association between mood disorders and migraine. Psychological factors frequently co-exist with many headache disorders. Treatment of a co-existing mood disorder with cognitive behavioural techniques, may therefore reduce the impact of migraine.

Methods: All patients underwent an examination by a neurologist and psychologist. The diagnosis was done according the International Headache Classification. For the psychological assessment 4 scales are used: the Cognitive Behavioural Assessment for Evaluation of Outcomes (CBA-VE), the Eysenck Personality Questionnaire Revised (EPQ-R) *short scale* version, the Somatization Scale from the SCL-90R (SOM), and a generic scale for the study of self-esteem (SES). The Headache Impact Test (HIT-6) was also administered. Pharmacological prophylaxis was prescribed to all patients (Ph), while those disabled by more frequent migraine

received also a psychological intervention (Ph+Psy). The outcome was evaluated after 6 months.

Results: 54 patients (34 W and 10 M) were included. Mean age was 39.4 ± 13.2 years. 36 patients received only pharmacological prophylaxis, while 18 received also the psychological intervention. The results of the 4 scales used for the psychological assessment showed statistically significant difference only for the CBA-VE scores in the dimensions of anxiety (28.2 ± 10.6 *vs* 21.4 ± 12.1 p=0.05), depression (28.3 ± 10.7 *vs* 20.6 ± 13.3 p=0.04), and psycho-social trouble (24.5 ± 13.4 *vs* 16.3 ± 11.7 p=0.02). The HIT-6 was higher in Ph+Psy with respect to Ph patients (62.4 ± 4.2 *vs* 57.0 ± 6.6 p=0.07). At the outcome evaluation 61.1% of Ph+Psy with respect to 33.3% Ph patients (p=0.05) showed reduction of the frequency of migraine with mean HIT-6 of 44.8 ± 12.5 *vs* 48.5 ± 5.3 p=0.6, and lower rates of dropouts (11.1 *vs* 47.2% p<0,01).

Conclusions: These results indicate that the use of psychological techniques can help people cope with their pain more effectively. It would thus appear logical to view medical and psychological approaches as potentially synergistic rather than mutually exclusive in the prophylaxis treatment of migraine.

P393

Family Psychiatric History Influences Healthcare Utilization and Disability among People with Severe Migraine

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Objectives: To examine the relationship between family history of psychiatric disorders and disability and healthcare utilization.

Background: Migraine is highly comorbid with anxiety and depression. Familial aggregation of both migraine and depression are well recognized. Family history of psychiatric disorders could influence healthcare utilization, particularly for nonpharmacologic treatments.

Methods: We conducted a secondary analysis of baseline data from the Treatment of Severe Migraine Trial. People with severe migraines ($n = 232$) were recruited from referrals and flyers. During clinical assessment, neurologists asked participants about the number of family members with anxiety and depression, and previous headache treatment history. Participants completed measures of disability (Headache Disability Inventory) and psychiatric symptoms [Beck Depression (BDI) and Anxiety (BAI) Inventories]. Only participants with complete histories of previous treatment ($n = 225$) were included in these analyses. A series of regressions examined the relationship between disability and headache healthcare utilization and family history of depression and anxiety, alone and controlling for psychiatric symptoms.

Results: Participants were 78.7% women with a mean age of 39.5 (SD = 10.0); 15.6% reported family history of anxiety, and 29.3% reported family history of depression. In the last two years, participants reported seeing a physician for headaches 3.1 (SD = 3.8) times, with 28.4% going to urgent care. 39.1% of participants reported using nonpharmacologic treatment for headache in the prior two years, with the highest rates of chiropractic manipulation (27.1%) and massage (18.2%), and few using biofeedback (0.4%), relaxation training (4.4%), psychotherapy (1.8%), physical therapy (4.9%) or acupuncture (1.8%). Alone, family history of anxiety was associated with higher levels of disability, t(229)=2.23, p<0.05, r=0.15, although this was not significant [t(228) = 0.9, p> .05,*partial* r = .06) when controlling for BAI [t(229)=8.82, p<0.05, *partial* r=.50]. Controlling for BAI, family history of anxiety was associated with trying non-pharmacologic treatments for headache OR=2.56 (95% CI=1.21, 5.42), but no other health care utilization variable. Family history of depression was not associated with disability or healthcare utilization alone or controlling for BDI; the BDI was associated with the HDI [t(df)=-2.5, p<0.05, partial r=-.16] and trying non-pharmacologic treatments for headache [OR=1.05 (95% CI 1.00, 1.09)].

Conclusions: Reported family history of anxiety and depression did not independently contribute to disability beyond psychiatric symptoms. Family history of anxiety, but not depression, was associated with using non-pharmacologic treatments for headache. Participants reported low rates of utilization for nonpharmacologic treatments with grade-A evidence.

P394

Are Brown Scale for Attention-Deficit Disorder Scores Predictive for Compliance in Migrainous Patients?

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Objectives: To evaluate a possible relationship between high scores in Brown Scale for Attention-Deficit Disorder (ADD) and compliance in therapy and diary keeping.

Background: Compliance to therapy and recording of attacks in migraineurs is sometimes unsatisfactory. Well estabilished comorbidity with depression and anxiety disorders have been considered responsible, as well as the chronic nature of the illness and the patient beliefs in its essential benignity.

In recent years, there is a growing interest in adult ADD, due to its prevalence, co-morbidity, and negative psychosocial impact. The disorder can present in many ways, such as restlessness, dysphoria, lack of concentration, failure to plan activities and work. Epidemiological studies have demonstrated that ADD in adults is common, affecting an estimated 3 – 4% of the population, and recent findings point to a co-morbidity of migraine, based on the use of population surveys with questionnaires and following prescription patterns of anti-migraine and anti-ADD drugs.

Methods: We screened all consecutive patients who came to our Centre for Headaches in October and November 2012 with Beck Depression Inventory, STAI scales for anxiety and Brown Scale for ADD, the only validated tool for detection of ADD symptoms in Italian population.

All of our patients are requested to fill in a headache diary that we routinely record at every follow-up visit.

We included only patients with diagnosis of migraine, with or without aura, defined according to ICHD-II, >18 years old and in follow up for 1 year at least. Exclusion criteria were a diagnosis of other primary or secondary headache, psychiatric comorbidity and lack of comprehension of Italian language.

Compliance was evaluated by the investigator and scored on a 4-step grid ("excellent", "good", "poor", "absent") according to the filling in of diary and adherence to therapy of the previous year.

Evaluation of Brown Scales was conducted after assigning of compliances scores, to avoid bias.

A regression analysis was conducted to evaluate a possible influence of scores at Brown Scale for ADD on compliance.

Results: Sixty patients were eligible for study (48 women, 12 men), after exclusion of 7 patients with non-migrainous headache and 1 patient with bipolar disorder. Mean age was 46,78 years old, mean values of Beck, STAI I and II were, 9,6038, 41,9057 and 45,2453 respectively. Mean score at Brown Scale was 35,23.

Higher score at Brown Scale was predictive of worse compliance in filling in the headache diary ($p<0,05$), but not of worse adherence to therapy.

All results are controlled for sex, age and depression and anxiety scores.

Conclusions: ADD is a frequent condition in adult population and often comorbid with migraine.

It is possible that higher scores at Brown Scales, validated for ADD initial detection, could be predictive factors for lack of compliance in reporting attacks of migraine on headache diary, our best tool to evaluate effectiveness of preventive and acute therapy.

These interesting results would benefit from a replication on a larger sample.

P395

Does Posttraumatic Stress Disorder Influence the Relationship between Psychological Trauma and Headache in Veterans?

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Objectives: To examine the influence of posttraumatic stress disorder (PTSD) symptoms on the relationship between psychological trauma and headache in veterans of the conflicts in Iraq and Afghanistan (OEF/OIF).

Background: Psychological trauma and PTSD have been associated with higher rates of headache. It is unclear whether the relationship between trauma and headache is independent of PTSD, or if this relationship occurs primarily in the context of PTSD. OEF/OIF Veterans have high rates of headaches, traumas, and PTSD.

Methods: This study examines cross-sectional survey data from the Women Veterans Cohort Study from 228 male and 323 female OEF/OIF veterans (total $n = 551$) who were recruited through mailings sent to 8465 OEF/OIF veterans in New England, Indiana and Illinois, or flyers in Connecticut and Indiana. 693 veterans completed the baseline survey from 7/2008-12/2011. 551 veterans responded to the study inclusion item, "During the past 12 months, have you taken prescription medication for

headaches," which is nonspecific to headache type and identifies clinically significant headache. Measures included PTSD symptoms (Post-traumatic Stress Disorder Checklist, Military Version) and trauma [Traumatic Life Events Questionnaire, Combat Exposure Scale, and military sexual trauma (sexual harrassement and rape)]. Logistic regression examined associations between trauma and headache. Single mediator models were later estimated using the bias-corrected bootstrap method. Where assumptions were met, PTSD was tested as a mediator between trauma and likelihood of taking prescription headache medication.

Results: 139 veterans reported taking prescription headache medication in the prior year. Alone, a higher number of lifetime traumas was associated with higher odds of taking prescription medication (OR = 1.10, 95% CI = 1.01, 1.16). PTSD symptoms mediated this association [Indirect effect =.009 (SE=.002), 95% CI (.004, .014)]. A greater number of childhood (OR = 1.07, 95% CI = 1.03, 1.12) and adulthood interpersonal traumas (OR = 1.06, 95% CI = 1.02, 1.10) were both associated with higher odds of taking prescription headache medication. PTSD symptoms mediated both of these associations [Childhood indirect effect=-.012 (SE=.004), 95% CI (.005, .022); Adulthood indirect effect=-.018 (SE=.005) 95% CI (.008, .030)]. Neither combat trauma (OR = .97, 95% CI = .94, 1.01) nor rape (OR = .77, 95% CI = .39, 1.51) was associated with taking a prescription headache medication. Notably, military sexual harassment was associated with decreased odds of taking prescription headache medication (OR = .57, 95% CI = .38, .86) but the assumptions of mediation were not met.

Conclusions: This preliminary evidence suggests that PTSD symptoms may play an important role in the relationship between psychologically traumatic events and headache. The relationship between traumatic events occurring during military service and headache may differ from other traumatic events.

P396

Relations between Alcohol Use and Migraine among Young Adults

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Objectives: To assess relations between alcohol consumption variables and migraine.

Background: Research on relations between alcohol use and migraine has produced mixed findings, likely attributable in part to the debated role of alcohol in precipitating migraine attacks. Many migraineurs identify drinking alcohol as a trigger for migraine attacks (Fukui et al., 2008; Kelman, 2007), but little research has explored whether specific alcohol consumption variables (eg, frequency, quantity, binge episodes) distinguish migraineurs from those without migraine or are related to impact of migraine. The current study supplements explored relations between these alcohol variables and migraine-related variables in young adults, a population of interest because of their high rates of alcohol consumption and migraine.

Methods: 192 students (72.9% female, M age = 19.84) completed a battery of headache and psychological measures including the Rutgers Alcohol Problem Index (RAPI; White & Labouvie, 1989) and the Daily Drinking Questionnaire (DDQ; Collins et al., 1985). Ninety-three students were identified as migraineurs using a structured headache diagnostic interview (87% female; 93.5% with episodic migraine) and also completed the Migraine Disability Assessment Questionnaire (MIDAS; Stewart et al., 2001). MANOVA was used to quantify mean differences in consumption variables (frequency, quantity, binge episodes, alcohol-related negative consequences) between episodic migraineurs and controls. Among episodic migraineurs, multivariate regression analyses assessed the variance in headache impact (frequency, severity, and disability) attributable to these alcohol variables.

Results: Migraineurs reported having 7.13 drinks/week (vs 9.37 for controls), drinking on 1.55 days/week (vs 1.94 for controls), and engaging in 2.39 binge episodes during the past month (vs 2.63). The overall MANOVA comparing groups on these drinking-related variables was nonsignificant, $F(4,181) = 1.603$, $p = .176$. The multivariate regression analysis with the combined criterion variables was also nonsignificant, $F(12, 204) = 1.326$, $p = .206$. Headache frequency, severity, and disability were not individually associated with any of the consumption variables (R^2s= 0.1% - 3.9%).

Conclusions: Young adults with episodic migraine do not differ from those without migraine in frequency or quantity of alcohol consumption, severity of alcohol-related negative consequences, or number of binge episodes. Among a college population, alcohol consumption appears largely unrelated to the impact of migraine. Given the prevalence of migraineurs who report alcohol as a trigger, these data highlight a need for future studies to assess how migraineurs assign causality to alcohol as a trigger and to probe its role as a trigger through further experimental manipulations.

P397

Epicrania Fugax: Relationship between Severity and Psychological Profile in a Large Series of Patients

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Objectives: Our aim was to analyze the relationship between the frequency and intensity of pain paroxysms, response to treatment and several psychological variables in a large group of patients diagnosed with Epicrania Fugax (EF).

Background: EF is a novel condition consisting of brief painful paroxysms stemming from a particular area of the head, and quickly radiate forwards or backwards with a wide linear or zigzag movement through the territories of different nerves. Pain intensity is usually moderate or severe, and quality mostly electric.

Methods: 24 patients (16 women, 8 men; mean age 49.6, SD 16.9) fulfilling the proposed diagnostic criteria for EF were recruited at the headache units of two hospitals; 21 of them had forward EF, while 3 had backward EF. Personality traits (NEO-FFI; Costa & McCrae, 1992), perception of stress (PSS; Cohen, Kamarck & Mermelstein, 1983), usual coping strategies (Brief COPE; Carver, 1997), and psychiatric symptoms (SCL-90-R; Derogatis, 1983) were assessed. Pain frequency was measured using an ordinal scale, and pain intensity was evaluated using a 10-point visual analogue scale (usual, minimum and maximum intensity, plus a composite measure resulting of arithmetic mean).

Results: Intra-group analyses (Spearman's rho) showed significant negative associations between frequency of episodes and self-blame (-0.55; $p<0.05$), venting (-0.68; $p<0.01$), neuroticism (-0.56; $p<0.01$), hostility (-0.50; $p < 0.05$), paranoid ideation (-0.51; $p<0.05$), psychoticism (-0.05; $p<0.05$), and interpersonal sensitivity (-0.56; $p<0.01$). Intensity was inversely related to venting (-0.50; $p<0.05$), obsessive-compulsive symptoms (-0.50; $p<0.05$) and agreeableness (-0.60; $p<0.01$). Non-parametric tests (Kruskal-Wallis) showed significant differences in the distribution of hostility among patients with complete, partial, or no response to treatment ($c^2 = 7.41$; $p<0.05$).

Conclusions: Some psychological variables normally associated with negative health outcomes were linked to a minor severity in EF patients. Neuroticism, self-blame, hostility, paranoid ideation, psychoticism and interpersonal sensitivity were related to lesser frequency of pain paroxysms, while obsessive-compulsive symptoms were related to lesser pain intensity. Moreover, patients scoring higher in hostility showed a better response to treatment. We can consider a possible restriction in the experience of emotions in patients suffering from EF. As a rule, the aforementioned variables might be indicative of negative health outcomes, but they may also reveal a better capability for experiencing emotions. This hypothesis is reinforced by the inverse relationship between the capability for expressing emotions in response to stress (venting) and the severity of pain symptoms in our patients with EF.

P398

Confusional Migraine: A Further Understanding of Its Symptomatology and Possible Comorbidities

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Objectives: As new International Classification of Headache Disorders are considered, we offer some presentations of confusional migraine, a migraine variant.

Background: Confusional migraine is a term used by many clinicians that has not been placed in the ICHD. Recent literature reveals that the diagnosis of confusional migraine is no longer confined to children, it can occur in adults. However, little is known about these patients since it is a rare disorder.

Methods: We present four new cases with cognitive problems and behavioral changes occurring in distinct confusional states with confusional migraine as a possible unifying diagnosis. We looked at the cognitive presentation, migraine characteristics, comorbid mood, anxiety and sleep disorders, history of abuse and family history of migraine, epilepsy and psychiatric disorders. We report findings on the neurological exams, neuropsychiatric rating scales, EEG and MRI.

Results: Descriptions of the episodes included inattentiveness, disruption of awareness, emotional "lability/storm" unresponsiveness, and acute loss of tone with speech difficulties. Neurologic examination revealed that cognition was well preserved on limited in office testing. Migraine attacks included photophobia and phonophobia in 75% and accompanying sensory symptoms (scalp

allodynia, burning or tingling, facial paresthesias, left hemibody numbness) in 75%. All had one or more psychiatric diagnoses (75% mood disorders, 50% anxiety). All had sleep problems (75% insomnia, 25% sleep walking disorder). Half reported a history of physical abuse. There was a family history of psychiatric disorder, epilepsy and migraine in 75%, 50% and 50% respectively. All four patients had EEGs which did not show any epileptiform activity. Brain imaging was non-contributory to the clinical symptoms.

Conclusions: We propose that confusional migraine may be more common than initially thought. Interestingly, all four patients had underlying mood and/or anxiety disorders as well as sleep disorders. Thus, patients with confusional migraine may have a mixed bag of comorbid diagnoses. Confusional migraine should be included in the ICHD criteria, and future work should be undertaken to elucidate a common paradigm implicating confusional migraine and its comorbidities.

P399

Bio-Neurofeedback and Cognitive Behavioral Therapy Combined with Pharmacologic Therapies in Patients with Primary Headache

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Objectives: To describe the usefulness of the Bio-Neurofeedback technique and CBT combined with medication treatment in patients suffering from primary headache.

Background: Taking into account the limitations of abortive and preventive headache treatments, behavioral therapy combined with biofeedback techniques BNF-BCT constitute a therapeutic modality with rigorous scientific methodology that improves the quality of life for migraine sufferers providing multifaceted and comprehensive treatment. To our knowledge, in Colombia there is not any other a clinical experience or studies on this topic.

Methods: Through an observational study patients with primary headache (PHA) were evaluated before and after the BNF-BCT. The behavioral therapy was performed at least once a week for at least five sessions and included: BFB (EMG) in frontal muscles, relaxation techniques, creative visualization and positive self-affirmations. Clinical characteristics were evaluated though different variables; impact questionnaires MIDAS and HIT-6 were screened before and after BNF-BCT Protocol. In addition, affective disorders were looked at, displaying the typical cognitive schema of those evaluated. Nonparametric statistical tests were used.

Results: 78 patients were included. 91% (n = 71) were women, with an average age of 44±14 years with an average headache evolution time of 15 +13.4 years. 52.6% of patients had associated affective psychological disorders such as depression and anxiety. Only 6.4% had no associated symptoms in the prodromal phase or during the headache chronification stage. The majority of subjects reported hours or days prior to headache associated symptoms as nausea-vomiting (50.0%), phonophobia (65.4%) and photophobia (56.4%). 84.6% of patients used preventive and abortive medications, while just 6.4% were using painkillers.

52.5% of patients had endured headache for over 10 years, while the remaining 47.4% have had it for a period between 1 to 10 years.

At the beginning of BNF-BCT, through HIT-6 66.7% of patients scored in the severe headache impact and 21.8% reported moderate impact.

Regarding the MIDAS the monthly headache days were 17.7 +9. After BNF-BCT (average sessions 11 SD: 7.6), the HIT-6 score improved in 46.2%, while worsen in 9% of patients. MIDAS score significantly reduced afterbehavioral treatmenton average6 days (17.7+-9 days of pain/ month versus 11.6 +-9.3, P <0.0001); similar results were obtainedwiththe average abortive consumption per week (from 4.5+-3.4to 2.7+-1.8 (p <0.0001).

Taking into consideration the years of chronification and response to BNF-BCT, it was found better results in the group of patients with less than 10 years (41% of the population. N = 32, 53.1%), than subjects with more than 10 years (59%, n = 46, 41.3%).

Conclusions: Biofeedback can be used in the context of behavioral interventions as a proven successful non-medical treatment for PHA. The results of this study support the usefulness in our population; it seems patients with shorter evolution time do better.

P400

Psychotherapist Administered Biofeedback Provides Headache Improvement and Associated Psychological Benefits

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Objectives: This study was performed to determine the impact of time-limited biofeedback treatment provided by a trained psychotherapist on headache sufferers.

Background: Subjects volunteered to be a part of the study and were referred for treatment by their neurologist in hopes that biofeedback treatment would help control their pain. Most subjects continued to take preventive medication.

Methods: Headache frequency, intensity, and level of impairment were recorded in a self-report questionnaire asking subjects to rate each factor before and after their six sessions of treatment.

Results: After six sessions, results showed a decrease in frequency, intensity, and level of impairment for the majority of clients. In addition, there were a number of supplementary benefits including an improvement in quality of sleep and the management of general stress and anxiety.

Conclusions: The results suggest that the administration of biofeedback by a trained psychotherapist provides benefits for patients that go beyond pain reduction and should be considered regularly as a headache treatment option.

P401

Onset Headache in First-Ever Ischemic Stroke: A Study of Taiwan Stroke Registry in 11,523 Patients

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Objectives: To assess if onset headache is an ominous sign in patients with first-ever ischemic stroke.

Background: An association between headache and ischemic stroke is well-known but its clinical significance is not determined. Discrepancy in definitions might have led to mixed results.

Methods: A large population of ischemic stroke patients was obtained from the Taiwan Stroke Registry, a government-funded prospective study recruiting 42,883 patients with acute stroke since August 1, 2006. Ischemic stroke subtypes were classified by the TOAST criteria. Clinical features and impact on stroke outcomes, including in-hospital stroke-in-evolution, changes in NIHSS at discharge, and Barthel index and modified Rankin scale (mRS) up to six months after stroke were compared between those with and without onset headache.

Results: After excluding patients with hemorrhagic stroke, younger than 18 years old, a previous stroke history, and poor communication, the final analyzed sample was 11,523 patients. Of them, 848 patients reported having onset headache (7·4%). Patients with specific etiology, large artery atherosclerosis, or cardio-embolism were more likely to have onset headache than those with small vessel disease. Patients with onset headache were younger, predominantly female, and more likely to have posterior circulation ischemic lesions. Compared to patients without onset headache, those with onset headache had a lower frequency of stroke-in-evolution (4.5% vs. 6.7%. adjusted RR: 0.67, 95% CI: 0.53-0.76, $p<0.001$), greater improvement in NIHSS score upon discharge (0.08 vs. -0.20, $p=0.02$), and higher mean Barthel index scores (86.5 ± 24.0 vs. 83.9 ± 25.3, adjusted difference: 1.3, 95% CI: -.06-2.89, $p=0.032$) and a lower frequency with mRS higher than 2 (27.6% vs. 31.5%, adjusted RR: 0.89, 95% CI: 0.79-0.99, $p=0.022$) at one-month follow-up. There was also a trend for better functional outcome in three- and six-month follow-ups.

Conclusions: With a well-characterized definition, this large-scale study demonstrated onset headache is associated with modest but significantly better outcomes after stroke. Onset headache depicts a characteristic group of stroke patients and should be explored in evaluating patients with acute stroke.

P402

Reversible Cerebral Vasoconstriction Syndrome and Cervical Artery Dissection in 20 Patients

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Objectives: Our study aims at describing clinical-radiological characteristics in a prospective series of patients having both confirmed reversible cerebral vasoconstriction syndrome (RCVS) and cervical artery dissection (CAD).

Background: RCVS is a clinical-radiological syndrome characterized by severe acute headaches, with or without seizures and focal signs, and a multifocal constriction of cerebral arteries resolving spontaneously within three months. A few cases of CAD associated with RCVS have been reported.

Methods: From January 2004 to December 2011, we prospectively recruited patients with confirmed RCVS, based on angiographically proven reversible vasoconstriction, and CAD.

Results: Twenty patients (18 females, 2 males) had RCVS and CAD. Main associated conditions were migraine (12/20) and postpartum (5/18). Clinical features included severe headache in all patients, neck pain in 15, focal neurological deficit in 9, and seizures in 4. Pain was the only symptom in 10 patients. All patients had multifocal cerebral vasoconstriction. Twelve patients had brain lesions, cortical subarachnoid haemorrhage in 11, posterior reversible encephalopathy syndrome in 4, intracerebral haemorrhage in 3, and infarcts in 4.

CAD involved one artery in 13 patients and multiple arteries in 7. CAD mostly affected vertebral arteries (25 of 30 CAD). Only one vertebral CAD was associated with a related symptomatic infarct.

At 3 months, 18 patients had fully recovered, all patients showed reversal of cerebral vasoconstriction, and 21 dissected arteries had normalized whereas 9 arteries had not, showing residual stenosis (7) and/or aneurysm (3).

Conclusions: Our study suggests that the association of RCVS and CAD is not so rare. It points to the need for a systematic study of cervical arteries in RCVS, and of intracranial arteries in CAD patients with worsening or recurrent headache.

P403

Withdrawn by the author.

P404

Reversible Cerebral Vasoconstriction and Cervical Carotid Vasoconstriction in Migraineurs

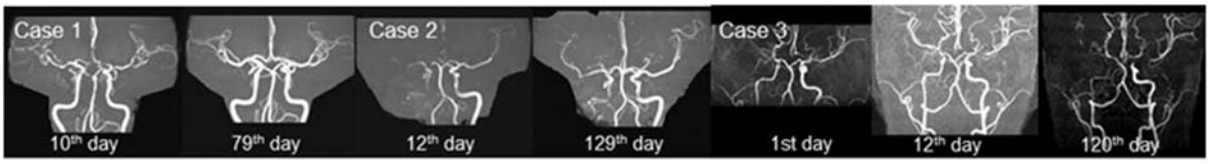
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Objectives: The purpose of this study is to evaluate clinical characteristics of cerebral vasoconstriction in migraineurs.

Background: Reversible cerebral vasoconstriction syndrome (RCVS) had been become a topic as one of the conditions responsible for thunderclap headache. Recently there are a few reports of cervical carotid vasoconstriction (CCV) of unknown etiology. Cerebral vasoconstriction in migraineurs should not be misdiagnosed because the risk of stroke may increase if they use triptans.

	Case 1	Case 2	Case 3
Age, Gender	40, female	41, female	40, female
previous headache	migraine without aura	migraine without aura	migraine with aura
Trigger factor	Caesarean section	unknown	unknown
Character of headache	intermittent, sharp, severe pain, different from previous headache	intermittent, sharp, severe pain, different from previous headache	continuous, moderate pain, same as previous headache except for lasts 3 days
Blood pressure	hypertensive	hypertensive	normal
Intracranial vessels	multiple constriction and dilatation	multiple constriction and dilatation	multiple constriction and dilatation
Extracranial vessels	normal	normal	constriction
Course of vasoconstriction	normalized at 79 days	normalized at 129 days	improved once, exacerbated at 120 days
Complication	none	subarachnoid hemorrhage	cerebral infarction



Methods: Patients who visited our Headache Clinics between August 2010 and December 2010, and had been diagnosed as having cerebral vasoconstriction were prospectively assessed. MRA was repeated until cerebral vasoconstriction improved.

Results: One hundred and eight patients were diagnosed as having migraine and underwent MRI. Reversible cerebral vasoconstriction was confirmed in 3 patients (2.8%). Clinical characteristics and neuroimagings of these cases were as follows. Case 1 and 2 were diagnosed as having RCVS. Case 3 was diagnosed as having idiopathic CCV.

Conclusions: Dysfunctional regulation of cerebral vascular tone under the predisposition and/or precipitating factors might be the central element in the pathogenesis of RCVS, but relationship between RCVS and CCV remains unclear. From the present cases and the review of past reports, both conditions were common in 30s and 40s, more women. However, patients with CCV were more migraineurs, has less frequent thunderclap headache, more frequent cerebral infarction, and long duration of repeated vasoconstriction. Sympathetic dysfunction is suggested in migraineurs even during headache-free period, and may be more strongly influenced in CCV than RCVS. Cerebral vasoconstriction is not uncommon among migraineurs. The pathogenesis of cerebral vasoconstriction may be multifactorial. Further clinical data are required to elucidate this intriguing condition.

P405

Diagnostic Criteria for the Pseudotumor Cerebri Syndrome in Adults and Children

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Objectives: To update the diagnostic criteria for the pseudotumor cerebri syndrome based on advances made since the last revision in 2002.

Background: Problems with the term IIH, over- and misuse of the diagnosis "IIH without papilledema," greater awareness of the associated radiologic abnormalities, and a better understanding of this condition in children and what constitutes a normal CSF opening pressure in this age group, necessitate a revision to the nomenclature [pseudotumor cerebri syndrome (PTCS)] and diagnostic criteria for all age groups.

Methods: We revised the 2002 classification and diagnostic criteria.

Results: 1. Required for diagnosis of the PTCS

A. Papilledema

B. Normal neurological examination except for cranial nerve abnormalities

C. Neuro-imaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on magnetic resonance imaging (MRI), with and without gadolinium, for obese females, and MRI, with and without gadolinium, and MR venography for others. If MRI is unavailable or contraindicated, contrast-enhanced computed tomography may be used.

D. Normal CSF composition

E. Elevated LP opening pressure (> 250 mm CSF in adults and > 280 mm CSF in children (250 mm H2O if the child is not sedated and not obese) in a properly performed lumbar puncture

2. Diagnosis of PTCS without papilledema

In the absence of papilledema, a diagnosis of PTCS can be made if B-E from above are satisfied, and in addition the patient has a unilateral or bilaterial sixth nerve palsy.

In the absence of papilledema or sixth nerve palsy, the diagnosis is "suggested" but not established if B-D from above are satisfied, in addition to A and C below.

A. Elevated LP opening pressure (> 250 mm CSF in adults and > 280 mm CSF in children (250 mm H20 if the child is not sedated and not obese) in a properly performed lumbar puncture

B. Unilateral or bilateral abducens nerve palsy

C. Neuroimaging signs (at least three):

i. Empty sella

ii. Flattening of the posterior sclerae

iii. Distention of the perioptic subarachnoid space +/- a tortuous optic nerve

iv. Transverse venous sinus stenosis.

Conclusions: Further study will determine the specificity and sensitivity of these criteria.

P406

HIV and Headache: A Case-Control Study

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Objectives: The aims of the present study were to **c**ompare the prevalence and headache characteristics between those infected or not by HIV virus.

Background: Headache is one of the most common medical complaints reported by individuals suffering from human immunodeficiency virus (HIV), but limited and conflicting data exist regarding their prevalence and characteristics.

Methods: Case-control study. Cases: consecutive HIV infected patients who sought medical assistance in the AIDS clinic of Hospital Oswaldo Cruz and Hospital Correia Picanço; CD4+ T lymphocyte $> 500/mm^3$, without the use of highly active antiretroviral therapy (HAART). Controls: consecutive patients who sought medical assistance in the Basic Health Care Units (general practice physician) for several reasons but without history of HIV infection. A semi-structured interview, the Headache Impact Test (HIT-6) and the Hospital Anxiety and Depression Scale were used.

Results: Two hundred thirty-five patients were interviewed, 80 of them with HIV infection. The mean age of the study group was 38 years (SD=17); 62% were women. The headache prevalence in HIV group was 90% and among those without HIV was 67% ($p<0.01$; chi-square test). The HIV group had significant lower frequency and lower impact of headache. There were no differences between the groups regarding migraine and tension-type headache prevalence, headache intensity or depression and anxiety symptoms.

Conclusions: Patients with HIV infection had a higher prevalence of headache compared with those without history of HIV infection, but had a lower frequency and impact of headache.

P407

Frequency of Chronic Headache Resulting Stroke

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Objectives: Our study was to determine whether the percentage of the stroke patients with a chronic headache as its consequence, treated in our hospital during 2011, differs from the data in similar centres in the EU and the US.

Background: Apart from direct and evident neurological deficiencies specifically related to localisation of lesion,-stroke patients, both in acute and later stages, develop numerous functional disorders and complications. Headache is a common symptom in pre-stroke and ongoing stroke patients and is not uncommon as a consequence of a stroke.

Methods: During the year 2011, 5,476 stroke patients were treated in St. Sava Hospital. 4,005 patients survived. Out of them, 3610 were ischemic stroke patients and 395 were hemorrhagic stroke patients.Our data have been obtained based on the regular monthly check-ups of the patients. The patients came for these check-ups with questionnaires and calendars where they circled each day with a headache. The criterion for the diagnostics of chronic headaches has been set up according to the criteria defined by HIS, which means that the patients have suffered from headaches for 15 days or more over a period of six months.

Results: Our study shows that 761 patients have had chronic headache as a consequence of a stroke, which makes 19.1% of the total number of patients.

Conclusions: Having compared these results to those in studies conducted in the EU and the US, which show 16 – 20% of the patients, we have not established a significant difference in the percentages of stroke patients with a chronic headache as its consequence.

P408

Secondary Trigeminal Neuralgia Caused by Pharyngeal Squamous Cell Carcinoma – A Case Report

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Objectives: This case report is to present atypical trigeminal neuralgia that may be misdiagnosed as classical trigeminal neuralgia or temporomandibular joint disorder.

Background: Trigeminal neuralgia (TN) is characterized by recurrent paroxysms of unilateral facial pain that typically is severe, lancinating, and activated with cutaneous stimulation. To be more exact, there are two types of TN, classical TN and atypical TN. The feature of classical TN is the same as forementioned things and the feature of atypical TN is constant, burning pain. The cause of atypical TN includes aneurysm, tumor, and multiple sclerosis.

Methods: We describe the case of a 49-year old male presenting with right sided facial pain. He was diagnosed with temporomandibular joint disorder in the dental clinic and he was on medical treatment, but symptoms were aggravated day by day. He was referred to pain clinic for further evaluation. Radiologic evaluation, including MRI, showed a parapharyngeal tumor.

Results: We consult to the department of oncology, he was scheduled for radiation and chemotherapy.

Conclusions: The clinical factors of suspicion for atypical TN are constant, burning nature of pain, pain of multidermatome level, sensory deficit, age under seventies, male gender. Moreover, we should consider not only intracranial tumor but also paraphayngeal tumor for underlying disease generating atypical TN.

P409

Retrospective Analysis of Headache Patients Treated by Neurosurgeons at Emergency Department in Japanese Rural Area

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Objectives: In some area, headache (HA) has been believed to be initially treated by neurosurgeons to triage subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), cerebral infarction (CI), arterial dissection and/or brain tumor. In rural area with sparse physicians as well as neurologist, neurosurgeons would be initial HA doctors. We have introduced neurosurgery hotline to bypass any physicians and to triage stroke as well as traumatic brain injury to shorten the diagnostic process and to initiate stroke treatment as soon as possible with the policy of "Time is Brain". Here we reviewed our registries at emergency department (ED) visitors during off-hour and clarify the profile of headache patients of our small community.

Background: We are only board certified stroke doctors. Patients showing stroke suggestive symptoms are all directly referred to us, in addition to head injuries and several types of seizures. We reviewed our cases for the last 3 years and report the prevalence and clinical features of stroke. The hotline received emergency calls during off-hours between 5:30 PM and 8:45 AM and whole holiday hours.

Methods: We studied 110 consecutive HA patients of all 546 hotline registry during 3 years of periods. All but 2 patients received at least one of or both or all of CT, MRI and lumber puncture. We retrieved clinical information

Primary HA	50 (45.5%)
Stroke	27 (24.5%)
hypertension	17 (15.5%)
inflammatory disease	6
sinusitis	3
epilepsy	2
BPPV	2
skull fracture	1
hearing disturbance	1
hyperventilation	1
hypoglycemia	1
unknown	1

	Stroke HA (n=27)	Non stroke HA (n=83)	p value Odds Ratio (95%CI) if applicable
age	62.7±2.7	53.5±2.32	p=0.015
Male: female	17:10	36:47	p=0.12
ambulance	19 (70.4%)	16(19.3%)	p<0.0001 9.95 (3.75-26.34)
admission	26 (96.3%)	8 (9.6%)	p<0.0001 269.75 (39.4-1732.5)
Onset to arrival (min) (excluded pts beyond 1day after onset)	727.0±322.2 (110.2±33.2)	1068.2±221.9 (281.7±34.1)	p=0.22 (p=0.003)

including, HA type, final diagnoses, prognosis, transfer methods and interval from onset of HA to ED arrival.

Results: Total 104 CT scan (92.7%), 46 MRI (41.8%) and 12 lumbar punctures were performed to investigate HA. 27 stroke (24.5%) were documented, following 48 primary HA (43.6%). In stroke, there were 14 SAH, 6 ICH, 5 vertebral artery dissections and 2 CI. 35 patients (32.7%) were transferred by ambulance car with 19 of 27 stroke (54.9%) and 11 of 14 SAH prevalence. Stroke patients were older (62.7 years vs. 53.5, p=0.015) and more transferred by ambulance car (70.4% vs. 19.3%, p=0) with shorter interval from HA onset (110.2minutes vs. 281.7, p=0.003) than non stroke HA.

Conclusions: Aged HA patients transferred by ambulance car highly predict stroke related HA. Further investigation should be performed to triage life threatening HA. In this area, HA patients seemed to take the privilege of HA and stroke triage. Neurosurgeons have the important role to treat stroke patients in the areas with sparse HA doctors.

P410

New Persistent Daily Headache with Normal Neurological Findings – Rare Primary or Secondary Phenomena Caused by Carotid-Cavernous Fistula?

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Objectives: We report a case of a patient which has diagnosed with CCF initially presented with persistent daily headache followed by promptly neurological progression.

Background: Carotid cavernous fistulas (CCF) are a dural arteriovenous fistulas which include pathological communications between the arterial system and the venous cavernous sinus situated at the wall of the cavernous sinus (CS). It can be demonstrated by wide range clinical presentations, like ophthalmic signs and symptoms (proptosis, chemosis, and visual loss), cranial nerve pareses, bleeding from the cranial structures and intracranial hemorrhage.

Methods: Twenty eight years old women has presented with 3 months history of daily left side headache, predominantly localized in left eye profound, without free after analgotherapy. Parallel with headache development she described sensation as a heart sound in pain area. Her mother died since some brain AV malformations. On examination, she had no ophthalmoplegia, proptosis and chemosis with normal neurological status. Auscultation under her left eye has found a whir.

Results: Digital subtraction angiography was performed and revealed a left side ophthalmic and facial venous dilatation with CS dilatation during all the time beginning from early arterial phase. As a result of panangiography detected a direct fast flow CCF, without presentation of left ICA intracranial parts with promptly retrograde venous swelling into the ophthalmic and facial venous and petrous sinus. During three days in neurological examination have occurred fully left side ophtalmoplegia with diplopia, left side ptosis and hypestesis in V1 area. The stent assisted coil embolization with complete occlusion of the fistula was performed with completed clinical recovery.

Conclusions: In the small number of cases CCF can be presented by minimal symptoms such as new persistent daily headache. This condition must be diagnosed and treated promptly since it has a high risk of clinical progression and irreversible neurological demages.

P411

Giant Cell Arteritis Associated with Orbital Pseudotumor

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Objectives: To present a patient with giant cell arteritis (GCA) associated with orbital pseudotumor.

Background: GCA is a systemic inflammatory vasculitis of unknown etiology that affects medium and large sized arteries. It characteristically affects the elderly and can result in a wide array of systemic, neurologic, and ophthalmologic complications of which visual loss and permanent visual impairment are a major cause of morbidity. Orbital pseudotumor, also known as Idiopathic Orbital Inflammatory Syndrome (IOIS) is a benign, non-infective, inflammatory condition of the orbit and can be a rare presenting sign of GCA.

Methods: Case report.

Results: An 83-year-old woman presented to the emergency department (ED) with a 5-day history of right-sided headache and facial pain. The pain was located in

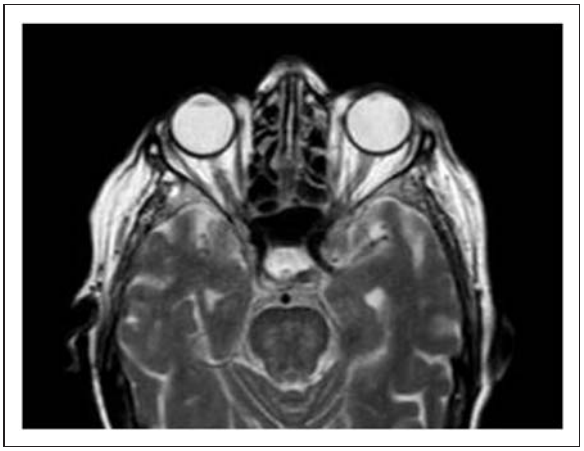
the right frontotemporal and periorbital regions, was gradual in onset, severe in intensity, throbbing, constant in quality and associated with ipsilateral lacrimation, decreased vision and jaw claudication. She also reported a 20-pound weight loss over 2-weeks, myalgias and fatigue.

Exam was significant for allodynia over the right V1-V3 dermatomes and right temporal artery tenderness. Visual acuity was 20/70 in the right eye and 20/50 in the left. Labs revealed an erythrocyte sedimentation rate (ESR) of 127 and c-reactive protein (CRP) of 3.7. Right temporal artery biopsy revealed occlusive calcified atherosclerosis with no evidence of GCA. T1 weighted images on MRI of the brain and orbits with gadolinium demonstrated enhancement of the right optic nerve sheath and surrounding retro-bulbar fat consistent with IOIS. Based on high clinical suspicion of GCA, she was started on prednisone 60mg daily. Symptoms improved and she was discharged on prednisone 60mg daily.

One month later, after stopping prednisone for a week, she presented with sudden onset bilateral vision loss. Her examination was unchanged with the exception of bilateral visual acuity to hand motion only. ESR and CRP remained elevated at 50 and 13.2 respectively. MRI of the brain and orbits without gadolinium revealed improvement of the previously seen increased right-sided retro-bulbar signal. The patient was treated with high dose intravenous steroids for 3 days with improvement in visual function and was discharged on prednisone 60mg daily. ESR several months later was 31.

Conclusions: IOIS can be an uncommon presentation of GCA and clinical suspicion for GCA should be high in cases of IOIS, even in the absence of other symptoms.





P412

Acute Headache with Encephalopathy Featuring a Transient Diffusion Weighted Imaging Splenium Lesion in Herpes Simplex Virus Encephalitis

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Objectives: To describe a patient who presented with severe headache, fever and encephalopathy and was found to have a transient diffusion weighted imaging (DWI) lesion in the splenium of the corpus callosum.

Background: Reversible splenium lesions have been described in various clinical contexts, many of which may feature headache prominently, including epilepsy syndromes, anticonvulsant withdrawal, hypoglycemia, and numerous infectious meningoencephalitides. However, this association has not been previously reported with HSV, the most commonly diagnosed severe encephalitis.

Methods: Case report from a tertiary medical center.

Results: A 20-year-old male presented with headache, fever, confusion, visual hallucinations, and nausea over two days. Lumbar puncture revealed a lymphocytic pleocytosis and 2439 copies/mL of HSV on polymerase chain reaction. MRI brain showed a centrally located lesion in the splenium of the corpus callosum, hypointense on T1-weighted and hyperintense on T2-weighted and FLAIR images. It demonstrated restriction on DWI and was hypointense on corresponding apparent diffusion coefficient mapping. Additionally, the patient had hyperintensities on T2-weighted, FLAIR, and to a

milder extent DWI images in the medial temporal lobes and right basal ganglia. He improved markedly after a 28 day course of acyclovir but was left with residual frequent headaches, imbalance and memory loss. These imaging findings largely resolved on repeat MRI six days later and completely resolved nineteen days later.

Conclusions: Disorders featuring secondary headache, including HSV encephalitis, may be associated with a transient DWI lesion in the splenium. When encountered in meningoencephalitis, this abnormality may not be particular to a specific pathogen but instead relate to the degree of acquired white matter pathology. The etiology of the splenium lesions is not fully understood but may relate to intramyelinic edema and inflammatory infiltrates or osmotic demyelination caused by fluid imbalance. This association may be underrecognized even in HSV encephalitis based on the lesion's transient radiographic presence.

P413

Hadache in HIV-1 Infected Patients

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Objectives: The present study was performed in HIV-1 infected patients without cerebral complications in order to investigate the prevalence and features of "headache attributed to HIV infection", but also to investigate the prevalence of primary headaches and their changes during HIV infection. The possible correlations between headache and clinical features of HIV infection (duration of infection, antiretroviral therapy, CD4 cell count, etc.) were also considered.

Background: Although Headache attributed to HIV/AIDS was coded to point 9.3 of the International Classification of Headache Disorders (2004), not many studies have been performed in this field. The identity of a specific headache due to HIV infection is still controversial. In addition, the presence of primary headaches (migraine, tension type headache, etc.) has not been considered in most studies.

Methods: We performed a retrospective study in 130 consecutive HIV-1 infected patients without cerebral complications and 130 age and sex matched healthy controls.

All patients were visited in blind by two different neurologists expert in the headache field. A detailed questionnaire was used to record the features of HIV infection (duration of infection, CD4 cell count, antiretroviral therapies, etc.). The diagnosis of headache was established according to the IHS classification criteria. The prevalence and features of primary headaches were studied in patients and controls. Any kind of headache which began after the HIV infection was considered.

Results: At the time of the study, a history of migraine was present in 29 patients (22%) and 16 controls (12%). The features of migraine did not change after the diagnosis of HIV infection, but a considerable number of patients, 13/29 (45%), developed migraine after the infection. Tension-type headache was present 25 patients (19%) and 33 controls (25%). Out of the 25 patients with tension-type headache, only 15 (12%) developed the headache after the infection. In 6 patients (5%) headache was related to the intake of a specific antiretroviral therapy.

The prevalence of migraine was significantly higher in patients that in controls ($p<0.05$). No correlation was found between this headache and the clinical features of the HIV infected patients. The relatively high prevalence of migraine in patients may be due to a vascular involvement in HIV infection.

Conclusions: It is not clear if the "tension-type headache" that occurred in our 15 patients after the infection may be considered as a "headache attributed to HIV infection". It is possible that the new treatments for HIV infected patients changed their clinical evolution as well as the occurrence of a specific headache.

P414

Are Occlusal Devices Effective on the Headache Improvement in Subjects with Temporomandibular Disorders? A Systematic Review

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Objectives: The aim of this review is to assess whether the treatment with occlusal devices is effective to improve headache in TMD patients.

Background: There is a concept that the TMD management of primary headache patients may headache pain frequency. Although some studies already were done to determine the efficacy of occlusal devices on headache pain improvement associated to TMD, their results have not been pooled as a systematic review.

Methods: A structured literature search was conducted in MEDLINE and other databases. All randomized controlled trials (RCT) for occlusal appliances treatment in TMD and headache patients were considered. Selection criteria included Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) and evaluation of headache in intensity and/or frequency. A quality analysis was conducted using PEDro scale.

Results: Of 2128 references, 3 RCT were included. The total sample was 205 subjects diagnosed with myofascial pain and/or arthralgia or osteoarthritis. The occlusal devices tested are stabilization, prefabricated, resilient and control appliances. Headache improvement ranges from 30-50% at the 12 months follow-up independent of device type.

Conclusions: Despite these positive results, the evidence available is insufficient to support the use of occlusal devices in the management of headache associated with TMD.

P415

Three-Dimensional Ultrasound Based Analysis of Cervical Spine Motion – Clinical Significance in Cervicogenic Headache

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Objectives: To investigate the dysfunction in anatomical structures of the craniocervical junction in persons with cervicogenic headache (CEH).

Background: Restriction of the range of motion (ROM) in the cervical spine as well as symptoms and sign of neck involvement are part of the main criteria of cervicogenic headache. CEH i s often worsen by neckmovement, sustained awkward head position, external pressure of the cervical or occipital region on the symptomatic side. Neck pain and cervical muscle tenderness is also prominent in primary and secondary headache but is not necessarily related to restriction in the cervical range of motion.

Methods: A case control study of 46 consecutive persons with CEH, 22 consecutive with headache attributed to whiplash associated headache (WLaH) and 19 consecutive persons with migraine. The criteria of the Cervicogenic Headache International Study Group (CHISG) were used for diagnosing CEH; otherwise the criteria of the International Classification of Headache Disorders (ICHD II) were applied. All participants had a clinical interview, and a physical and neurological examination. Cervical range of motion (ROM) was measured with the Zebris CMS20 ultrasound based motion analyses system (Zebris Meditac GmbH, Isny, Germany). The first aim was to evaluate the ROM in the sample of patients with CEH, WLaH and migraine to determine if the cervical ROM could discriminate between those groups. And the second aim was to determine whether the ROM is improving after blockade of the greater occipital nerve in patients with CEH. All participants were assessed in all neck movements actively and passively. Participants with cervicogenic headache were examined before and after blockage of the greater occipital nerve.

Results: To be presented at congress.

Conclusions: To be presented at congress.

P416

Chronic Migraine after Cocaine Use

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Objectives: To describe a patient who developed chronic migraine after snorting cocaine and to review literature of similar cases.

Background: Cocaine is a powerfully addictive drug that has serious neurologic consequences from its use. The potential neurological side effects of cocaine use include intracranial hemorrhage, ischemic stroke, cerebral vasculitis, brain abscess and psychiatric illnesses. Cocaine-induced headaches are estimated to occur in over 60% of users related to cocaine use. There are three types of headaches described with its use; an immediate bi-temporal, short-lasting headache, a second type of headache occurring during binge use located in the frontal region and the third type of headache during withdrawal from cocaine. All these headaches are short lasting up to 72 hours and only one case is reported to have lasted 1 week. There are no reported cases of chronic migraine developing after a single cocaine use except for one abstract from 1989 describing 6 patients with self-limited headaches from cocaine use lasting 4 weeks to 9 months.

Methods: This is a case report and review of literature.

Results: The patient is a 22-year old right-handed male college student who presented with chronic daily headaches that started 6 hours after snorting cocaine and

had been persistent for 9 months. He had intermittently snorted cocaine three times, prior to this event and had not experienced any headaches. His pain was described as a very intense, throbbing, 9/10 at its worst, located in the bi-temporal region, and radiating posteriorly, superimposed on a constant background headache of 2-3/10 with daily exacerbations to 5/10 to 6/10. He has zero headache free days per month and experiences 10 severe headache days per month. There is no proceeding aura, or any associated neurological symptoms. Triggers for the headache include sleeping too much and alcohol consumption. Patient reported no previous history of headaches and there was no family history of migraine headaches. His neurological examination and MRI imaging of the brain were unremarkable. According to the International Headache Society Guidelines cocaine-induced headache onset is within the first hour after use and the headache should resolve within 72 hours. The diagnostic criteria include bilateral pain, a frontotemporal location, a pulsating quality, and being aggravated by physical activity. Our patient is unique in the fact that his headache started 6 hours after cocaine use, and has persisted for the past 9 months even though he completely stopped using cocaine. He fulfills the I.H.S criteria for chronic migraines.

Conclusions: One case is described in which chronic daily migraine developed after snorting cocaine. Cocaine blocks the serotonin uptake and alteration in central pathways of serotonergic transmission has been shown in chronic migraine. We hypothesize that the cocaine use may have triggered the onset of chronic migraine via central neurotransmission dysfunction of the raphe-cortical serotonergic pathway. More research is necessary to confirm our findings.

P417

Masticatory Muscle Tenderness in Temporomandibular Disorders and Primary Headaches Patients

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Objectives: To evaluate association between anterior temporalis (AT) tenderness to palpation, parafunctional habits and diagnostic of masticatory muscle disorders, tension type headache (TTH) and migraine.

Background: The association between headache and temporomandibular disorders (TMD) is not fully understood. Both conditions are highly frequent with similar clinical presentation, besides the main complaint of head pain, such as muscle tenderness to palpation, the presence of trigger points, and a very strong impact in the patient's quality of life.

Methods: Retrospective analysis was conducted with patient records of the Orofacial Pain Clinic of Bauru School of Dentistry, among 1996 and 2009. Diagnostic of masticatory muscle disorders followed the American Academy of Orofacial Pain guidelines and International Headache Society criteria were used to diagnose TTH and migraine. According to physical examination, patients were classified in two groups: presence (group I) or absence (group II) of AT tenderness to palpation. Self-reported presence of parafunctional habits was also addressed. Chi-Square test with a 5% of significance accounted for statistical analysis.

Results: A total of 635 dental records were analyzed. Mean age was 35.7 years and 84% were women. Tenderness to palpation was found in 52% of the entire sample and 80% presented parafuncional habits. Eighty six percent (86%) of group I was diagnosed with masticatory muscle disorders, 34% with TTH, 16% with migraine and 84% reported parafunctional habits. Among those with parafunctional habits, 75% had masticatory muscles disorders, 27% had TTH and 13% had migraine. Significant association was found between presence of tenderness to palpation and parafunctional habits ($p=0.009$), masticatory muscle disorders ($p<0,001$) and TTH ($p<0,001$).

Conclusions: Anterior temporalis tenderness to palpation is associated with masticatory muscles disorders, TTH and frequently found in patients with parafunctional habits. Processes of trigeminal sensitization may account for these findings suggesting a sharing of pathophysiology mechanisms.

P418

Subarachnoid Hemorrhage Resulting Vasospasm and Related Headache

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Objectives: The **aim** of our study was to determine frequency and intensity of the headache following vasospasm after SAH, using transcranial color dopler ultrasonology (TCD) for diagnosis of middle cerebral artery (MCA) spasm.

Background: Vasospasm of a cerebral vessel remains a major source of morbidity and mortality after subaracnoid hemorrhage (SAH) and can expose the patient to a delayed ischemic deficit (1-7% of all strokes). Vasospasm occurs in 70% of patients after SAH and can begin 3–14 days after the first bleed, most commonly between 7–10 days. Patients may go "in and out" of vasospasm throughout 21days. Symptoms of SAH include a severe headache with a rapid onset, that belongs to symptomatic headaches and is classified in the 6th group (IHS classification).

Methods: The study included 69 patients (age 55+/-10 years) after aneurysmal SAH, admitted to the St Sava Hospital from January 1 to December 31,2011. At least one DSA (used as the reference standard) was performed between day 3 and 14 after SAH. At the same time TCD ultrasound was performed routinely every 24–48 hours to monitor possible development of vasospasm and its gravity. A blood flow velocity of more than 120cm/s suggested severe vasospasm. Changes in vessel diameter are inversely proportional to the mean flow velocity (MFV). MCA/ICA index and blood flow velocity (BFV) of the M1 and M2 branches were measured with TCD and compared with clinical findings of the presence of headache, its frequency and intensity established by taking the history from the patients or relatives.

Results: PSV and MFV for both M1 and M2 were significantly higher in patients with spasm than in those without spasm ($p>0.01$) and MCA/ICA index was >3. The ROC curve identified the best cut-off point for M1 (PSV250; MFV125 cm/s) and for M2 (PSV160; MFV 80 cm/s). Comparison of TCD and DSA was possible in 58 cases. DSA showed vasospasm in 46 cases, confirmed by TCD in 31 cases (67%). About one third of sufferers have no symptoms apart from the characteristic headache. Those with mild to medium spasm (MFV–M1 $<$ 120 cm/s) described headache as a dull lingering pain. Those with severe vasospasm (MFV $>$ 200 cm/s) experienced sudden and strong pain that referred to a "thunderclap headache", which further increased to a headache described as "like being kicked in the head", or the "worst ever". This headache often pulsated towards the occiput (the back of the head).

Conclusions: Although headache starts suddenly its further intensity may increase gradually. Our results confirm that frequency rate and intensity of headache is proportionate to vasospasm and that severe headache is most common in patients with vasospasam of high degree, occuring between 3-7 days after SAH. The study also proves that TCD is a convenient, safe and effective method that can be used to confirm rapidly the clinical findings and is certainly much less "invasive" than cerebral angiography.

P419

The Outcomes of Interventional Pain Management for Treatment of Intractable Headaches Refractory to Conventional Medical Managements

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Objectives: The objectives of this abstract presentation is to highlight the importance of considering interventional pain management approach and making proper referrals for treatment of intractable primary or secondary headaches.

Background: Secondary headaches account for about 2% of non-traumatic headache disorders. The prevalence of secondary headaches increases with advancing age, most probably due to degenerative changes in the cervical spine and vascular disorders. As such, the prevalence of secondary headaches can be as high as 11% in those over 75 years of age. Diagnosis and appropriate treatment of this condition historically has been very challenging for primary care physicians and even for neurologists.

Methods: Between May of 2011 and May of 2012, a total of 88 patients with a variety of intractable head pain conditions were referred to our center due to lack of response to all the conventional preventive/abortive therapies. Every patient had seen at least one primary care physician or internist and at least one neurologist. The average duration of headache activity was 6.5 years. A variety of target specific interventional pain management procedures were implemented to treat this group of intractable head pain conditions.

Results: This study demonstrates an interestingly high percentage of secondary headaches as our center usually receives referrals with difficult to treat head pain conditions. Headaches due to cervical facet joint arthropathy (referred pain due to convergence of somatic afferents from cervical nerves and trigeminal nucleus caudalis onto the same segments of cervical spinal cord), were the most prevalent condition across all age groups. This condition responded extremely favorably to controlled double block technique for cervical medial branch nerves, followed by radiofrequency ablation of the offending nerves resulting in complete to near complete resolution of the intractable head pain. The next most successful outcomes occurred following cervical epidural steroid injections and sphenopalatine ganglion blocks using a trans- nasal application of 4% lidocaine on a cotton-tipped applicator. Overall we successfully have treated 80.7% of the referred patients with an interventional pain management approach.

15.9% of patients were diagnosed with classic migraine and responded to medical management with optimization of their preventive and abortive medications and 3.4% were diagnosed with hemicrania continua and were treated successfully with indomethacin.

Conclusions: This study reflects the importance of considering appropriate interventional pain management techniques to treat intractable head pain conditions. In 80.7% of the referred patients this approach virtually resulted in the resolution of difficult to treat headaches and commitment to polypharmacy. In our study only 19.3% of our patients required optimization of medical management to control the headache activity.

P420

New Daily Persistent Headache with Migraine Features in Association with Multiple Cranial Neuropathy, Primary or Secondary Headache?: A Case Report

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Objectives: To highlight the difficulty to make definitive diagnosis in a case of a difficult to treat patient with a new daily persistent headache (NDPH) with migraine features, secondary to an inflammatory systemic disease.

Background: Managing the headache patient, specially the one with recent daily onset can be a difficult task. Altought not approved in the ICHD-2 criteria, NDPH can frequently share migraine features making such classification problematic. In 30% of patients CM can be abrupt. A strong possibility exists that many patients with NDPH simply have CM, with similar underlying biology. Many migraine-like headaches (MLH) have been previously described.

Methods: Retrospective case report.

Results: We report a previously healthy 51-year-old man who developed left ear tinnitus and bilateral diminished hearing during a one-year period. Three months later, he went onto tympanostomy tube placement without significant improvement. Two months later, he presented to the emergency room (ER) with sudden onset throbbing headache, moderate to severe intensity, of global localization, associated with nausea, photophobia, severe cranial allodynia and worsening with physical activity that did not respond to OTC analgesics. A diagnosis of acute sinusitis was made, receiving antibiotics for 8 days. A week later, due to the headache, he returned to the ER and had a paranasal sinuses CT scan that reported bilateral otomastoiditis and nasal rim compression causing nostrils obstruction, he went onto nose decompressing surgery, with no headache relief. A couple of weeks later, he developed left peripheral facial nerve palsy, with headache worsening. Because of this he underwent left mastoidectomy. Because of no treatment response he had a MRI of the brain done, which showed bilateral otomastoiditis with postsurgical changes in the left side, and leptomeningeal enhancement of the cerebellopontine angle. A lumbar puncture (LP) showed lymphocytic response with no other relevant abnormalities. One month after he complained of dysphagia and worse bilateral hearing loss, a fibronasolaringoscopy showed right vocal cord palsy associated with X cranial nerve compromise. After an intensive workout, the only persistent abnormal findings had been high erythrocyte sedimentation rate, elevated C-reactive protein and lymphocytic response on the CSF after three LP. A chest CT scan showed diffuse bronchial infiltration, although not conclusive, pulmonary and meningeal tuberculosis or neurosarcoidosis were suspected and treatment was given for both conditions; bacterial partially treated sub acute meningitis was ruled out. Nevertheless, after three months of in-patient managment the headache has been refractory to any sort of abortive and preventive treatment (oral, nerve block, IV infusion).

Conclusions: NDPH likely is a heterogeneous syndrome; many different secondary and primary headache disorders may be overlooked when considering a such diagnosis.

P421

Systemic Lupus Erythematosus (SLE) Presenting as Thunderclap Headache

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Objectives: To describe a secondary thunderclap headache caused by Neuropsychiatric Systemic Lupus Erythematosus (NPSLE).

Background: Thunderclap headache presents as an instantaneous severe headache. Secondary causes are common, including subarachnoid hemorrhage or reversible cerebral vasoconstriction syndrome. Since there can be a number of other etiologies, an extensive work up for secondary causes is necessary. Headache is frequently

diagnosed in patients with SLE, with prevalence rates varying from 66-80%. Headache is included as a criterion for NPSLE and is included in the standard measure for NPSLE disease activity. Migraine and tension-type headaches are the two most common phenotypes. Thunderclap headache has not been previously described. We present thunderclap headache as a likely manifestation of NPSLE.

Methods: Case Report.

Results: A 51 year old woman with no previous history of headaches developed a sudden onset, severe, 10/10 headache. The headache started while she was doing light housework and reached maximum intensity within seconds. Pain was located in the right retro-orbital and frontal regions, stabbing in quality, associated with mild nausea and photophobia. In the ER, she also complained of blurry vision and right arm paresthesias and numbness. Evaluation included CTA, MRI brain and lumbar puncture, all of which were normal except for MRI which showed extensive white matter disease in a non-specific pattern. The day following admission, her paresthesias recurred and she underwent repeat MRI/A which did not show an acute infarct or stenosis. Her initial thunderclap headache lasted for several hours, but on discharge, she continued with moderate daily headaches. She was seen in follow up, and further work up revealed an elevated ANA. She was started on steroids. Although not certain, it is plausible that her thunderclap headache was caused by NPSLE, given that she has no other clear explanation.

Conclusions: Several studies have shown that headaches are more common in patient with SLE than in controls. One study showed a prevalence of 75.7% in SLE patients compared with 66% of controls. Another case control study showed that 36% of patients with SLE had migraines without aura, higher than in control patients. NPSLE occurs in up to 56% of all patients with SLE. The neuropsychiatric manifestations range from change in mood and cognition to more dramatic manifestations, including psychosis, seizures, cerebrovascular accidents and headaches**.** A case report describes NPSLE mimicking hemiplegic migraines in a 39 year woman with 2 episodes of mild left hemiparesis, blindness in left visual field and aphasia lasting 2 hours, followed by nausea and non-pulsatile headache on each occasion. A skin biopsy of her rash showed SLE. The authors proposed that SLE should be considered in the differential for hemiplegic migraines. However, there are no previous reports of thunderclap headache as a manifestation of NPSLE. If additional cases are collected, NPSLE could be considered as a cause of thunderclap headaches.

P422

Treatment of Episodic Tension-Type Headache with a Novel Formulation of Ibuprofen Sodium

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Objectives: To evaluate the overall efficacy and onset of analgesia of a novel formulation of ibuprofen sodium (IBU_{Na}) tablets compared to standard ibuprofen (IBU) tablets and placebo in the treatment of episodic tension-type headache (ETTH).

Background: Tension-type headache is the most common type of primary headache and is often treated with over-the-counter (OTC) analgesics such as IBU. Rapid onset of action is a desirable attribute of OTC analgesics; therefore, considerable effort has been expended to develop faster-absorbed and therefore potentially faster-acting formulations. A novel tablet formulation containing 256mg of IBU_{Na} (equivalent to 200mg of standard IBU) has recently been developed.This formulation is absorbed faster than standard IBU tablets and as fast as solubilized IBU and IBU lysinate, and has a faster onset of action than standard IBU in the treatment of dental pain.

Methods: This was a randomized, double-blind, single-center, parallel-group study. Subjects 18 to 65 years of age with a history of $\geq$4 ETTH attacks of at least moderate severity per month for the previous 6 months were eligible. Subjects who reported to the study center with at least moderately severe baseline headache pain were randomized 2:2:1 to receive a single oral dose of IBU_{Na} tablets (2×256mg; equivalent to 400mg standard IBU), Motrin® tablets (IBU_{Mot}; 2×200mg), or placebo. Primary endpoints were the time-weighted sum of pain relief rating (PRR) and pain intensity difference (PID) scores over 3 hours (SPRID 0-3), and time to meaningful pain relief (TMPR) as assessed by the double-stopwatch method. Secondary endpoints included time to first perceptible pain relief (TFPR) confirmed by TMPR; sum of PRR and PID scores (PRID) at 1, 2, and 3 hours post-dose; and time-weighted sum of PRR, PID, and PRID scores over 2 and 3 hours post-dose.

Results: A total of 226 eligible subjects were randomized to IBU_{Na} (n=91), IBU_{Mot} (n=89), and placebo (n=46). Demographics and baseline characteristics were comparable between groups. Both IBU_{Na} and IBU_{Mot} had significantly better mean SPRID 0-3 scores than placebo ($P<.001$), but were not significantly different from each other. Results for summed secondary endpoints were similar. Median TMPR was significantly faster for subjects in both active treatment groups (IBU_{Na}=40.6 min and IBU_{Mot}=48.5 min) than in the placebo group (>180 min;

$P<.001$). Although TMPR was not significantly different between the IBU_{Na} and IBU_{Mot} groups using the protocol-specified statistical analysis ($P=.253$), a *post-hoc* analysis that assigned higher weight to earlier timepoints suggested that IBU_{Na} provided faster TMPR and TFPR than IBU_{Mot} ($P=.022$ and .020, respectively). No adverse events were reported.

Conclusions: This study demonstrates that a novel formulation of IBU_{Na} is effective and safe in the treatment of ETTH, with a numerically faster onset of analgesia than standard IBU tablets. A *post-hoc* analysis suggested that IBU_{Na} is appreciably faster-acting than standard IBU.

P423

Pericranial Tenderness in Chronic Tension-Type Headache. The Akershus Study of Chronic Headache

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Objectives: To explore the relationship between chronic tension-type headache (CTTH) and pericranial muscle tenderness in a population-based sample.

Background: Few data excist on CTTH in the general population. Several studies have shown that pericranial muscle tenderness is increased in tension-type headache sufferes, however, the mechanisms involved are not fully understood.

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 and examined by neurological residents. The questionnaire response rate was 71% and the rate of participation in the interview was 74%. The International Classification of Headache Disorders II was used. Pericranial muscle tenderness was assessed by a total tenderness score (TTS) involving 8 pairs of muscles and tendon insertions. Cross-sectional data from the Danish general population using the same scoring system were used for comparison.

Results: The tenderness scores were significantly higher in women than men in all muscle groups. The TTS of both gender was significantly higher in those with than without co-occurrence of migraine (19.4 vs 16.8, $p = 0.02$). The analysis by gender showed the same tendency (in men 13.8 vs 11.5, $p = 0.2$, and in women 20.5 vs 19.0, $p = 0.2$). The linear regression analysis revealed that the TTS of both gender was significantly associated with decreasing age ($p < 0.01$) and increasing headache intensity ($p = 0.04$). The TTS was not influenced by medication overuse or headache duration, i.e. hours per day, days per month or years. People with CTTH had a significantly higher TTS compared with the general population.

Conclusions: People with CTTH have increased pericraniell tenderness. Increased pericranial muscle tenderness is associated with co-occurrence of migraine. Future studies should adress whether the increased muscle tenderness is primary or secondary to the headache.

P424

The Effectiveness of Etoricoxib Plus Lidocaine Patches 5% in the Treatment of Allodynia in Chronic Daily Tension Headache (CDTH)

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Objectives: The objective of the study is to evaluate the effectiveness of the combination therapy of Etoricoxib tapering plus lidocaine patches 5% in the treatment of allodynia of CDTH.

Background: Most common among adults, "tension-type" headaches may appear periodically (episodic, less than 15 days/month) or daily (chronic, more than 15 days/month), these headaches may last from 30 minutes to several days. Chronic daily tension headaches (CDTH) come and go over prolonged period. On the other hand, allodynia, meaning "other pain," is a pain that results from a stimulus that is not normally painful. Up to 80% of persons with migraine experience at least one symptom of allodynia during a headache attack. Allodynia is not referred pain, although it can occur outside the area stimulated. It is also not hyperalgesia, which is a pain stimulus more painful than usual.

Methods: 150 patients, evaluated according to IHS classification at the Pain & Headache Center, IMC, KSA, were randomly allocated to receive either Etoricoxib tapering alone or in combination with lidocaine patches 5% for 3 months. First group (N=76) received Etoricoxib tapered over 30-day period (60mg BID [8days], 90mg OD [10days], 60mg OD [12days]) in combination with the application of lidocaine patches daily applied for 12 hours to the allodynic area at bed time for 3 months.

Second group (N=74) received only Etoricoxib taper for 3 months. Inclusive criteria: 66 males, 84 females; ages between 25-70 years, with a mean of 47. Exclusive criteria: pediatrics, patients older than 60, with uncontrolled diabetes and blood pressure; pregnancy and other neurological deficits.

Results: Average improvement of 79%, as per numeric pain scale, was seen in patients receiving combination therapy (Etoricoxib and lidocaine patches 5%), appreciated within 3 days and sustained for up to 12 months. However, an average improvement of only 60% was seen in patient receiving Etoricoxib taper alone, appreciated within 3 weeks and sustained for 6-9 months.

Conclusions: Patients receiving Etoricoxib plus lidocaine patch 5% showed more significant, faster symptomatic improvement and sustained effect for longer period than those receiving only Etoricoxib taper.

P425

Reduction of Current Tension-Type Headache Pain Intensity after a Sitting Position Neck and Upper Thoracic Spinal Massage and Manipulation

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Objectives: To investigate whether a simple manual technique could be effective in reducing current tension-type headache pain intensity.

Background: The risk of development of medication-overuse headache limits use of analgesic drugs in treatment of acute headaches. Headache sufferers are frequent users of complementary techniques such as manual therapies and chiropractic care. However, there is already no rigorous evidence that manual therapies have positive effect in the evolution of tension-type headaches.

Methods: A total of 19 subjects (all males; mean age: 24.9±5.3 years) with an onset of a tension-type headache (TTH), underwent a simple neck and upper thoracic massage and manipulation. Headache pain intensity was measured on referral, immediately after and one-hour after the massage and manipulation, using a verbal analogue scale ranging from 0 to 10.

Results: Mean headache pain score on referral was 5.0±1.5; and reduced to 1.7±1.4 immediately after (P<0.0001) and 0.9±1.4 one-hour after the intervention (P=0.006). 13 subjects (68.4%) did not demand analgesic drug during follow-up, and no adverse event or headache pain intensification occurred. In logistic regression analysis, "subjects' age", "headache pain score on referral" and "headache location" were not significantly associated with 50% or more reduction in the headache pain intensity.

Conclusions: The study showed that our simple sitting-position neck massage and cervico-thoracic manipulation technique significantly reduced the pain intensity of a current tension-type headache.

Parameter		Measure
Age (years)		24.9±5.3
Headache pain score on referral (out of 10)		5.0±1.5
Headache laterality	Unilateral	2 (10.5%)
	Bilateral	17 (89.5%)
PRP50 (at least 50% reduction of headache pain intensity) immidiately after the manipulation	Yes	12 (63.2%)
	No	7 (36.8%)
PRP50 (at least 50% reduction of headache pain intensity) after one hour of the manipulation	Yes	17 (89.5%)
	No	2 (10.5%)
Drug demand during one hour after the manipulation	Yes	6 (31.6%)
	No	13 (68.4%)
Pleasure level from the manipulation	Excellent	7 (36.8%)
	Very good	8 (42.1%)
	Good	4 (21.1%)

Exposure Parameter	Odds Ratio (95% CI)	P value
Age (years)	0.84 (0.65 – 1.08)	0.178
Headache pain score on referral (out of 10)	0.51 (0.004 – 64.59)	0.787
Headache location (bilateral compared to unilateral headache)	0.99 (0.51 – 1.92)	0.966

P426

Is Indomethacin Still Required? Long-Term Course in 19 Patients with Hemicrania Continua

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Objectives: We aim to analyze the long-term course of a series of 19 patients diagnosed with hemicrania continua (HC) and the requirement of indomethacin over time.

Background: Hemicrania continua (HC) is an uncommon primary headache, characterized by continuous unilateral pain, and superimposed exacerbations frequently associated with autonomic features. According to the International Classification of Headache Disorders, 2nd Edition (ICHD-II), a complete response to therapeutic doses of oral or parenteral indomethacin is required as a diagnostic criterion. It is considered an unremitting syndrome but its natural history is not well-known. There are cases in the literature documenting HC remission after treatment with indomethacin but the role of this drug as a disease-modifying agent is under discussion.

Methods: We evaluated consecutive patients with HC attended in an outpatient headache office located in a tertiary hospital over a five-year period (January 2008 to January 2013). In every patient we gathered demographic and clinical variables. We assessed indomethacin response with a standard oral trial up to 250 mg per day during 10 days. To confirm HC diagnosis we took special care to assure complete response to indomethacin before discontinuation of the therapy due to side effects. In those patients with a prolonged tolerance to the initially effective dosage, we analyzed their long-term course.

Results: Forty five patients (34 females, 11 males) out of 2130 (2.1%) attended in the mentioned clinic during inclusion period were diagnosed with HC. Mean age at diagnosis was 51.3 $\pm$ 14.8 years (range: 22-76). In all patients pain was strictly unilateral. Temporal pattern was always chronic and unremitting. Patients rated the continuous pain 5 $\pm$ 1.6 and exacerbations as 8.3 $\pm$ 1.3 on a verbal analogical scale (VAS). All of them presented exacerbations, and 12 (26.7%) did not report associated autonomic symptoms. All our cases responded to indomethacin; in 20 of them (44.4%), and due to side effects, alternative treatments were required. Follow-up was not possible in five patients and in one additional case diagnosis was too recent. So we finally considered long-term course with indomethacin in 19 patients (15 females, 4 males, and mean age at diagnosis 52.7 $\pm$ 16.6 years). They were proposed to reduce indomethacin dose every 3 to 6 months in order to check headache intensity. All patients were able to decrease indomethacin from an initially established effective dosage of 144.7 $\pm$ 36.8 milligrams (range 50-250) to 40.8 $\pm$ 41 (0-100) milligrams, after 11.1 $\pm$ 5.2 months (range: 3-21). In 6 cases a suppression of indomethacin was achieved; 3 of these patients and 11 among those with a partial dose reduction presented a persistent mild pain that they preferred to a higher dose of indomethacin.

Conclusions: Long-term course in our series suggests that, at least in a subset of patients, indomethacin could alter the natural history of Hemicrania Continua.

P427

Long-Term Headache and Stroke Outcomes in Reversible Cerebral Vasoconstriction Syndrome (RCVS)

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Objectives: i) To assess headache and stroke outcomes using validated measures ii) To determine the impact of RCVS on health related quality of life (QoL).

Background: RCVS is characterized by acute onset of severe headaches, with or without neurologic deficit with evidence of reversible cerebral vasoconstriction. Natural history and long term outcomes of RCVS have not been thoroughly investigated.

Methods: Prospective cohort analysis of patients recruited from the RCVS registry was conducted. Validated questionnaires were mailed to the patients. The forms included: Headache screening form, Headache Impact Test (HIT-6), Migraine Disability Assessment Test (MIDAS), Barthel Index (BI), EuroQoL (EQ-5D-5L) and Patient Health Questionnaire (PHQ-9).

Results: The RCVS registry had a total of 57 patients. Three patients refused, 26 were lost to follow-up, 8 never replied, and 20 participated. Median follow-up time from diagnosis to answering questionnaires was 91.5 months (range 10-254). Of the 20 patients (90% female), 19 (95%) presented with thunderclap headache and had ischemic stroke (50%), subarachnoid (45%) or intracerebral (15%) hemorrhage. Eleven (55%) patients continued to have headache, but majority (91%) reported improvement in character with only 1 patient having worsening. Headache impact on life measured by HIT-6 showed that 2 (13%) patients had a severe impact (HIT score $\geq$60). The mean MIDAS score was 10.67 and 2 (13%) patients had severe disabling headaches (MIDAS score$\geq$ 21). Sixteen (94%) patients were independent by BI scores $\geq$ 85 (11 patients scored 100). EQ-5D-5L measurements showed that 12 (71%), 14 (82%) and 12 (71%) patients had no problems with mobility, self-care and leisure respectively.

PHQ-9 scores revealed that only 1 (6%) patient had severe depression (PHQ score 20-27).

Conclusions: These data on long term outcomes in patients with RCVS suggests that half of them will continue to have headache, although decreased in severity and frequency. Although close to three-quarter of patients suffered an initial ischemic stroke or hemorrhage, almost all were independent with little disability. Pain and anxiety however decreased the QoL.

P428

Headache and Transient Ischaemic Attacks: Features of Neurological Clinics, Hemodynamics and Stroke Risk in Patients with Different TIA Subtypes

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Objectives: Objective is to study the frequency, location, characteristics, features of neurological clinics, hemodynamics, DW-MRI findings, and prognostic role of headaches (H) which occurred in TIA patients according to diferent TIA subtypes to increase the efficiency of secondary stroke prevention.

Background: Transient ischemic attacks (TIA) are strong predictors of subsequent stroke, disability and death. Nearly half of all strokes occur within the first 2 days after TIA. Headache is a frequent premonitory symptom of cerebral ischemia. However, clinical features and prognostic role of it in patients with differnt transient cerebralishaemia subtypes (as to TOAST criteria) isn't clear yet.

Methods: The clinical, Doppler ultrasound, DW-MRI, transthoracic echocardiography diagnosing has been made for 178 patients in acute period of TIA. Cases were reviewed by two neurologists to establish the correlation with the diagnosis. TIAs were divided into 2 groups according to the H: 1-TIA with H temporarily related to other symptoms of TIA (n=61(34.3%)) and 2-without H (n=117(65.7%)). Development of stroke was considered the primaryendpoint.Observation period was 2 years.

Results: Stroke developed in 27 (40.9%) patients after TIA with H and in 18 (16.1%) cases - without it (OR (95%CI)=19,6 (19.09-20.1), $p<0.001$). Patients with TIA onset of H had a significantly greater volume ($p<0.05$) and duration ($p<0.001$) of neurological deficit, presence of acute ischaemic lesion on DW MRI ($p<0.05$) compared with persons with TIA without H. Most often H were determined for cardioembolic (39.4%) and small-vessel occlusion (25.8%) TIA. TIAs manifested by frontal H was more frequently associated with TIAs in the carotid territory; occipital-nuchal headache was more common in vertebrobasilar TIA($p<0.05$).

Conclusions: The duration and volume of the neurological deficit as the risks of stroke were higher in patients with TIA with H than without it and differ depending on TIA pathological subtypes and vascular territory.

P429

Cardiac Cephalagia in a Patient with Unstable Angina: The First Case Report

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Objectives: We reported a case of headache associated with unstable angina.

Background: The relationship between headache and ischemic heart disease had been recognized since 1978 by Walter HC. The term of cardiac cephalalgia was defined by Lipton and diagnostic criteria was published in the second edition of the International Classification of Headache Disorders. Cardiac cephalalgia is a rare disorder, currently there is only 36 cases reported worldwide.

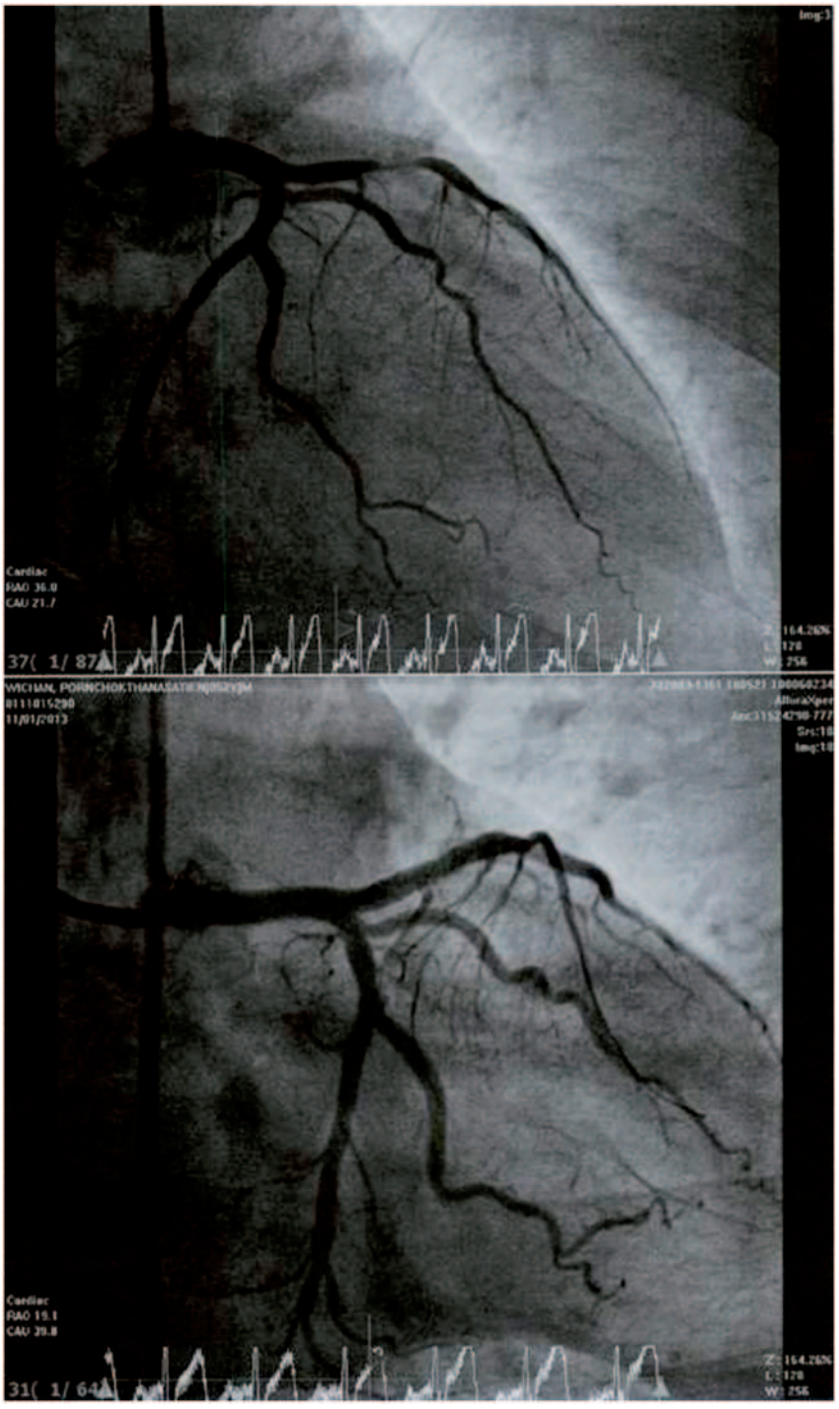
Methods: We reported a case of cardiac cephalagia and reviewed the relevance published literatures.

Results: A 52 year-old Thai male presented to the Comprehensive Headache Clinic at Bangkok Hospital Medical Center with progressive side-locked headache while walking for 1 week. After walking for 500 meters, he had chest pain followed by left-sided throbbing headache. The pain is moderate intensity at left temporal area, without nausea or vomiting. There was no photophobia, phonophobia, or any autonomic symptoms. The attack occcurs approximately 3 times per day, each episodes last for a few minutes, and went away after rest. There was no history of previous headache or head injury. His cardiovascular risk factors are hyperlipidemia and heavy smoker.

His neurological examination was unremarkable. Brain MRI and MRA showed no intracranial abnormality. Cardiologist consultation was done. Resting ECG showed right bundle branch block. Exercise stress test showed no change in baseline ECG, no chest pain, and no headache during exercise. He was diagnosed as unstable angina and was prescribed medications.

10 days later, he was admitted to the hospital due to frequent chest pain and more severe headache. ECG did not show any significant changes. Laboratory tests showed elevated cardiac enzymes. He was diagnosed with Non-ST elevated myocardial infarction. Coronary angiogram showed 85% tubular narrowing at left anterior descending artery. Percutaneous coronary intervention was performed. The final angiogram revealed no residual stenosis and TIMI III flow. After the procedure, his headache subsides, and resolved completely in 3 days. On last follow up, 2 weeks after the intervention, he reported no headache.

Conclusions: Our patient fitted almost all of the criterias for cardiac cephalalgia. The missing criterias are nausea which occur in only 23% of cases and myocardial infarction which presented later. From this patient, we postulated that unstable angina can also produce headache



similar to cardiac cephalalgia, and that a patient with this symptom could develop myocardial infarction later on. In our knowledge, this is the first case that presented with headache associated with unstable angina who later developed myocardial infarction. The ICHD-II criteria for cardiac cephalalgia might need to be revised

P430

Headache in Hospitalized Patients. Analysis of 35 Cases

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Objectives: To evaluate causes of headache in hospitalized patients.

Background: Headache is a pain syndrome secondary to multiple causes, in addition to the primary forms. In the ambulatory setting and urgent care, the prevalence of primary headaches is higher. Headache in an inpatient can be worrisome for the treating physician, even more in the context of an underlying cause of admission. Currently, there are no studies reporting the prevalence of headaches in inpatients.

Methods: We evaluated 1324 hospitalized patients in a community hospital, between May and October 2011, of which 35 fulfilled inclusion criteria.

Results: Primary headache was diagnosed in 45.7%; whereas 54.3% had secondary headaches. Migraine was the main primary headache. Headache atributed to hypoxia was the most common secondary headache, found mostly in patients admitted for surgical reasons, or associated to pulmonary infections.

Conclusions: In our study, the frequency of primary and secondary headaches in hospitalized patients was similar.

P431

Catastrophic Reversible Cerebral Vasoconstriction Syndrome Associated with Serotonin Syndrome

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Objectives: To report fulminant cases of reversible cerebral vasoconstriction syndrome (RCVS) in the setting of serotonin syndrome (SS).

Background: RCVS is characterized by acute onset of severe headaches, with or without neurologic deficit, with evidence of reversible cerebral vasoconstriction. It is often benign and prognosis is generally considered favorable. In the largest prospective study on RCVS, only 4% of patients were disabled from strokes and there were no fatalities.

Methods: Case series.

Results: Case 1

A 45-year old female with depression on escitalopram presented to a hospital with thunderclap headache and confusion. She was given intravenous dihydroergotamine and multiple doses of hydromorphone. Initial MRI brain showed T2 hyperintensities in the cerebellum fossa resembling Posterior Reversible Encephalopathy Syndrome. Repeat MRI 2 days later showed focal T2 hyperintensity in the frontal subarachnoid space consistent with a bleed. She also intermittently spiked fevers and developed rigidity. Ten days after symptom onset, she acutely deteriorated becoming comatose with decrebrate posturing. Repeat imaging revealed large bi-hemispheric infarcts with significant edema. A cerebral angiogram showed severe segmental vessel narrowing in all vascular distributions. Infusion of intra-arterial (IA) nicardipine resulted in minimal improvement. Aggressive medical and surgical management of raised intracranial pressure was unsuccessful. Worsening examination and imaging prompted withdrawal of care.

Case 2

A 57-year old female with depression on wellbutrin and citalopram with recent dose increase was admitted with dizziness. She developed acute confusion followed by a seizure and unresponsiveness. On examination, she was rigid, diaphoretic, febrile, and tachycardic with labile blood pressures and subsequently developed decerebrate posturing. CT and MRI of the brain showed bilateral parieto-occipital strokes with normal brainstem. Cerebral angiogram showed severe diffuse irregularities predominantly in the posterior circulation and IA nicardipine was administered with slight improvement. A subsequent angiogram 8 days after symptom onset showed improvement of the vascoconstriction. She clinically improved and was eventually discharged.

Serum/cerebrospinal fluid testing for vasculitis in both patients was negative and both were treated with verapamil.

Conclusions: Both cases satisfied Sternbach criteria for SS and although reversal of cerebral vascoconstriction was not demonstrated in Case 1, this likely represents a forme fruste of RCVS. Serotonergic agents are known triggers of RCVS, but the concurrent presence of SS likely precipitated the malignant course in our patients. Severe clinical and angiographic manifestations should be considered as part of the spectrum of RCVS.

P432

Tilted Metamorphopsia as an Accompanying Symptom of Nummular Headache: A Case Report

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Objectives: We aim to report a non-previously described symptom associated with nummular headache.

Background: Inverted or tilted perception disorder consists of the illusion of a visual field rotation, with no other changes in the characteristics of the objects or the scene. Its most frequent etiology is cerebral ischemia although it has been described in association with other conditions, including migraine. Nummular headache was incorporated in the Appendix of the ICHD-II. It is defined as a pain circumscribed to a rounded area of the head surface. The pain probably stems from extracranial sensitive branches of the trigeminal nerve.

Methods: A 21 year-old-woman presented with a 3-year history of an episodic pain confined to a circular area of 5 x 5 cm over her left frontal scalp. Pain attacks occurred three times per week and lasted between 20 and 60 minutes. Pain was described as pressing, with an intensity of 5 out of 10 on a visual analogue scale. No triggers were identified. Pain episodes were consistently accompanied by photopsias, photophobia and phonophobia, and were aggravated by physical activity. Moreover, during pain attacks the patient perceived objects as tilted 30 degrees in the frontal plane in a counterclockwise direction. The neurological exam was unremarkable. Brain magnetic resonance imaging and blood tests including erythrocyte sedimentation rate and antinuclear antibodies were obtained with no abnormalities. Gabapentin achieved a nearly complete response.

Results: The perception of spatial orientation relies on visual, vestibular and propioceptive inputs integrated at higher-level cortical networks. The reported cases of tilted vision have been linked to a variety of cerebral lesions, mainly located in the parieto-occipital region and the vestibulo-cerebellar system. During the migraine aura, patients may experience different visual phenomena, including scintillating scotomas, fortification spectra, polyopia, palinopsia, dyschromatopsia, and metamorphopsias (i.e. changes in shape, size or orientation of the perceived objects). All these visual disturbances are probably related to cortical spreading depression. On the other hand, nummular headache has been classified among the epicranias. The confinement of the pain and the local enhancement of pain sensitivity to a small cranial area suggest a peripheral origin. Nevertheless, some migrainous features, such as nausea, photophobia, phonophobia, or pain exacerbation by physical activity, have been occasionally encountered in patients with nummular headache. Here we report a patient with a nummular-type of headache with visual aura and other migraine accompaniments.

Conclusions: According to the present description, central mechanisms might be involved in some cases fulfilling diagnostic criteria for nummular headache. Alternatively, this patient might be suffering from an atypical migraine with aura with a well-circumscribed pain.

P433

Diagnostic Dilemmas with Acute Headache Attacks and Seizures

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Objectives: To review the diagnosis and treatment of a young man with uncontrolled seizures masquerading as acute headache attacks in the pre-ictal and ictal phases.

Background: Headaches and seizures are comorbid, sharing pathophysiological mechanisms and common clinical features. Typically the delineation or correlation between the two is clear. However, comorbid diseases present challenges in both differential diagnosis and concomitant diagnosis. Although the overlap of these two entities is well known, seizures presenting as acute episodic headache attacks in the pre-ictal and ictal phases has not been well described. Headache has been reported to be the most predominant clinical manifestation of seizure, although rare. Pre-ictal and ictal headaches are typically short-lived, and the patient may be amnestic for this pain given the altered awareness during the seizure. Continuous video EEG can facilitate the diagnosis of comorbid epilepsy and migraine.

Methods: An extensive chart review focused on the atypical features of acute headache attacks, the use of continuous video EEG, and anti-epileptic medication selection was performed. A literature search on headache and epilepsy was completed and analyzed.

Results: The patient presented with unrelenting acute headache attacks, and due to the patient's complicated prior neurologic history and risk factors for seizure, the patient was recorded with continuous video EEG for 24 hours. Interestingly, four seizures were captured on this recording, which correlated with the patient's headache attacks. Despite the patient being unaware of ictal phenomena, clinical signs of seizure were captured on video. Electrographically, the events were stereotyped with a clear ictal pattern lasting 3-5 minutes, with evidence of rhythmic theta slowing in the right centro-temporal leads prior to a generalized delta seizure pattern. With optimization of anti-epileptic medications and control of the seizures, the headaches resolved.

Conclusions: The differentiation of transient neurologic changes poses diagnostic challenges and differentiation between etiologies can be difficult based on history alone. This case demonstrates the importance of identifying atypical features of headache that could suggest an underlying seizure disorder. In addition, the importance of the use of continuous video EEG is evident as a correlation between the ictal EEG pattern and the symptoms of the patient was apparent. Anti-epileptic medication selection in patients with concurrent seizures and headache should be aimed at optimization of treatment with minimization of polypharmacy to reduce side effects. While the link between headaches and epileptic seizures is being researched, there are still deficiencies. Literature review emphasizes the need for further research into the relationship between acute headache attacks and seizure in the pre-ictal and ictal phases on a pathophysiological, clinical, and treatment basis.

P434

Sumavel for Cyclic Vomiting Syndrome in Adults: A Case Report

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Objectives: To highlight Cyclic Vomiting Syndrome (CVS) in Adults and present a case report of successful abortive therapy with Sumavel.

Background: Originally thought to be a pediatric disease, CVS is a profoundly disabling disorder that affects adults as well as children. It is characterized by recurrent, stereotypic episodes of incapacitating nausea and vomiting, separated by completely asymptomatic intervals. Up to 93% of patients experience prodromal symptoms, marked by nausea, pallor, heightened sensory sensitivity, and and fatigue. Most sufferers can identify "triggers" that precipitate attacks, such as menstruation, lack of sleep, certain foods, extreme physical exertion, and stress.

The most common acute treatments are IV fluids and potent anti-emetics, but a recent open-label clinical trial in Japan showed efficacy of intranasal or injectable sumatriptan in Pediatric CVS. Because of its similarity to "abdominal migraine", therapeutic trials have been conducted with traditional migraine preventives, such as amitryptiline, topiramate, propranolol, and cyproheptadine, which have shown promise in preventing recurrent attacks.

The prevalence of CVS is unknown, but sufferers usually experience long delays in diagnosis and frequent misdiagnosis.

Results: Case Report: Mrs. P is a 29 year old white female with a history of infrequent migraines since late adolescence. Her migraines were typically moderately-severe, associated with mild nausea (never vomiting), photophobia and osmophobia. They responded well to triptans. Family history was positive for migraine, including a sister who had been diagnosed with "abdominal migraine" in childhood.

At age 25, Mrs. P experienced the abrupt onset of CVS. She had no history of any prior gastrointestinal complaints, and an evaluation by an academic gastroenterologist was unrevealing.

Attacks would stereotypically begin on first awakening and persist until bedtime, with severe nausea and vomiting all day. No previous treatments had ever afforded even partial or temporary relief, including prescription antiemetic suppositories. She had never tried a triptan for an attack, since—with no associated headache—she had not related the vomiting episodes to migraine.

With her most recent attack, Mrs. P was instructed to use Sumavel in a therapeutic trial. Immediately after the injection, she was able to sleep. When she awoke an hour later, she felt well. Her appetite returned and she remained asymptomatic. In her four years of suffering with CVS, this was the first attack that had ever been aborted or even minimally ameliorated.

Conclusions: CVS not only is highly co-morbid with migraine, but it has been found to share a high association with two migraine-associated mitochondrial DNA polymorphisms. With these clinical and biologic associations, and with CVS's response to migraine preventives, controlled studies are warranted to assess its response to injectable sumatriptan.

P435

An Unusual Case of Short Lasting Unilateral Neuralgiform Headache with Conjunctival Tearing (SUNCT) with Prolonged Aura and Onset during Sexual Orgasm Responding to Topiramate

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Objectives: We report a case of SUNCT with prolonged aura with onset of first attack during sexual orgasm responding to high dose topiramate.

Background: Trigeminal Autonomic Cephalalgia (TAC) are rare. Cluster headaches comprise the majority of them with SUNCT being the rarest and shortest in duration. Majority of cases of SUNCT are primary with a few cases occurring secondary to posterior fossa or pituitary lesions. Although activities like exercise or blowing of nose can trigger SUNCT, onset during sexual orgasm has not been described. Short lasting sensory aura has been described in TACs but prolonged aura has not been described so far in relation with SUNCT. Lastly treatment of SUNCT is difficult; with lamotriginebeing the commonest effective reported. Topiramate has been shown to be effective in SUNCT but the doses used have been lower. Topiramate is particularly effective in treating migraine with aura.

Methods: A 42 year female with previous history if infrequent migraines and visual aura (MA) experienced severe acute left occipital, temporal and peri-orbital pain during orgasm. This was associated with ipsilateral lacrimation, conjunctival injection and rhinorrheoa. It lasted 2 minutes with a spontaneous recurrence after 20 minutes. The severity and frequency of pain episodes increased over the next several days with a maximum of 40 episodes a day and 16 attacks an hour. During a typical attack she would get several small stabs, each lasting for 2-3 seconds, with the total duration of the attack being 15-150 seconds. She complained of mild double vision on looking to the left, reduced hearing on the left and veering to the left on walking. On examination she had left conjunctival injection with Horner's Syndrome, partial left sixth nerve weakness, mild left sensorineural deafness and minimal cerebellar signs all on the left side with ataxic gate. All signs resolved completely within 3 weeks except a partial residual Horner's syndrome. Her CT head, CT angiogram, MRI with gadolinium and diffusion weighted imaging with enhanced views of pituitary were normal with normal serum prolactin.

Results: A diagnosis of SUNCT with prolonged aura was made and the patient was commenced on lamotrigine but failed to notice any benefit on 100 mg bd. A trial of indomethacin was given but she develped a rash on 50 mg tds without getting any relief. She failed to respond to Greater Occipital Nerve Block. She developed drowsiness on a small dose of carbamazepine and experienced no improvement with Gabapentin at a dose of 2.4 gm per day. She was put on topiramate to which she responded initially with reduction of day time attacks followed by complete resolution at a dose of 400 mg bd.

Conclusions: This is the first reported case of SUNCT with prolonged aura with onset during sexual orgasm and responsive to high dose topiramate. We feel the excellent response to topiramate is related to the duration of aura.

P436

How To Diagnose Mild or Moderate Form Headaches Caused by Symptomatic Cyst of the Septum Pellucidum

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Objectives: We have experienced four mild or moderate cases of headaches caused by symptomatic cyst of the septum pellucidum (sCSP). We considered important points for diagnosis of these headaches in their data including cerebrospinal fluid (CSF) pressure and the ocular fundus in a few of four cases.

Background: Headaches caused by sCSP are extremely rare. Clinical features of severe form of these are known as intolerable headaches with vomiting. But mild or moderate form headaches are not known well. In our former study, we revealed characteristics of mild or moderate form of them.

Methods: We have experienced four cases of headaches caused by sCSP from May 2007 to December 2012. MRI of all cases revealed an expansive CSP. All of them had mild or moderate headaches. We gave them questionnaires

asking about clinical features in headache. We checked effects of oral administration of isosorbide on their headaches.

Results: Case 1 is a 30-year-old man. His headache started 2 years ago. It is like occipital neuralgia, sharp and very short lasting pain, without nausea, vomiting, photophobia, phonophobia and aggravation by routine physical activity. He felt headache everyday, but it is a momentary pain. In this case we didn't examine CSF pressure and the fundus of the eye. Oral administration of isosorbide is effective as same as Case 3 and 4. Neurosurgeons performed endoscopic fenestration toward the CSP, and after the operation his headache completely vanished.

Case 2 is a 36-year-old woman. Her headache started 16 years ago. It is moderate bilateral throbbing pain like migraine with nausea, phonophobia and aggravation by routine physical activity without vomiting and photophobia, but it ceased spontaneously within 30 minutes without any medication. Frequency is once a month. CSF pressure was 200 mmH_2O and no papilledema were observed.

Case 3 is a 36-year-old woman. Her headache started 2 months ago. It is continuous moderate bilateral throbbing pain with photophobia, phonophobia and aggravation by routine physical activity without nausea and vomiting. No papilledema were observed. Her headache aggravated gradually. Several months later she recovered spontaneously.

Case 4 is a 18-year-old man. His headache started 6 years ago. It is moderate bilateral throbbing pain like migraine with photophobia, phonophobia and aggravation by routine physical activity without nausea and vomiting, but it ceased spontaneously within 20 minutes with no medication. Frequency is fifth a month. CSF pressure was 280 mmH_2O and no papilledema were observed.

Conclusions: We thought the clinical features of mild or moderate form headaches caused by sCSP is like migraine without vomiting, but duration is within 30 minutes. It is extremely shorter than migraine. Their CSF pressure was not so high and no papilledema were observed. We thought revealing clinical atypicality, checking effects of oral administration of isosorbide and MRI are the most important points for diagnosis.

P437

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Program Author Index

Aamodt, A.H OR21
Aaseth, K P423
AbdElKarim, E.H P385, P424
Abdiche, Y.N P371
Abramova, M P270
Abu-Raddad, E P367, P370
Àfra, J P213
Ahmed, F P71, P146, P375, P376, P435, P437
Ahmed, M P250
Ahn, A P140
Ahn, A.H P221
Aiello, C P200
Ailani, J P13, P111
Aja, S P347
Akcali, D OR7
Akdal, G P92, P177, P271
Akerman, S OR14, P307, P310, P312, P326
Akgun, H P72, P235
Akor, F P250
Akuzawa, S P353
Alay, S P72, P235
Albas, M P34
Alberto da Silva de Jesus, C P51
Albertson, B.K OR4
Alexa, T P282, P359, P379
Algra, A P176
Alkilani, R P250
Allais, G P17, P19, P20, P228
Allaria-Lapierre, V P169
Allen, J OR26
Allen, J.R P128
Al-Shaikh, E P192, P229
Alvarado, X P40
Alvarez, F.I P381
Alvarez-Sabin, J P210, P212
Ambrosini, A P213
Amezcua, L P182
Amin, F.M OR2, P316
Amlal, S OR15
Amrutkar, D P356
Anda, T P409
Andrade, C.C P103
Andrasik, F P49
Andree, C P187
Andreou, A.P OR19
Andress-Rothrock, D P73
Andron, G P359
Andron, G.D P282
Angst, M P59
Annanthan, S P150
Antonelli, A P251, P274
Anttila, V OR18, P212
Arai, M P436
Arakawa, I P76
Araki, N P142, P373
Arantes, A.A P106
Arbel-Ornath, M P314
Argibay, D P347
Arkink, E.B OR15
Arreguin, A P314, P315
Arsava, E.M P335
Asano, Y P70, P142
Aschenbrenner, C P125
Asgari, F P185, P193, P204
Asghar, M.S OR2, P316
Ashina, M OR2, OR11, P316, P358
Ashina, S P199
Ashkenazi, A P111
Aslan, T.S P245
Atkinson, E.J P211
Aurilia, C P171, P336
Aurora, S P24
Aurora, S.K P14
Avery, R P335
Avins, A.L P175
Ay, H P335
Ayama, M OR3
Ayata, C P314, P315, P335, P374
Aydinlar, E.I P114
Aylward, B.S P254, P257, P267, P268
Ayta, S P130, P263, P271
Babyn, P P321
Baca, S.M OR1, P331
Bacskai, B P314
Baggaley, S P330
Baggaley, S.K P284
Bahr, S P151
Bakar, M P50
Bakels, F P208
Balci, B.D P92
Bamford, C.C P159
Banihashemi, M P185, P193, P204

Baradaran, H.R P425
Barbanti, P P17, P20, P171, P228, P336
Barløse, M OR11
Barmettler, G OR23, P260, P337
Baron, E P1
Baron, E.P P154
Baron, J P432
Bastidas, J P281
Bates, E.A P151
Bathulapalli, H P395
Baykal, B P177
Beach, M.E P6, P54
Beams, J.L P149
Becerra, L OR23, P260, P337
Belcher, A P314
Bell, K.R P364
Bellini, B P246
Benatto, M.T P56
Benavente, L P62
Bender, S.D P111
Bendtsen, L P199, P219
Benedetto, C P17, P19, P20, P228
Benemei, S P357
Benschop, R P370
Berek, K P187
Bergum, M P222
Berliner, R P111
Berlutti, G P171
Bernstein, C P5
Bernstein, J.A P192
Bevilaqua-Grossi, D P56, P68, P78, P98
Bhatt, D.K P355
Bianchi-Marzoli, S P104
Bigal, M.E P56, P68, P78, P98, P231, P232
Bilchik, T.R P360
Blaauw, B.A P166, P168
Blair, S P284
Blandini, F P354
Bloudek, L P189
Blume, H.K P362
Blumenfeld, A P111
Boele, H.-J P333
Bogdanov, V.B OR5
Bohotin, C.R P282, P359, P379
Bolay, H OR7
Bonassi, S P171, P336
Bonavita, V P47
Bond, D.S P170
Bono, F P285, P290
Bonte, M P198
Borowsky, R P321
Borsook, D OR23, P260, P269, P337
Borsuk, A P400
Bosco, A P28
Boukobza, M P402
Bousser, M.-G P402, P403
Bozorg, A P433
Bracaglia, M P53, P332
Brandt, C.A P395
Brasil, A.L P184
Braunstein, D P169
Bravo, T P14
Brawn, J P337
Brennan, K.C OR5, P151, P284, P330
Brighina, F P196, P259
Broessner, G P187
Browning, R P67
Bubes, V OR30
Buckanie, N P143
Bulger, R P286, P287
Buonanotte, C.F P430
Burch, R P5, P125, P421
Burcin, C P403
Buring, J.E OR30, P186
Burns, T.L OR25
Burstein, R OR23, P16, P337
Buse, D P24
Buse, D.C OR9, OR28, P42, P44, P46, P60, P61, P65
Bush, J P188, P252
Bussone, G P17, P19, P20, P49, P74, P104, P109, P228, P338
Cabrera, J P205
Cady, R P4, P28, P67
Cady, R.K P6, P54, P67
Cahill, D P250
Calabrese, L P427
Calhoun, A.H P126, P203, P434
Calleja, S P62
Calvert, S.E P258
Camprodon, J P398
Can, A P374
Cantú Macías, J.A P361
Caparso, A OR8, OR11, P132, P135
Cappabianca, P P47
Capuano, A P255, P256
Cardillo, G P47
Cardona, A.M P399
Carothers, J P4, P11
Carvalho, A.F P106
Carvalho, D.S P108, P148
Carvalho, G.F P56, P68, P78, P98
Carvalho, M.F P106
Casciani, C P255
Celik, Y P350
Cernuda, E P62
Cernuda-Morollon, E OR29, P52
Cerutti, R P277
Chaibi, A P37, P118
Chamberlin, L.A P128

Chamberlin, N P315
Chance, M P119
Chandwani, B P223
Chang, Y.-H P230
Charles, A OR1, P14, P93, P324, P331, P369
Charles, A.C P85
Charleston IV, L P111
Chaudhry, P P279
Chauvel, V.I OR22
Chaves, T.C P56, P68, P78, P98
Chen, N P343, P344
Chen, P.-K P401
Chen, S.-P P293
Chen, W.-T P317
Chen, Y.-T P162, P163
Cheung, C OR10
Chiacchierini, R.P P14
Chiba, S P102
Chim, H P119
Chisholm, D P183
Chou, D.E P84
Christensen, S.L.T P355
Chronicle, E.P P372
Chu, M.K OR13, P31
Chung, C.-S P368
Chung, H.-J P249
Church, M.M P63
Citti, M P256
Clark, T.S P48
Climov, M P314
Cloninger, C.R P253
Cobb, K.M P252
Coffey, C.S P128
Colaizzo, E P413
Collins, E P367, P370
Condello, C P394
Conidi, F P82, P140, P366
Connors, E P15, P25
Consolo, F P259
Conti, P.C.R P232, P305, P414, P417
Cooper, W P24
Coppola, G P53, P213, P332
Cormand, B P210, P212
Corroo, J P84
Cortelli, P P17, P20, P228
Cortes, D.S P106
Cortez, M P330
Cortijo, E P426
Costa, Y.M P305, P414, P417
Couch, J.R P363
Coveney, S P172
Covington, E P96
Craig, W P8
Crum, A.V P284
Cruz, R.O P106
Csati, A P346
Cuadrado, M.L P397, P432
Cummiford, C.M P322
Cunanan, C P60
Cunha, C.L P224
Cunha, C.O P150
Curcio, M P285, P290
Curone, M P17, P20, P104, P228
Cutrer, F.M P211
Dach, F P56, P68, P78, P98, P101, P232
Dahlem, M.A P288
Dakka, Y P295
Dall'armi, V P171, P336
D'Amelio, M P259
D'Amico, D P104, P109
Daneshmand, A P335, P374
Danser, A.H.J P215, P227
Dash, P.D P214
DaSilva, A.F P200, P283, P322
Datta, S P286
Dave, H.N P88
David, P P230
Davis, R.E P396
Dawn, B.C P43
Dayal, A.K P225, P238
de Almeida, T.J.C P244
De Col, R OR6
de Coo, I.F P133
De Felice, M P352
De Gaalon, S P403
de Hoon, J P367, P370
de Koning, P.J.H OR2
de la Cruz, C P347, P397, P426, P432
de la Cruz González, J.G P361
De Marinis, M P413
De Pasqua, V P280, P341
de Resende, D.F P103
De Simone, R P47
De Souza, J.A P107
de Tommaso, M P308
de Vries, B P212, P216
De Vries, R P215
de Zeeuw, C.I P333
DeBoer, M P200, P322
Deboer, M.D P283
Deelder, A.M P208
Demirkaya, S P72, P235
Demirtas, M.Z P275
Dexter, J.K P6, P54, P67
Dhadwal, S P223, P301
Di Clemente, L P213
Di Lorenzo, C P53, P332
Di Tola, M P261
Diaz, E.A P79
Diener, H.-C P143, P327, P340

Dietz, C.J OR1
Digre, K.B P284, P405
Dikmen, S.S P364
Dikomitis, L P198
Dilekoz, E OR7
Ding, M P221
Disco, C P134
DiTommaso, C P364
Djupesland, P.G P23
Dobi, D P113
Dodick, D P1, P58, P121, P154, P230
Dodick, D.W P2, P14, P111, P352
Doelger, Z.W P180
Dolezil, D P83
Donaldson, S P250
Dondas, A P282, P359, P379
Donepudi, R.V P225
Dong, C P178
Donnelly, M P431
Donnet, A P169
D'Onofrio, F P17, P228
Dorsch, A P362
DosSantos, M.F P200, P283, P322
Driscoll, M.A P395
Ducros, A P402, P403
Duggan, D.T P266
Duminskaya, M P270
Durbin, D P362
Durham, P P67
Durko, A P144
Dusaran, M P424
Dussor, G P313
Dussor, G.O P352
Dux, M OR6
Dyb, G P166, P168, P243
Ebine, T P226, P328, P339, P345
Ecklund, D.J P128
Eda, T OR3
Edvinsson, L P320, P346
Eftekhari, S P320
Egeo, G P171, P336
Eikermann-Haerter, K P314, P315, P335, P374
Eisenach, J.C P125
Elchami, Z P79, P385, P424
Eller, M P63
Elliott, M.B OR4
Ellison, J.B P192
Engstrøm, M P329, P334
Eraslan, D P233
Eriksson, N OR18
Erling, T OR21
Eroglu, E P72, P235
Ertas, M P177
Ertsey, C P219
Esposito, F P47
Esposo, E P35
Eun, B.-L P249
Eun, S.-H P249
Eyde, N P352
Fadic, R P32
Fahrenkrug, J P358
Fanning, K P60, P61, P65
Fanning, K.M OR9, OR28
Fartushna, O.Y P428
Fataki, M P213
Fataki Likale, M P45, P280, P341
Fayed, D P385
Fernandez-Cadenas, I P210, P212
Fernandez-Morales, J P210, P212
Ferracini, G.N P68
Ferrari, M.D OR10, OR15, P87, P90, P95, P133, P137, P197, P208, P216, P227, P314, P333
Ferreira, G.F P107
Ferreira, G.N P103
Fidanci, H P275
Files, J P230
Filho, P.F.M P107
Filiz, A OR7
Fillingim, R.B P221
Fimiani, C P413
Finkelman, M P223
Finos, L P213
Fischer, T P121
Florencio, L.L P56, P68, P78, P98
Fofi, L P171, P336
Fokin, I.V P160
Fontana, A P390
Ford, S P126
Foster, S P21
Fouad-Terazi, F P91
Franc, J P402
Francis, F.M P262, P299, P302, P304, P377
Frantal, S P89
Fredrick, J OR19
Freeman, M P433
Freitag, F P6, P25, P54
Freitag, F.G P48
Fried, N.T P311
Friedman, D.I P111, P279, P405
Fuh, J.-L P162, P163, P293, P317, P323
Fujii, N P218
Fujiwara, S P202
Funakubo, M P226, P328, P339, P345
Furuya, D P115
Furuyama, H P102
Galasso, D P413
Galdezzani, J.P P231
Galego, A.R P231

Gardener, H P178
Garza, I P384
Garza Martínez, A.T P361
Garza-Villarreal, E.A P361
Gaul, C OR8, P132, P135
Gelfand, A P175
Gelfand, A.A P241, P242
Geppetti, P P357
Gerdes, L P129
Geyer, H.L P386
Ghiotto, N P86
Giannotti, G P387
Giantomassi, M.C P78
Gil-Gouveia, R OR17
Ginoza, L P41
Giordano, G P259
Glorioso, P P390
Glümer, C P164, P165
Goadsby, P P121
Goadsby, P.J OR14, OR19, OR-WA, P14, P63, P84, P86, P93, P141, P241, P242, P307, P310, P312, P326, P348
Goicochea, M.T P32
Goksan Yavuz, B P391
Gold, M P26
Goldstein, J P12, P26, P58
Gomez, S P400
Gonçalves, A.L P122, P148
Gonçalves, M.C P56, P68, P78, P98
González, M P62
González-Gutiérrez, J.L P397
Goodman, A OR8, P132, P135
Gordon, J P365
Gordon, S P33
Goto, M OR24
Gottesman, R.F P170
Gould, L P321
Goulet, J P395
Gower, B.A P214
Grabova, S P113
Graff-Radford, S P15
Grande, R.B P423
Gratz, K.L P75
Gravdahl, G.B OR21
Gray, S P28
Grayzel, D P367, P370
Grazzi, L P49, P74, P338
Greco, R P354
Green, L P80, P294, P416
Green, M P15
Green, M.W P147
Grewal, T.S P42, P43, P46
Griesser, J P7, P12
Grosberg, B.M P46, P386
Grossman, T.B P238
Grubenhoff, J P248
Guaschino, E P86, P196
Guerra, C P57
Guerrero, A.L P347, P397, P426, P432
Guidetti, V P246, P251, P261, P274, P277
Güler, G P263, P271
Guo, S OR11
Guo, Z P237
Gupta, S P355, P356
Guyuron, B P119
Haan, J OR10, P95, P133, P137, P216
Håberg, A P319
Hagen, K OR21, P168, P319, P329, P334
Hagen, M P26
Haghdoost, F P173, P185, P193, P204
Haider, B P194
Hajiyeva, N P199
Hajj-Ali, R P427, P431
Hakyemez, B P50
Halker, R P1
Hall, C.B P190
Hall, T P322
Hamada, J P306, P378
Hamada, Y P378
Hamer, J.D OR20, P396
Hammond, E.R P214
Han, S.R P325
Hands, A P48
Handy, T.C P321
Hansen, A.E OR2
Hansen, J.M P93, P331, P358
Harding, T.M P69
Hargreaves, R OR14
Hariz, M OR12
Hashemirad, F P127
Haskell, S.G P395
Hastriter, E P154
Hatef, B P127
Hayashi, T P115
Hay-Schmidt, A P356
Haythornthwaite, J.A P170, P214
He, J.-P P170
He, L P343, P344
Heber, A P327
Heir, G.M P150
Helenius, J P335
Hernández-Díaz, S P397
Herrero, S P347, P426
Herrero-Velázquez, S P432
Hershey, A.D OR26, P128, P188, P248, P252, P254, P257, P267, P268
Hirata, K OR3, P105, P110
Hirata, K.H P76

Hishida, R P436
Hoang-Tienor, A OR25
Hoffman, J.M P364
Hoffmann, J OR14, P307, P310, P326
Hoffmann, M.B P316
Hoggan, R.N P284
Holick, M.D P266
Holle, D P143, P327, P340
Holme Hansen, E P164, P165
Holmen, J P222
Holmen, T.L P168
Holroyd, K.A P393
Holt, J.L P221
Honda, M P409
Honda, N P373
Honningsvåg, L.-M P319
Hooper, D.C OR4
Horn, P P252
Hougaard, A OR2, P316
Houle, T.T P75, P125, P129, P174
Hsu, C.Y P401
Hudry, E P314
Huh, B P58
Hunt, M P230
Hunter, J.A P36
Huston, C P36
Huynh, C.H P175
Hyson, M P131
Iacovelli, E P53, P255, P332
Ibrahimi, K P227
Iezzi, E P213
Iijima, K P380
Ilgaz Aydinlar, E P233, P391
Imai, N P206
Incesu, C.E.M P233, P391
International Headache Genetics Consortium OR18
Ishikawa, T OR3
Issa, M.B P79
Ito, Y P142
Iwanami, H P110
Iwashita, T P226, P328, P339, P345
Jabarra, C.P P107
Jacobs, D P59
Jacobsen, L.M P166, P222
Jacobson, A.S P175
Jaffe, K.M P362
Jahangiri Noudeh, Y P425
Jansen-Olesen, I P355, P356
Jaramillo, E P420
Javanmard, S.H P173
Jean Henri, R P117
Jennings, C P21
Jensen, R OR8, P132, P135, P199
Jensen, R.H OR11, P164, P165, P219
Jessel, S P264
Jevoux, C.C P10, P112, P184, P388
Jian, P P237
Jimenez-Chinea, R P433
John, S P159, P427, P431
Johnson, A P269
Johnson, T P365
Johnston, M.M P85
Jones, J.M P157
Jones, R.T OR1
Jordan, M.J P221
Jordan, S.E P85
Joshi, S P145
Joshi, S.G P9
Jurno, M.E P103, P244
Kabbouche, M P188, P252, P257
Kabbouche, M.A P254, P267
Kacperski, J P254, P257, P267
Kairalla, J.A P221
Kaiser, E.A P209
Kaiser, R P400
Kaku, H P353
Kalidas, K P1, P154, P300
Kanavakis, G P39
Kanazawa, N P378
Kang, D P221
Kang, T.-H.H P77, P120
Kaniecki, R P94
Kaniecki, R.G P167
Kantor, D P66, P389
Karakiliç, S P275
Kardon, R.H P209
Karli, N P34, P50
Kashikar-Zuck, S OR26
Kato, Y P115, P142
Katsarava, Z P143, P327, P340
Katz, B.J P284
Katz, M.J P190
Kaufmann, D OR5, P151
Kawabata, S P292
Kawamata, R OR24
Kayama, Y P328, P339, P345
Kedia, S P248, P253
Keilman, A P247
Keles, F P314
Kellerman, D P15, P24, P28
Kellstein, D P422
Kempe, A P248, P253
Kempner, J P181
Kernmayer, M P245
Keselman, I P324
Keyvani, M P73
Khalil, M P71, P146, P375, P376, P437
Kikuchi, T P373
Kim, B.K P97

Kim, B.-K OR13, P31
Kim, H.-W.W P77, P120
Kim, H.-Y P408
Kim, J.-M OR13, P31
Kim, M P296
Kim, W.-S P249
Kim, Y.-O P249
King, C.D P221
Kisialiou, A P213
Kitagawa, Y P380
Kitamura, E P306, P378
Klein, B.C P111
Kline, M.T P149
Knackstedt, H.K P415
Knake, S P143
Ko, M P230
Kobayashi, H P436
Koekoek, B.K P333
Koeppe, R.A P322
Koppen, H OR15, P333
Korbee, L.L P128
Kori, S P15, P24, P25, P189
Kothari, S.D P309
Koutstaal, B P333
Kowa, H P217, P220
Krel, R P152
Krisht, K.M OR5
Kristoffersen, E.S P124
Krogh, A.-B P195
Kroner, J P257, P268
Kroner, J.W P128, P254, P267
Kruger, J OR25
Kruit, M.C OR15, P333
Kruja, J P113
Krymchantowski, A.V P10, P112, P184, P388
Kuburas, A P209
Kuchibhotla, K P314
Kulich, R P39
Kumar, S.R P129
Kuroshima, K P292
Kurth, T OR30, P186
Labruijere, S P215
Laender, V.R P244
Lagrata, S OR12
Laguerta, M.G.B P35
Lai, K.-L P317
Láinez, J.M OR8, P132, P135
Lal, S P291
Lambru, G OR12, P136
Lammers, G.J P197
Lampl, C P187, P194
Lantéri-Minet, M P132, P135, P169
Lara, O P309
Larrosa, D OR29, P52, P62
Larsen, V.A OR2, P316
Larsson, B P195
Larsson, H.B.W OR2, P316
Lattarullo, C P314
Launer, L.J OR15, P333
Lebel, A P260, P269
Lebron, D P266
LeCates, S OR26, P188, P252
LeCates, S.L P128
Lechner, A P187
Lee, C.-B P368
Lee, D.J P266
Lee, J.H P374
Lee, K.-H P249, P273
Lee, K.-S OR13, P31
Lee, S.B P325
Lee, S.W P129
Lennerz, J.K P342
Leonardi, M P109
Leston, J.A P32
Lettich, A P2, P154
Leubitz, A P265
Levin, L.S P192, P229
Levy, D OR16
Levy, W P300
Leyva, R P422
Li, X P15
Lieba-Samal, D P89
Lin, K.-H P163
Linde, M OR21, P86, P168, P183, P195, P319, P329, P334, P372
Linder, S P287
Linder, S.L P286
Lio, R P69
Lipton, R.B OR9, OR28, P7, P14, P42, P43, P44, P46, P60, P61, P65, P190, P199, P204
Lirng, J.-F P323
Lisotto, C P18, P298
Liu, G P405
Liu, L P205
Ljubisavljevic, S P410
Lo Noce, A P251, P274
Loder, E P5, P125
Londoño, L P57
López-López, A P397
Lopez-Mesonero, L P426
Louter, M P212
Louter, M.A P87, P95, P137, P197, P216
Love, T P322
Love, T.M P283
Lovell, B P154
Lu, B P24, P25, P28
Lu, P P237
Luca, A P282, P359, P379
Lucas, S P25, P200

Lucas, S.M P364
Lucchese, F P246, P251
Lucchese, S.A P100
Lundqvist, C P124, P234, P423
Luthringshausen, G P187
Luu, A.K.S P309, P318
Lyngberg, A.C P199
MaassenVanDenBrink, A P215, P227
Macaya, A P210, P212
Macci, J.P P107
MacGregor, E.A P234
Macolino, C.B OR4
Magalhaes e Silva, C.S P103
Magayano, D P385
Maggioni, F P134, P298
Magis, D P45, P213, P280, P289, P341
Mahmoud, R P4, P11, P23
Mainardi, F P134, P298
Majdoleslam, B P127
Majko, E P113
Maleki, N OR23, P260, P269, P337
Maloney, G P39
Manack, A.N P44, P60, P61, P65
Manaka, S P76
Mangano, S P390
Mangione, S.A P354
Maniyar, F P435
Maniyar, F.H OR-WA
Manning, P P188, P252
Manos, G P121
Manouchehri, N P173, P185, P193, P204
Marandino, R P106
Marchese, M P47
Marcus, R P121
Mardekian, J P205
Marfil Rivera, A P361
Mariano, B P35
Marin, J.C.A P141
Marinazzo, D P308
Markowitz, S P1
Markowitz, S.Y P154
Marmura, M.J P13
Marshall, S P172
Marske, V P60
Martelletti, P P315
Martikainen, I.K P283, P322
Martin, A.T P229
Martin, G.V P192
Martin, P.R P123
Martin, V.T P192, P229
Martinez, M.S P35
Martínez-Camblor, P P52
Martins, I.P OR17
Martins, M.L P244
Martins-Oliveira, M P307, P312
Maruki, Y P70, P142
Masjedi, S.S P185, P193, P204
Maslowski, E P322
Massaro, M P399
Massaro, M.M P57, P191, P281
Massoud, R P424
Masuda, R P306, P378
Materazzi, S P357
Matharu, M OR12, P136
Mathew, P P1
Mathew, P.G P2, P9, P145
Mathews, M P96
Matsuda, H P373
Matsumori, Y P202
Matsumoto, S OR24
Mauser, E P201
Mawet, J P402
May, A OR8, P132, P135
Mayboroda, O.A P208
Mayer, A P230
Mazman, S P72, P235
Mazza, M.R P285, P290
McAllister, P.J P360
McCrory, D.C P372
McDermott, M.J P75
McGuire, B P369
Meadows, K P21
Mechanic, J P59
Mecum, T P36
Medgyessy, Z P29
Mednick, T P152
Mehta, N P223
Meilán, A OR29
Meissner, A P208
Melemedjian, O P313
Melhado, E.M P231
Mello, M.T P108
Mendez, J.M OR5
Mendonça, A.P.P P106
Merikangas, K.R P170
Messali, A P189
Messina, J P4, P23
Messina, J.C P11
Messlinger, K OR6, P342
Mezzapesa, D P308
Micallef, J P169
Mickleborough, M.J.S P321
Mignolet, J.-Y P289
Mijo, S P113
Miller, R P119
Miller, S OR12, P136
Miller, W.J P94
Milovanovic Kovacevic, N.J P407
Milovanovic-Kovacevic, N P418
Mimura, T P373

Minen, M.T P393, P398
Minster, A P260
Mirambel, A P79
Mishra, L P155, P272
Mitchell, E P178
Mitrovic, A.V P38
Mitsufuji, T P142, P303
Mitten, E P172
Miyamoto, M P105
Miyamoto, T P105
Miyashita, K P239
Mody, I OR1
Mogilner, A P58
Mohammad, S P258
Mollik, M.A.H P207, P240
Momoi, M.Y OR24
Monica, V.S P362
Montaner, J P210, P212
Monteith, T OR-WA
Monteith, T.S P178
Montella, S P47
Montieth, D P367, P370
Moreira, C P349
Moreira Filho, P.F P244
Moriya, Y P218
Moscarelli, M P390
Moscato, D P27
Moscato, F.R P27
Moses, J P247
Moskowitz, M.A P315
Motaghi, M P173
Motegi, R P239
Mowls, D P276
Mowrey, W P190
Moynahan, V.L P75
Mulder, M.J.H.L P297
Mulero, P P432
Mulleners, W.M P372
Mullin, K P2, P147
Multon, S OR22
Munksgaard, S.B P219
Muñoz, I P397
Myren, M P356
Nacopoulos, D.A P159
Naegel, S P143, P327
Nagai, T P345
Nagata, E P218
Nägel, S P340
Nahas, S.J P88
Nakashima, K P217, P220
Nam, S.-O P249
Napchan, U P111
Nappi, G P86, P196, P278, P354
Nardello, R P390
Narouze, S P58
Nascimento, T.D P200, P283, P322
Nassini, R P357
Natali, F P169
Negro, A P314, P315, P335
Negru, A P379
Negru, A.L P282, P359
Neilson, J P22, P55
Nelson, T.D P257, P268
Nesbitt, A.D P141
Nett, R P54
Neuhuber, W.L OR6, P342
Newman, L P7
Ni, K P353
Nicholson, R.A P180
Nicolodi, M P138, P139
Niddam, D.M P317
Nishiyama, K P306, P378
Nobre, F P101
Nobre, M.E P148
Nojima, S P436
Norris, L.L P158
Nozaki, Y OR24
Numao, A P105
Nusser, J.I P342
Obermann, M P143, P327, P340
Obmann, S.-M P187
O'Brien, H P257
O'Brien, H.L P188, P252, P254, P267
O'Carroll, C.P P6
Ogel, K P391
Oh, K OR13, P31
Oh, M P296
Ojha, A P167
Öksüz, N P130, P263, P271, P275
Okuma, H P380
Olesen, J OR2, P316, P355, P356
Oliveira, A.B P108
Oliveira, A.G OR17
Olsen, K.S P358
Omboni, S P18, P19, P20
Omland, P.M P329, P334
O'Neill, C P7, P12, P21
Ordas, C.M P397
Ortiz, G.A P430
OShea, A P36
Oshinsky, M.L P311
Osipova, V.V P99
Ossipov, M.H P352
O'Sullivan, E.M P172
Ota, I P292
Oz, O P72, P235
Özal, S P275
Ozbek, S.E P50
Özge, A P114, P130, P263, P271, P275
Padamsee, A P236

Paemeleire, K P198
Paiva, E.S P224
Paletta, R P285, P290
Palm-Meinders, I.H OR15, P333
Palotie, A OR18, P212
Parikh, S P247
Park, J.E P181
Park, J.W P325
Park, K.-H.H P77, P120
Park, K.Y P335
Pascini, T.M P103
Pascual, J OR29, P52, P62
Patel, S P230
Paulsen, R P125
Pavlovic, J P2, P190
Pavlovic, J.M P42, P43, P44, P46
Pearlman, L P315, P335
Peatfield, R P382
Peck, K.R P396
Pedersen, L.M P166, P222
Pedraza, M.I P347, P426, P432
Pelliccia, A P171
Pellicoro, M P308
Pelzer, N P176, P216
Peñas, M.L P347, P432
Peng, K.-P P162
Penzien, D.B P174
Peres, M.F.P P51, P108, P122, P148
Peterlin, B.L P170, P214
Petersen, J P358
Petescia, M P277
Petretta, V P17, P228
Petty, S P322
Peugh, J P268
Pezzola, D P17, P18, P19, P20, P228
Picarelli, A P261
Pierce, M P7, P12, P21
Pierelli, F P53, P213, P332
Pierric, G P117
Pinessi, L P18, P394
Piovesan, E.J P224
Ploug, K.B P355
Pons, J P371
Poolman, P P209
Porporatti, A.L P305, P414, P417
Porreca, F P352
Porta-Etessam, J P397
Porter, J.A.H P174
Postma, R P208
Poulsen, K.T P371
Powers, S.W OR26, P128, P248, P254, P257, P267, P268
Pozo-Rosich, P P210, P212
Pradel, V P169
Pradhan, A.A.A P369
Presaghi, F P277
Pressman, A.R P175
Pripp, A.H P222
Pruitt, A.P P434
Puchimada, B P150
Quarantelli, M P47
Quarshie, V P375, P376
Quattrone, A P285, P290
Queiroz, L.P P231
Radhakrishnan, K P247
Rafiei, L P173
Raggi, A P109
Raieli, V P259
Rajpal, A P371
Ramachandran, R P355, P356
Ramalingam, V P315
Ramirez, A.C P381
Ramón, C P52
Ramos, E P205
Ranieri, A P47
Rao, R P291
Rasul, F OR12
Rausch, J OR26
Ravid, S P33
Rea, B.J P209
Ready, D.M P153
Recober, A OR25, P209, P309, P318
Reddi, S P411
Reed, D P119
Reed, K P58
Reed, K.L P286, P287
Reed, M.L OR9, OR28, P42, P43, P44, P46, P60, P61, P65
Regnerus, J P69
Reider, A.C P241, P242
Reiner, P.B OR27
Renger, J OR14
Resende, D.F P244
Rho, Y.-I P249
Ribeiro, G.A P224
Ribeiro, R.T P108, P122, P148
Richer, L P8, P22
Richer, L.P P55
Rigaux, P P289
Riggins, N.Y P63
Rijsman, R.M P197
Rist, P.M P186
Rivara, F.P P362
Rizzoli, P P5
Robbins, M.S P111, P225, P238, P386, P412
Robertson, C.E P2, P111, P384
Robinson, R.C P48
Rocha-Filho, P.A.S P116, P406
Rodríguez, C P432
Romundstad, S P222

Rosen, I P314, P315
Rosen, N.L P201
Rosenberg, J.D P170
Rosenow, F P143
Rossi, H.L P309, P318
Rossi, P P196, P278
Rosso, A.L P170
Rostrup, E P316
Rothner, A.D P247, P264, P265, P276
Rothrock, J.F P73
Rowe, B P8
Rowe, V.D P36
Rozen, T.D P149
Rozniecki, J.J P144
Ruiz, M P426
Rundek, T P178
Rupert, M.P P286
Russell, M.B P37, P118, P124, P234, P423
Russo, A.F P209
Ruttledge, M.H P141
Ryan, C P172
Saadatnia, M P173, P185, P193, P204
Sacco, R.L P178
Sahai-Srivastava, S P80, P182, P294, P416
Sahota, P P100
Saiz, A OR29
Sakai, F P70, P142
Saladino, M P390
Šaltyte-Benth, J P124
Salvati, A P308
Salvi, E P251, P261, P274
Salvino, D P285, P290
Sampaio, F.A P150
Sances, G P86, P196
Sanchez, P.A P399
Sand, T OR21, P329, P334
Sàndor, P.S P213
Sandoval, V P138, P139
Sandrini, G P354
Santamarta, E OR29
Santamorena, G P392
Santangelo, G P259
Santiago, M P178
Sara, Y OR7
Sarov, M P402
Sasso D'Elia, T P45, P213, P280, P289, P341
Sato, H P328
Saunders, G.H P151
Sava, S.L P45, P280, P289, P341
Savi, L P18, P394
Sawant, P.M OR5
Schankin, C OR-WA
Schankin, C.J P63
Scheman, J P96
Scherer, J P367, P370
Schick, D P412
Schiff, A P33
Schim, J P111
Schmid-Ott, G P29
Schoenen, J OR8, OR22, P45, P132, P135, P213, P280, P289, P341
Schoonman, G.G P90, P197
Schuetz, T P367
Schüler, M OR6
Schulman, R.A P81
Schulz, N.A OR5
Schwartz, D.P P43
Schwedt, T P1, P154, P230
Schwedt, T.J P2
Schweiger, C P187, P194
Schytz, H.W OR11
Scola, R.H P224
Scrivani, S P39, P223, P337
Segers, A P188, P252
Seidel, J P315
Seiler, K P342
Selb, J OR11
Selekler, M.H P179
Sener, D.K P50
Seng, E.K P393, P395
Sengul, B P314, P374
Sergeev, A.V P99
Serrano, D OR9, P42, P43, P44, P46, P60, P61, P65
Sette, G P17, P228
Shahar, E P33
Shanahan, P P136
Shand, B P32
Shapiro, R.E OR27
Sharan, A P58
Sharma, S P30
Sheikh, H.U P9, P145, P421
Shelton, D.L P371
Shevel, D P161
Shevel, E P161
Shibata, M P226, P328, P339, P345
Shimazu, T P142
Shimizu, T P76, P226, P328, P339, P345
Shimohata, K P239
Shimohata, T P239
Shin, H.E P325
Shorser-Gentile, L P315
Sierra, J.M P347
Sigman, E P41
Silberstein, S P58
Silberstein, S.D P7, P13, P14, P111
Siller Reyes, M.F P361
Silva, Jr., A.A P184
Sinacore, J P291
Siva, A P245

SJM Chronic Migraine Study Investigators P58
Slavin, K P58
Smith, T.R P180
Smith, Y.R P322
Smitherman, T.A OR20, P75, P174, P396
Snopkova, E.V P99
Solano, J.M P281
Sollars, C.M P42, P43, P46
Sood, R P30, P150
Souza, J.A P103
Spasic, M P410
Speciali, J.G P56, P68, P78, P98, P101, P232
Spierings, E P223
Spierings, E.L.H P236, P297, P301, P360
Spinner, W P152
Spitaleri, C P259
Sprenger, T OR-WA, P348
Sretenovic, S.L P38
Stakic, J P167
Standley, K P433
Stanic, A.I P38
Starling, A.J P14
Stefanidou, M P147
Steiner, T P183
Steiner, T.J P179, P245
Stensland, S.Ø P243
Stepanova, I P270
Stewart, K.S P363
Stijnen, T P90
Stillman, M P91, P427
Stock, D P121
Stojanov, D P410
Stokes, A P349
Stokes, H P349
Stolk, L P215
Stovner, L.J OR21, P319
Straand, J P124
Stramaglia, S P308
Strop, P P371
Stuginski-Barbosa, J P232, P305, P414, P417
Sullivan, A.K P211
Sullivan, S P257, P268
Sullivan, S.M P128, P254, P267
Sunagawa, Y P150
Supronsinchai, W OR14, P326, P348
Suzuki, K P105
Suzuki, N P226, P328, P339, P345
Suzuki, S P105
Sweeney, B P172
Sylvie, C P117
Tabeeva, G.R P99
Taimoorazy, B P419
Taiwan Stroke Registry Investigators P401
Tajaddini, M P173
Tajti, J P346
Takagi, K P436
Takashima, R P105
Takigawa, H P217, P220
Takizawa, S P218
Takizawa, T P328, P339, P345
Tanahashi, N P115, P142
Tannous, R P79
Tarantino, I.S P36
Tarantino, S P255, P256
Tarash, I P369
Tasdelen, B P114, P263, P271
Tasdemir, S P72, P235
Taskapilioglu, O P50
Tassorelli, C P86, P278, P354
Tat, T P223
Tatsumoto, M OR3, P110
Tavares, N.F.P P103
Teernstra, O.P.M P137
Tegeler, C.H P129
Tegeler, C.L P129
Tekes, K P219
Teles, M.C.M P107
Temkin, N P362, P364
Tepe, N OR7
Tepper, S P96, P189, P427
Tepper, S.J P214
Terwindt, G.M OR15, P87, P90, P95, P133, P137, P176, P197, P208, P212, P216, P227, P333
Tfelt-Hansen, P P3, P383
Thaler, R.E P229
Thekkootu, N.P P146
Thekkootu Pisharam, N P71
Theriot, J P330
Theriot, J.J OR5
Theysohn, N P340
Thomas, D P30
Thoresen, S P243
Thyssen, D P314
Tietjen, G.E P214
Toghae, M P127
Tokuoka, K P380
Tomkins, E P141
Toriumi, H P226, P328, P339, P345
Toros, F P130, P263, P271
Torres, R.C.S P406
Torrini, A P138, P139
Tran, D.P P360
Tranquilli, C P171
Triggiani, L P387, P392
Trimboli, M P285, P290
Tripathy, A P155
Tripathy, A.K P272
Trotta, G P308
Tsai, K P189

Tufik, S P108
Tull, M.T P75
Tullo, V P17, P19, P20, P228
Turkel, C.C P44
Turkish Headache Prevalence Study Group P177
Turner, D.P P129, P174
Turner, I.M P67, P69
Tyburski, A.L OR4
Tye, A.E P209
Uchino, K P427, P431
Uglem, M P329, P334
Ugurlu, C P80, P182, P294, P416
Ugurlu Uludüz, D P245
Uitterlinden, A.G P215
Ulas, U.H P72, P235
Uluduz, D.U P130
Umlas, E P385
Unekawa, M P226
Unlu, E P350
Unno, Y P404
Ura, S P292
Usai, S P49, P74
Uygunoglu, U P245
Vaisman, J P58
Valastro, C P277
Valença, M.M P156
Valenzuela, R P32
Valeriani, M P255, P256
Valerio, R.C P244
Valguarnera, F P17, P228
van Buchem, M.A OR15, P333
van den Maagdenberg, A P212
van den Maagdenberg, A.M P314
van den Maagdenberg, A.M.J.M P216
van den Meiracker, A.H P227
van der Geest, J P333
van der Maagdenberg, A.M.J.M P208
van der Sar, S.A P208
van der Willik, D P176
Van Hecken, A P367, P370
van Holsbeeck, H P200
van Noorden, M.S P87
van Oosterhout, W.P P227
van Oosterhout, W.P.J P87, P90, P95, P197, P208
van Someren, E.J.W P197
van Zwet, E.W P87, P90, P95
Vanadia, F P259
VanOwen, K.R P36
VanValkenburgh, P P331
VanValkenburgh, P.G P351
Vargas, B P230
Vargas, J.R OR5
Vatankhah, N P425
Vaughan, P P188
Vaughn, P P252
Vecchio, E P308
Vecsei, L P346
Vega, J P52, P62
Verbiest, M.M.P.J P215
Vermeersch, S P367, P370
Vetvik, K P124
Vetvik, K.G P234
Viana, M P86
Viganò, A P45, P213
Vigevano, F P255, P256
Vila-Pueyo, M P210, P212
Villate, S.G P430
Vintayen, E.V P386
Volcy, M P57, P191, P281, P381, P399, P420
Vollbracht, S P411
Vollbracht, S.E P42
Vongvaivanich, K P429
Wagner, G P245
Wainger, B P5
Wallace, B P253
Walters, A.B OR20
Wang, H P237
Wang, J P362
Wang, P P343, P344
Wang, S.-J P162, P163, P293, P317, P323, P401
Wang, S.L P182
Wang, Y P237
Wang, Y.-F P293, P323
Warabi, T P102
Ward, T.N P214
Warfvinge, K P346
Warner, J.E.A P284
Watanabe, Y P105
Wayne, P P125
Wei, X P313
Weibelt, S P73
Weller, C.M OR10
Wells, R P1
Wells, R.E P2, P125
Wentzel-Larsen, T P243
Wermer, M.J.H P176
Werneck, L.C P224
Westergaard, M.L.S P164, P165
White, L.W P214
White, M.K P185
White, S P188, P252
White, S.H P151
White, S.K P128
Wienecke, T P358
Wilbrink, L.A OR10, P95, P133, P137
Wilcox, K P151
Will, K P286, P287
Willems, S P198
Williams, M.A P170

Winegarner, D.M P36
Winner, P P25
Winrow, C.J OR14
Winsvold, B P212
Winsvold, B.S P166, P222
Wisdom, P P363
Wöber, C P245
Wöber-Bingöl, Ç P245
Woeber-Bingoel, C P89
Woeber, C P89, P187
Wollmann, D.R P224
Woo, S.B P273
Worley, A P247
Wright, C P178
Wurm, W P187
Wuschitz, A P187
Yalcin, N P314, P315, P374
Yalinay Dikmen, P P233, P391
Yamagata, T OR24
Yamaguchi, S P373
Yamazaki, K P436
Yao, L P64
Yasuda, T P380
Yeomans, D.C P59
Yildirim, V P130, P263
Yohannes, E P119
Yoo, T.-W.W P77, P120
Yoshida, K P292
Young, W.B P111, P181
Yu, E.S P314, P315, P374
Yucel, M P235
Zanchin, G P18, P134, P298
Zandifar, A P173, P185, P193, P204
Zandifar, E P173, P185, P193, P204
Zandifar, S P173, P185, P193, P204
Zaric, N.L P407, P418
Zarifoglu, M P34, P50
Zava, D P17, P18, P19, P20, P228
Zebenholzer, K P89, P187
Zekja, I P113
Zesch, H.-E P245
Zhao, J OR16
Zheng, Y P96, P374
Zhou, L P91
Zielman, R P208
Zitman, F.G P87, P95
Zonderman, A.B P170
Zoukhri, D P223
Zrinzo, L OR12
Zubieta, J.K P283
Zubieta, J.-K P322
Zuluaga, M.I P191
Zwart, J.-A P166, P168, P212, P222, P243
Zyuzin, J P324

Program Keyword Index

5HT 1B/1D agonists P5, P9, P18, P19, P20, P169, P205, P310, P358
Abortive therapy P1, P13, P22, P81, P131, P141, P146, P154, P180, P182, P434
ACM P418
Acute OR2, P141, P282, P349, P359, P379, P433
Acute migraine therapy OR14, OR19, P1, P2, P3, P4, P6, P7, P9, P10, P12, P13, P14, P16, P17, P21, P26, P29, P67, P121, P126, P180, P183, P228, P238, P252, P358
Acute therapy P2, P111, P172, P205, P238, P357, P425
Acute treatment P1, P8, P54, P131, P159, P191, P248
Adolescent P195, P245, P269, P277
Adolescent migraine P8, P22, P55, P128, P188, P250, P252, P254, P255, P257, P263, P268, P271, P273, P286, P287, P366
Adolescents P243, P248, P362
Adverse events P25, P372, P386, P426
Almotriptan P18, P19, P20
Alternative P29, P41, P207, P387, P425
Analgesics P165, P183, P283, P325, P364
Anger P251
Angina OR28, P429
Basilar P9
Behavior OR7, OR27, P101, P151, P209, P240, P263, P268, P282, P311, P313, P338, P352, P365, P369, P379, P397, P398
Behavioral treatment P48, P96, P123, P125, P368, P392, P399, P400
Biomarkers P55, P138, P139, P178, P208, P214, P218, P219, P221, P222, P224, P330
Botox P69, P71, P83, P375, P376, P384, P437
Botulinum toxin P117, P120, P297, P384
Botulinum toxin A P67, P71, P74, P152, P375, P376
Botulinum toxin type A P71, P83, P144, P381, P437
Brainstem OR-WA, P156, P300, P328, P350, P355
Calcium channel P314
Cavernous angioma P145
Central sensitization OR4, P53, P56, P70, P137, P280, P341, P369
Cervicogenic headache P64, P85, P118, P272, P415, P419
Cervicogenic migraine P85, P366, P385
CGRP OR4, P52, P67, P121, P209, P215, P223, P227, P320, P342, P352, P355, P356, P357, P367, P370
Childhood OR24, OR25, P33, P130, P195, P244, P245, P249, P250, P252, P253, P256, P267, P269, P270, P272, P273, P275, P362
Chronic daily headache P31, P33, P34, P35, P36, P38, P47, P55, P79, P116, P149, P284, P285, P325, P366, P375, P410, P416, P421, P424, P437
Chronic headache OR12, P37, P39, P40, P41, P96, P124, P138, P164, P165, P191, P199, P206, P242, P281, P360, P363, P399, P407, P419, P420
Chronic migraine OR9, OR26, OR29, P27, P34, P37, P42, P43, P44, P45, P46, P48, P49, P51, P52, P53, P54, P55, P57, P58, P62, P63, P64, P66, P67, P68, P69, P70, P71, P72, P73, P74, P78, P82, P83, P109, P181, P191, P201, P216, P224, P232, P242, P254, P281, P311, P338, P347, P369, P371, P375, P376, P378, P381, P386
Chronic pain P43, P232, P297, P305
Chronic tension-type headache P34, P37, P424
Classification P44, P102, P114, P133, P234, P298, P413, P420
Clinical P84, P86, P96, P108, P121, P207, P284, P291, P367, P370, P401, P411, P412
Clinical characterization OR17, P86, P91, P93, P102, P107, P114, P130, P171, P188, P255, P259, P261, P270, P292, P296, P297, P301, P330, P331, P398, P406, P414, P428, P430, P431, P436
Cluster P85, P143
Cluster headache OR10, OR11, P95, P133, P134, P137, P142, P143, P144, P145, P146, P148, P156, P327, P382
Cognitive constructs OR27, P274
Cognitive impairments OR17, P50, P190, P237, P321, P366
Comorbidity P42, P43, P75, P87, P95, P130, P163, P167, P170, P197, P229, P246, P258, P271, P302, P305, P335, P394, P395, P417
Convergence P304
Cortical excitability OR15, P53, P280, P283, P314, P315, P321, P332, P334, P335, P374
Cortical spreading depression (CSD) OR1, OR5, OR7, OR22, P151, P226, P288, P306, P308, P314, P315, P316, P324, P331, P339, P348, P353, P374, P378
Cost-effectiveness P81, P203
Daily headache P435
Daily triptans P169, P361

Demographics OR9, OR28, P46, P172, P201, P207
Depression P43, P87, P95, P96, P123, P137, P237, P240, P251, P274, P398
DHE P3, P15, P24, P25, P28, P63, P84, P136
Diagnosis P39, P44, P103, P133, P148, P161, P174, P184, P202, P223, P225, P297, P301, P349, P363, P405, P415
Dietotherapy P307, P312
Disability OR17, P33, P46, P46, P68, P69, P78, P96, P109, P171, P181, P196, P246, P261, P277, P387
Disease modification P6
Divalproex sodium OR7
Dizziness P76, P92, P97, P98, P177, P271, P363
Doctors P116, P160, P201
Domestic violence P243
Double-blind study P26
Drug effects P139, P327, P372, P382, P426, P436
Drug interaction P5, P75
Drug treatment P1, P151, P203, P269, P381, P388, P422, P426, P435
Economics P153, P183, P201
Education P2, P154, P160, P161, P198, P201
Educational model P159
Efficacy P26, P84, P96, P132, P387
Epidemiology OR13, OR24, OR25, OR30, P60, P61, P65, P66, P95, P163, P164, P165, P167, P168, P169, P170, P171, P175, P176, P178, P183, P186, P187, P188, P190, P192, P195, P196, P197, P199, P200, P201, P202, P207, P216, P234, P243, P246, P248, P319, P362, P363, P423, P427
Episodic headache P6, P42, P43, P46, P54, P125, P126, P130, P181, P214, P280, P322, P341, P389, P422, P433
Estrogen P215, P226, P227, P234
Facial pain P39, P150, P152, P221, P223, P282, P297, P299, P301, P346, P359
Familial hemiplegic migraine P314, P384
Family P257, P393
Frovatriptan P17, P18, P20, P228
Gabapentin P389
Gabapentine P432
Genetic markers OR18, P173, P210, P211, P212, P216, P217, P220, P223
Headache OR13, OR14, OR16, P30, P31, P35, P64, P89, P94, P100, P101, P108, P113, P129, P140, P144, P154, P155, P171, P175, P179, P184, P195, P196, P222, P249, P265, P269, P276, P279, P289, P295, P313, P319, P321, P322, P323, P352, P360, P362, P363, P400, P419, P428, P433
Headache diagnosis P77, P102, P120, P150, P172, P176, P213, P225, P230, P290, P347, P349, P403, P409, P430, P435, P436
Headache disorders OR4, P85, P104, P116, P256, P292, P298, P406, P409, P411, P421, P429, P436
Headache education P156, P159, P160, P278
Headache impact P102, P173, P180, P232, P246, P284, P427
Headache practice P153, P157, P158, P185, P193, P204, P206
Hemicrania continua P149, P275, P300, P426, P437
History P99, P155, P156, P335
Hormones OR22, P166, P226, P307
Hypothalamus OR-WA, P197, P307, P312
Hypothesis OR11
Hypoxia P146, P430
Impact OR17, P87, P179, P181, P245, P273, P333
Indirect costs OR17
Inflammation OR4, P207, P240, P282, P313, P318, P359, P379
In-hospital consultation P159, P191
Insomnia OR20, P31, P360
Internet P246
Iron P146
Ischemia P162, P333, P428, P431
IV therapy P191, P266
Lamotrigine P374
Lumbar puncture P47, P290, P295, P323
Medication overuse P49, P153, P169, P172, P325, P375
Medication overuse headache P32, P38, P45, P164, P165, P219
Medications P1, P182, P422
Memory P363, P398
Menstrual cycle P226, P231, P236
Menstrual migraine P228, P231, P234, P235, P236, P237, P239
Meta-analysis P372
MIDAS P46, P106, P127, P233, P391, P399
MIDAS score P69, P102, P387
Midbrain reticular formation P326
Migraine OR1, OR3, OR7, OR9, OR14, OR15, OR17, OR18, OR19, OR-WA, OR21, OR24, OR25, OR28, P3, P9, P15, P18, P19, P20, P23, P24, P25, P28, P30, P36, P50, P57, P75, P76, P78, P84, P85, P87, P89, P90, P91, P97, P101, P103, P105, P106, P107, P112, P114, P116, P123, P130, P137, P162, P163, P166, P169, P170, P175, P178, P182, P184, P189, P190, P194, P197, P199, P200, P208, P209, P211, P213, P214, P216, P222, P229, P230, P232, P233, P236, P244, P245, P247, P251, P253, P259, P274, P289, P296, P306, P309, P312, P314, P315, P316, P317, P318, P320, P321, P322, P326, P328, P329, P332, P333, P334, P335, P336, P337, P340, P343, P345, P353, P354, P355, P356, P357, P360, P367, P368, P373, P374, P383, P389, P391, P392, P393, P394, P433, P436
Migraine and mixed headache disorders P120, P404, P419
Migraine costs P160
Migraine headache OR2, OR23, P36, P44, P81, P99, P115, P121, P175, P230, P243, P269, P296, P351, P352, P396

Migraine impact OR27, P167, P181, P202, P254
Migraine phases P93, P334, P341
Migraine prophylaxis P73, P82, P100, P110, P122, P125, P151, P183, P284, P371, P372, P375, P380, P381, P382, P384, P387, P388
Migraine rescue medication P380
Migraine with aura OR1, OR19, P36, P80, P86, P88, P93, P100, P162, P218, P237, P250, P279, P288, P308, P315, P316, P331, P335, P340, P348, P350, P384, P416
Migraines OR13, OR30, P11, P154, P161, P174, P186, P192, P226, P231, P250, P267, P370, P373, P390
Migrainous P76, P296
Migrainous headache P420
Misdiagnosis P120
Mitochondria P311, P379
Naratriptan P142, P239
Nasal spray P23, P59
Neurocognition P50, P321
Neurosarcoidosis P420
New daily persistent headache P420
Nitric oxide P310, P342
NSAIDs P16, P17, P59, P203, P228, P422
Number needed to treat P372
Opioids P39, P73, P180, P283
Outcome P57, P99, P153, P191, P240, P281, P419, P427, P428
Outcomes research P13, P48, P99, P180, P189, P203, P372, P387, P401
Pain-free P134, P389, P426
Paroxysmal headache OR12, P150, P264, P275
Pathophysiology OR2, OR5, OR7, OR11, OR15, OR16, OR-WA, P53, P62, P91, P209, P213, P221, P227, P255, P300, P306, P307, P308, P308, P309, P311, P313, P316, P317, P318, P320, P326, P332, P333, P338, P340, P346, P347, P348, P354, P358, P378
Patient preference P2, P107, P116, P206
Pediatric OR24, P195, P242, P248, P258, P260, P267, P362, P390
Pediatric migraine P8, P22, P55, P128, P241, P242, P250, P255, P256, P258, P259, P262, P263, P266, P271, P275
Periaqueductal gray OR-WA, P350
Peripheral nerve stimulation P58, P281, P289
Personality P253, P392, P397
Pharmacoeconomics P203, P205
Pharmacoeconomy P183, P205
Pharmacokinetics P367
Pharmacology OR14, P151, P357, P358, P369, P370, P378, P389
Placebo P283, P377
Preference P393
Prevention P45, P57, P94, P172, P207, P281, P381, P428
Preventive P6, P45, P54, P141, P370, P386
Primary afferents OR16, P221, P313
Primary care P106, P172, P206, P364
Prodrome P71, P87, P90, P194
Productivity P179
Prolonged aura P86, P314, P435
Prophylactic therapy OR21, P58, P66, P72, P81, P289, P345, P376, P378, P379, P383, P390
Prophylactic treatment OR12, P34, P127, P140, P149, P368, P371, P374, P380
Prophylaxis P76, P106, P311, P386, P389
Prophylaxis therapy P142, P357, P371, P373, P376
Psychological P43, P75, P393
Psychological factors OR13, OR20, OR27, P66, P108, P240, P243, P253, P257, P391, P392, P395, P397, P398
Psychological treatment P39, P392, P399, P400
Psychophysiology P221
Quality of life P94, P98, P125, P180, P232, P240, P245, P254
Randomized controlled trial OR8, P26, P37, P58, P118, P122, P123, P125, P127, P135, P284, P422
Refractory headache OR12, P57, P57, P117, P152, P286, P419
Refractory migraine P47, P64, P127, P252, P281, P433
Response rate P184
Rizatriptan P18, P19, P20, P361
rTMS P45, P329, P334
Self-efficacy P125
Sensitization P16, P47, P137, P309, P313, P327
Serotonin OR22, P5, P431
Serotonin receptor P353
Sinus P298
Sinus headache P192
Sleep P31, P82, P95, P105, P257, P263, P315, P360, P398
Sleep apnea P31, P36
Sleepiness P31, P36
South India P304
Spectrum of headaches P291, P420
Spine P149, P415
Spontaneous intracranial hypotension P303
Stroke OR28, OR30, P42, P88, P113, P162, P319, P335, P401, P402, P407, P409, P418, P427, P428
Subdivision P44
Sumatriptan P4, P7, P9, P11, P12, P21, P205, P352, P434
Symptomatology P268, P340, P406
Symptoms OR9, P90, P91, P114, P143, P296, P336
Telephone calls P158
Tension-type P106, P116
Tension-type headache OR24, P123, P130, P166, P192, P199, P218, P243, P245, P263, P271, P344, P360, P422, P423, P425, P430

Tension-type headaches P161, P174, P184
Therapeutic gain P361, P400
Therapy P15, P24, P25, P28, P49, P74, P84, P134, P141, P144, P171, P189, P282, P283, P297, P354, P359, P361, P373, P414
Thunderclap headache P293, P402, P403, P418, P421, P431
Topiramate P374, P435
Transcranial magnetic stimulation OR19, P14, P45, P288
Transdermal P7, P12
Transformation OR9
Transformed migraine P55
Treatment OR12, P23, P37, P39, P47, P83, P106, P111, P118, P131, P147, P151, P152, P184, P238, P258, P284, P285, P383, P393
Trexima P126
Trigeminal ganglion OR4, OR6, P59, P215, P320, P328, P339, P342
Trigeminal nerve OR10, OR16, P23, P30, P119, P150, P152, P294, P301, P306, P408
Trigeminal nucleus caudalis OR4, OR7, OR14, P30, P215, P311, P326, P327, P345, P355, P356
Trigeminovascular system OR6, OR11, P23, P30, P209, P221, P259, P306, P307, P312, P318, P320, P330, P336, P339, P340
Triptan P2, P9, P11, P17, P22, P23, P228, P358
Triptans OR28, P1, P2, P3, P13, P14, P30, P76, P154, P189, P205, P269, P361
Venous compression P270
Work loss P127, P181
Zolmitriptan P18, P19, P20, P361