ABSTRACTS

A054

Electrophysiological profile of FHM1 and FHM2 patients

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Background Familial hemiplegic migraine is associated with genetically dysfunctioning ion channels or pumps which is thought to facilitate cortical spreading depression and hyperexcitability. In the common forms of migraine the brain is characterised interictally by a habituation deficit in information processing. As the pathophysiological link between FHM and the former remains unproven, it seemed of interest to explore habituation in FHM patients.
Objectives As part of the EUROHEAD project, to assess habituation in genotyped FHM patients from the Danish population sample.
Methods In 9 FHM patients (5 FHM1, 4 FHM2, mutations R583Q, C1369Y and R763C, R202Q) and 7 healthy volunteers (HV) we recorded visual evoked potentials (VEP), intensity dependence of the auditory evoked potential (IDAP) and the nociception-specific blink reflex (nsBR).
Results FHM patients had a more pronounced habituation during VEP ($p = 0.007$) and nsBR recordings ($p = 0.023$) than HV. There were no significant differences for IDAP, but the slope tended to be steeper in FHM, despite quasi normal habituation at 80 dB. Pain thresholds (nsBR) were significantly higher in FHM patients ($p = 0.039$).
Conclusions Contrary to the common forms of migraine, FHM is not characterized by a deficient, but rather by an increased habituation in cortical/brain stem evoked activities. Although these results need to be confirmed, this suggests that pathophysiological mechanisms are different between FHM and migraine with or without aura.

A055

Prevalence of primary headaches and cranial neuralgias in men and women aged 55 to 94 years (Bruneck Study)

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Background Headaches are among the most common neurological disorders. Aim of the current study was to estimate the prevalence of all primary headaches and cranial neuralgias in the general community, thereby strictly adhering to the 2004 classification of the International Headache Society (ICHD-2).
Methods This evaluation was part of the prospective population-based Bruneck Study. During the 2005 follow-up, 574 men and women aged 55–94 years underwent extensive neurological and laboratory examinations involving a standardized headache interview designed to comply with ICHD-2 criteria.
Findings In the Bruneck Study population the lifetime prevalence of all primary headaches combined and of cranial neuralgias was 51.7% and 1.6%, respectively. Tension-type headache (lifetime prevalence, 40.9%) and migraine (19.3%) emerged as the most common types of headache and both showed a female preponderance (prevalence ratios, 1.3 and 3.3). Hypnic headache and trigeminal neuralgia occurred at rates much higher than previously assumed. In men and women aged 55 to 94 years the one-year prevalence of primary headaches was high at 40.5%. In this age range tension-type headache, migraine and trigeminal neuralgia all caused significant impairment of health-related quality of life (HRQoL).
Interpretation The Bruneck Study confirmed the high lifetime prevalence of primary headaches and cranial neuralgias in the general population and provides first valid prevalence data for all types of primary headaches based on 2004 ICHD-2 criteria. In the elderly primary headaches comprised a substantial health burden and caused significant impairment of HRQoL.

A056

Headache by Multiple Sclerosis (MS) and Sjogren Syndrome (SS) in the same Family

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Objectives This study intends to investigate the coexistence of headache and common clinical features of MS and SS, as observed between two heterozygote sisters.
Methods A 40-year-old female patient, who was diagnosed with major MS, has also been suffering from severe headache of various duration.
Results The 32-year-old sister of the above patient had developed SS confirmed by gland biopsies, but she also reported non pulsating headaches of different severity and variation alike her sister.
Conclusion It is likely that cephalalgia is a common neurological complication between various autoimmune diseases, such as MS and SS.

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B080

Nitrogelycerin induced delayed Sensitization of Meningeal Nociceptors mediated by GC-cGMP and pERK

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Systemic administration of the nitric oxide (NO) donor GTN triggers in migraine a delayed migraine. Mechanisms underlying this headache are unclear but may involve sensitization of meningeal nociceptors.

We used In vivo extracellular recordings made from the trigeminal ganglion of anesthesized rats to examine changes in the mechanical sensitivity of meningeal nociceptors in response to GTN, local manipulation of the GC-cGMP signaling cascade or local inhibition of ERK phosphorylation. Immunohistochemistry was used to examine dural pERK following GTN administration.

GTN, applied either IV or topically to the dura produced a progressive increased in the mechanosensitivity of meningeal nociceptors, an effect commencing 120–180 min following systemic infusion. Topical adminstration of GTN or SNAP, another NO donor mimicked the sensitizing effect of GTN infusion. Topical administration of cGMP, or a PDE-5 inhibitor mimicked the sensitizing effect of GTN while the PKG inhibitor ODQ blunted the GTN-induced sensitization. Systemic GTN administration doubled the number of ephrinB2-positive dural arterioles expressing pERK at 4 hours, while topical administration of PD98059 which prevents ERK phosphorylation blunted the sensitizing effect of GTN.

We propose that, in migraineurs, the delayed migraine headache evoked by GTN is mediated, at least in part by delayed mechanical sensitization of meningeal nociceptors and that this neuronal effect is dependent on local meningeal, non-vasodilatory action of the NO-PKG second messenger cascade, an effect that relies on endothelial pERK expression in meningeal arterioles.

B081

Functional condition of the trigeminal system in unilateral headaches

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The functional condition of the trigeminal systems is analysed in unilateral headaches before and after therapy. 42 patients with cervicogenic headache (CEH), 21 patient with a migraine and 14 patients with cluster headache (CH) are surveyed. Control group have made 20 person without a headache.

It was investigated to patients: intensity of a headache on the visual analog scale, neuroortopedic investigation, the blink reflex with an estimation of the latent periods (LP) of early (R1) and late (R2) components (on a background of a headache).

At CEH was detected decrease R1 and R2 on the side of a headache. Whereas at patients with a migraine the R2 components are increased from both sides. At patients with CH all LP are increased from the 'pain' side.

B082

Glycine receptors modulate neurotransmission in the trigeminocervical complex of the rat

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Objectives Strychnine-sensitive glycine receptors (GlyR) located in the spinal cord mediate inhibitory neurotransmission onto nociceptive neurons. We examined neurons activated by microiontophoretically applied L-glutamate and NMDA in the trigeminocervical complex (TCC) linked to middle meningeal artery (MMA) and V1 or V2 cutaneous receptive field afferents to determine whether they could be modulated by glycine and the GlyR antagonist strychnine.
Methods Extracellular electrical activity of wide-dynamic-range neurons ($n = 22$ in six rats) in the TCC, responding to brush and pinch on the cutaneous receptive fields, and to electrical stimulation of the MMA was recorded. Rats were anesthetized and their cardio-respiratory parameters were maintained within physiological limits.
Results Microiontophoretically applied glycine inhibited the neuronal response to L-glutamate (21/22 cells tested) and NMDA (6/6) in a dose-dependent manner, reaching significance at higher currents (generally <–100 nA; $P < 0.05$). When concurrently applied to the neurons with glycine, strychnine increased the depressed firing rate toward pre-glycine control levels in some cells stimulated by L-glutamate (8/15), and most cells stimulated by NMDA (4/5). Firing rates were excited above baseline levels evoked by L-glutamate (15/21) and NMDA (5/5) when strychnine was singularly applied. Glycine reversibly inhibited the neuronal response to cutaneous receptive field stimulation (6/10) and to stimulation of the MMA (12/14; $P < 0.05$).
Conclusions These data suggest that, like the analogous inhibitory $GABA_A$ receptors, GlyR may be involved in the pathophysiology of head pain and represent a target for anti-migraine therapeutics.

B083

Plasma nociceptin levels decrease after trigeminal stimulation

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Background Approximately 70% of neurones in the human trigeminal ganglion exhibit nociceptin immunoreactivity and express nociceptin receptor mRNA. In these cells nociceptin is colocalized with CGRP and substance P, marker peptides of the trigeminovascular system, suggesting a role for nociceptin in the regulation of neuropeptide release from trigeminal nerve terminals. In an experimental setting exogenous nociceptin dose-dependently inhibited neurogenic dural

vasodilatation, and human studies demonstrated lower circulating nociceptin levels in patients with migraine without aura and the active phase of cluster headache, arguing for a possible role of nociceptin in neurovascular headache.
Objective To examine the effect of trigeminal ganglion stimulation on circulating nociceptin levels.
Methods We performed the unilateral electrical stimulation of the trigeminal ganglion in the rat and used a radioimmunoassay method to assess nociceptin levels in the ipsilateral external jugular vein.
Results The stimulation of the trigeminal ganglion caused a significant decrease in nociceptin levels of the ipsilateral external jugular vein (1.74 ± 1.07 vs. 4.22 ± 0.019 pg/ml in sham-operated controls, $p < 0.001$). Pretreatment with sumatriptan or ergotamin prevented this decrease. Pretreatment with the Ca2+-antagonist nimodipine resulted in highly increased nociceptin levels (21 ± 1.32 pg/ml, $p < 0.01$).
Conclusion The stimulation of the trigeminal ganglion leads to a significant decrease of circulating nociceptin levels that can be prevented by 5-HT agonists. Whether this decrease is due to increased synaptic turnover, increased cleavage or any other mechanism, is yet to be clarified.

B084

Headache and pineal cysts: a case control study

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Objectives The aim of this study was to investigate the relationship between pineal cysts and headache and to determine the relevance of cyst size in this context.
Methods We conducted a case control study with chart review of patients who consulted the neurological department between 1999 and 2006. Patients with pineal cysts were identified and when available, the cyst diameter was measured. Control patients were randomly matched for age, sex, year of consultation and the existence of a brain scan. Headache diagnoses were identified on the basis of the patient records. The relationship between headache and pineal cysts was investigated by a Chi-square test. In patients with pineal cyst, the diameter of pineal cysts was compared between patients with and without headache (t-test).
Results 51 patients (41 f, 10 m) with pineal cyst were identified. 51% were suffering from headache (thereof 50% migraine). In the control group (no pineal cyst), only 25% had headache (thereof 31% migraine). There was a significant relationship between headache and pineal cysts ($p < 0.025$). Cyst diameter could be determined in 32 patients. We found no significant difference in diameter between the groups with and w/o headache (mean diameter 11.2 ± SD 3 mm versus 11.4 ± SD 5 mm).
Conclusion Our data provide evidence for a relationship between pineal cysts and headache. The existence of headache was not related to the cyst size. On the basis of these results, further prospective studies on the pathophysiological significance and mechanisms of headache related to pineal cysts are warranted.

B085

C-reactive protein levels in migraine patients is similar to that of controls

The Reykjavik Study

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Objectives C-reactive protein (CRP), a marker of inflammation is associated with cardiovascular disease. Risk of stroke and coronary heart disease is increased in migraineurs with aura. CRP has been suggested to be abnormal among migraineurs, possibly through repeated vascular inflammation. Migraineurs have been reported to have an overrepresentation of individuals with abnormal CRP (>3 mg/L) levels in a small study. We examined the proposed association in a large population-based study.
Methods We studied 2907 men and 1251 women (age 55.5, SD 9.1 years) who participated in the Reykjavik Study [1967–1996] and had serum available to measure hsCRP with standard assays. Migraine was diagnosed using a modified version of the IHS criteria, defined as two or more of the following symptoms: nausea/vomiting, unilateral location, photophobia, visual disturbance during/just before headache (visual aura), numbness on one side during/just before headache. Mean levels of CRP (log-transformed) were calculated using linear regression, adjusting for age and sex.
Results CRP was similar in migraineurs and controls (1.15 vs.1.28 mg/L, $p = 0.11$). Compared to controls, CRP was lower in migraineurs without aura, (1.28 mg/L vs. 0.93 mg/L, $p < 0.0013$) but similar in migraineurs with visual aura (1.28 vs. 1.36 mg/L, $p = 0.48$). CRP was higher in migraineurs with visual aura compared to migraineurs without visual aura (1.36 vs. 0.93 mg/L, $p < 0.0035$).
Conclusions In a population-based study of men and women, overall CRP levels were not associated with migraine status. Migraineurs without visual aura had significantly lower CRP levels both compared to controls and to migraineurs with visual aura.

C041

Comparative Study of the Referrals to Neurologists for Headache at the Adult's and Children's Emergency Departments of General Hospitals in Greece

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Aim of the study To compare the profile of headache in the pediatric ED with the corresponding adult ED and search out for possible discrepancies with the ICHD.

Patients and methods This is a comparative study of data recording from adults and children ED of two General Hospitals in Athens. Demographical and clinical data concerned the headache profile, diagnosis, other diseases, management and evolution of the patient condition were recorded. A comparison of the two groups data during 1-year period has been done. Student's test and spearman's p for correlation were used for the statistical analysis.
Results Women overpresented in adult Ed in contrast to children ED were equal percentage of girls and boys. Secondary headache diagnosis was less than primary headache in the two ED. Special investigations (CT scan) has been used 86% in children ED and 40% in adults ED. The useful of IHS classification is speculated. In general the emergency physicians are unable to use correctly the ICHD classification because the larger number of patients visits for assessment in a very limited time. Although there is a great effort the last years for the classification of headache a brief flexible classification according to the ICHD is perhape necessary for the implementation in the Emergency Department.

C042

The prevalence and association of sleep disorders (SDs) and cephalalgia in adolescents

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Objectives To discern the prevalence association of sleep disorders (SDs) cephalalgia. To identify risk factors.
Methodology Study retrospective revision clinical history 172 adolescents aged 14–18 with cephalalgia. HIS criteria for diagnosis of cephalalgia. A survey was conducted later with general data.SD diagnosis according to international criteria.
Results Adolescents with cephalalgia showed difficulty falling asleep, waking up in the middle of the night or very early, and/or not feeling rested on waking. Family background, season and level of stress also seem to affect the risk of cephalalgia and SD. Males (60%) females (40%). Unrestful sleep 66.6% Waking up at night 47.3% Talking in sleep 42.7% Difficulty falling asleep 22.7% Wakes up drowsy 12% Family relationships regular 69.3%, good 26.4%, bad 4.3%. Analyzing SD types, prevalence of drowsiness when waking up, unrestful sleep and waking during the night. Among females, prevalence of difficulty getting to sleep and frequent awakenings. Among males, prevalence of drowsiness on awakening. Statistically significant association SDs and lack of affection in family relationships.Depression and anxiety as a result of regular or poor family relations are precipitating factors for onset of SDs.
Conclusions A high number of adolescents with cephalalgia presented SDs and family relations played a predominant role. It is necessary to continue researching to determine what happens first: SDs or cephalalgia.Early detection and simultaneous treatment of both conditions necessary. Also necessary to create good personal and family habits to sleep better.

D123

The role of intracranial venous system in the pathogenesis of chronic tension type headache (CTTH)

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Materials and methods Twenty-nine patients with CTTH (IHS 2nd edition criteria) were evaluated with overall headache assessment, pericranial muscle tenderness score, head-down tilt test (HDTT), blink reflex, and cerebral MR-venography. According to the MR-venography the patients were divided into two groups: group 1 (n = 16) without, and group 2 (n = 13) with intracranial venous pathology.
Results Mean age of onset (1 = 43, 2 = 33.65 years) and duration of headache (1 = 4.66, 2 = 12.04 years) in the two groups were significantly different ($p < 0.02$). Clinically, the patients in group 2 more frequently suffered from night and morning headaches (1 = 37.5%, 2 = 53.8%), they were more likely to describe their headache as daily (1 = 37.5%, 2 = 69.2%) or related to physical strain (1 = 31.3%, 2 = 61.5%). The severity of myofacial syndrome was significantly higher in group 2 (score 34.73 vs. 41, $p < 0.05$), mostly due to the left-side muscles. The most frequent abnormalities on MR-venography in group 2 were hypoplasia of the left transverse sinus in 61.5% and its aplasia in 30.8% of patients. HDTT showed a more significant change in headache severity in group 2 (1 = 1.31, 2 = 2.69 by VAS scale, $p < 0.01$). In blink reflex studies group 2 patients showed a longer latency of the late component (R2), both ipsilateral and contralateral, than in group 1 patients ($p < 0.05$).
Conclusions CTTH is a clinically and possibly pathogenetically heterogeneous disease. In patients with CTTH certain clinical markers exist that allow the clinician to suspect an intracranial venous pathology. The patients with intracranial venous abnormalities are likely to suffer from increased intracranial pressure, either venous or liquor.

D124

Chronic headache in Korean geriatric patient

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Chronic headache impose considerable burden in old age patient because of their polypharmacy and medical cost. In Korean, their prevalence is not known very well but presumed to be very high. There are many medical system including orietal (herb,acupuncuture) medicine, western medicine, and shamanism becacuse of their very long historical background. So chronification factor is diverse than other country. In clinic base, many old age chronic headache patients seek alternative medicine rather than western medicine. So their symptom duration is very long (mean 1.2 year). And especially herb medication case, their symptom is very intractable with preventional drug. So we must recognize and educate the people as chronic headache is treatable and curable disease and early treatment is very important as other oriental backgroud country.

E098

Cervical dystonia in patients with chronic daily headache

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Objectives This study was conducted to assess whether Cervical Dystonia (CD) is more prevalent in patients with Chronic Daily Headache (CDH) than in the general population. Although CD prevalence in the US is currently 8.9 per 100,000, many patients with mild CD frequently go undiagnosed. Our objective was to identify headache patients with comorbid CD.
Methods Eighty-five patients with CDH (Silberstein and Lipton Criteria) from five tertiary headache centers, and 75 age and body index-matched controls without headache were evaluated. Assessment of CD was made using a standardized examination protocol including videotaping. Videotapes were reviewed by two blinded movement disorder specialists to assess whether CD was present. Final diagnosis of CD was made by another movement disorder specialist with a formal office visit for those patients suspected of having CD after the video screening.
Results None of the controls had features of CD. Of the headache patients, 71% (60/85) had muscle tenderness/pain upon palpation of the neck and shoulders. The most prevalent postural abnormalities included head tilt (19%, 16/85), shoulder elevation (8%, 7/85), and head rotation (2%, 2/85). After the video review seven headache patients were suspected of having CD. After the office visit the diagnosis of CD was confirmed for four patients. The resultant 4.7% CD prevalence is approximately 525 times greater than in the general population.
Conclusion Cervical Dystonia may be a component of Chronic Daily Headache. Comprehensive evaluation of Chronic Daily Headache patients should include a movement disorder protocol designed to identify Cervical Dystonia.

E099

Referrals to neurologists for headache at the emergency department of a general hospital in Greece

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Aim of the study Aim of the study is to evaluate the records of patients coming for headache to the ED of a General Adults Hospital of Athens during a period of 20 years and on the other hand the impact of IHS classification to the headache population visits in the ED of the hospital.
Patients and methods The period of the last 20 years 130,899 patients visited the ED for Neurological Disorders. 44,205 complained for headache. Data evaluated according to the IHS classification. Demographical and clinical data as well as the first and final diagnosis of headache were evaluated. Comparison of the data has been done between the period before and after the use of IHS classification and with the headache population of the Neurological outpatient clinic (OC). A statistical analysis was performed. Student's test and spearman's p for correlation were used for the statistical analysis.
Results The one forth of visits in neurological ED is for Headache women were overpresented in the ED as well as in the outpatient clinic. The age ranged from 30–50 years. There was a preponderance of the socially underprivileged. Primary headaches had a higher preponderance the first 14 years in comparison with the last 6 years when the IHS classification is more familiar. Chronic headache was the common cause of visits in the ED.
Conclusions The role of IHS classification is important for the management of headache in the ED department and there is a need to have guidelines brief and flexible according ICHD for application by the emergency physician.

E100

Chronic tension type headache, anxiety disorder and prophylaxis with pregabalin

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Objectives Anxiety is frequently associated with tension type headache and pregabalin has been recently suggested as a therapy for this disorder. We evaluated the efficacy and tolerability of pregabalin for chronic tension type prophylaxis in refractory patients.
Methods 36 patients with refractory chronic tension type headache according to International Headache Society criteria were evaluated. Headache frequency, severity (measured by Analogical Visual Scale) and anxiety associated (according to Hamilton Scale) before and after treatment with pregabalin were studied. The patients had failed an average of 3.2 prophylactic drugs prior to pregabalin. The average pregabalin daily dose was 180 mg and the average duration of treatment was 157 days.
Results The average number of days with headache per month was reduced in the entire study population from 20.1 before pregabalin treatment to 16.3 after its initiation and headache severity was reduced from 7.1 to 5.2. The reduction in these two parameters was proportional to the reduction in anxiety ($r = 0.89$). On the other hand, anxiety was reduced from 22.0 to 17.1. Pregabalin was well tolerated, the principal adverse event was somnolence and none patient abandoned the treatment because of that.
Conclusion Pregabalin has efficacy in tension type headache and anxiety disorder prevention. According to our results, a better control of associated anxiety may improve tension type headache and pregabalin may be a safe and effective agent in tension type headache prophylaxis. Double-blind studies are warranted to confirm these findings.

E101

Ophthalmoplegic Migraine – Suggestions for Revision of Nosology based on Normal Imaging in 4 patients

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Objectives 1. To report on 4 patients with recurrent migrainous headaches and III nerve palsy who fulfilled the criteria for Ophthalmoplegic Migraine (OM) BUT in whom there was no post-contrast enhancement of the oculomotor nerve on MR imaging. 2. To suggest a revision to the nosological status of this entity.
Methods 4 patients (males aged from 6 to 60 years) who presented with features suggestive of OM are included. All patients underwent routine MR imaging with gadolinium contrast and TOF intracranial MRA. CSF examination was carried out in all patients. All were treated with antimigraine prophylactics and none received steroids. Details of the history and findings have been discussed.
Results In contrast to recent literature reports, all four patients included here failed to show enhancement of the cisternal segment of the third cranial nerve on MRI following gadolinium during the acute phase. All responded well to antimigraine prophylactics.
Conclusion Based on findings in 4 patients with OM seen in our practice we wish to point out that 1. OM can be seen at any age 2. Post contrast enhancement on MR is not seen in all patients with features of OM 3. Based on post contrast cisternal enhancement on MR imaging, OM could be categorised as a migrainous variant with no enhancement OR as an inflammatory variant with enhancement. Till such time that this nosological debate is resolved, the Classification Committee could better position this entity in the Appendix.

E102

Migraines in patients with intracranial aneurysms prior to their rupture

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Background The purpose of this study was to reveal the frequency of migraines prior to rupture of intracranial aneurysms (IAs) and the prevalence of risk factors for IAs in patients with IAs who suffered from migraines compared to controls in the Urals region of Russia.
Methods The studied population consisted of 199 cases with treated IAs (96 men and 103 women, mean age 43.2 years) and 146 patients of healthy controls without headaches and IAs (94 men and 52 women, mean age 38.4). We studied clinical interview, detailed physical examination and pedigrees.
Results The frequency of migraines in patients with IAs prior to their rupture was 42.7%: migraines without aura – 41.7%, migraines with aura – 1.0%. The following risk factors were significantly more common in patients with IA who suffered from migraines compared with controls: (1) history of previous arterial hypertension (OR = 17.3, 95% CI = 8.5–35.1, $p < 0.0001$); (2) the presence of 3 or more of visible markers of connective tissue dysplasia (OR = 11.4, 95% CI = 6.0–21.7, $p < 0.0001$); (3) family history of intracranial haemorrhages (OR = 5.8, 95% CI = 1.8–18.7, $p = 0.001$); (4) family history of ischemic strokes (OR = 8.1, 95% CI = 2.9–22.6, $p < 0.0001$); (5) family history of IAs ($p = 0.003$). Smoking, use of oral contraceptives, alcohol consumption and diabetes were not significantly associated with IAs in these patients.
Conclusion Patients with migraines who have multiple signs of connective tissue dysplasia, arterial hypertension, family history of haemorrhages, strokes, IAs are at increased risk of developing IAs. They are recommended screening examination of cerebral vessels.

E103

No effect of deep brain stimulation of the posterior hypothalamus on thermal nociception in cluster headache

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Objective Deep brain stimulation (DBS) of the posterior hypothalamus has been shown to be clinically effective in drug-resistant chronic cluster headache. In a small sample significant changes of electrical and pressure pain thresholds have been observed. Our aim was to evaluate the influence of DBS on thermal nociception.
Methods Three groups were investigated: chronic cluster headache patients with unilateral DBS of the posterior hypothalamus (n = 11), strictly unilateral chronic cluster headache patients without DBS and ongoing attacks (n = 15) and healthy controls (n = 19). Perception and pain thresholds for hot and cold stimuli were presented bilaterally to all subjects supraorbitally, at the forearm and the lower leg. In DBS patients, thresholds were determined with the stimulator activated for a longer period and 30 min after deactivating the stimulator.
Results DBS patients in 'on' condition showed no significant changes of their trigeminal or brachial thermal thresholds compared to the 'off' condition. The only significant change was an increase in the cold perception threshold in the 'on' condition of the contralateral leg ($p = 0.013$). A comparison between all groups including non-DBS patients and healthy controls showed significant differences of mainly perception thresholds.
Conclusion Given the impressive clinical results, short-time DBS of the posterior hypothalamus in cluster headache does not seem to influence trigeminal or brachial thermal nociception. It does not appear to effect pain thresholds as such and could therefore be highly specific. These data are in contrast with recent PET data in patients, showing activation of large parts of the pain matrix by hypothalamic stimulation.

E104

Influence of questionnaire on incidence of adverse events in OTC use of acetylsalicylic acid in observational trials

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Objectives Assessment of influence of questionnaire on adverse event reporting in the OTC treatment of migraine with acetylsalicylic acid (ASA).
Methods Two different questionnaires were used to investigate side effects of 1000 mg effervescent ASA used for the treatment of migraine in a pharmacy-based observational study (PHOBS) on 296 patients reporting 578 migraine attacks: group I patients described adverse events (AEs) via an open-end question, whereas group II recorded AEs via closed-end questions in a check list of known side effects of ASA and fatigue, unlikely to be associated with the drug.
Results Questionaires influence the incidence of AEs reporting: group II (302 attacks) reported a two-fold incidence compared to group I (276 attacks) (16.6% vs. 8.3%). In both groups most frequently reported AE was stomach pain (5.4% and 6.3%) known as most frequent side effect. The open-end question did not induce the documentation of events unlikely related to the substance. The symptom fatigue ranked second in group II (5.6%). Patients may not distinguish symptoms of the disease (nausea, vomiting) and AEs caused by the medication. This is supported by 3 RCTs with ASA with incidences of AEs of 8.6%, 16.2% and 12.9%. Physicians`adjudication yielded 0.6%, 4.1% and 4.7% drug-related AEs.
Conclusion Questionnaire-type influences the rate of patient-reported AEs in PHOBS. Closed-end questionnaires lead to more AEs than open questions. In the light of much lower side effect rates evaluated by physicians the influence of questionnaire on rate of patient-reported side effect has to be considered when planning observational studies and interpreting their results.

E105

Randomized double-blind, placebo-controlled trial of high-flow inhaled oxygen in acute cluster headache

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Introduction In cluster headache attacks (CH), there is a rapid onset of very severe pain, requiring effective abortive relief. Subcutaneous and intranasal triptans are used to good effect, as is high-flow inhaled oxygen, although there is a lack of clear evidence for the latter.
Methods Eighty-one patients (66 male) with episodic cluster headache (ECH) and 28 patients (23 male) with chronic cluster headache (CCH), aged 21–65, who were naïve to high-flow oxygen, were randomized into a placebo-controlled, double-blind crossover study. Patients treated four CH attacks using two treatments each of air placebo or 100% oxygen at 12 L/min, for 15 minutes. Each patient recorded the results in a diary. The primary end point was relief at 15 minutes, defined as pain free or that the patient recorded adequate relief if the diary was not available, assessed across all treated attacks for CH patients as one cohort. The study was approved by the appropriate Ethics Committee. Multilevel Multivariate Analysis with MLwinN (www.ioe.ac.uk) was employed to test the primary endpoint.
Results Fifty-seven patients with ECH and nineteen with CCH were available for the intention-to-treat analysis. For the primary end point the difference between oxygen, 78% (n = 150) and air, 20% (n = 148) was significant (Wald test, $\chi^2 = 66.7$, $P < 0.001$). There were no important adverse events.
Conclusion This is the first adequately powered, placebo-controlled study of high-flow oxygen in acute cluster headache and it is clearly positive. The data provide a strong basis for the provision of this well tolerated treatment for the treatment for the treatment of this devastatingly severe primary headache.

F112

Efficacy of 1,000 mg effervescent aspirin: individual patient data meta-analysis of three trials in migraine

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Objectives Migraine is often associated with health consequences including impaired quality of life, and the cost of treating migraine headaches places a significant financial burden on patients who suffer from migraines. Aspirin is widely accepted as a treatment option for migraine pain relief and could provide an alternative not only for treatment of moderate migraine attacks, but also for severe migraine attacks.
Methods The efficacy and safety of 1,000 mg effervescent aspirin (eASA) was evaluated in comparison to 50 mg sumatriptan and placebo in an individual patient data meta-analysis of three randomized, placebo-controlled, single-dose migraine trials. Pain-relief at 2 h, pain-free at 2 h and sustained pain-free up to 24 h were calculated.
Results For eASA, the response rates were 51.5% (95% CI: 46.6–56.5%), 27.1% (95% CI: 22.6–31.4%), and 23.5% (95% CI: 19.3–27.7%). For sumatriptan, the response rates were 46.6% (95% CI: 40.0–53.2%), 29.0% (95% CI: 23.0–34.9%), and 22.2% (95% CI: 16.7–27.6%). The corresponding rates for placebo were 33.9% (95% CI: 29.1–38.6%), 15.1% (95% CI: 11.5–18.7%), and 14.6% (95% CI: 11.0–18.1%). The treatment effect of eASA and sumatriptan were significantly different from placebo ($p < 0.001$), but differences between eASA and sumatriptan were not significant.
Conclusion This individual patient data meta-analysis provided evidence that eASA 1,000 mg is as effective as sumatriptan 50 mg for the treatment of acute migraine attacks and has a better side effect profile. This is also true for patients with moderate as well as severe headache at baseline. Patients therefore should be advised to use eASA first for migraine attacks and use a triptan in case of no response.

F113

Effection of acupuncture treatment on migraineurs

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Objectives The efficacy of acupuncture for migraineurs has been demonstrated in many clinical trials. Transmagnitic Stimulation (TMS) has been used to show increased cortical excitability in migraineurs, and the threshold increases with preventive medicine on migraine patients. The aim of this research to assess the efficacy of acupuncture as a therapy in treating migraineurs, we propose using TMS to objectively assess cortical heperexitability in migraineurs pre and post treatment with acupuncture. together with a headache diary kept by the patients.
Methods 21 headache patients were recruited. They underwent 10 acupuncture treatment sessions with TMS performed before the first acupuncture session (TMS1), at the last session (TMS2) and 2 months after the last session (TMS3). A headache diary was also used to record details in migraine frequency/duration/pain score from before acupuncture to 2 months after the last session of acupuncture.
Results The phosphene threshold was increased in 17 out of 21 patients, but remaining 4 patients had no changed with comparison between TMS2 and TMS1 ($P < 0.001$); and 16 out of 21 patients increased in their phosphene threshold, but 3 patients had no changed and 1 patient decreased at their 2 month after the last session TMS test (TMS3) compared to the initial condition (TMS1) ($P < 0.001$). Migaraine attacts are reduced in 14 patients in terms of pain frequence/score /duration at their 2 months after the last session of acupuncture.
Conclusion this study showed that migraine attacks and cortical excitability were reduced with the use of acupuncture treatment. Acupuncture is effective on migraineurs.

F115

Topiramate in migraine prevention: Comparison between two different posologies

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Objective Topiramate is one of the most studied drugs in migraine prevention. It has demonstrated a high effectiveness, although side effects are its limiting factor. We try to compare efficacy and safety between once daily and twice daily doses of topiramate in migraineurs.
Methods 52 migraine patients according to the International Headache Society criteria were divided into two different groups. The first one (31 patients) with a single night dose, and the second one (21 patients) with a twice daily dose of topiramate (75–150 mg/day depending on response). They were followed for 6 months. There were no significant differences in sex, age or migraine type between groups. Studied items were: number of days with migraine, severity, use of acute medication and side effects. Afterwards statistical analysis was carried out.
Results There were no significant differences with regard to number of days, severity or use of acute medication between the two groups. However, certain side effects were less in the once daily group including paresthesias and cognitive disorders.
Conclusions Once daily topiramate dose may be useful in migraine prevention. Comparing with twice daily dose, the single night dose represents an easier posology, the same effectiveness and a best profile of side effects.

F116

Variation in almotriptan efficacy with different migraine prophylactic medications

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Objectives Efficacy of different triptans as treatment of acute migraine has been widely demonstrated. However there are still scarce data on its variation under prophylactic drugs. We evaluate the effect of most common migraine preventive medications (propranolol, flunarizine and topiramate) on the response to almotriptan.
Methods 120 patients with episodic migraine according to International Headache Association criteria were classified depending on the prophylactic treatment they were taking in the following groups: no preventive treatment (35 patients), propranolol (26 patients), flunarizine (25 patients) and topiramate (34 patients). Headache severity according to Analogical Visual Scale before and after almotriptan intake and side effects of this treatment were evaluated. The average follow-up was 168 days.
Results Almotriptan was effective in all groups. A significant better response was advised in propranolol group. In the rest of the groups the response was similar. Principal side effects were fatigue and drowsiness and they were similarly presented in all groups. However no patient abandoned the treatment because of them.
Conclusions Almotriptan was an effective and well tolerated medication in both control and under prophylactic treatment groups. Almotriptan in propranolol-treated patients seems to be more effective than in other groups. A possible answer could be the profile of these patients with a more benign migraine since propranolol is in most cases the first line of treatment. Double-blind studies are warranted to confirm these results.

F117

Treatment of medically intractable cluster headache by occipital nerve stimulation: long term follow up 13 patients

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Objectives To report on the outcome and long term follow up of 13 patients treated with occipital nerve stimulation (ONS) for medically intractable chronic cluster headache.
Background Cluster headache features repeated attacks of excruciating, severe headache. Chronic cluster headache can be medically intractable and treatment with cranially invasive or neurally destructive procedures can be offered.
Methods Thirteen patients with medically intractable chronic cluster headache were implanted with electrodes for occipital nerve stimulation. All patients were stimulated bilaterally, although the first patient initially unilaterally. Data was collected retrospectively for demographics, diagnosis, previous treatment, follow up duration, ONS settings, patient's estimate of frequency/severity/duration of attacks, patient's overall view of outcome, estimate of percentage change in cluster headache, complications and description of result if the ONS had been off for a period of time.
Results At a median follow up of 19 months (range 4–35 for bilateral stimulation) three patients estimated they improved by 90% or more, two by 40–60%, five by 20–30% and three no improvement. Triptan use reduced for five patients, was unchanged for six and two were not using triptans for other reasons. Ten patients said they would recommend ONS to similarly affected patients, one wouldn't and two were not sure. Adverse events of concern were battery depletion in four patients and electrode migration/failure in three. Generally, patients reported deterioration in their attacks if their ONS stopped working.
Conclusions Occipital nerve stimulation seems to offer a safe, effective treatment option for some patients with medically intractable chronic cluster headache.

F118

Reduced expression of calcitonin gene related peptide in mice with the familial hemiplegic migraine (FHM) 1 mutation

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Introduction The FHM1 R192Q mutation in the *CACNA1A* gene that encodes the pore forming α_{1A} subunit of $Ca_V2.1$ channels is associated with increased calcium influx, increased neurotransmitter release and reduced threshold and increased speed of cortical spreading depression. Elevated CGRP levels in migraine and the clinical efficacy of CGRP receptor antagonists suggest that CGRP-related mechanisms have a role in migraine pathophysiology.
Objective To investigate the level of expression of CGRP in trigeminal ganglion neurons of the R192Q (FHM1) mutant mice.
Method Mice were intracardially perfused and following fixation, the trigeminal ganglia (TG) were dissected out and cryoprotected in sucrose for 48 hours. TG were cut into 20 µm sagittal sections, reacted with anti-CGRP and visualised with avidin fluorescein using the ABC amplification system. CGRP positive cells (CGRP-ir) were counted blinded to the study group in areas where they were clustered and expressed as a percentage of the total number of neurons in the area. Adjacent sections were counterstainedwith Cresyl Violet to provide estimates of the number of neurons in counted regions.
Results There is a decreased percentage of CGRP-ir cells in trigeminal ganglion neurons of mutant mice (n = 8; 17.6, 13.4–21.1, median, interquartile range) compared to wild-type (n = 7; 24.6, 17.9–35.3; U = 365, $p < 0.001$). Cell diameters are being determined to make the same comparison.
Conclusion Expression of CGRP appears to be reduced in trigeminal ganglion neurons of FHM1 R192Q mutant mice. These data open the possibility that the *CACNA1A* mutation can alter CGRP-related transmission in the trigeminovascular system.

F119

Difference in triptan effect in patients with migraine and early allodynia

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Introduction Animal experiments indicate that the beginning of a migraine attack is first characterized by peripheral sensitization of C fibers located in the dura and in the vascular walls of the trigeminal nerve (1). In the course of the attack sensitization becomes central, which is clinically manifested by allodynia of the face and head. The aim of our study was to determine whether the response rate to various triptans differs in migraine patients with and without aura and with marked, early or interiktal allodynia.
Method The intention was to treat three consecutive definite migraine attacks within 1 hour of commencement of the attack. Patients were randomized in five treatment groups: Group I, zolmitriptan 2.5 mg; Group II, eletriptan 80 mg; Group III, naratriptan 2.5 mg; Group IV, frovatriptan 2.5 mg; Group V, zolmitriptan 5 mg nasal spray.
Results Each of the five treatment groups included six patients. While treatment with zolmitriptan (oral), naratriptan und frovatriptan showed no statistically significant change in VAS as compared with treatment with sumatriptan 100 mg and baseline, a statistically highly significant improvement in VAS was achieved with eletriptan 80 mg ($p = 0.028$ after 2 h, $p = 0.028$ after 4 h) and with zolmitriptan nasal spray 5 mg ($p = 0.028$ after 1 h, $p = 0.028$ after 2 h, $p = 0.027$ after 4 h).

Discussion The study results indicate that pain and central sensitization reflected as allodynia can be reduced by using eletriptan 80 mg and zolmitriptan 5 mg nasal spray instead of sumatriptan in patients with early allodynia.

F120

Nurse-based education: an office-based comparative model for education of migraine patients

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Background A person with migraine needs to be prepared to make therapeutic decisions on her own. For this reason, patients often need education to understand the nuances of managing migraines. In this study an educational CD-ROM/DVD that described the pathophysiology was utilized by nurses in an office-based primary care setting for patient education.
Objectives 1) Identify educatonal information that assisted migraine patients with managing migraine more effectively; 2) Encourage patients to intervene during the mild headache phase of migraine; 3) Measure education related changes in patient satisfaction and confidence regarding management of migraine; 4) Measure changes in nurse satisfaction and confidence in educating migraine patients; 5) Compare the effectiveness of 3 methods of delivery of nurse-based migraine education.
Methods 180 migraineurs at 21 primary care practices were divided into 4 groups: Group A watched the CD-ROM/DVD in the office with a nurse available for questions; Group B was given the CD-ROM/DVD by a nurse who recommended the content; Group C received the CD-ROM/DVD from a nurse without comment; Group D received no educational material. Patients and nurses answered a pre- and post-study Migraine Questionnaire. Patients filled in a Treatment Diary online within 24 hours of treating a migraine. Nurses completed a Satisfaction Questionnaire.
Results There was significant improvement in correct responses on the post-test for patients and nurses in Groups A, B, and C but not in Group D. The percentage of correct responses was directly and statistically significantly correlated with the involvement of the nurse in the educational effort.

F121

Intramasseteric botulinum toxin injection is as effective as oral overnight splint in nocturnal bruxism

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Objectives Nocturnal bruxism(NB) is a cause of secondary headache and facial pain. Oral overnight splint is an effective means of management in about 80% of the patients. Botulinum toxin is known to prevent involuntary muscle spasms and subsequent pain. We compared these two treatment methods with an open label cross-over study in 13 NB patients.
Methods Patients filled a self-assessment form about their facial, jaw or temporomandibuler pain on awakening in the morning. We examined patients within 2 hours after awakening for sensitivity in temporal, masseter, lateral pterygoid, sternocleidomastoid and trapez muscles, and weakness of jaw closing. Patients were evaluated four times: In the beginning (pre-sp), after 2 months of oral full-arch maxillary overnight splint application (post-sp), after 2 months of wash-out period after which a sum of 60 IU of Botox® were applied into masseter muscles (pre-bx) and 2 months after the injection (post-bx).
Results The mean ± SD of total pain and total sensitivity scores follows: Pain was 9.1 ± 3.7, 2.5 ± 3.7, 12.7 ± 7.0, 1.4 ± 2.1; sensitivity was 11.6 ± 5.2, 9.9 ± 5.0, 13.3 ± 5.4, 4.1 ± 3.7; and weakness was 4.2 ± 3.2, 1.1 ± 1.8, 3.8 ± 2.3, 0.7 ± 1.4 at pre-sp, post-sp, pre-bx and post-bx, respectively. The results were analysed by Wilcoxon test. Pain and weakness were significantly decreased with both treatments. Muscle sensitivity was significantly decreased with botulinum toxin.
Conclusion To our knowledge, there isn't any study comparing overnight splint treatment with botulinum toxin injection in NB. This study suggests that botulinum toxin is an equally or more effective treatment alternative for patients with NB, especially who find overnight splints uncomfortable.

F122

Migraine free rates across 4 attacks treated with sumatriptan 85 mg RT Technology™ and naproxen sodium 500 mg vs PBO

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Objective To evaluate the consistency of migraine free response to a fixed-dose combination of sumatriptan and naproxen sodium (SumaRT/Nap) across up to 4 migraine attacks when treated in an early intervention (EI) paradigm (mild within 1 hour).
Methods In two (S1 : N = 646; S2 : N = 620) identical, randomized, multi-center, double-blind, multiple-attack, EI trials in adult migraineurs (ICHD-II), subjects were randomized to five sequence groups. In four sequence groups, subjects treated 3 attacks with SumaRT/Nap and one with a randomly interspersed placebo. In the fifth arm, patients treated four migraine attacks with SumaRT/Nap. Summarizing across attacks, we reported that SumaRT/Nap was superior to placebo on 2-h pain freedom (PF) and 2–24-h sustained pain freedom (SPF) (Lipton 2006). This secondary analysis used repeated measures techniques (GEE) across attacks for migraine free (MF; no pain, no associated symptoms, no rescue) correcting for baseline variation and multiplicity.
Results Patient demographics were similar to other migraine studies. For Study 1 and Study 2 (S1/S2), 44%/43% of patients were migraine free on SumaRT/Nap at 2 hours across all attacks compared to 21%/17% for placebo using GEE ($p \leq 0.001$). At 4 h, 69%/66% were migraine free on SumaRT/Nap

across all four attacks compared to 36%/31% for placebo ($p \leq 0.001$). To support this analysis, migraine free rates were determined for each attack (Ranges; SumaRT/Nap: 42%–45%/39%–45%; Placebo: 17%–26%/10%–23%) and were significantly better than placebo on all attacks ($p \leq 0.001$). In over 1100 patients treating over 3300 migraine attacks, SumaRT/Nap was generally well tolerated.
Conclusions SumaRT/Nap demonstrates consistently better migraine free rates compared to placebo in an EI paradigm.

F123

The validation of a new headache-specific quality of life instrument in migraineurs

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Background The deleterious effect of primary headaches on the sufferers' quality of life (QOL) has been abundantly documented using both generic and headache-specific instruments. The currently used questionnaires focus on a limited number of factors and therefore may not be sensitive enough to detect the effect of headache type and headache characteristics on QOL, despite the obvious clinical differences. We have devised a comprehensive questionnaire that may be more sensitive to the burden of headache.
Objective To validate this new questionnaire on a group of migraineurs.
Patients and methods We included 117 migraineurs (14 males; mean age: 36.2 years, SD: 11.6). Reliability was assessed by calculating Cronbach's alpha of all items. Content validity was examined by calculating the correlation of the items with subscales of the generic QOL measure SF-36. The correlation of the patients' migraine characteristics with the questionnaire's items was used to assess criterion validity. The reliability and validity assessments were performed in conformity with the standards of classical test theory.
Results The questionnaire demonstrated good internal consistency (Cronbach's alpha = 0.8973). Content validity was adequate; most 'physical' items of the new questionnaire showed significant correlations with the bodily pain and role physical SF-36 subscales and most 'psychical' and 'mental' items were correlated with the vitality, role-emotional and mental health SF-36 subscales. Criterion validity was adequate, with headache severity being correlated with most of the items.
Discussion In this preliminary study the comprehensive headache-specific quality of life instrument showed adequate psychometric properties.

F124

In vitro pharmacological and molecular investigations of K_{ATP} channels in rat dural arteries

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Objectives Dilatation of meningeal (dural) arteries causes a throbbing, unilateral migraine-like pain in patients, indicating that these structures are involved in migraine. When used in clinical trials, vasodilatory K_{ATP} channel openers like levcromakalim and pinacidil cause headache as one of the primary side effects, indicating that K_{ATP} channels may be involved in headache and migraine pathogenesis. PNU-37883A is a potent blocker of the Kir6.1 subtype of K_{ATP} channels. We examined the mRNA expression profile of K_{ATP} channel subunits in the rat middle meningeal artery. Furthermore, we studied the possible in vitro inhibitory potentials of PNU-37883A on K_{ATP} channel openers levcromakalim, pinacidil and P-1075 in isolated rat middle meningeal arteries.
Methods mRNA expression of K_{ATP} channel subunits was studied in isolated rat middle meningeal arteries by quantitative real-time PCR. The in vitro effect of PNU-37883A on the K_{ATP} channel openers was studied in rat middle meningeal arteries mounted in wire myographs.
Results Of the five K_{ATP} channel mRNAs detected (Kir6.1, Kir6.2, SUR1, SUR2A and SUR2B), the expression levels of Kir6.1 and SUR2B transcripts were predominant. The three K_{ATP} channel openers caused dilatation of isolated rat middle meningeal arteries. The responses were blocked by PNU-37883A at 10–7 and 3×10–7 M.
Conclusion Our results indicate that Kir6.1/SUR2B is the major K_{ATP} channel complex in the rat middle meningeal artery and that PNU-37883A can block the in vitro dilatory effect of K_{ATP} channel openers levcromakalim, pinacidil and P-1075 in rat middle meningeal arteries.

F125

In vitro pharmacological and molecular investigations of K_{ATP} channels in rat cerebral arteries

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Objectives Dilatation of large cerebral arteries causes a throbbing, unilateral migraine-like pain in patients, indicating that these structures are involved in migraine. When used in clinical trials, K_{ATP} channel openers like levcromakalim and pinacidil cause headache as one of the primary side effects, indicating that K_{ATP} channels may be involved in headache and migraine pathogenesis. A selective blocker could thus prove an efficient new prophylactic treatment strategy for migraine. The K_{ATP} channel blocking effects of PNU-37883A (a selective blocker of the Kir6.1 subtype) was examined together with the mRNA expression profile of K_{ATP} channel subunits in rat basilar and middle cerebral arteries.
Methods The vasodilatory effects of levcromakalim, pinacidil and P-1075 were examined in precontracted segments of rat middle cerebral and basilar arteries mounted in

wire myographs and pretreated with different concentrations of PNU-37883A. The expression of the different subtypes of K_{ATP} channels was examined in rat middle cerebral and basilar arteries by quantitative real-time PCR.
Results PNU-37883A significantly attenuated the response to all three K_{ATP} channel openers at doses of 10^{-7} and 3×10^{-7} M. The K_{ATP} channel openers were less potent in the middle cerebral artery. The expression studies showed that Kir6.1 and SUR2B are the prevalent K_{ATP} channel mRNA transcripts in rat middle cerebral and basilar arteries.
Conclusion Kir6.1/SUR2B is the major K_{ATP} channel subtype in middle cerebral and basilar arteries. PNU-37883A proved efficient at blocking the vasodilatation caused by K_{ATP} channel openers, and may be a promising model drug for future therapeutically applicable drugs of this class.

F126

The in vivo effect of the selective K_{ATP} channel blocker PNU-37883A in rat dural arteries

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Objectives Dilatation of meningeal (dural) arteries causes a throbbing, unilateral migraine-like pain in patients, indicating that these structures are involved in migraine. When used in clinical trials for respiratory and cardiovascular diseases, vasodilatory K_{ATP} channel openers like levcromakalim and pinacidil cause headache as one of the primary side effects, indicating that K_{ATP} channels may be involved in headache and migraine pathogenesis. PNU-37883A is a potent blocker of the vascular K_{ATP} channels. However, its in vivo use is limited as doses above 15 mg/kg are cardiotoxic in experimental animals. Our aims were, within the therapeutic interval, to evaluate the possible in vivo inhibitory effect of PNU-37883A on K_{ATP} channel opener induced dilatation of the rat middle meningeal artery, using levcromakalim, pinacidil and P-1075 as K_{ATP} channel openers.
Methods The in vivo effect of PNU-37883A was examined in the genuine closed cranial window model, which allows for real-time visualization and measurement of the middle meningeal artery diameter during the administration of vasoactive drugs to anaesthetized rats.
Results PNU-37883A (0.5 mg/kg) significantly inhibits the in vivo dilatory effect of levcromakalim (0.025 mg/kg), pinacidil (0.38 mg/kg) and P-1075 (16 μg/kg) in rat middle meningeal arteries at a dose 30 times below the cardiotoxic limit established in experimental animals.
Conclusion PNU-37883A is a potent inhibitor of K_{ATP} channel opener induced dilatation of the rat middle meningeal artery in vivo and may serve as a model molecule for the development of future target specific anti-migraine drugs.

F127

Item response modeling in the development of a new headache-specific quality of life instrument

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Background Item response modeling (IRM) is a new and powerful theoretical framework for analyzing multiitem scales and is probably better suited for test development than classical test theory. Among other advantages, IRM can evaluate the measurement properties of each item, can give reliable estimates of whole test score based on a subset of questions (the basis for computerized adaptive testing), and can give more realistic estimates of measurement precision.
Objective To demonstrate the usefulness of IRM by examining the responses of a migrainous sample to a new headache-specific quality of life (QOL) questionnaire.
Patients and methods A sample of 117 migraineurs (14 males; mean age: 36.2 years, SD: 11.6) filled in a 24-item QOL questionnaire with 5-point Likert sclae responses. Statistical analysis was done with TestGraf98 and ConstructMap 4.3, software specially developed for IRM.
Results The analysis of option characteristic curves suggested that four response categories were adequate in 18 of the 24 items. Cronbach's alpha was 0.89 signifying good reliability. Exploratory factor analysis confirmed that a main factor was responsible for 47% of the total variance. Of the 24 items 23 showed adequate fit to a partial credit model.
Discussion Item response modeling is useful in the development of QOL instruments. After due refinements, the new headache-specific QOL instrument may be useful as a short yet multi-domain assessment method.

F128

Influence of patients's self-selection of OTC analgesics on efficacy perception in ETTH and migraine

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Objectives Hypothesis is that the degree of satisfaction triggers the repeated use of the same brand/substance when patients buy OTC analgesics. To evaluate possible differences in the perception of efficacy a pharmacy-based epidemiological cohort study was performed comparing 3 analgesics: 1. acetylsalicylic acid (ASA), 2. acetaminophen (APAP), 3. combination of ASA, APAP and caffeine (AAC).
Methods Patients requesting the respective analgesic in the pharmacy were asked to document their pain intensity on a 100 mm VAS prior to and after 15, 30, 45, 60, 90, 120, 180, 240 min after drug intake. Efficacy parameters were calculated time to 50% percent pain relief, and time till reduction of pain intensity to 10 mm VAS, percentage of patients with 50% pain relief at the different time points, global assessment of efficacy on a 4-point VRS.
Results Median time to 50% pain relief was 30.9 min (ASA; N = 1159), 34.5 min (APAP; N = 1015), 30.9 min (AAC; N =

887) ($p < 0.001$ for ASA and AAC vs. APAP). Time needed to reduce pain intensity to 10 mm was significantly shorter for ASA (47.5 min) and AAC (44.1 min) than for APAP (53.9 min). ASA and AAC showed faster onset of pain relief reaching significance after 15 and 30 min. after intake. Global assessment of efficacy was good/very good in 90.5% (ASA), 90.1% (AAC) and 82.7% (APAP).

Conclusion Whereas some RCTs have shown slightly superior efficacy of AAC vs. ASA and APAP this self-selection based study revealed no difference between ASA and AAC. However APAP showed less efficacy and a longer time to onset of pain relief. The results show that the self-selection by patients – based on former experience – may influence efficacy perception.

F129

Headache disability in Kenya is not inability

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Objective To study headache associated disability in a group of medical students at the Kenyatta National Hospital.

Methods Cross Sectional Survey.

Results Between October 1994 and January 1995 we conducted a survey on headache characteristics on medical students at both the Kenya Medical Training Centre and the Medical School of the University of Nairobi. Six hundred and twenty-five (87%) of the 711 students surveyed admitted having had at least one episode of headache in the last 6 months. Using the International headache society (IHS) case criteria 314 students (50%) had tension type headache, 240 (38%) migraine headache and 71 (12%) unclassified headache. Eighty-six percent of the students with headache had their working ability disturbed to various degrees. Eighty-five percent of the students reported that their social activities were interfered with by headache. Migraine headaches had the greatest impact on both the working and social activities at a p-value of 0.0005 and 0.0004 respectively. One hundred and forty-one students (23.6%) had missed at least 1 day of work or school in the last 1-year as a direct result of the headache. There was an association between headache severity with working ability and social effect. There was no association between the days students missed work or classes with the severity of the headache. No gender difference was found in the headache associated disability.

Conclusion Headache is a prevalent condition with disability both in working and social activities.

F130

Cost-effectiveness of migraine therapy: non-prescription analgesics vs a selective serotonin receptor agonist

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Objectives Compare cost-effectiveness of non-prescription analgesics and a prescription selective serotonin 1b/1d receptor agonist for the treatment of migraine headache (patient perspective).

Methods A decision analytic model was constructed (Microsoft® Excel®) to compare aspirin/acetaminophen/caffeine combination (AAC) (Excedrin® Migraine), ibuprofen (Advil® or Motrin® Migraine), and sumatriptan (Imitrex®) for the treatment of migraine headache. Efficacy data were from two randomized, double-blind, placebo-controlled trials: AAC versus ibuprofen, AAC versus sumatriptan. Effectiveness in the model was defined as total sum of pain relief scores at 4 hours (TOTPAR4) (AAC = 8.9, ibuprofen = 7.1, and sumatriptan = 6.9). Higher TOTPAR4 scores indicated greater pain relief. Drug dosing was based on product labeling. Assumptions included two migraine episodes/month for all agents and one physician visit/year for sumatriptan. Cost of therapy included non-prescription per unit drug costs (AAC = $0.10 and ibuprofen = $0.16), prescription drug co-payment (sumatriptan = $50/month), and physician visit co-payment (sumatriptan = $19.92/visit). Drug co-payment and number of tablets/prescription (12) were based upon interviews with managed care decision-makers. All costs were 2007 US dollars. Univariate sensitivity analyses were conducted.

Results Cost of therapy per migraine episode was $0.20 (AAC), $0.32 (ibuprofen), and $9.16 (sumatriptan). Cost per one point improvement in pain relief score at 4 hours was lowest for AAC ($0.02), followed by ibuprofen ($0.05), then sumatriptan ($1.33). Sensitivity analyses indicated the model input with the most influence on the AAC cost-effectiveness ratio was the average retail price per tablet/caplet.

Conclusion AAC is a cost-effective treatment for migraine headache, resulting in the lowest cost per one point improvement in pain relief score at 4 hours.

F131

Magnesium salts as add-on therapy in refractory migraine

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Objectives Magnesium deficiency has been shown to play a potential role in the pathogenesis of migraine and although a few clinical trials have produced preliminary evidence of therapeutic efficacy in both acute and prophylactic treatment, more studies are still warranted. We evaluated the efficacy and tolerability of a combination of different magnesium salts for migraine prophylaxis in refractory patients.

Methods Thirty-two patients, with International Headache Society-defined episodic migraine, were initiated on a combination of magnesium salts (28.68 mg magnesium bromide, 765.20 mg magnesium hydroxide, 1.36 mg magnesium fluoride and 0.12 mg magnesium iodide) a day as add-on therapy, which was titrated to the double dose. The patients had failed an average of 3.8 migraine prophylactic drugs prior to magnesium. Headache frequency and severity before and after treatment initiation were compared.

Results Statistically significant improvements in headache severity ($P < 0.05$), and frequency ($P < 0.05$) were evident after 1 month of magnesium therapy and persisted after 7 months

of treatment. Magnesium salts were well-tolerated and the most common side effects were diarrhea and abdominal pain. Only one patient discontinued the treatment because of these adverse events.
Conclusions These results suggest that magnesium salts as add-on therapy may be safe and effective for migraine prevention and may be useful in refractory patients.

F132

Precision dosing of Dihydroergotamine (DHE) by inhalation

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Objectives Dihydroergotamine (DHE) is a proven, effective migraine therapy, particularly when administered by IV. Other administration routes have inconsistent pharmacokinetic (PK) properties, creating therapeutic variability. More consistent and titratable inhaled DHE delivery closely mimicking IV administration protocols may provide great benefit in migraineurs, including: rapid onset, self administered dose titration. This work aimed to show that the Tempo™ Inhaler, by precisely coordinating dose administration with patient inhalation, could enable consistent dosing of DHE. The consistency and resulting PK response were determined via in vitro clinical release testing and human clinical trial use.
Methods (1) In vitro testing: Pharmacopoeial methods confirmed Delivered Dose (DD, dose exiting Tempo mouthpiece) and Fine Particle Dose (FPD, (2) Clinical trial: Clinical trials compared the PK profile of DHE 0.22, 0.44, 0.88 and 1.32 mg FPD delivered by the Tempo Inhaler to 1.0 mg IV administered DHE 45® in healthy subjects.
Results Highly consistent aerosol performance was confirmed during clinical release testing: DD, 0.39 ± 0.02 mg and FPD, 0.22 ± 0.02 mg. Clinical evaluation showed DHE with 0.88 mg FPD achieved Tmax just slightly longer than 1.0 mg IV: 5 vs. 10 min respectively. The PK profiles post-Tmax and AUC0-inf were closely comparable to 1.0 mg IV. Intersubject variability via inhalation was comparable to IV. In addition, Cmax with inhalation was 13X lower than IV and was associated with less frequent adverse effects, including nausea.
Conclusion Inhalation administration of DHE using Tempo Inhaler provided highly consistent aerosol performance, shown to correlate with consistent IV DHE dosing during clinical investigation in humans.

ScS5-4

Novel gene causing Retinal Vasculopathy with Cerebral Leukodystrophy, Raynaud's phenomenon and migraine

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Introduction Previously, we described a large Dutch family with hereditary vascular retinopathy (HVR) – recently renamed to Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)-, Raynaud's phenomenon, and migraine and mapped the responsible gene to a locus on chromosome 3p21.1-p21.3. Additional genetic testing revealed that the RVCL haplotype in this family increased the risk for both Raynaud phenomenon and migraine.
Objective To identify the underlying gene for RVCL and investigating its functional consequences.
Method Sequencing of 33 candidate genes in the disease locus on chromosome 3. Generation and testing of cDNA constructs of wildtype and mutant RVCL gene product in cellular assays to test the functional consequences.
Results The gene causing RVCL in the Dutch family was identified. The gene affects a very basic cellular process. Several European and non-European RVCL families have been identified with mutations in the same gene. Functional studies of RVCL mutants hint to a unifying mechanism of protein mislocalisation causing disease.
Conclusion The causative gene was identified in a large Dutch family with a complex phenotype of retinal vasculopathy, Raynaud's phenomenon and migraine. Our results implicate that the gene is involved in the maintenance of vascular integrity and thus contributes to the pathogenesis of these diseases. Detailed future studies of RVCL mutations may teach us much about homeostasis of the endothelium, and events leading to premature vascular aging.

ScS5-5

Double-blind placebo-controlled trial of tonabersat in the preventive management of migraine

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Background Tonabersat, with its unique stereospecific binding site in brain, has been shown to reduce the frequency and amplitude of experimentally induced episodes of cortical spreading depression and to inhibit cerebrovascular responses to trigeminal nerve stimulation.
Aim To study the potential for tonabersat as a migraine preventive.

Methods A randomized double-blind placebo-controlled multi-center parallel group study recruited patients with migraine with and without aura experiencing between two and six migraine attacks per month. After a 1-month baseline they received tonabersat 20 mg daily for 2 weeks and 40 mg daily for a further 10 weeks. The primary endpoint was the change in mean number of migraine headache days comparing the third month and the baseline period in the ITT population for placebo (n = 65) and tonabersat (n = 58).
Results At the primary endpoint there was a 1.0 (0.33, 2.39, 95%CI, p = 0.14) day reduction in migraine days. There were twelve secondary endpoints. In the third month of treatment the responder rate defined as a 50% reduction in migraine attacks was 62% and 45% for tonabersat and placebo, respectively (P Conclusion-Tonabersat was generally well tolerated with the dataset supporting further exploration of this compound in larger controlled trials.
Disclosure This study was supported by Minster Research Ltd.

ScS5-6

CGRP receptor inhibition reduces neuronal activation in the spinal trigeminal nucleus

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Objectives Calcitonin gene-related peptide (CGRP) is abundant in a subset of intracranial afferents that are implicated in the generation of headaches. Intra- and extracranial nociceptive afferents project to spinal trigeminal neurons, the activity of which is thought to indicate headache and facial pain. The CGRP receptor antagonist BIBN4096BS reduced headache in migraine patients (Olesen 2004) and lowered the activity of spinal trigeminal neurons with meningeal input in animal experiments (Fischer 2005). In the present study we examined whether CGRP receptors contribute to activation in the spinal trigeminal nucleus following noxious stimulation, c-fos expression was used as a marker.
Methods Male Wistar rats were anaesthetized with isofluorane. Intravenous application of 900 µg/kg BIBN4096BS or vehicle within 10 min was followed by infusion of 915 µg/kg capsaicin or vehicle within 30 min. After further 90 min the animals were transcardially perfused with paraformaldehyde. Cryostat sections of the brainstem caudal to the obex were processed for immunolabeling of the fos protein, augmented by a horseradish peroxidase-conjugated avidin-biotin complex and stained with diaminobenzidin.
Results C-fos immunoreactive cells within the layers I–II of the spinal trigeminal nucleus were counted. In vehicle-treated animals 4 ± 1 and in capsaicin treated animals 31 ± 5 cells per section were c-fos positive. Pre-treatment with BIBN4096BS reduced capsaicin-induced fos production to 14 ± 2 cells per section. A reduction in fos positive cells was seen at all levels within 6 mm caudal to the obex.
Conclusion Our results suggest that CGRP receptors are critically involved in the increased activity of central trigeminal neurons following noxious input.

ScS5-7

Opportunity for early intervention in a clinical trial setting

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Objectives Early intervention (EI) while pain is mild and within an hour improves migraine treatment outcomes. In practice, many patients do not use EI, in part because of non-compliance. In two identical studies comparing sumatriptan 85 mg RT Technology™ and naproxen sodium 500 mg with placebo we examine both treated and untreated attacks to explore the feasibility and the barriers to successful application of EI strategies.
Methods Subjects were instructed to treat up to 4 attacks with study drug (SD) using EI and to record untreated attacks and the reasons for not treating. For the purposes of this exploratory analysis, the data from both studies were combined.
Results In these studies, 1,266 patients recorded information on over 14,000 migraine attacks. Only about 30% of attacks were treated with SD. In the 70% of attacks not treated the two most common reasons for not treating were awakening with (30%) or quickly progressing to (20%) moderate or severe pain. Overall about 48% of migraine attacks were judged to be treatable using the EI paradigm.
Conclusions These are the first prospective data which illustrate that less than half of migraine attacks were treatable within an hour of onset of an attack and while pain is mild.