POSTER SESSION II

I: Preventive treatment

P2-I1

Evaluation of the glyceryltrinitrate (GTN) human migraine model as a possible tool for prophylactic drug development: effect of valproate in a double-blind cross-over study

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Objective Due to the intermittent and unpredictable nature of migraine, a human model would be helpful in the study of new migraine compounds. GTN evoked headache has been fully investigated in migraine patients. Besides an immediate headache during infusion, migraine patients experience a delayed headache that resembles the patients' spontaneous migraine attacks and fulfils IHS criteria. Efficacy of valproate in the GTN model would support the usefulness of this model in drug development.
Methods 12 subjects with migraine without aura, in a randomized double-blind cross-over study. Valproate 1000 mg or placebo was given daily for a minimum of 13 days, followed by a 20-min intravenous infusion of GTN 0.25 μg/kg/min on both study days. Headache was registered for 12 h after the infusion and its intensity was scored on a scale from 0 to 10. Fulfilment of IHS criteria was recorded up till 24 h.
Results 12 subjects completed the study. The response was identical on both study days in 6 subjects. Of these 1 did not develop headache at all, 2 took rescue medication at the onset of delayed headache and did not fulfil IHS migraine criteria on either study day. 2 reported migraine that fulfilled IHS 1.1 on both study days. 1 reported migraine on both study days that fulfilled IHS 1.1 except having only photophobia and not phonophobia before taking rescue medication. Of the remaining 6 subjects, 4 fulfilled IHS 1.1 after placebo but not after valproate. 2 reported migraine after placebo but not after valproate. However, it did not quite fulfil IHS criteria. After valproate a non- significant reduction compared to placebo were seen in subjects with GTN evoked migraine IHS 1.1 (2 *vs* 6, $P=0.09$). Also a non-significant reduction of peak headache was seen after valproate compared to placebo (mean 4.8 *vs* 3.1, $P=0.10$). IHS criteria 1.1 is a very hard endpoint since the subjects could treat their headache/migraine at any time and before fulfilling IHS 1.1. Subsequent analyses of the data revealed, however, that on placebo, 9 subjects reported migraine, fulfilling IHS 1.1 or 1.1 except only having photo- or phonophobia and not both before taking rescue medication. This was reduced to 3 subjects after valproate ($P=0.01$).
Conclusion Valproate reduced all headache parameters, but none of the primary endpoints to a statistically significant degree, possibly due to the small number of subjects. The size of the effect was similar to that of valproate in clinical trials. The study therefore suggests that the GTN migraine model is valid and could be suitable for the testing of future prophylactic migraine drugs. Several possibilities exist for further improvement of the model.

P2-I2

The cost-effectiveness of a prophylactic migraine programme as contrasted to pharmacological migraine treatment

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Objective To compare the cost-effectiveness of utilizing the Mundo Method Programme with conventional therapy for patients in a managed care practice who were migraine sufferers receiving chronic maintenance care.
Background Migraines afflict 24 million Americans usually women between 10 and 40 years of age. The Mundo Method Programme, a self-care prophylactic oriented educational programme, seeks to prevent and control migraines by emphasizing body-mind awareness, elimination of headache triggers and stress reduction. Mundo therapy training, similar to biofeedback, is self-applied touch therapy with focused concentration to abort migraines.
Methods A retrospective analysis of programme questionnaires, baseline and follow-up ($n=78$) 1995 through 1999 of clients who self-assessed their headaches as migraines according to IHS criteria. Number of headaches reported before and after the programme, use of medications, and the use of the Mundo therapy were collated. 87% were women, age range 17–62. Encounter data for this group was not available to link cost of prior maintenance treatment. A second retrospective review analyzed the cost of migraine pharmacological therapy for 10 patients being treated over 1 year (9/1999 to 9/2000) identified through pharmacy profiles and billing data. The mean cost of abortive medications and office visits for migraines was $2187/year. Adding the cost of emergency visits and diagnostic imaging increased this to $2639.
Results Analysis of the 78 cases in the Mundo programme showed a 65% reduction in the number of headaches and 52% decreased use of abortive medication. Of note, prior to programme, only 17% (9% after) were on prophylactic drug treatment. 97% reported greater self-control of their headaches. Cost was $210 per person to the managed care network. Applying this projected 65% reduction in the number of headaches to the medically managed group

($2187) would realize a potential cost reduction of $1421 per patient.
Conclusion Cost reduction is noted in the decreased cost/client/year as evidenced by a decreased use of abortive and acute therapy and increased self-control. The benefits of the programme in increased personal quality of life and increased social quality of life through decreased days lost to missed work/school/social activities are related to the reduction of migraine occurrence in the survey comments. The findings that biofeedback, stress reduction, relaxation and trigger avoidance reduce frequency of headaches is consistent with the literature. A pretest/post-test design identifying encounter costs, prophylactic contrasted with pharmacological, is recommended.

P2-I3

Quality of life, disability and migraine prophylactic therapy

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Introduction Migraine prophylactic therapy is indicated to diminish frequency and intensity of crises when migraine attacks are more than two a month. MIDAS and SF-36 questionnaires could be powerful instruments for physicians to evaluate the disability and quality of life of migraineurs. Their use has shown how these features are ameliorated after prophylactic therapy.
Objective We performed a study to evaluate the quality of life and disability in a group of migraineurs before and after prophylactic therapy. We evaluated the utility of both questionnaires in clinical practice and the impact of a chronic drug therapy on the quality of life.
Materials and methods A prophylactic therapy, either with propranolol, lisuride, amitriptyline and flunarizine, was prescribed to 43 outpatients, attending the Headache Center, Department of Neurosciences, University of Cagliari. Patients were evaluated with MIDAS and SF-36 questionnaires before and after three months of therapeutic regimen. Statistical analysis was performed using Student's *t*-test.
Results Following therapy, 43 patients showed a statistically significant ($P < 0.05$) average decrease of MIDAS score of 19 points. An average, statistically significant ($P < 0.05$) elevation of total score was evident in every domain of the SF-36 scale, particularly in RF, RE, AS, and DF areas.
Conclusions This study has demonstrated that prophylactic therapies have a relevant role in decreasing disability and ameliorating the quality of life in migraineurs, and also that the chronic use of a drug does not interfere with the quality of life. The questionnaires are also valid tools to specify practical guidelines and give an estimate of economical costs of migraine. Further information given by SF-36 could integrate the clinical evaluations in fields of interest not investigated by MIDAS such as the reasons for disability that are not related only to pain.

P2-I4

Carbamazepine, controlled-release, for migraine prophylaxis

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Objective To study a new dosage form of a well-established anticonvulsant as a prophylaxis agent for migraine headache previously refractory to prior conventional therapies.
Study design and methods 30 patients were entered into this study, all with at least IHS-criteria migraines (1.1,1.2, 1nd 1.7). Many ($n = 20$) had coexistent tension-type headaches for an average duration of 5.2 years. All patients had at least 4-h migraine headaches per month; 8 patients had chronic daily headaches in addition to migraines. Most ($n = 24$) had been tried on other anticonvulsant prophylaxis therapy, including divalproex sodium, gabapentin, tiagabine and even carbamazepine. Controlled-release carbamazepine (Carbatrol) was started at 200 mg in the evening once daily and titrated by 200 mg each week to 600 mg per day. At times, 200 mg in the morning and 400 mg in the evening was the regimen, depending on how it was tolerated. Some patients were also increased to 400 mg twice a day. After initial titration of therapy, the average duration of active therapy was 4 months. Patients kept headache diaries and rated the severity of their headaches on a 0–10 numeric rating scale (NRS).
Results 14 patients reported an average of 67% reduction in frequency of their migraines. 4 patients reported no change in the pattern of their headaches. 4 patients dropped out due to side-effects (nausea and GI disturbance) and 10 patients are still in the titration phase of the study. 10 patients were able to taper off or reduce the dosage of their other anticonvulsant prophylaxis medications.
Conclusions This open-label study demonstrates effectiveness of controlled-release carbamazepine as a prophylaxis agent for refractory migraines and other headaches. This is complementary to its action in reducing other pain syndromes, such as neuropathic pain and trigeminal neuralgia. It is well tolerated and may be tried as prophylaxis even when other neuronally active agents have not been successful in reducing headache severity and frequency. The preliminary results in an ongoing study extend our available option for treating resistant migraines and they warrant further research using double-blind methods.

P2-I5

A retrospective chart review demonstrating the efficacy of topiramate for prophylaxis of migraine

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Objective Topiramate is a novel agent approved for treatment of epilepsy. Open-label reports and pilot double-blind trials suggest a role for topiramate in migraine

prophylaxis. We had previously reported a chart review of 98 refractory migraine patients treated with topiramate. For this chart review we utilized topiramate prophylaxis earlier in the treatment sequence.

Methods A chart review was performed on patients started on topiramate between 5/4/99 and 11/17/00. 107 patients were included who were diagnosed with migraine (with or without aura) and on topiramate for migraine prophylaxis with at least one follow-up visit at four or more weeks. Charts were reviewed for frequency of mild or moderate/severe headaches and side-effects at baseline and all follow-up visits.

Results The 28-day headache frequency was reduced from 21.0 ± 8.7 to 17.1 ± 9.6 ($P = 0.0001$) for all types of headache; mild headaches were reduced from 7.5 ± 6.9 to 5.7 ± 6.4 ($P = 0.02$) and moderate/severe headaches were reduced from 13.4 ± 7.4 to 11.4 ± 8.6 ($P = 0.02$). A subgroup analysis of patients failing >5 prior preventives ($n = 54$) demonstrated a reduction in all types of headache from 19.9 ± 9.9 to 15.2 ± 9.3 ($P = 0.0004$); mild headaches were reduced from 6.9 ± 7.3 to 5.3 ± 6.4 ($P = 0.09$) and moderate/severe headaches were reduced from 12.9 ± 7.2 to 9.9 ± 7.3 ($P = 0.004$). Patients failing 35 prior preventives ($n = 53$) proved more refractory: all types of headache were reduced from 22.1 ± 7.3 to 19.1 ± 9.5 ($P = 0.04$), mild headaches were reduced from 8.2 ± 6.5 to 6.2 ± 6.5 ($P = 0.09$) and moderate/severe headaches were reduced from 13.9 ± 7.7 to 13.0 ± 9.5 ($P =$ NS). Of patients experiencing a $\geq 50\%$ reduction in headache frequency, the response rate for each type of headache was: mild headaches (36%); moderate headaches (37%); severe headaches (39%) and all types of headache (23%). The $\geq 50\%$ reduction rate for patients receiving topiramate as their only migraine preventive ($n = 40$) was as follows: mild headaches (33%); moderate headaches (25%); severe headaches (43%) and all headaches (23%). The most common adverse effects (AEs) were drowsiness, paresthesias, decreased memory, altered taste and decreased appetite. Average patient weight was reduced from 183 to 177 lb ($P = 0.0001$) with 76% of patients experiencing weight loss. 27 patients (25%) discontinued topiramate therapy; 12 due to lack of efficacy and 15 due to AEs. The median topiramate dose was 75 mg daily (range 25–300 mg/day).

Conclusions The results demonstrate the clinical efficacy of topiramate in migraine prophylaxis. In contrast to our previously reported series in which patients with mild headache obtained less benefit, topiramate therapy was significantly able to reduce the frequency of both mild and moderate/severe headaches.

P2-I6

Prophylaxis of migraine with topiramate: a retrospective analysis

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Objective To assess the efficacy and tolerability of topiramate for prophylaxis of migraine and cluster headache, based on a retrospective chart analysis.

Methods Patients diagnosed with transformed migraine (TM), episodic migraine (EM) or cluster headache (CH), and who received topiramate either as add-on therapy or monotherapy, were selected from patient charts. The parameters examined included mean 28-day migraine frequency, migraine severity, number of headache days per month, number of abortive medication tablets per month, patient global evaluation, and MIDAS scales.

Results One hundred 78 patients ($N = 96$ TM; $N = 12$ CH; and $N = 70$ EM) were included in the retrospective analysis. Patients began topiramate therapy by using 25 mg/day for the first week, and increased the daily dose by 25 mg/ week to a maximum of 200 mg/day. Topiramate was used as add-on therapy for TM and CH patients, and as first-line monotherapy in EM patients who had no previous prophylactic therapy. The mean dose of topiramte for all patients was 87.5 mg/day. For patients with TM, migraine frequency decreased from 6.3/28 days to 3.7 ($P = 0.005$). Mean severity decreased from 7.1 to 3.8 on a 10-point scale, with 10 representing the most severe pain ($P = 0.003$). The number of headache days per month decreased from 22.1 to 9.6 ($P = 0.001$), and the mean number of abortive medication tablets decreased from 28.7/month to 10.6 ($P = 0.001$). Patient global evaluation demonstrated substantial or moderate improvement in 53% of patients with TM who used topiramate as add-on therapy. MIDAS scale values decreased from 90.21 to 24.86 ($P < 0.0001$). The 70 EM patients who were administered topiramate as first-line therapy exhibited a decrease in migraine frequency (5.8/28 days to 1.9, $P = 0.001$), while migraine severity decreased from 8.1 to 2 ($P = 0.003$). 61% of patients reported marked improvement. Seven of 12 CH patients exhibited a $>65\%$ reduction in 28-day migraine frequency; 2 exhibited a 40–60% reduction; and 3 had no improvement. CH patients demonstrating improvement also responded better to acute treatment. The most common adverse effects were paresthesias (12%), weight loss (12%), cognitive effects (11%), and dizziness (6%). Eight patients discontinued topiramate due to adverse effects; cognitive effects were the most common reason. No patient discontinued topiramate treatment due to lack of efficacy. Twelve per cent of patients lost more than 5 lbs during treatment (range 5–120 lb).

Conclusion Both as an add-on therapy and first-line monotherapy, topiramate yielded significant reductions in migraine frequency, migraine severity, number of headache days, and use of abortive medications. Topiramate appears to be well-tolerated and useful in the treatment of cluster headache. Further double-blind, placebo-controlled trials are indicated.

P2-I7

Topiramate: a case series study in migraine prophylaxis

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Objective To determine the efficacy and tolerability of topiramate for the prophylaxis of episodic and chronic migraine, based upon a retrospective chart review.

Methods Patients diagnosed with either episodic migraine (EM) or chronic migraine (CM) who had continued topiramate therapy for at least 6 weeks were selected from an electronic medical record system. The parameters examined included demographics, headache frequency, headache severity, concomitant use of other medications, and incidence of adverse events. A paired *t*-test was used to compare parameters before and after treatment.
Results Seventy-four patients were identified (6 males and 68 females). Fifty patients were diagnosed with CM and 24 with EM (6 with aura and 18 without). Among patients with CM, mean headache frequency was 25.7 per 28 days. Mean headache severity was 6.3 on a scale of 0–10, with 10 representing the most severe pain. Among patients with EM, mean headache frequency was 9.9 per 28 days. Mean headache severity was 6.0. Eighty-six per cent of all patients used abortive migraine medication at least 3 days/week. Among all patients, 15 (20%) were on monotherapy and 59 (80%) were on polytherapy. Sixty of 74 patients (81%) began topiramate therapy at 25 mg/day for the first week, which was increased by 25 mg/week to 100 mg bid (200 mg/day). Fourteen patients began topiramate therapy at 15 mg/day for the first week, which was increased by 15 mg/week. The mean daily dose for all patients was 208 mg, and the mean duration of treatment prior to analysis was 133 days. Mean headache frequency decreased from 20.6 per 28 days to 13.6 for all patients ($P<0.001$), from 9.9 to 5.1 for EM patients ($P<0.02$) and from 25.7 to 17.7 for CM patients ($P<0.01$). Headache frequency was reduced by at least 50% in 44.6% of all patients, 58.3% of EM patients, and 38.0% of CM patients. Among all patients, headache severity was reduced from 6.2 to 4.8 ($P<0.001$). Headache severity was reduced in EM patients (6.0–4.8, $P<0.001$) and in CM patients (6.3–4.8, $P=$NS). Seventy-four per cent of patients reported using less abortive medication. Migraine duration was shorter for 58% of EM patients. The number of years with CM, a diagnosis of depression, and the presence of a more severe psychiatric disorder did not correlate with a change in headache frequency ($P=$NS). The most common adverse events were paresthesias (25%), cognitive difficulties (15%), dizziness (4%) and nausea (4%). Six patients (8%) discontinued topiramate, 2 due to adverse events and 4 due to ineffectiveness. Mean weight loss was 6.9 lb.
Conclusions These study results suggest topiramate is effective in reducing headache frequency, severity, and duration in patients with EM and CM. Psychiatric comorbidity did not effect treatment outcome.

P2-I8

Topiramate: effective prophylaxis treatment for refractory migraines and mixed headaches

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Introduction In the prophylaxis treatment of migraine headaches, virtually all anticonvulsants that are currently marketed (perhaps more properly termed neuronal stabilizing agents or neuromodulators) have been shown to have efficacy. This may be concordant with the theory that migraines and perhaps other headaches are reflective of a brain disorder. Topiramate has unique mechanisms of action: blockade of sodium channels and AMPA/kainate glutamate receptors, agonist activity at GABA-A receptors, together with weak carbonic anhydrase activity. Preliminary evidence from this ongoing study, and from other investigators, has suggested that topiramate may be effective for migraine prophylaxis.
Methods Patients with chronic migraines, with or without other headache types were recruited from the population of a headache clinic and were enrolled in this open-label study. Topiramate was started at 25 mg per day, with weekly titration to 100–150 mg per day over 4–6 weeks. Active treatment continued over at least three months, although some patients have been treated up to a year or longer. Additional dosing titration was accomplished during ongoing treatment with topiramate. The average dose for successfully treated patients was 325 mg per day, usually in two doses (range 75–1600 mg). Patients were instructed to keep headache diaries, rating the frequency and severity of their migraines and other headaches. They used a 0–10 numeric rating scale (NRS) to rate the severity of their symptoms.
Results 98 patients were placed on topiramate. Most (76) had failed attempts at prophylaxis with neuronal stabilizing agents such as divalproex sodium, gabapentin, carbamzepine and other agents. Many ($n=49$) had coexisting cervical or lumbar neuropathic pain syndromes. In 60 evaluable patients, migraines decreased in frequency by an average of 70.5% per month. Remaining headaches were about 57% less severe, on a 0–10 NRS. 16 patients dropped out due to side-effects, mainly paresthesias, cognitive difficulties or non-benefit. 18 patients were just begun on therapy or did not follow the protocol instructions; 6 were lost to follow-up.
Conclusions Topiramate prophylaxis therapy was well tolerated and effective in reducing the frequency and severity of chronic migraine headaches in a refractory headache clinic population. Double-blind, placebo-controlled studies are warranted.

P2-I9

Topiramate is indicated in cluster-migraine

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Objective Determine whether topiramate is indicated for preventative treatment of cluster-migraine.
Background Topiramate demonstrates migraine efficacy in randomized controlled trials and in open label clinical experiences. Unfortunately, preventative selection is often difficult and usually determined by comorbid illnesses. However, it would be helpful if migraine diagnosis could define an appropriate preventative agent. Topiramate has shown efficacy in migraine and cluster headache, thus it may have efficacy in the cluster-migraine overlap syndrome, migraine with cluster features (MWCF).

Methods MWCF represents unilateral International Headache Society migraine associated with at least one symptom of ipsilateral orbital-nasal autonomic dysfunction (lacrimation, conjuctival injection, ptosis, eyelid edema, rhinorrhea or nasal congestion). Chart review was performed on all MWCF patients who were treated with topiramate from October 1997 to October 2000. The primary endpoint was defined as ≥50% reduction in migraine frequency. A significant reduction in headache or aura severity represented secondary endpoints. Endpoints were assessed after two to three months of treatment.

Results Fifteen subjects were identified, all women. Age range 38–62 years, mean 51.5 years. Five had chronic or transformed migraine and 10 episodic migraine. Aura was present in three; one multiple auras and another prolonged aura. Topiramate was adjunctive in 13, and monotherapy in two. Topiramate dose range 25–400 mg/day; mean 112.5 mg/day. Migraine improved in 14 (93%). Twelve (80%) had significant improvement with ≥50% reduction in migraine frequency. Two improved per secondary endpoints. Only one patient failed, a chronic migraine sufferer on adjunctive treatment. In chronic migraine sufferers there was no significant change in daily headache when assessed at three months. However, at six months one had a reduction in daily headache to once weekly. One monotherapy patient dropped out after two weeks of treatment because of dizziness and paresthesias but was assessed at two months with ≥50% reduction in migraine frequency. There were no other dropouts. Paresthesias occurred in two others, and one each had dysgeusia and drowsiness, and another had anxiety, depression and confusion. Seven patients had weight loss.

Conclusions Topiramate demonstrates efficacy, safety and tolerability in the treatment of migraine with cluster features. The high efficacy suggests a possible selection bias in favor of a migraine variant or phenotype likely to be topiramate responsive. Thus, specific migraine diagnosis or characteristics may define which preventative is most appropriate. This preliminary report suggests that topiramate is indicated for cluster-migraine prevention. However, randomized controlled trials are recommended.

P2-I10

Long-term therapy with topiramate reduces migraine frequency and severity: a retrospective chart analysis

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Objective To assess long-term efficacy and tolerability of topiramate for the prevention of migraine, utilizing a retrospective chart review.

Background Several antiepileptic drugs, including topiramate, appear to have utility in a variety of neurologic conditions such as neuropathic pain and migraine. Long-term efficacy and tolerability of these agents for the prevention of migraine have not been widely reported.

Design and methods Patients treated for >1 year with topiramate for migraine prevention were included. Chart review included demographics, baseline headache frequency, prior preventive medications, topiramate dose, reduction in migraine frequency (≥50%) and severity (≥2-point reduction on a 4-point migraine severity scale; 0=no pain, 3=severe or debilitating pain), and incidence of adverse events (AEs).

Results Thirty-seven female patients were included in the analysis, ranging in age from 19 to 60 years (mean = 42). Seventeen patients (46%) had migraine with aura. The mean number of years with migraine was 20 (range 3–50). Twenty-seven patients (73%) failed one or more (mean = 3.2) prior preventive medications. The mean duration of therapy was 2.3 year (range 1.3–3.9). The mean daily dose of topiramate was 295.3 mg (range 50–1600); 14 patients (38%) received ≤100 mg/day and 8 patients (22%) received 125–200 mg/day. Most patients (92%) received topiramate monotherapy. Only 3 patients (8%) received combination therapy. Thirty-one patients (84%) experienced a ≥50% reduction in monthly migraine frequency and 28 of 37 patients (76%) experienced a ≥2-point reduction in migraine severity while on topiramate therapy. No serious AEs were reported. The most common AEs were paresthesias ($n=8$), and confusion ($n=4$). Six patients discontinued therapy, 4 for lack of efficacy and 2 for AEs (diarrhoea, confusion). Sixteen patients experienced weight loss (mean 18.4 lb, range 10–68 lb).

Conclusions To our knowledge, this is the first report on the long-term utility of topiramate in migraine prevention. Topiramate therapy was well tolerated. A large majority of topiramate-treated patients experienced fewer, less severe migraine headaches.

P2-I11

Neuromodulation of late life migrainous accompaniments with topiramate therapy

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Objective To describe neuromodulation of late life migrainous accompaniments using prophylactic topiramate therapy.

Background Late life migrainous accompaniments – scintillating scotomas, numbness, aphasia, motor weakness and dysarthria – may occur for the first time after the age of 45 and complicate the diagnosis of cerebrovascular disease, particularly transient ischemic attacks. Treatment can be difficult for many reasons but cardiac disease and drug tolerability pose challenges in choosing a prophylactic medication for the older patient.

Topiramate is being evaluated currently as a migraine prophylactic agent. As a neuromodulator, topiramate blocks repetitive firing, enhances GABA inhibition, reduces glutamate, and affects voltage-gated Na^+ and Ca^{++}

channels, all of which may be important in interrupting migraine. Those characteristics, in combination with its cardiac safety profile, make topiramate an appealing drug to evaluate in the older patient with persistent migrainous accompaniments.

Design and methods Ten patients with persistent periodic neurologic phenomena (scintillating scotoma, parathesias, vertigo) were identified. All were over 65 years of age and one had a previous history of migraine with aura. After thorough evaluation to exclude causes of transient ischaemia, topiramate therapy was begun. Patients were treated with dosages beginning at 15 mg/day, increasing by 15–30 mg every four days, up to 100 mg BID. No significant adverse events were reported by the patients.

Results All 10 patients achieved complete resolution of their neurologic symptoms within 2 weeks of initiating topiramate.

Conclusions The anticonvulsant, topiramate, may represent an effective and safe therapy for treatment of late life migrainous accompaniments by modulating cortical hyperexcitability.

P2-I12

Levetiracetam as prophylaxis for resistant headaches

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Introduction Levetiracetam, a new anticonvulsant, was recently introduced in the USA for the treatment of seizures. It has an unknown mechanism of action. Using the rationale that virtually all commercially available anticonvulsants have shown efficacy in the treatment of migraines and other headache types, we decided to utilize this agent in the treatment of a headache clinic population with chronic refractory headaches. This initial open-label study with a neuronal stabilizing agent such as levetiracetam was undertaken on the premise that migraines and perhaps other headaches are a manifestation of an underlying neuronal dysfunction in the brain.

Methods and study design 30 patients from an existing headache clinic population were chosen for prophylaxis therapy with levetiracetam. All had been treated with other neuronal stabilizing agents (anticonvulsants) and had failed or responded poorly to these attempts at prophylaxis therapy. Each patient in the study had tried at least two agents and 18 patients had tried up to 4 different agents. Most ($n = 25$) were on at least one agent at the time levetiracetam was added. All patients had an average of at least 2 migraine episodes per week (IHS criteria) with additional tension-type headaches. 16 patients had additional cervical or lumbar radiculopathy symptoms, cervical whiplash injuries, failed neck surgery or traumatic brain injuries prior to onset of their severe headache pattern. Levetiracetam was started at 250 mg in the evening, with weekly increases. A one-month run-in period to 1000 mg twice a day was used. Further dosage adjustments were then made during active therapy. Patients kept headache diaries and rated severity of headaches on a 0–10 numeric rating scale (NRS).

Results 14 patients reported a better than 50% reduction in their migraine frequency and severity with 3 months of active therapy. Dosage was adjusted in some cases to 4500 mg per day in two or three doses. 12 patients were able to discontinue or taper the bulk of their prior prophylaxis medications during treatment with levetiracetam. 8 patients had no response, or discontinued the medication due to side-effects ($n = 3$). 4 patients had 25–50% decreases in their headache patterns and 4 are in the run-in phase.

Conclusions These preliminary results from an ongoing study using levetiracetam as migraine prophylaxis may add a new therapeutic strategy to existing available therapies with neuronal stabilizing agents. This may be very useful in treating refractory headache patterns that have failed multiple prior attempts at headache stabilization using neuronally active agents. These results may warrant a double-blind trial of levetiracetam in migraine prophylaxis.

P2-I13

Levetiracetam for preventive treatment of migraine

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Objective To assess the efficacy of the new anticonvulsant levetiracetam (Keppra, LEV) for preventive treatment of migraine.

Background and methods Antiepileptic drugs are increasingly recognized to be helpful in migraine treatment. LEV, a promising anticonvulsant of unknown mechanism, has been tried in a small number of headache patients. We gave 62 patients with refractory migraine with (10) and without aura (40) as well as daily headache (12) LEV beginning at 500 mg BID and increasing as needed to 1500 mg BID. Other preventive and abortive medications were continued. Patients reported headache frequency, duration and severity as well as side-effects at 1, 2 and 3 months.

Results Ten patients discontinued LEV because of side-effects (drowsiness, nausea, increased headache, tics and 'weird' feelings) or lack of efficacy. Headache frequency and severity were significantly less on LEV, although not in the first month and not at doses below 1500 mg/day. The infrequent side-effects increased at the more effective higher doses.

Conclusions LEV reduced the frequency and severity of refractory migraine with modest side-effects. Gradual titration to relatively high doses of this antiepileptic drug may be required for migraine therapy. Further study of LEV in headache and pain is appropriate.

P2-I14

Lamotrigine efficacy in migraine prevention

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Objective To show that lamotrigine has efficacy in the treatment of migraine with and without aura and chronic daily headache.
Background In a randomized controlled trial, Steiner et al. showed a lack of preventative migraine efficacy for lamotrigine. However, that study was flawed by the exclusion of 50% of the study population on the basis of being placebo responders or non-compliant during the single-blind placebo run in phase, too high a lamotrigine starting dose (200 mg/day), and changing the lamotrigine dose during the trial. Subsequently, open label studies by D'Andrea et al. and Lampl et al. suggested efficacy for migraine aura and migraine with aura, but not for migraine without aura.
Materials and methods Sixty-five patients with migraine or chronic daily headache seen between September 1999 and August 2000 were compassionately prescribed lamotrigine. Data was collected regarding demographics and efficacy was recorded after two or three months of treatment. The primary efficacy endpoint was a $\geq$50% reduction in severe headache frequency. Secondary endpoints included a $\geq$50% reduction in mild and moderate headache frequency or aura frequency.
Results 30 patients were excluded from analysis; 10 were non-compliant (six never started the medication), eight were lost to follow-up, one lack of benefit, and 12 adverse events (4 increased headache, 3 rash, 2 abdominal discomfort, 1 pruritus, 1 ataxia). 35 patients had adequate lamotrigine therapy, and efficacy was assessed at three months in 30 and two months in five. There were 26 women and nine men; age range 32–79 years, mean 48.4 years. 24 patients had transformed or chronic migraine, seven episodic migraine and four had hemicrania continua. Lamotrigine dose ranged from 25 to 200 mg/day, mean 55.1 mg, median 50 mg/day. Treatment was adjunctive in 34 patients. 48.6% (17/35) of patients showed significant improvement with a $\geq$50% reduction in severe headache frequency, the primary endpoint. However, overall efficacy was 57.1% (20/35). 18 patients had aura and 66.7% (12/18) had a $\geq$50% reduction in headache frequency. There were nine analgesic rebound or overuse patients and only one improved significantly. There were seven non-rebounding chronic migraine without aura patients and eight with aura; 28.6% (2/7) without aura and 50% (4/8) with aura improved significantly. Surprisingly significant improvement was noted in 75% (3/4) of hemicrania continua patients.
Conclusion This open label experience suggests supplementary evidence in favor of lamotrigine efficacy as a migraine preventative. Effectiveness was improved when aura was present and diminished by analgesic overuse. In some intractable populations, chronic migraine with aura and unexpectedly hemicrania continua, benefit was demonstrated. On the basis of these findings, additional randomized controlled trials are recommended.

P2-I15

Preventive treatment of migraine with zonisamide

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Objective To assess the efficacy of the new anticonvulsant zonisamide (Zonegran, ZNS) for migraine prevention.
Background and methods ZNS is a new antiepileptic drug which reduces glutamate-mediated excitatory neurotransmission, inhibits excessive nitric oxide production, scavenges hydroxyl and nitric oxide radicals and inhibits carbonic anhydrase. These mechanisms may be relevant to migraine as well as epilepsy. We gave ZNS to 34 patients with migraine with and without aura who were resistant to other preventive and abortive treatments. ZNS was begun at 100 mg/day and increased as tolerated to 400 mg daily. Other medications were continued, including abortive treatments but not analgesics. Patients reported frequency, duration and severity of headaches as well as side-effects at 1, 2 and 3 months.
Results Headache severity was significantly reduced, and the other measures decreased with ZNS treatment. Paresthesias, fatigue, anxiety and weight loss were acceptable side-effects which often resolved; more bothersome side-effects were agitated dysphoria (2) and difficulty concentrating (2), which prompted discontinuation. Nine other patients discontinued ZNS because of perceived lack of efficacy.
Conclusions ZNS, like other neuromodulating anticonvulsants, may be efficacious for migraine prevention. It reduced headache severity and was well tolerated; at least some of the patients who stopped it due to apparent inefficacy may have responded with a longer trial. Prospective study in a larger population is appropriate.

P2-I16

Zonisamide in the treatment of headache disorders

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Introduction Zonisamide, an anticonvulsant recently introduced in the US has a unique combination of pharmacologic actions: it inhibits voltage-gated Na^+ channels and also blocks T-type calcium channels. Both of these mechanisms may play a role in headache and pain modulation, possibly via neuronal stabilization.
Methods 33 patients, taken from an active headache clinic population, were selected for open-label treatment with zonisamide. All had refractory migraines and mixed headache disorders, by IHS criteria. All had failed, or had responded poorly to prior trials with other anticonvulsants as prophylaxis therapy, and most ($n=27$) had failed at least 2 such agents. 8 had chronic migraines alone, with an average of 9 migraines per month. The rest of the patient sample had tension-type headaches along with migraines (average of 7.7 episodes per month).

Zonisamide was started as add-on therapy to other prophylaxis agents. 100 mg was given in the evening or at bedtime every third day for 4–5 doses. Then, it was increased to every other day for the same number of doses before beginning on a daily regimen. Dosage was changed every 2–3 weeks and in some cases was as high as 600 mg/day. Headache frequency and severity were reported by patients using diaries. Severity was reported on a 0–10 numeric rating scale (NRS).

Results 6 patients reported a 65% or better decrease in frequency of migraines and other headaches; 8 reported 25–50% decrease in their symptoms. 9 patients did not respond or were non-compliant with the protocol; 4 of these patients stopped the medication due to side-effects. 10 patients have just been started on the medication and are in the titration phase of therapy.

Conclusions Zonisamide may have efficacy in a difficult-to-treat refractory headache population. These initial data, generated open-label and ongoing, suggest zonisamide may, like virtually all other neuronal stabilizing agents (anticonvulsants), have efficacy where older agents have failed to provide relief of headache symptoms. This potentially useful agent for headache prophylaxis should be studied in a double-blind manner.

P2-I17

Asthma + migraine in childhood and adolescence: prophylactic benefits with leukotriene receptor antagonist

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Objective To evaluate the prophylactic benefits of montelukast, a potent cysteinyl leukotriene receptor antagonist on asthma plus migraine patients.

Materials and methods Treatment of 6 outpatient asthma + migraine sufferers (3 males and 3 females, aged between 9 and 13 years) were evaluated on a prospective open-label study design using sodic montelukast 5 mg (SINGULAIR®) once at night for 24 weeks. Prophylaxis and diagnosis was established for asthma according to the International Consensus Report on Diagnosis & Management of Asthma (1992) and for migraine using the IHS criteria (1988) modified by Winner et al. (1995). Frequency of attacks was measured by patients' notes on a standard calendar currently adopted at DITH.

Results All patients experienced a decrease in asthma attacks during treatment. No relevant side-effect was reported. Patient data and migraine improvement are presented in the table at the foot of the page, where M = male; F = female; MA = migraine with aura; MO = migraine without aura.

Conclusions Leukotrienes are pro-inflammatory mediators derived from the metabolism of arachidonic acid via 5-lipooxygenase. Leukotriene antagonists for asthma prophylaxis are currently available. Perivascular inflammatory reaction in the intracranial trigeminovascular system is accepted in the pathophysiology of migraine attack. Sheftell et al. (ASH meeting 1999, oral presentation) reported a greater than 50% decrease in frequency and intensity of attacks during two months of prophylactic use of montelukast 10 mg in 10 of 14 adults migraine sufferers. The results suggest a beneficial effect of montelukast toward decreasing the frequency of migraine and asthma attacks during 24 weeks of medication in this small sample of young patients. This treatment indicates safe and efficacious benefits from prophylactic control of asthma migraine comorbidity.

P2-I18

Preventative treatment of migraine headache with rofecoxib and montelukast

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Introduction The use of NSAIDs has long been known to be effective in migraine prevention. Work by Sheftell (1) has demonstrated partial efficacy of montelukast in migraine prevention.

Table for abstract P2-I17

Patient ID	Age (year)	Sex	Diagnosis of headache	Reported calendar of attacks: Estimation to 4 weeks	During 4 weeks before treatment	During first 8 weeks of treatment	During second 8 weeks of treatment	During third 8 weeks of treatment
F.C.N	9	M	MA	3	6	3	1	1
R.D.L.	11	M	MO	8	3	1	1	0
T.P.S.	13	M	MO	8	6	1	1	0
V.M.S.P.	12	F	MA	12	8	3	2	2
K.F.R.	12	F	MO	20	8	2	2	2
D.O.S.	13	F	MO	8	4	2	0	2

Study purpose To assess the efficacy of a COX-2 inhibitor, NSAID, rofecoxib combined with montelukast in migraine prevention.
Study design Prospective, open label of rofecoxib 12.5 mg daily combined with montelukast 10 mg daily for 12 weeks in migraine without aura. Patients had 2–12 migraine attacks per month. Interval headaches were less than 15 days per month and distinguishable from their migraines. Previous preventative medications were allowed if dose had been stable for 8 weeks prior to study initiation.
Results There were 33 patients enrolled, 25 females and 6 males. 31 patients had evaluable data. 2 patients dropped out in the first month of treatment due to adverse effects. The mean number of migraine attacks at initiation was 6.4 attacks per month. At the end of 12 weeks, the migraine frequency was reduced to 2.3 per month ($P < 0.001$). 25 of 31 patients had at least a 50% reduction in their migraine frequency. 2 patients had transient adverse effects but continued on the study. There were 6 patients who had been on previous preventive medication. There was no statistical difference in their response rate compared to patients on no prior preventative medication ($P < 0.05$). There was no change in the occurence rates of interval headache. Long-term use of 4–40 weeks additional use demonstrated no increased risk of adverse effects nor dimunition in the response rate.
Conclusion The combination of rofecoxib and montelukast was a highly effective, well-tolerated preventative treatment for migraine headache. The combination of the 2 agents produced more favorable results with less adverse events than have been found in previous clinical trials of an NSAID or monteluskast alone.

Reference

1 Sheftell F et al. Headache, 1999; 39:381.

P2-I19

Rofecoxib for migraine prophylaxis

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Objective To demonstrate the effectiveness of rofecoxib in the prevention of migraine.
Methods and materials Rofecoxib was prescribed to a series of patients presenting to an outpatient clinic with complaint of migraine headaches. The study was conducted in a retrospective chart review fashion. 25 patients with IHS criteria for migraine headache were treated with rofecoxib 25 mg per day, in addition to their usual abortive medications. Migraine types include migraine with and without aura, mixed migraine/tension and post traumatic migraine. Initial headache frequency was recorded. On subsequent follow-up (range 4–8 weeks), headache frequency was again recorded, as well as adverse side-effects or reason for discontinuation.
Results 16 of 25 patients (64%) reported a significant reduction in frequency of their headaches post-treatment, defined by reduction in frequency of at least 50%. Rofecoxib appeared to be equally effective for all migraine subtypes. Rofecoxib appeared to be well tolerated at the dose of 25 mg per day. 4 of 25 patients discontinued the medication, and only 2 (8%) did so because of untoward side-effects. Side-effects reported were pelvic pain and malaise. No patient discontinued rofecoxib because of GI intolerability. Two patients discontinued rofecoxib due to poor response. One patient discontinued rofecoxib because her migraines were completely controlled resulting in headache recurrence after discontinuation. After reintroducing rofecoxib, complete migraine control was once again achieved.
Conclusion Rofecoxib appears to be an effective, well-tolerated medication for the prophylaxis of migraine headache. Additional investigation of this medication on a larger scale is warranted.

P2-I20

Prophylactic treatment of migraine with tizanidine

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Objective To assess the efficacy of the alpha-2 adrenergic antagonist tizanidine (Zanaflex, TZD) as an adjunct to the prophylactic treatment of refractory migraine.
Background and methods TZD has been widely used to treat spasticity, tension headache, analgesic rebound headache, and as an adjunct to the multifaceted treatment of transformed migraine. It may also have a role in migraine preventive therapy, and with early use may prevent the emergence of daily headache. We gave TZD to 22 patients with frequent episodic migraine with and without aura who had not responded to anticonvulsants or antidepressants, and whose attacks were incompletely controlled by abortive agents. TZD was started at 4 mg nightly and increased to 16 mg nightly or in divided doses as tolerated. Other migraine medications were continued but analgesics were not. Patients reported headache frequency, duration and severity as well as side-effects after 1, 2 and 3 months.
Results TZD in doses of 4–16 mg per day significantly reduced the severity and duration of headaches, and caused a less marked reduction in their frequency. Thirteen of the 22 patients could not continue the effective TZD dose or chose to stop TZD due to sedation, fatigue or weakness.
Conclusions TZD may be a useful adjunct to other preventive medications for the prophylactic treatment of migraine. We found the sedative effects to be limiting, however, even with bedtime dosing. More gradual titration and the recent availability of a smaller size may improve the tolerability of TZD for sensitive patients.

P2-I21

Acute effect of acetazolamide on familial hemiplegic migraine (FHM)

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Background Acetazolamide, a carbonic anhydrase inhibitor, is a treatment effective in the episodic ataxia type 2 and it has already been used successfully in FHM prophylaxis. Distinct types of mutations in the CACNA1A gene have been identified in these different autosomal dominant disorders.
Objective To evaluate the efficacy and tolerance of acetazolamide in the treatment of acute FHM attacks.
Material and methods We studied a 15-year-old male affected, since the age of 11 years, with attacks of scotoma in the peripheral visual field, lasting 15–20 min, followed by right (occasionally left) hemiparesthesia, including the hemiface and the hemitongue, hemiplegia and aphasia. These symptoms usually persist for 24 h. A migrainous throbbing headache, with nausea and vomiting, develops 30–60 min after the beginning of visual aura. Attacks may be provoked by trivial trauma or by stressful events. Brain MR and interictal neurological examination were normal. His mother had suffered two attacks of migraine with visual aura, hemiplegia and aphasia. The patient was treated with simple analgesics (acetyl salicylic acid or nimesulide) for five consecutive FHM attacks, in two associated with zolmitriptan (2.5 mg), and for three other consecutive attacks with acetazolamide (500 mg per os) at the beginning of aura symptoms, and zolmitriptan (2.5 mg) at the beginning of the migrainous headache.
Results Simple analgesics with or without zolmitriptan, were without benefit on aura symptoms, which still lasted 24 h, and gave limited headache relief. Duration of aura symptoms, including the hemiplegia, were significantly shortened to 1.5–2 h after acetazolamide. Zolmitriptan was effective on headache and associated symptoms in 1–1.5 h. No adverse events were reported.
Conclusion This preliminary study suggests that acetazolamide is a safe and effective acute treatment of prolonged and disabling neurologic symptoms of FHM, especially when prophylaxis is not feasible due to a low frequency of attacks.
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P2-I22

Flunarizine and migraine: a prospective study on long-term prophylactic effectiveness

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Introduction In a previous naturalistic study, we evaluated the efficacy of prophylactic treatments and the existence of a post-treatment remission period in a group of outpatients affected by migraine with or without aura attending our headache centre.
Objective The objective of this study was to evaluate the long-term effectiveness of prophylactic therapy with flunarizine and the presence of a well being period after repeated cycles of therapy.
Materials and methods We chose our sample from a group of 81 responding patients out of a number of 114 subjects who performed the first preventive treatment with flunarizine. Thirty-two patients affected by migraine responding to the first preventive treatment with flunarizine (5 mg/day for at least three months) were followed up prospectively for 2–5 years during repeated cycles of preventive flunarizine therapy. We evaluated the efficacy of flunarizine using migraine index (frequency×intensity) before and after treatment and these data were statistically analysed with two-tailed Wilcoxon test for paired data. The percentage of patients who reported a period of partial (>50% decrease in the frequency of attacks) or total (lack of attacks) as well as the presence of side-effects during preventive therapy were detected.
Results All 32 patients repeated another prophylactic treatment with flunarizine: 30/32 patients (93.7%) responded during therapy and the post-treatment remission period was described in 19/30 patients (63.3%). A group of these patients were submitted to other preventive cycles of flunarizine therapy. The only side-effect observed was weight gain.
Conclusions Our data suggest that the efficacy of flunarizine during therapy was maintained in repeated preventive treatments and the partial or total remission period is present in at least 60% of patients even if its duration is reduced progressively.

P2-I23

The effect of mianserin on quality of life survey in migraine patients

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Migraine is one of the most observed primary headache types with a pronounced effect on general health and on the ability to take part in social activities. The management of migraine patients does not focus only on treatment of the headache but also on improvement in the quality of life. The purpose of this study was to evaluate the effect of mianserin, a tetracyclic antidepressant (2×10 mg), combined with a non-steroidal anti-inflammatory drug on quality of life survey in migraine patients. Fifty-four migraine patients, evaluated according to IHS criteria, were enrolled in this study (45F, 9M; mean age, 34±1.2). Mianserin was combined with a non-steroidal anti-inflammatory drug (naproxen sodium 2×275 mg [$n=34$] or nimesulide 2×100 mg [$n=20$]) and used for approximately 1 month. Quality of life survey was assessed using Medical Outcome Study (MOS) Short Form Health Survey (SF-36).

The SF-36 Health Survey is an instrument used for the assessment of the health-related quality of life of patients. The survey was constructed for self-administration by people 18 years of age and older. Evaluated parameters are physical functioning, limitations due to physical health, limitations due to emotional problems, energy-fatigue, emotional well being, social functioning, pain and general health. Mianserin therapy combined with non-steroidal anti-inflammatory drug, in migraine patients for one month improves significantly all the parameters assessed and related to quality of life. As it is well known that migraine diminishes quality of life, the management of migraine should also be addressed to the effect of the therapy on quality of life. In this study, we present the beneficial effect of mianserin (2×10 mg) on quality of life in migraine patients.

P2-I24

Buspirone as an adjuvant therapy in the prophylaxis of refractory migraine: case studies

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Objectives Stress is a recognized precipitating factor in migraine. It has been suggested that the physiological and psychological responses to stress in migraine patients are different from the non-sufferers (1). Buspirone, a 5-HT2a agonist, is an effective anxiolytic drug with many pharmacological effects. Buspirone has been observed to be effective in tension headache (2). The aim of this pilot open study was to assess buspirone's efficacy as an adjuvant therapy in the prophylaxis of migraine attacks.
Patients and methods Ten female migraine patients, aged between 22 and 85 years, were prescribed buspirone 10 mg twice daily initially for 6 weeks in an open study. They all had normal CT/MRI scan of head, but EEG was abnormal in 2 patients. 5 were suffering from migraine with aura and 3 had migraine without aura. Three others fulfilled the criteria for chronic tension-type headache (CTH) (IHS, 1988). Buspirone was prescribed when all other pharmacological treatment options were exhausted. The concomitant prophylactic drugs were sodium valproate, verapamil, baclofen, a non-selective beta adrenoceptor blocking drug and pizotifen. Patients were not taking any other regular medication. They were seen at an outpatient clinic and were instructed to keep a migraine diary. The average frequencies of attacks per month were 4 in migraine and 20 in CTH patients. Patients who improved and were able to tolerate the medication, received buspirone for 12 months or longer depending on the clinical progress.
Results At the end of 6 weeks' treatment, the average frequencies of attacks per month were reduced to 1.5 and 8 in migraine and CTH groups, respectively. Six patients observed 30–90% (average 62%) reduction in the migraine frequency and 4 patients maintained the improvement for 7–12 months. They were selected for long-term therapy. The attacks were also of shorter duration and less severe, but they were not specifically monitored. Buspirone was discontinued for adverse reactions, such as spacing out and general slowness, in 2 patients. One patient suffered from a seizure following 2 weeks' medication and buspirone was stopped. Two other patients did not take buspirone for longer than 2 weeks due to poor motivation and/or fear of side-effects.
Conclusion In the dosage used, in this open pilot study buspirone appears to be an effective adjuvant therapy for the prophylaxis of migraine and related headaches. However, clearly further long-term placebo-controlled study involving a larger patient population is necessary to verify buspirone's efficacy in migraine prophylaxis.

References

1 Holm JE et al. Headache 1997; 37:221–7.
2 Mitsikostas DD et al. Acta Neurol Scand 1997; 96:247–51.

P2-I25

Use of chlordiazepoxide/amitriptyline combination for long-term migraine prophylaxis

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Forty-four migraine patients who had more than 5 migraine attacks per month were given 5 mg chlordiazepoxide and 12.5 mg amitriptyline combination as migraine prophylaxis. Patients ranged in age from 20 to 75 years and were followed for 5 years. Migraine abortive drugs were allowed for acute attacks, but no other prophylactic drug was permitted. All patients had at least a 50% reduction in frequency of attacks over the 5-year period. Duration and intensity were also reported to be less. No serious side-effects were reported. The combination drug appears to be as effective as higher doses of amitriptyline and prophylaxis occurs at much lower doses when combined with chlordiazepoxide. This study suggests that the combination drug of 5 mg chlordiazepoxide and 12.5 mg amitriptyline is an effective migraine prophylactic agent working as effectively as higher doses of amitriptyline alone, but without the accompanying side-effects.

P2-I26

Preventing headache by intervening during prodrome: what predicts success?

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Objective To review patient diaries from a previously reported study to determine if one is able to characterize the prodrome symptoms that were associated with success in terms of preventing moderate to severe headaches.
Methods Prodrome precedes headache by up to 48 h, is characterized by a variety of symptoms, and is distinguished from aura. Migraineurs who are able to recognize prodrome symptoms may be able to intervene and prevent headache.

Naratriptan, a long-acting 5HT-1 agonist, has been shown to prevent headache in patients with documented prodrome (1). Adult migraineurs who were aware of prodrome symptoms preceding headache by 4–24 h recorded onset of prodrome and symptoms, time of naratriptan 2.5 mg administration, and headache onset and severity. A posthoc analysis was conducted to compare prodrome symptoms that preceded headaches that were successfully prevented with those prodrome symptoms that were followed by headache, despite intervention with naratriptan.

Results 20 patients documented 84 prodromes and took naratriptan 2.5 mg at the point when they felt the headache was inevitable. A moderate or severe headache was prevented in 68/84 (81%) prodrome treatments. Of the successfully treated prodromes, 54/68 (79%) were not followed by headache and 14/68 (21%) were followed by mild headache. Successful intervention (none or mild headache) was most frequently preceded by the following prodrome symptoms: irritability 29/68 (43%), change in nausea 29/68 (43%), and muscle pain/tenderness 27/68 (40%). Similar prodrome symptoms were reported for those headaches that were not prevented, suggesting that further research is needed to identify which prodrome symptoms may predict success, in terms of preventing headache. However, time of naratriptan administration may be more important for preventing headache than recognizing specific prodrome symptoms.

Conclusion Preventing headache by intervening during prodrome may be possible if the intervention can be administered at an optimal time. This requires that migraineurs are able to recognize prodrome symptoms that predict success. More studies are needed to determine these symptoms and to optimize the timing of the intervention.

Reference

1 Cephalagia 2000; 20:122–6.

P2-I27

The role of naratriptan as a prophylaxis to the menstrual migraine: a pilot comparative to naproxen study

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Objectives Menstrual migraine is a monthly nightmare for many young women, starting 1–3 days before or after the menstruation onset. Triptans are the treatment of choice for attack therapy, but a small percentage of them require specific prophylaxis. NSAIDs drugs, as well as estrogen supplements, have been used for this purpose. Naratriptan, a second-generation triptan without associated adverse events and rebound phenomena, could be used as a short duration prophylactic treatment. The aim of this study is to evaluate the usefulness of Naratriptan as prophylaxis for true menstrual migraine.

Patients and methods Fifteen young women, mean age 29-year-old, with regular cycle and menstruation as the only trigger of migraine, were enrolled in this open study, comparative to NSAIDs study, which lasted 6 months. During the first 3 months, they were requested to keep a headache and menstruation diary card and were under treatment with NSAID (Naproxen 500 mg/day) that started 3 days before the expected onset of menstruation and was taken the 3 first days of bleeding. During the second quarter, all patients were under treatment with Naratriptan, 2.5 mg/day for 6 days (-3 up to $+3$ days from the menstruation onset). The results of the second quarter were compared with those of the first one for each patient.

Results 12 of the 15 women (80%) treated with Naratriptan and 8/15 (54%) treated with Naproxen had no attack. Three women under Naratriptan had an attack of mild intensity and short duration.

P2-I28

Can vagus nerve stimulation help migraine?

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Objective To investigate whether epileptic patients treated with vagus nerve stimulation (VNS) and suffering from migraine experience relief of headaches following VNS implantation.

Background The mechanism of action of VNS used for control of epilepsy is not completely understood. Hypotheses include secondary activation of multiple central nervous system structures by the Nucleus Tractus Solitarius (NTS), including reticular activating system and cerebral cortex. NTS also projects to amygdalo-hippocampal complex, thalamus, hypothalamus, and spinal trigeminal nucleus, all structures implicated in migraine. It is therefore suggested that vagus nerve stimulation could potentially help control migraine by modifying the activity of these different structures.

Methods We identified all the patients in the VNS registry of the department of Neurology of the University of Oklahoma ($n=34$). These individuals were contacted and information was collected by telephone with standard form by the first author (M.E.L.). Patients were screened for diagnosis of migraine according to IHS criteria. The outcome measurement used was the average monthly frequency of migraine attacks, which was assessed in three time periods: (I) 3 months before VNS placement; (II) 3 months immediately after VNS placement; (III) 4–6 months after VNS placement. Improvement was defined as at least 50% reduction in the frequency of attacks from before to after VNS placement. Patients unable to give accurate answers were excluded.

Results Of the 34 identified patients in the registry, 5 could not be contacted and 4 were excluded for lack of accurate information due to mental retardation. Of the 25 patients from whom adequate information was obtained, 10 (5M/5F) had

IHS-defined migraine. Of these, 8 improved, 2 did not improve and none became worse. Improvement occurred in the first 3 months after placement of VNS (period II), and was maintained over the next 3 months (period III) in all patients who showed improvement. The two who did not improve in period II did not show late improvement (period III) either.
Conclusion These observations suggest that VNS may produce improvement of migraine by decreasing the frequency of attacks. The study has to be interpreted with great caution since data were retrospective and the sample was small. Multiple confounding factors might play a role such as improvement of seizure condition and effect of VNS on mood, currently under intense investigation. Nonetheless, this study suggests that the effect of vagus nerve stimulation in migraine warrants further study.

P2-I29

A randomized, double-blind placebo-controlled parallel group study of thioctic (or alpha-lipoic) acid, 1600 mg po in migraine prophylaxis

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Objectives To assess the prophylactic antimigraine effect of thioctic acid (Thioctacid®) in a randomized controlled trial (RCT). Thioctic acid (alpha-lipoic acid) is known to enhance energy metabolism in mitochondria and of proven benefit in diabetic neuropathy. Impaired mitochondrial phosphorylation potential may play a role in migraine pathogenesis (Montagna et al., 1994) and enhancers of mitochondrial energy metabolism, such as high-dose riboflavin, are effective in migraine prophylaxis. After an open pilot study indicated a possible benefit, we performed an RCT of oral thioctic acid in the prophylactic treatment of migraine.
Material and methods Five Belgian centres recruited 54 migraineurs (48 migraine without aura, 10 with aura; mean age 38 ± 8 year; 7 males). They received placebo for a 1-month run-in period and were included in the randomized double-blind phase, if they had presented at least 1 attack. Forty-four patients received either placebo ($n = 18$) or thioctic acid 600 mg p.o./day ($n = 26$) for 3 months. Seven patients dropped out after 2 months (2 in the placebo arm, 5 in the verum); their data were included according to the last-value-carried-forward method. The trial was interrupted before the planned 80 patients were enrolled, because of slow recruitment in some centres and time limitation in drug quality.
Results Monthly attack frequency was reduced between run-in and the third month of randomization after thioctic acid, but not after placebo ($P = 0.034$). There was, however, no significant difference in attack frequency between the first run-in month and the average of the randomized 3 months, nor in headache days. The proportion of responders (50% reduction in monthly attack frequency) was not significantly different between placebo (11%) and thioctic acid (19%). Within group analyses showed a significant reduction of attack frequency ($P = 0.002$), headache days ($P = 0.008$) and headache severity ($P = 0.042$) on average in patients treated with thioctic acid, but no significant reduction in the placebo group. No adverse effects were reported. The reasons for drop-outs were inefficacy and in 1 patient rhinitis.
Conclusions This RCT does not demonstrate a clinically meaningful advantage of thioctic acid over placebo in migraine prophylaxis. On various secondary outcome measures, there is nonetheless an indication for a beneficial effect of thioctic acid. As this study was underpowered because of premature interruption, a large multicentre trial of this compound, which has an excellent tolerance, may be worthwhile.

P2-I30

Open-label trial of high-dose Coenzyme Q10 as a migraine preventive

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Objectives To assess the efficacy of high-dose Coenzyme Q10 as a preventive treatment for migraine headaches.
Background The true pathogenesis of migraine is unknown. Clues from magnetic resonance spectroscopy studies and DNA analysis suggest that migraine, in a subset of individuals, is a direct result of mitochondrial impairment. At present, there are very few efficacious migraine preventives and fewer without significant side-effects. Coenzyme Q10 is a naturally occurring substance and an essential element of the electron transport chain. It has been the most extensively studied agent for the treatment of mitochondrial disorders. If indeed migraine results from mitochondrial dysfunction, then Coenzyme Q10 could be a successful migraine preventive.
Methods 32 patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with Coenzyme Q10 at a dose of 150 mg/day. Study subjects had to have had a migraine history for at least one year and have experienced between 2 and 8 migraines per month. No one was on preventive therapy within two months of Coenzyme Q10 administration. Total study length was four months with a one-month baseline period and three-month therapy phase. Each patient kept a study diary to monitor migraine frequency and intensity.
Results 31 of 32 patients completed the study. One patient was lost to follow-up. 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. 93.5% had at least a 25% reduction in number of days with migraine. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after three months of therapy which was a statistically significant response ($P < 0.0001$). Mean reduction in migraine frequency after one month of treatment was 13.1% and this increased to 55.3% by the end of three months of therapy. There were no

side-effects noted with Coenzyme Q10. Because of the small number of males in the study and individuals less than age 30, we were unable to comment on any sex or age group differences in response to Coenzyme Q10. In the attacks that did occur, Coenzyme Q10 did not appear to significantly reduce headache intensity.

Conclusion From this open-label investigation, Coenzyme Q10 appears to be a good migraine preventive. The data suggest that Coenzyme Q10 starts to work within four weeks of initiation but usually takes five to 12 weeks to yield a greater than 50% reduction in days with migraine. Placebo-controlled trials are now necessary to determine the true efficacy of Coenzyme Q10 in migraine prevention.

P2-I31

Creatine phosphate as a prophylactic agent in migraine. A pilot study

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Objective To determine the efficacy and safety of creatine in the prevention of migraine in a pilot study.

Background 31P-MR spectroscopy has shown decreased levels of phosphocreatine, the high energy phosphate buffer, in the brains of migraineurs. Creatine is a precursor of phosphocreatine, and it is used to increase mass and aerobic fitness of muscles.

Design and methods Eight patients suffering from migraine without aura (2 males and 6 females, aged 29–42 year) gave informed consent to a pilot double-blind *vs* placebo study of creatine. After a run-in time of 6 months, patients were randomly allocated in a cross-over design to a placebo or creatine phosphate, 5 g per os 4 times a day in soluble form for one week followed by 5 g once a day for 3 months (wash out period of 3 months). The number and intensity of the migraine attacks, the days free from migraine and the consumption of analgesic medications were calculated for each trial period. Patients underwent blood and urine and standardized lactic effort tests prior to and at the end of each trial period. Statistical analysis was performed by means of Paired Student's *t*-test.

Results All patients finished the study and there were no untoward clinical or laboratory effects. Creatine administration resulted in no statistical differences in any of the variables analysed. Peak effort lactic levels were reduced after creatine.

Conclusion Creatine administration was safe but did not show beneficial effects in the prevention of migraine attacks, at least at the dosages and treatment duration used here. Further studies, on more patients, and with different dosages may be needed.

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P2-I32

Effect of changes in nutrition and lifestyle on migraine: the patient's experience

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Objectives To evaluate the effect of changes in nutrition, consumption of alcohol, lifestyle and environmental factors in migraine patients and migraine-free controls.

Patients and methods Sixty-six consecutive patients suffering from migraine with and/or without aura and 45 migraine-free controls completed a semistructured interview covering demographic data, headache characteristics, changes in nutrition (including alcohol, cheese, dairy products, chocolate, cereals, caffeine, food additives, fruits, vegetables, nuts, etc.) and lifestyle or environmental factors (including stress, sleeping habits, intake of meals, hunger, smoking, oral contraceptives, physical activity, exhaustion, bright light, noise, etc.) and the effect of such changes on headache. Patients with overuse of analgesics, ergotamines and/or triptans as well as patients with relevant organic and/or psychiatric disorders were excluded. The subjects gave informed consents. All interviews were performed by the same person (JH) either personally or by telephone. For statistical analysis, SPSS-WIN 10.0 was used.

Results Patients and controls were comparable regarding age, sex, educational level and profession. In migraine patients, 19.7% had changed nutrition and 35.4% had changed lifestyle because of headache; another 19.7% and 23.1%, respectively, reported changes because of other reasons. In the controls, the corresponding percentages were 4.4% and 6.7% (changes due to headache) and 35.6% and 42.2% (other reasons). Changes in nutrition most commonly included alcohol, red wine, chocolate, cheese and caffeine. Statistically significant differences between migraineurs and controls were found in only 2 of 19 factors, i.e. alcohol ($P<0.001$) and red wine ($P<0.05$). Changes in lifestyle most commonly comprised stress, oral contraceptives, smoking, sleep, and intake of meals. None of a total of 12 factors differed between patients and controls. Changes in nutrition were rated effective by few subjects (migraineurs: 11.5%, controls 5.6%). Changes in lifestyle, however, were rated effective significantly more often (migraineurs: 41.0%, $P<0.05$, controls: 22.7%, $P<0.05$). The difference in the efficacy of lifestyle changes between patients and controls was on the border of statistical significance ($P=0.05$).

Conclusions Between 40 and 60% of patients with migraine and migraine-free controls change nutrition and/or lifestyle in order to improve their headaches. Changes in nutrition are rated effective by few subjects, whereas changes in lifestyle are related to an improvement of headache by more than 40% of the migraine patients and by more than 20% of the migraine-free controls.

P2-I33

Nutritional profile and intermediate metabolism of B12 vitamin: a novel physiopathological and therapeutic approach for migraine. An open study on 70 patients

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Objective The aim of our study is to evaluate in migraineurs eventual alterations in food behaviour, gastrointestinal problems with or without clinical evidence of nutrient deficiency (above all, vitamins and minerals), repercussion of corrective therapy on migraine, and possible physiopathological interpretation.
Materials and methods During the period from January to December 2000 we studied 70 consecutive patients (48 F) with a mean age of 33.8 (SD 12.6) years who were suffering from migraine with or without aura (IHS 1988 criteria). We did an open study in 5 stages: T0: first visit; T1: starting of corrective therapy; T2, T3, T4: follow-up controls.
Results 80% of patients followed an unbalanced diet (excessive consumption of animal proteins, acid fats, simple carbohydrates rather than complex ones; small quantities of vegetable proteins, vitamins and mineral salts) and disproportionate consumption of main meals and snacks. The average water consumption was 781.4 mL/24 h without thirst (37.1%). In 91% of cases at least one gastroenteric symptom was present (14.3% diarrhoea, 63% nausea and/or gastralgia). Furthermore, symptoms of lack of vitamin A were found (photophobia 72%; nyctalopia 48.6%), of vitamin B12 and cobalt (cold feet 48.6%; limb cyanosis 14.3%; joint and muscle pain 54.3%; cold hands 34.3%; cramps 48.6%; and paraesthaesias at upper and lower limbs 45.7–40%). Clinical data were confirmed by following laboratory results: increase of plasma osmolarity (38.6%); reduction of B12 vitamin serum concentration (64.3%); and serum concentration of cobalt below normal limits (57.1%). After the therapy aimed to correct these deficiencies, migraine index values were found significantly reduced ($P < 0.001$) with respect to basal ones.
Conclusions The crucial point from a physiopathological point of view is represented by a possible dysfunction of vitamin B12; other mechanisms can be the production of abnormal vasoactive substances by bacterial flora and change of the homeostatic balance.

P2-I34

A placebo-controlled, double-blind trial of magnesium with riboflavin and feverfew for the prevention of migraine headaches

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Introduction Current prophylactic agents for migraine have limited efficacy and a high side-effect profile. Three 'natural' supplements – magnesium, riboflavin, and feverfew – have each demonstrated efficacy for migraine prevention in placebo-controlled trials. Differences in therapeutic mechanisms suggest the possibility that a combination of these agents may offer further efficacy with a low side-effect profile.
Methods Some 120 patients are to be randomized in a 1:1 ratio to receive either the combination supplement or placebo, in order to produce evaluable results for 96 patients. Patients log their headache frequency and severity for a one-month run-in, and then a 3-month trial period. The primary endpoint measure is change in number of migraine attacks. Secondary endpoints include: per cent of patients with at least 50% decrease in migraine attacks; and changes in number of: migraine attacks month 1 and month 3, migraine days, doses of triptan medication, and migraine quality-of-life scores.
Results Statistical design allows for an evaluation of the data after a total of 48 patients have completed the study. Results for the first 48 patients will be reported.
Conclusion A new therapeutic product which combines magnesium, riboflavin, and feverfew is evaluated.

P2-I35

Fish oil vs olive oil in the management of recurrent migraine headaches in adolescents

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Objective To examine whether dietary supplementation with fish oil rich in very long-chain n-3 polyunsaturated fatty acids (PUFA) can alleviate recurrent migraine headaches in adolescents.
Background Recent reports have suggested that increasing dietary intake of n-3 PUFA results in formation of less potent inflammatory mediators, and attenuates inflammatory processes that may affect adolescents.
Design and methods 27 adolescents with frequent migraine headaches for at least 1 years (mean 4+1 years) participated in a randomized, double blind, crossover study consisting of 2 month fish oil, 1 month washout period, and 2 month placebo (olive oil). Participants self-assessed severity and duration of headache episodes throughout the study. At the end of every 2-month treatment period, participants rated the effectiveness of treatment on a 7-point Likert Scale (1 'not

effective, not worthwhile'; 4 'moderately effective, moderately worthwhile'; 7 'totally effective, totally worthwhile'). A score of >4 was considered as improvement.

Results 23 adolescents (16 girls, 7 boys, mean age $15+1$) completed the study. Compared with frequency of headaches before the study, there was a significant ($P<0.0001$) reduction in headache frequency during fish oil treatment and during olive oil treatment but no significant (NS) difference between treatments. Likewise, self-assessment on the 7-point faces pain scale revealed a significant reduction in headache severity during fish oil treatment ($2.9+0.5$, $P=0.01$) and during olive oil treatment ($3.5+0.4$, $P=0.03$) compared with headache severity before the study ($5.0+0.3$), and no significant difference between treatments. Patients' ratings revealed that 87% experienced reduction in headache frequency, 74% experienced reduction in headache duration, and 83% experienced reduction in headache severity during fish oil treatment, compared with 78% who experienced reduction in headache frequency, 70% who experienced reduction in headache duration, and 65% who experienced reduction in headache severity during olive oil treatment (NS). About 91% would recommend fish oil to friends/relatives with headaches *vs* 91% who would recommend olive oil (NS).

Conclusions Patients experienced a similar reduction in frequency, duration, and severity of headaches during treatment with fish oil and during treatment with olive oil. The overwhelming improvement suggests that the effect should not be dismissed as simply a placebo effect. In fact, results of this preliminary study suggest that both fish oil and olive oil may be beneficial in the treatment of recurrent migraine headaches in adolescents. Further studies are warranted to compare each of these treatments with other interventions.