

FACT SHEET

Research at the City of London Migraine Clinic

HEADACHES AND HORMONES

Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study

Objective: To assess the effect of perimenstrual estradiol supplements on menstrual attacks of migraine associated with estrogen withdrawal.

Methods: Women with regular menstrual cycles and menstrual migraine or menstrually-related migraine completed an initial three-cycle assessment confirming eligibility for a six-cycle crossover study using estradiol or placebo to prevent menstrual attacks of migraine. Women collected early morning samples of urine daily for laboratory assay and used a fertility monitor to identify peak fertility associated with ovulation. Estradiol gel or placebo was first applied on the tenth day following the first day of peak fertility and continued daily until, and including, the second full day of menstruation. Women kept a daily migraine diary and continued their usual treatment for migraine. The main outcome was the number of days during gel use on which a migraine occurred.

Results: Data from 35 women were available for a paired analysis. Percutaneous estradiol was associated with a 22% reduction in migraine days (RR 0.78, 95% CI 0.62 to 0.99, $p = 0.04$); these migraines were less severe and less likely to be associated with nausea. This was, however, followed by a 40% increase in migraine in the 5 days following estradiol vs placebo (RR 1.40, 95% CI 1.03 to 1.92, $p = 0.03$).

Conclusion: Although perimenstrual percutaneous estradiol showed benefit during treatment, this was offset by deferred estrogen withdrawal, triggering post-dosing migraine immediately after the gel was stopped. Further work could assess if this could be avoided by extending the duration of treatment with estradiol.

MacGregor EA, Frith A, Ellis J, Apsinall L, Hackshaw A. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. Neurology 2006;67:2159–2163

Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen

Objective: To investigate the association between urinary hormone levels and migraine, with particular reference to rising and falling levels of estrogen across the menstrual cycle in women with menstrual and menstrually-related migraine.

Methods: Women with regular menstrual cycles, who were not using hormonal contraception or treatments and who experienced between one and four migraine attacks per month, one of which regularly occurred on or between days 1 – 2 of menstruation, were studied for three cycles. Women used a fertility monitor to identify ovulation, conducting a test each day as requested by the monitor, using a sample of early morning urine. Urine samples were collected daily for assay of estrone-3-glucuronide, pregnanediol 3-glucuronide, follicle-stimulating hormone, and luteinizing hormone. All women kept a daily migraine diary and continued their usual treatment for migraine.

Results: Of 40 women recruited, data from 38 women were available for analysis. Compared with the expected number of attacks, there was a significantly higher number of migraine attacks during the late luteal/early follicular phase of falling estrogen and lower number of attacks during rising phases of estrogen.

Conclusion: These findings confirm a relationship between migraine and changing levels of estrogen, supporting the hypothesis of perimenstrual but not postovulatory estrogen “withdrawal” migraine. In addition, rising levels of estrogen appear to offer some protection against migraine

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Poster: MacGregor EA, Frith AA, Ellis J, Aspinall L. Estrogen 'withdrawal': a trigger for migraine? A double blind placebo-controlled study of estrogen supplements in the late luteal phase in women with migraine. 11th International Headache Congress. Rome, September 2003. POSTER PRIZE

MacGregor EA, Frith A, Ellis J, Apsinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 2006;67:2154-2158

Predicting menstrual migraine with a home-use Fertility Monitor

A home-use fertility monitor was used to time perimenstrual prophylaxis in 27 women with menstrual or menstrually-related migraine. Cycle length variability was mostly caused by follicular phase variability; the postovulatory luteal phase was relatively constant. The monitor accurately identified ovulation in >90% of cycles, enabling prediction of menstruation and precise timing of perimenstrual prophylaxis. Ninety-seven percent of women found the monitor useful in predicting menstrual migraine attacks.

Poster: MacGregor EA, Frith AA, Ellis J, Aspinall L. Predicting and preventing menstrual migraine: use of the Clearplan fertility monitor. 11th International Headache Congress. Rome, September 2003 (Poster Prize)

MacGregor EA, Frith A, Ellis J, Apsinall L. Predicting menstrual migraine with a home-use Fertility Monitor. Neurology 2005;64:561-3

Differences between migraine attacks related to menses and non-menstrual attacks - symptoms, duration

Diary data from 155 women were analyzed using within-woman analysis. Compared with all other times of the cycle, migraine was 1.7 times more likely to occur during the 2 days before menstruation and 2.1 times more likely to be severe and 2.5 times more likely to occur during the first 3 days of menstruation and 3.4 times more likely to be severe. This confirms that migraine at menstruation is different from nonmenstrual attacks, even within individuals.

MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. Neurology 2004;63:351-3.

The effect of natural oestrogen supplements on migraine during the pill free week of combined oral contraception

Context: Migraine in the pill-free interval of combined oral contraceptives is reported by many women, but there is little published information on possible mechanisms and treatments.

Objective: To determine whether the use of natural oestrogen patches affected the occurrence and severity of migraine during the pill-free interval.

Design: A double-blind, placebo-controlled, randomised, crossover study.

Setting: The City of London Migraine Clinic.

Participants: Fourteen women with migraine during the pill-free interval.

Interventions: 50 µg oestradiol patches (Evorel™) used during the pill-free interval for two cycles versus placebo for two cycles (total four cycles).

Main outcome measures: Number of pill-free intervals (zero, one or two) during which migraine occurred; number of days of migraine; severity of migraine; number of days of migraine accompanied by nausea, vomiting and/or photophobia.

Results: Complete data were available for 12 women and for two cycles for one woman. Use of 50µg oestrogen patches during the pill-free interval showed a trend towards reducing the frequency and severity of migraine.

Discussion: These results were not as good as expected. However, we had originally aimed for 20 eligible women to participate in the trial, but only 14 were recruited and only 12 completed the study with full data for analysis.

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Conclusion: The results of this pilot study suggest that use of 50 µg oestrogen patches during the pill-free interval may reduce the frequency and severity of migraine at that time. This study should be repeated with larger numbers of women and a higher dose of oestrogen.

MacGregor EA, Hackshaw A. Prevention of migraine in the pill-free week of combined oral contraceptives using natural oestrogen supplements. J Family Planning and Reproductive Healthcare 2002; 28(1):27-31

Headaches and migraine in a specialist menopause clinic

Objectives: Epidemiological studies suggest that migraine and headache worsen during the climacteric. The authors noted that women attending a specialist hospital-based menopause clinic frequently reported vasomotor and other common climacteric symptoms but few spontaneously reported headache or migraine. The aim of this study was to assess the prevalence of migraine and headache in women attending this clinic.

Methods: Seventy-four women consecutively attending the Menopause Clinic at St Bartholomew's Hospital were questioned about headache. Those with a positive response were further interviewed to obtain a headache diagnosis.

Results: Headache was found to be a common symptom affecting 57 per cent of women in the 3 months before attending a specialist menopause clinic. Migraine affected 29 per cent of patients in the preceding 3 months. This condition was associated with significant disability: 80 per cent of women reported that attacks were more frequent than once a month; 75 per cent reported that the attacks were severe; 50 per cent reported that the duration of treated attacks was longer than one day.

Discussion: The high prevalence of headache and migraine in this group suggests that perimenopausal women should routinely be asked about headache and offered appropriate advice. This should include optimal attack therapy and strategies for preventing attacks, which may include hormone replacement therapy (HRT). Further studies are warranted to evaluate the relationship between climacteric symptoms, headaches, migraine and HRT.

Poster: International Headache Society Congress 1997; British Menopause Society Congress, 1998.

MacGregor EA, Barnes DS. Migraine in a specialist menopause clinic. Climacteric 1999; 2: 218-23

Effect of different types of HRT on migraine

This questionnaire of members of Migraine Action studied the subjective effects of different types of HRT. The results suggested that oral oestrogens were associated with deterioration of migraine and non-oral routes were associated with improvement. This preliminary study refuted the myth that HRT should not be given to women with migraine, but that routes of delivery associated with minimal oestrogen fluctuations can have a favourable effect.

MacGregor EA. Effects of oral and transdermal estrogen replacement on migraine. Cephalalgia 1999; 19: 124-5



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Oestrogen as a trigger for migraine aura

Objective: To assess the association between estrogen replacement therapy and migraine aura.

Background: Estrogen replacement therapy is increasingly used by perimenopausal and postmenopausal women for management of menopausal symptoms and for long-term protection against osteoporosis and arterial disease. There are few reports about the effects of estrogen replacement therapy on migraine.

Methods: Case reports were collected from women developing migraine aura related to use of estrogen replacement therapy.

Results: Four patients who developed migraine aura associated with the use of estrogen replacement therapy are described. In all cases, reducing the dose of estrogen or changing the route of delivery was associated with loss of aura.

Conclusion: These findings suggest that high levels of estrogen in women using replacement therapy can trigger migraine aura.

MacGregor EA. Estrogen replacement: a trigger for migraine aura? Headache 1999; 39: 674

Headaches and Hormones – subjective versus objective assessment

Objective: To determine the subjective assessment of the effects of hormonal events on headaches and migraine by subjective assessment in a 2 groups of women attending the City of London Migraine Clinic: Group One: those who thought that their attacks of migraine were associated with their menstrual periods. Group Two: those who did not think their attacks were associated with their menstrual periods. The subjective assessment was compared against an objective assessment of the link using diary cards.

Design: A consecutive series of 100 women attending the clinic with migraine were questioned by one of the doctors (HI) regarding the effects of specific hormonal events on their attacks of migraine and other headaches. Each woman was asked whether or not they felt that their migraine attacks were related to menstruation. All women were then asked to keep a record of their migraine attacks and menstrual periods over the following 3 months.

Patient selection: 100 women, 22 migraine with aura and 78 migraine without aura. Eighty-four were still menstruating, 11 were post-menopausal and 5 had had a hysterectomy.

Results: Of 84 women still menstruating, 42 (50.6 per cent) thought that their attacks were related to menstruation (Group One) and 41 (49.4 per cent) did not (Group Two). One woman was uncertain of any relationship between migraine and menstruation and was excluded from further study. Women in Group One were only slightly more likely to notice a relationship between age at onset of migraine and age at menarche. Premenstrual symptoms of weight gain, abdominal distension, depression and irritability, affected more women in Group One. Women in Group One obviously reported a worsening of their attacks of migraine around the time of menstruation. However, women in Group Two reported an increase in the number of non-migraine headaches at this time. Women in Group One were in general, adversely affected by the oral contraceptive pill and their headaches improved during pregnancy. Twenty of the 83 women completed the 3 month record of migraine and menstrual periods, 16 from Group One and 4 from Group Two. From this self-selected group 3 women (15 per cent) fulfilled criteria for 'menstrual' migraine and a further 3 women (15 per cent) fulfilled criteria for 'menstrually-related' migraine. These 6 women were all from the self-assessed Group One and all were diagnosed as having migraine without aura.

Conclusions: Many women when questioned link their attacks of migraine to the menstrual cycle and these women also report a greater influence of hormonal events on their attacks of migraine. However, when prospective records were kept, only a small number of women

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(15 per cent) were found to have exclusively 'menstrual' migraine, most having attacks at other times in addition. The results support the belief that 'menstrual' migraine attacks are of migraine without aura. These findings confirm that the terms 'menstrual' migraine and 'menstrually-related' migraine should only be used when strict criteria are fulfilled, enabling future studies to explore the pathophysiology of 'menstrual' migraine with fewer confounding triggers. Such criteria should also be met before specific hormonal treatment is considered.

MacGregor EA, Igarashi H, Wilkinson M. Headaches and Hormones: Subjective versus objective assessment. Headache Quarterly 1997; 8: 126-36

Migraine and menstruation

Objective: To define the term "menstrual" migraine and to determine the prevalence of "menstrual" migraine in women attending the City of London Migraine Clinic.

Design: Women attending the clinic were asked to keep a record of their migraine attacks and menstrual periods for at least 3 complete menstrual cycles.

Results: Fifty-five women completed the study. "Menstrual" migraine was defined as "migraine attacks which occur regularly on or between days -2 to +3 of the menstrual cycle and at no other time". Using this criterion, 4 (7.2%) of the women in our population had "menstrual" migraine. All 4 women had migraine *without* aura. A further 19 (34.5%) had an increased number of attacks at the time of menstruation in addition to attacks at other times of the cycle. Eighteen (32.7%) had attacks occurring throughout the cycle but with no increase in number at the time of menstruation. Fourteen (25.5%) had no attacks within the defined period during the 3 cycles studied.

Discussion: A small percentage of women have attacks only occurring at the time of menstruation, which can be defined as true "menstrual" migraine. This group is most likely to respond to hormonal treatment. The group of 34.5% who have an increased number of attacks at the time of menstruation in addition to attacks at other times of the month could be defined as having "menstrually related" migraine and might well respond to hormonal therapy. The 32.7% who have attacks throughout *the* menstrual cycle *without* an increase at menstruation are unlikely to respond to hormonal therapy. The 25.5% who do not have attacks related to menstruation almost certainly will not respond to hormonal therapy

MacGregor EA, Chia H, Vohrah RC, Wilkinson M. Migraine and menstruation: a pilot study. Cephalalgia 1990; 10: 305-10



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OTHER RESEARCH

Water deprivation, migraine and headaches

Fifty migraineurs were asked if insufficient fluid intake could provoke their migraine attacks. Twenty replied "yes," 7 were doubtfully positive, and 23 said "no." In addition 14 of 45 migraineurs at a meeting of the British Migraine association (UK) also recognized fluid deprivation as one of their migraine triggers. Thus a total of 34 of 95 migraineurs knew that dehydration could provoke their attacks, a precipitant not recognized by the medical profession. This indicates that we can add fluid deprivation to our list of migraine precipitants. It would be interesting to know the extent to which it applies in other climates. Further research is needed into the mechanism of this precipitant.

Blau JN. Water deprivation: a new migraine precipitant. Headache. 2005 Jun;45(6):757-9

Objectives: To describe a new type of headache induced by water deprivation.

Background: Two medical students experienced headache over the previous 7 (C.A.K.) and 9 (J.M.S.) years when deprived of drinking water. In a tutorial on headache, they mentioned this precipitant, not recognized by the tutor (J.N.B.) or described in the medical literature.

Dialysis and post-alcohol headaches are widely attributed to dehydration, but simple water deprivation has not been documented as a headache precipitant.

Methods: Family members, colleagues, and acquaintances were asked whether they experienced a headache when deprived of fluids. If they had, information was obtained regarding the location and quality of the headache, whether activity or posture influenced the pain, and what amount of fluid and time was needed to relieve symptoms.

Results: Approximately 1 in 10 interrogated subjects experienced water-deprivation headache, aching in the majority and accentuated by head movement, bending down, or walking. The 34 subjects were divided into 2 groups according to the time taken to relieve the headache by drinking water: total relief within 30 minutes by drinking 200 to 1500 mL (mean, 500) occurred in 22 subjects, and within 1 to 3 hours by drinking 500 to 1000 mL (mean, 750) in 11 subjects; 1 subject required sleep in addition to fluid intake. Surprisingly, the Internet revealed many references to water deprivation inducing headaches.

Conclusions: Water-deprivation headache is common, recognized by the public, but not described in the medical literature. Here we delineate it as a primary headache, postulating that the pain arises from the meninges; that the brain is also involved is indicated by impaired concentration and irritability, although not studied in detail in this preliminary survey. We speculate that water deprivation may play a role in migraine, particularly in prolonging attacks. Further studies of serum osmolality could prove illuminating.

Blau JN, Kell CA, Sperling JM. Water-deprivation headache: a new headache with two variants. Headache 2004;44(1):79-83

Verapamil for cluster headache

Background: Verapamil is currently the best available prophylactic drug for patients experiencing cluster headaches (CHs). Published papers usually state 240 to 480 mg taken in three divided doses give good results, ranging from 50% to 80%; others mention higher doses—720, even 1200 mg per day. In clinical practice we found we needed to adapt dosage to individual's time of attacks, in particular giving higher doses before going to bed to suppress severe nocturnal episodes. A few only required 120 mg daily. We therefore evolved a scheme for steady and progressive drug increase until satisfactory control had been achieved.

Objective: To find the minimum dose of verapamil required to prevent episodic and chronic

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cluster headaches by supervising each individual and adjusting the dosage accordingly. **Methods:** Consecutive patients with episodic or chronic CH (satisfying International Headache Society (IHS) criteria) were started on verapamil 40 mg in the morning, 80 mg early afternoon, and 80 mg before going to bed. Patients kept a diary of all attacks, recording times of onset, duration, and severity. They were advised, verbally and in writing, to add 40 mg verapamil on alternate days, depending on their attack timing: with nocturnal episodes the first increase was the evening dose and next the afternoon one; when attacks occurred on or soon after waking, we advised setting an alarm clock 2 hours before the usual waking time and then taking the medication. Patients were followed-up at weekly intervals until attacks were controlled. They were also reviewed when a cluster period had ended, and advised to continue on the same dose for a further 2 weeks before starting systematic reduction. Chronic cluster patients were reviewed as often as necessary.

Results: Seventy consecutive patients, 52 with episodic CH during cluster periods and 18 with chronic CH, were all treated with verapamil as above. Complete relief from headaches was obtained in 49 (94%) of 52 with episodic, and 10 (55%) of 18 with chronic CH; the majority needed 200 to 480 mg, but 9 in the episodic, and 3 in the chronic group, needed 520 to 960 mg for control. Ten, 2 in the episodic and 8 in the chronic group, with incomplete relief, required additional therapy—lithium, sumatriptan, or sodium valproate. One patient withdrew because verapamil made her too tired, another developed Stevens-Johnson syndrome, and the drug was withdrawn.

Conclusions: Providing the dosage for each individual is adequate, preventing CH with verapamil is highly effective, taken three (occasionally with higher doses, four) times a day. In the majority (94%) with episodic CH steady dose increase under supervision, totally suppressed attacks. However in the chronic variety only 55% were completely relieved, 69% men, but only 20% women. In both groups, for those with partial attack suppression, additional prophylactic drugs or acute treatment was necessary.

Blau JN, Engel HO. Individualizing treatment with verapamil for cluster headache patients. Headache 2004;44(10):1013-8

Ponytail headache

Fifty of 93 females experienced headache from wearing a ponytail. Pain was experienced only at the site of the hair tie in 10 subjects, extending in others, forwards to the vertex (n = 5) or forehead (n = 7), laterally to the parietal region (n = 8) or temples (n = 3), downwards to the neck (n = 5), or to other areas (n = 12). Loosening the hair relieved pain immediately in 4 subjects, within half an hour in 32, and within an hour in 5 subjects; the remaining 9 subjects were uncertain of pain duration. This headache was preventable by wearing the ponytail more loosely tied. Ponytail headache, well known to females, is not described in the medical literature because the remedy is obvious, therefore those affected do not seek medical advice. This seemingly common headache provides an example of a pure extracranial headache arising from pericranial muscle fascia and tendon traction. Males almost certainly have similar experiences, but were not questioned in this study. Distinguishing intracranial from extracranial headache is essential in diagnosis and treatment. Further research on ponytail and other extracranial headaches could shed light on the mechanism of tension-type headache.

Blau JN. Ponytail headache: a pure extracranial headache. Headache. 2004 May;44(5):411-3

Treatment strategies for migraine

Objective: To determine which medications UK migraineurs have access to and assess the usage of these products in a 'real-life' setting.



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Research design and methods: Data were collected using an online questionnaire, which subjects were directed to by advertisements in pharmacies, a UK national newspaper, on the internet and information on the Migraine Action Association website and newsletters. Respondents were eligible for inclusion if attacks fulfilled International Headache Society criteria for migraine and/or if previously diagnosed by a physician as having migraine.

Main outcome measures: Respondents were asked to specify which products had been prescribed or purchased for migraine treatment. The pattern of use of these products was determined, including the reasons why respondents chose particular products to treat attacks.

Results: Of 3072 eligible respondents, the majority had purchased a variety of over-the-counter (OTC) medicines for treatment of attacks. Eighty-seven per cent had been diagnosed by a physician and were prescribed multiple products (average 1.68); 45% received triptans, but 26% were still prescribed products that were also available OTC. Over half (52%) of respondents initially used an OTC medicine to treat the last migraine attack. However, 73% required a second dose/product, mainly as a result of lack of efficacy of the first dose/product. Respondents using triptans were less likely to require a second dose/product than those not using triptans (52% vs.78%, respectively). The two main reasons for choosing a triptan to treat an attack were the need for quick control and the severity of the attack. Satisfaction with regard to migraine medication was higher among triptan-users than non-triptan users.

Conclusions: Medicines that are available OTC are often used as first-line therapy for migraine despite many migraineurs having access to prescription therapies such as triptans. Many migraineurs require a second dose/product, possibly indicating sub-optimal treatment efficacy. Physicians should consider the range of migraine-specific treatments available, including triptans, in order to develop a treatment plan that is based on the patient's needs and preferences.

MacGregor EA, Brandes J, Gendolla A, Giammarco R. Migraine treatment strategies: the global Migraine And Zolmitriptan Evaluation (MAZE) survey – Phase IV. *Curr Med Res Opin* 2004;20(11):1777-83

Impact of migraine on patients and their families

Objective: To investigate the impact of migraine on migraineurs and their families and evaluate migraineurs' preference for different treatment formulations. This study also assessed the prevalence and impact of migraine with menstruation.

Methods: Participants (n= 1028) from around the world (USA [39%], Canada [20%], Europe [37%] and other countries [4%]) completed an online questionnaire. Of these, 866 were migraineurs and 162 were non-migraineurs living with/related to migraineurs. Migraineurs were identified based on responses to a modified Kiel questionnaire and/or diagnosis of migraine by a doctor. Disability was quantified using the Migraine Disability Assessment Scale (MIDAS).

Results: Migraineurs missed more days from family/leisure activities than from work/school (mean 4.2 vs 2.4 days) in the previous 3months. On an additional 6.2days within the 3-month period, productivity at work/school was reduced by at least half. Inability and reduced ability (by at least half) to perform household work were reported on 6.0 and 6.5days, respectively. Of the women surveyed, 51% identified menstruation as a trigger for attacks and 6% reported attacks solely with menstruation (i.e. attacks occurred during menstruation on at least 9 out of 10 occasions), the latter associated with a higher pain score than other attacks. Living with or being related to a migraineur decreased non-migraineurs' ability to participate in home/family life (moderate/great impact 49%) and social/leisure activities (moderate/great impact 47%). In a trade-off analysis, 60% of treatment choice was driven by

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formulation type and 40% was driven by speed of onset. As migraine disability increased, speed of onset became more important.

Conclusions: This study confirms the significant burden of migraine on patients and families/cohabitants, highlighting not only reduced productivity and absences from work/school, but also time missed from family/social occasions. Many women identify menstruation to be associated with more painful attacks. Overall, in terms of treatment choice, formulation type was a more important driver than speed of onset; however, as migraine-related disability escalates, speed of onset becomes more important. To optimise migraine management, treatment choice should be based on individual patients' needs and preferences.

MacGregor EA, Brandes J, Eikermann A, Giammarco R. Impact of migraine on patients and their families: the Migraine And Zolmitriptan Evaluation (MAZE) survey – Phase III. *Curr Med Res Opin* 2004;20(7):1143-50

Migraine prevalence and treatment patterns

Objective: The objectives of the Migraine And Zolmitriptan Evaluation (MAZE) survey were to assess the prevalence of migraine in the general population across 5 different countries, to understand migraineurs' experience of migraine and its management on a global level, and to assess patient perceptions and preferences of current and future treatment formulations.

Methods: A two-phase, international survey was performed in France, Germany, Italy, the UK, and the USA, and involved a total of 5553 adults. In Phase I, ≥1000 adults from the general population in each country were interviewed by telephone using a routine consumer survey. The proportion of subjects meeting International Headache Society (IHS) criteria for migraine was assessed using an adapted Kiel headache questionnaire, whereas the impact of migraine on daily life was assessed using the Migraine Disability Assessment Scale (MIDAS) questionnaire. In Phase II, ≥100 clinically diagnosed migraineurs per country were recruited through their general practitioners and migraine clinics. Semi-structured interviews based on written questionnaires assessed the impact of, and attitudes toward, migraine and its treatments. Respondents also completed the MIDAS questionnaire. Patients also sampled a demonstrator version of the new orange-flavored orally disintegrating tablet of zolmitriptan.

Results: Phase I: An estimated 5% to 12% of the population in the different countries were classified as suffering from migraine, with most attacks categorized as fairly severe to very severe. Between 23% and 42% of migraineurs reported >24 attacks in the previous 12 months. Approximately one-half of all migraineurs did not seek medical advice. Of those who did consult a physician, only 3% to 19% were prescribed triptans. In all countries, the most commonly used current treatment was simple analgesics (22% to 54%). Phase II: Current migraine therapy was consistently effective in only 19% to 31% of patients, and only 21% to 50% of patients were satisfied with their current treatment. Many sufferers supplemented their prescription therapy with alternative management strategies, including herbal and homeopathic remedies, stress management, relaxation therapy, avoidance of trigger factors, and bed rest. Patients indicated that the most important attributes of migraine therapies are high efficacy and rapid pain relief. When asked to identify delivery options that they would like to see more of in the future, most patients (73%) specified "a dissolve-in-the-mouth tablet." Ninety percent of patients who sampled the demonstrator version of the zolmitriptan orally disintegrating tablet considered it to be "very easy" to use, and 99% stated it was suitable for use "anytime/anywhere."

Conclusions: In the general population samples we surveyed, there was a 5% to 12%



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prevalence of migraine across 5 different countries. As reported from previous epidemiologic studies, we found that many migraineurs still do not consult a physician. Despite high levels of disability, as assessed by MIDAS scores and evidenced by the need for bed rest during attacks, many migraineurs continue to treat their headaches with simple analgesics, which, if ineffective, leads to dissatisfaction with treatment. Patients desire a medication with high efficacy and a rapid onset of action, and an orally disintegrating tablet such as that used for the new zolmitriptan formulation, is a favored formulation and route of administration.

MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: results of the global migraine and zolmitriptan evaluations (MAZE) survey. *Headache* 2003;43:19-26

Aspirin: a randomised trial of mouth-dispersible aspirin to treat migraine attacks

Objective: To compare the efficacy of mouth-dispersible aspirin 900 mg and placebo in the treatment of migraine.

Background: Aspirin is widely accepted as an effective therapy for migraine. Previous studies have indicated that gastric stasis and delayed gastric emptying, which occur during migraine attacks, delay aspirin absorption. Mouth-dispersible formulations are considered to be more quickly absorbed than solid formulations and, therefore, may be more effective in treating migraine.

Design: Randomized, double-blind, placebo-controlled, crossover study in four specialized migraine clinics in the United Kingdom.

Methods: One hundred one patients diagnosed with migraine (according to the International Headache Society diagnostic criteria) participated in the study. Patients received either single doses of mouth-dispersible aspirin (3 x 300 mg) or placebo for moderate pain in the treatment of two migraine attacks. Rescue medication could be taken after 2 hours, if required. The primary efficacy parameter was response to therapy at 2 hours post-treatment. Other efficacy parameters were response to treatment, pain-free, and pain intensity at all other time points. Functional disability, nausea, vomiting, photophobia, phonophobia, symptom relief, patient and investigator global evaluation, use of rescue medication, headache recurrence, and palatability and convenience were also recorded.

Results: Of 101 patients, 73 took both treatments. At 2 hours, 48% of patients taking mouth-dispersible aspirin responded, compared to only 19% taking placebo ($P=0.0005$). Mouth-dispersible aspirin was significantly better than placebo for response to treatment ($P<0.05$) and pain intensity difference ($P<0.01$) at all time points from 30 minutes post-treatment; for pain-free ($P<0.05$) and use of rescue medication ($P<0.01$) from 3 hours post-treatment; for headache recurrence ($P<0.05$); and for patients' and investigators' global evaluations of efficacy ($P<0.0001$ in both cases).

Conclusions: Mouth-dispersible aspirin 900 mg is effective compared with placebo for the treatment of moderate migraine head pain, with relief seen from as early as 30 minutes after taking medication.

Poster: MacGregor EA, Dowson A, Hirst SG, Davies PTG. A Placebo Controlled Trial Of Mouth Dispersible Aspirin In Migraine. *Headache World* 2000, London, September 2000 (Poster Prize)

MacGregor EA, Dowson A, Davies PTG. Mouth-dispersible aspirin in the treatment of migraine. *Headache* 2002;42:249-255

Cluster headache triggers

Exercise, a hot bath, or elevated environmental temperature provoked cluster headaches, within 1 h, in 75 out of 200 patients. This new observation accords with recognised

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precipitants--alcohol, histamine, and glyceryl trinitrate--perhaps via generalised vasodilatation or hypothalamic activation.

Blau JN, Engel HO. A new cluster headache precipitant: increased body heat. Lancet 1999;18;354(9183):1001-2

Fluoxetine in the prophylaxis of migraine

Sixty-five patients needing migraine prophylaxis were recruited into a phase II, double-blind, placebo-controlled trial. After a 1-month placebo run-in, 53 patients met entry criteria with regard to attack frequency and were randomized, 27 to S-fluoxetine and 26 to matching placebo. Three failed to start treatment and there were 17 early discontinuations, 9 from S-fluoxetine, 8 from placebo, at similar times and for similar reasons. The primary efficacy variable was attack frequency and analysis compared decline-from-baseline in the two groups. This was earlier and greater (1.7 attacks/23 days, or 52%) on active therapy than on placebo (1.1 attacks/23 days, or 27%), and statistically significant in month 2 ($F=4.93$; $p=0.033$) and month 4 ($F=4.55$; $p=0.041$). As secondary measures of efficacy, migraine-days per month and Patient's Global Impression of Disease Severity coherently reflected the changes in attack frequency. Mean attack severity and acute medication use (doses per attack) were unaltered by either treatment. There were no serious adverse events. Withdrawals for adverse events were four from each group but none was considered causally related. The finding of greater efficacy of S-fluoxetine than of placebo should be interpreted conservatively, since the analysis in the final month was made on only half of the entered patients. It supports progression to phase III evaluation, which was the purpose of the study.

Steiner TJ, Ahmed F, Findley LJ, MacGregor EA, Wilkinson M. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia 1998; 18: 283-6

Zolmitriptan for treating migraine attacks

Zolmitriptan is a selective 5-HT_{1B/1D} receptor agonist for acute oral migraine therapy. This randomized, placebo-controlled, parallel-group study investigated the efficacy and tolerability of oral zolmitriptan (5, 10, 15 and 20 mg) in the treatment of single acute migraine attacks. Of 1181 patients randomized, 840 were evaluable for the primary efficacy analysis. Headache response rates (a reduction in headache intensity from severe or moderate at baseline to mild or no pain at 2 hours post-treatment) were similar across the zolmitriptan dose groups (66%, 71%, 69% and 77% for 5 mg, 10 mg, 15 mg and 20 mg, respectively) and were significantly higher than that for placebo (19%; all groups $P < 0.001$). A headache response was reported at 1 hour by 40-50% of zolmitriptan recipients (16% placebo). At 2 hours post dose, 39-47% of zolmitriptan-treated patients were pain-free, compared with 1% of placebo recipients. Headache recurrence occurred in 21-29% (upper 95% CI 37.1) of zolmitriptan-treated patients and in 65% (95% CI 38.3, 85.8) of placebo recipients. Zolmitriptan was well tolerated at each dose. The most commonly reported adverse events were asthenia, dizziness, paraesthesia and feelings of heaviness. Most adverse events were of mild or moderate intensity and were transient. The frequency of adverse events was dose-related. Although, zolmitriptan 5 mg exhibited the most favourable efficacy and tolerability profile, the dose response data suggest that lower doses would also offer significant efficacy.

Dahlof C, Diener HC, Goadsby PJ, Massiou H, Olesen J, Schoenen J, et al. Zolmitriptan, a 5-HT_{1B/1D} receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. Eur J Neurol 1998;5:535-43



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Warning symptoms of cluster headache

Warning symptoms in 150 cluster headache patients were studied by focusing on attacks occurring during waking hours. Warnings were divided into prodromes that started minutes before the pain of individual attacks (122 patients) and premonitory symptoms preceding the onset of cluster periods by days to weeks (12 patients). Pathogenetic and therapeutic implications are discussed.

Blau JN, Engel H. Premonitory and prodromal symptoms in cluster headache. Cephalalgia 1998;18:91-3

Abdominal pain in adult migraine

Recurrent abdominal pain in children, frequently diagnosed as "abdominal migraine," is thought to evolve into more typical migraine headache during the teens and twenties. If this transformation occurred, we would expect some adult migraineurs to retain abdominal pain; but we could not recall this symptom being mentioned by patients. However, without direct questioning the absence cannot be assumed. We, therefore, asked 100 migraineurs about abdominal symptoms during migraine attacks: only one experienced unexplained abdominal pain. We conclude that abdominal pain is not a feature in adult migraineurs, leading us to support the notions that: (1) recurrent abdominal pain of childhood has a number of causes; (2) abdominal migraine may be an incorrect attribution and is liable to be over diagnosed; (3) abdominal migraine requires more precise definition; (4) the transition from childhood abdominal migraine to adult migraine needs precise prospective study.

Blau JN, MacGregor EA. Is abdominal pain a feature of adult migraine? Headache 1995; 35: 207-9

Migraine consultations: differences between the problems reported by patients, GP and the specialist

Several studies have examined patients' attitudes to a consultation for migraine and other headaches. However, a patient's assessment of the problem for which they seek treatment may differ from that of the referring primary physician, which may, in turn, differ from the specialist's. This study set out to examine this triangle. The commonest reason for referral was failure of treatment response. This contrasted with the patient's different perception—an increase in the frequency of attacks, which we saw as headaches additional to migraine, accounting for failed treatment. Similarly, our view of the patient wanting reassurance paralleled their request for further information. These findings confirmed the hypothesis that recognizing and understanding a patient's fears were important factors towards a favorable outcome of a consultation. Several studies have examined patients' attitudes to a consultation for migraine and other headaches. However, a patient's assessment of the problem for which they seek treatment may differ from that of the referring primary physician, which may, in turn, differ from the specialist's. This study set out to examine this triangle. The commonest reason for referral was failure of treatment response. This contrasted with the patient's different perception—an increase in the frequency of attacks, which we saw as headaches additional to migraine, accounting for failed treatment. Similarly, our view of the patient wanting reassurance paralleled their request for further information. These findings confirmed the hypothesis that recognizing and understanding a patient's fears were important factors towards a favorable outcome of a consultation.

Blau JN, MacGregor EA. Migraine consultations: a triangle of viewpoints. Headache 1995; 35: 104-106

Behavioural patterns of migraineurs during attacks

A questionnaire study of the behaviour of 50 migraineurs during attacks which highlighted consistent withdrawal from stimuli, particularly through sleep. It was hypothesised that sleep

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may play a functional role in migraine by restoring normal brain metabolism.

Blau JN, MacGregor EA. Behavioural patterns of migraineurs during attacks - a functional role? Headache Quarterly 1995; 6: 30-33

Migraine and the neck

Fifty patients with migraine were asked about the occurrence of neck symptoms during different phases of their attacks, and if they felt the neck could act as a precipitant. Of the 32 reporting neck pain or stiffness, 10 noted symptoms during the premonitory phase, 30 during the headache phase, and 10 postdromally. In 7 cases the pain radiated into the shoulder and in 1 case into the lumbar region. These findings indicate extracerebral involvement of the migraine process and an overlap between the trigeminal and cervical distribution.

Blau JN, MacGregor EA. Migraine and the neck. Headache 1994; 34: 88-90

Behaviour during cluster headaches

Because cluster headache is short-lasting and tends to occur during the early morning hours, physicians rarely witness an attack. Accurate diagnosis is important because effective treatments are available. The diagnosis is made from the history of temporal pattern, reddening and tearing of the affected eye, and ipsilateral nasal congestion. An additional diagnostic aid is to invite patients to demonstrate how they respond to attacks. The pain, one of the worst known, causes extreme restlessness. 50 patients showed how they walk around, sit (or kneel) and rock, and clutch the affected side of the head. Diagnostic value apart, the patient will often be relieved to learn that bizarre behavioural responses are not a mark of insanity.

Blau JN. Behaviour during a cluster headache. Lancet 1993 Sep 18;342:723-5

What people can eat during migraine attacks

Although nausea and vomiting are diagnostic migraine symptoms, most patients can take tablets by mouth and a few say they can eat some food. This study was conducted to determine the proportion who could eat or drink, what was consumable and with what effect. One-hundred-and-nine migraineurs were asked what they could eat or drink at the beginning or height of their attacks; 59 could not take any food by mouth, but 50 could eat during the headache phase of their migraine attacks. Four ate normally, 5 took smaller amounts of their normal dietary intake, and 3 took lighter meals. Dry, carbohydrate foods were consumable by the remaining 38: a few had specific cravings, most stated the precise variety which, when eaten, reduced nausea, headache, other symptoms or length of attacks. Patients should therefore be encouraged to eat what they can tolerate, with their tablets taken as early as possible after the onset of attacks. Simultaneous nausea, tolerance or even craving for specific foods occur in other conditions, particularly high altitude headaches which share other features of migraine attacks. The observations in this paper support the notion that migraine is a central neuronal metabolic disturbance.

Blau JN. What some patients can eat during migraine attacks: therapeutic and conceptual implications. Cephalalgia 1993;13:293-5

Domperidone plus paracetamol in the treatment of migraine

This study was designed to evaluate the safety and efficacy of domperidone in combination with paracetamol in the treatment of migraine. Severity of headache, duration of migraine attack and overall efficacy of treatment were amongst the variables assessed in a randomized, double-blind, three-way cross-over comparison of 1 g paracetamol plus either



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domperidone 30 mg, domperidone 20 mg or placebo, taken at onset of headache. Forty-six patients attending the City of London Migraine Clinic completed the study. A significant difference was observed in the duration of the migraine attack: a median of 17.5 h with paracetamol alone was reduced to 12.0 h with the addition of domperidone 20 mg, and to 12.0 h with domperidone 30 mg. No significant adverse events were reported. A reduction in pain intensity and nausea was noted but this was not statistically significant. It was concluded that domperidone shortens the duration of a migraine attack and may help reduce headache and associated symptoms.

MacGregor EA, Wilkinson M, Bancroft K. Domperidone plus paracetamol in the treatment of migraine. Cephalalgia 1993; 13: 124-7

Aspirin in the prophylaxis of migraine

Grant from Laboratories for Applied Biology.

This study was in two parts: laboratory and clinical. A pilot study, using the Haemostatometer, was undertaken to assess the activity of calcium salicylate compared to aspirin, on platelets. Calcium salicylate was found to have minimal effect on haemostasis. This was followed by a double blind parallel study of 300 mg aspirin vs 292mg calcium salicylate taken daily for 3 months for the prophylaxis of migraine. The clinical trial was discontinued due to poor recruitment as many patients has already tried aspirin following press reports about its efficacy as a migraine prophylactic.

Number of headaches in patients attending the City of London Migraine Clinic

Patients with migraine attending a specialist clinic often have more than one type of headache. One hundred and two patients attending the City of London Migraine Clinic for the first time were asked: "What type(s) of headache do you think you have?" A separate diagnosis was made by the doctor, who was blinded to the self-diagnosis. On clinic diagnosis, 27 (26.5%) patients were found to have migraine plus an additional non-migraine headache. Compared with the self-diagnosis, 15 (56%) of these had correctly self-diagnosed two types of headache.

Laughey WF, MacGregor EA, Wilkinson MIP. How many different headaches do you have? Cephalalgia 1993; 13: 136-7

Changes in attendees at a migraine clinic over 20 years

This audit of patients attending the COLMC in 1991 was compared with similar data from 1970 to assess any demographic changes. The results showed a large increase in patients attending with migraine without aura, suggesting better recognition of this form of migraine. Peak age at attendance remained in the early 40s but an increasing proportion of women attended in 1991. Medication misuse headaches had not been recognised in 1970 but accounted for 10 per cent of patients attending in 1993. Patients attending for acute treatment had significantly reduced from 30 per cent of new patients in 1970 to less than 1 per cent in 1991 and was the reason for the difficulty in undertaking continued research on patients during attacks.

Poster: MacGregor EA, Wilkinson M. Migraine does it change. Presented at the International Headache Society Congress, 1993

Migraine: an informative method of communication

The Keypad Audience Response System can be used to obtain simultaneous Information from a large number of people in an audience. Answers to specific questions are transmitted from a keypad (pressed by each participant) to a computer. The results are

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displayed on a screen within 20 seconds, expressed as percentages of total responses to each question and presented as bar diagrams or pie charts.

At a meeting of the British Migraine Association, over 100 migraineurs learned how their attacks differed from, or resembled those of others. The speakers were able to clarify and discuss both questions and answers, which confirmed previous findings about attack duration, prodromes, postdromes, effect of pregnancy, oral contraceptives and the menopause. Three new points emerged which merit further study:

1. Hormone replacement therapy aggravated migraine in 42% of women, 27% noted an improvement, and 31% observed no alteration.
2. Twenty-five percent prefer to sit up during an attack.
3. Seven percent reported prolonged attacks (3-7 days).

The use of keypads at seminars or lectures is valuable in promoting enthusiastic audience participation, and the understanding of the diverse symptoms and manifestations of a condition. Although observations cannot be extrapolated to a wider population because all audience are a selected group, new points requiring research may be highlighted.

MacGregor EA, Blau JN. Migraine: an informative method of communication. Headache 1992; 32: 356-9

Handling of 5HT by platelets in migraine

There is little dispute that a link exists between 5-hydroxytryptamine (5HT) and migraine exists but the exact mechanism of an attack has yet to be established. The handling of 5HT by the platelet is regarded as a simple model of the handling of 5HT by nerve terminals. If differences are seen in how the platelets from migraineurs handle 5HT compared to those from a control population, it is possible that a similar difference exists in the nerve terminal. The Haemostatometer allows the rapid and simultaneous *in vitro* assessment of platelet function (shear induced haemostasis), coagulation and thrombolysis from non anticoagulated blood samples. In this study, a baseline comparison of haemostasis was made on 20 migraineurs between attacks and 20 controls. No differences were found in the results from each of the two groups. 5µM of 5HT was then added to blood taken from 10 migraineurs and 10 controls and the recordings were repeated. Again, no differences were found between the results from the two groups. In blood taken from both migraineurs and controls, the effect of 5HT was to significantly enhance clotting time and clot lysis. No effect was seen on primary aggregation. The possible reasons for and significance of these findings is discussed.

Poster: presented at the International Headache Society, 1991

MacGregor EA, Bird N, Ridler C, Wilkinson MIP. Handling of 5-hydroxytryptamine by platelets in migraine. Headache 1992; 32: 68-72

Ice-cream headaches

Sponsored by Walls Ice-Cream

Objective: To examine the characteristics of cold-induced headaches in a group of migraine patients, to compare these with their usual migraine headache and with cold-induced headache in a control population.

Design: Subjects completed a structured questionnaire recording previous headache history along with the characteristics of any headache produced during supervised palatal and pharyngeal application of ice cream.

Subjects: 70 consecutive patients attending the City of London Migraine Clinic, and 50 pre-clinical medical and dental student volunteers from Queen Mary and Westfield College.

Results: 27% of the migraine patients and 40% of the students reported previous ice cream headaches. 17% of the migraine patients and 46% of the students developed headache



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following palatal application or a swallow of ice cream. Typically the headache was of early onset ($x = 12.5s$) and short duration ($x = 21s$), with a tendency for anterior headache on the same side as a palatal stimulus, and bilateral headache following an ice cream swallow. However, a significant minority experienced a previously unreported headache of late onset ($x = 102s$) and long duration ($x = 236s$) which tended to occur particularly after swallowing ice cream and to be less well localised to the side of the cold stimulus. Ice cream appeared not to be a common trigger for migraine, and there was no significant correlation between site of ice cream headache and usual site of migraine.

Conclusions: These findings confirm that cold stimulation of the palate or pharynx commonly produces a headache. In contrast to previous studies, our results suggest that the 'ice cream headache' is less common in migraine patients than the general population. A similar pattern of headache was produced in both migraine patients and controls, and apart from the few for whom an ice cream headache may trigger a migraine, the ice cream headache seems not to have any special significance for migraine patients.

Poster: European Headache Federation, 1992

Bird N, MacGregor EA, Wilkinson MIP. Ice Cream Headache - site, duration and relationship to migraine. Headache 1992; 32: 35-8

Transcranial electrical stimulation in the prophylaxis of migraine

After 4 weeks baseline, 47 migraine patients were enrolled in a 4 month double-blind placebo-controlled crossover study to evaluate the efficacy and safety of cranial stimulation in the prophylaxis of migraine. The rationale for this study was the efficacy of TENS in the management of acute and chronic pain and the previous success of transcranial stimulation on acute migraine and tension-type headache. The results from the 31 patients who completed the study showed a trend to improvement in patients using the active device, although the results were not statistically significant.

Platform presentation: 9th Migraine Trust Symposium, 1992

Gap between the aura and the headache

The gap between the end of the visual aura and headache onset in classical migraine has been called the free interval. In a retrospective study of twenty-five migraineurs who had noted a gap, only three reported feeling normal at that time: twenty-two described alterations in mood, detachment from the environment or other people, fears, disturbances of speech or thought, or somatic symptoms. The interval lasted less than an hour in seventeen of the twenty-two but in five persisted for 1 to 5 hours. These symptoms suggest involvement of the frontal and temporal cortices as well as the hypothalamus; they do not conform to Leao's spreading depression or a vascular mechanism, but are in keeping with a diffuse cerebral process with focal manifestations.

Poster: Legarda I, MacGregor EA, Blau JN. Gap in migraine aura: implications for pathophysiology. 15th World Congress of Neurology, 1993

Blau JN. Classical migraine: symptoms between visual aura and headache onset. Lancet 1992; 340:355-6

ICS 205-930 for migraine prophylaxis

To investigate whether the novel, potent and highly selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist ICS 205-930 can prevent migraine attacks, we conducted simultaneously two randomized, double-blind, placebo-controlled, multicentre, international trials, involving a total of 204 patients, suffering from classic or common migraine. Both trials had the same parallel-group design (1 month baseline observation, followed by 3 months treatment) and both produced remarkably similar results. The primary efficacy parameter was the proportional reduction in attack frequency recorded after 3 months of treatment. Twenty-two patients withdrew prematurely from the trials and could not be

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assessed for efficacy. Mild to severe constipation was reported by about 50% of the patients on active treatment. None of the doses of ICS 205-930 tested (50 mg, 25 mg and 15 mg daily) produced a statistically significantly better result to reduce attack frequency than did placebo. However, confidence intervals for the difference in effect with placebo were wide, indicating that 15 mg ICS 205-930 may produce a 57% reduction in attack frequency as compared to placebo. The most unusual finding was that, for all efficacy parameters, the best results were obtained with the lowest dose (15 mg), the worst results with the highest dose (50 mg) and an intermediate effect with 25 mg. Such an inverse relation between dose and efficacy suggests a bell-shaped dose-response curve, implying that doses lower than 15 mg might well prove to be more effective. Thus, the present study has produced inconclusive, but intriguing results. Lower doses should be further investigated before drawing any definite conclusion on the efficacy of ICS 205-930 in the prophylactic treatment of migraine.

Ferrari MD, Wilkinson M, Hirt D, Lataste X, Notter M. Efficacy of ICS 205-930, a novel 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist, in the prevention of migraine attacks. A complex answer to a simple question. ICS 205-930 Migraine Study Group. Pain 1991;45:283-91

After the migraine

To determine the nature and duration of symptoms after the headache phase of migraine, 40 migraineurs (11 with and 29 without an aura) were given a questionnaire to complete on the day after a migraine attack. The most common symptoms that remained were physical and mental tiredness, subdued or depressed mood, impaired concentration, reduced physical activities and yawning; weak or clumsy limbs, head tenderness, neck ache or stiffness, impaired sight and altered fluid balance were less frequent. The number of symptoms ranged from 2 to 11 (average 6) per patient lasting for a mean of 18 h, usually the whole of the next day. Symptoms after the main migraine attack can help to diagnose migraine particularly when there is no aura before the onset of headache. Eliciting postdromes aids patient-doctor rapport and confidence. The range of symptoms lends support to the notion that the whole of the brain is involved in the aftermath of migraine attacks.

Blau JN. Migraine postdromes: symptoms after attacks Cephalalgia 1991;11(5):229-31

Similarities and differences between migraine with aura and migraine without aura

A preliminary study was undertaken to provide clinical evidence to support the hypothesis that: "Migraine with aura, migraine without aura and aura alone are the same condition, which differ in degree rather than pathophysiology." At the City of London Migraine Clinic, 50 patients consecutively attending the clinic with a past or present history of migraine with aura were questioned. Of the 50 patients questioned 36 (70%) had a combination of migraine with aura, migraine without aura and/or aura alone; i.e. 70% had had more than one type of migraine attack. The duration, severity and frequency of attacks did not differ between migraine with and migraine without aura. The results support the hypothesis that migraine with and migraine without aura, and aura alone are not separate conditions, because: (1) most patients suffer from more than one type of migraine attack; (2) there are no significant differences in the characteristics of the migraine attacks in the different groups; (3) there are no significant differences in the characteristics of the subjects.



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Ranson R, Igarashi I, MacGregor EA, Wilkinson M. The similarities and differences of migraine with aura and migraine without aura: a preliminary study. *Cephalalgia* 1991;11:189-92

Haemostasis in migraine

There has been much discussion about the role of platelets in the pathogenesis of migraine. A new in vitro technique using a custom built device called the Haemostatometer measures haemostasis, thrombolysis, and coagulation from non-anticoagulated, undiluted (native) blood. Using this device, data were analysed from blood samples taken from 10 migraineurs between attacks and 10 control subjects. Results showed no difference in haemostasis, spontaneous thrombolysis or coagulation between migraineurs and control subjects.

MacGregor EA, Chia HMY, Ridler C, Vohrah C, Wilkinson M. Haemostasis in migraine. *Cephalalgia* 1989; 9: 23-7

Common headaches

Questionnaires completed by 327 preclinical medical and dental students showed that 97.9% had experienced headaches, most frequently attributed to insufficient sleep (38.8%), mental stress (38.8%), alcohol (38.5%), excess heat (36.7%), reading (31.5%), excess noise (29.9%) or light (27.7%), and sleeping too long (23.5%). The frequency and duration of these and other headaches are listed. 8% of the headache group had consulted a doctor. Only 2.1% of all students had never experienced a headache. Two hypotheses are examined: (1) can headaches be normal?--delineated by their disappearing soon after the noxious stimulus has ceased; (2) can pain in the head, as elsewhere in the body, act as a warning and therefore have protective, even survival value?

Blau JN. Common headaches: type, duration, frequency and implications. *Headache* 1990;30(11): 701-4

Sleep deprivation headaches

Headaches due to insufficient or interrupted sleep are generally labelled "tension headaches" of psychogenic origin. In 25 healthy subjects, variable amounts of sleep loss (1-3 h for 1-3 nights) caused headaches lasting from 1 h to all day. The headache was most frequently a dull ache, a heaviness or a pressure sensation felt in the forehead and/or at the vertex. Simple analgesics, purchaseable without a doctor's prescription, completely or markedly reduced the head pain in 20-60 min. Headaches due to insufficient sleep differ from tension headaches in their site, duration and response to analgesics. Assuming that pain implies a regional dysfunction, headaches caused by sleep loss provide support for the notion that sleep has a restorative function in the brain.

Blau JN. Sleep deprivation headache. *Cephalalgia* 1990;10(4):157-60

Analgesic use in patients prior to attending the City of London Migraine Clinic

Eighty-three unselected patients attending the City of London Migraine Clinic for the first time were asked about their drug intake and use of alternative treatment.

Thirty-one of those questioned took *regular daily doses* of medication. Fifteen were taking a combination of drugs bought 'over the counter' (OTC) and drugs prescribed by their GP; eleven took OTC drugs only; and 5 took prescription drugs only. It was noticeable that those taking drugs prescribed both by the GP and obtainable over the counter were more likely than the other groups to be taking several drugs rather than a single type. Thirty-five of the 83 (42.2%) had tried alternative treatments for their attacks.

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MacGregor EA, Vohrah C, Wilkinson M. Analgesic use: a study of treatments used by patients for migraine prior to attending the City of London Migraine Clinic. Headache 1990; 30: 571-4.

Headaches in diabetic patients

Headaches affecting 117 insulin-dependent diabetic patients were studied. 50 developed 3 varieties of headaches associated with clinical hypoglycaemic episodes: (1) Brief headaches, contemporaneous with cerebral and autonomic symptoms, were relieved within minutes of ingesting carbohydrates (8 patients). (2) Prolonged headaches outlasting hypoglycaemic symptoms by 1-48 (average 4.3) hours, not relieved by food, occurred in 36 patients; 12 of these also had nausea, vomiting or photophobia. (3) Migraine headache. 11 of the 117 patients were migraineurs: in 6 of the 11 their typical migraines (2 classical and 4 common) were induced by hypoglycaemic episodes. 9 of the 50 had 2 types of headaches, easily distinguished by each subject. In the whole series of 117 patients, 9 had never had a headache in their life. The remainder had headaches associated with premenstrual tension, anxiety, alcohol or other causes.

Martins I, Blau JN. Headaches in insulin-dependent diabetic patients. Headache 1989;29(10):660-3



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Nimodipine for migraine prophylaxis

Nimodipine is a compound that is thought to block the influx of calcium through channels in vascular smooth muscle. This paper describes a double-blind parallel-group comparison of 40 mg nimodipine three times a day and placebo. Sixty-eight patients received treatment after a run-in period of 2 months, and of these, 57 completed 8 weeks or more of the trial. All but five of these completed the full 6-month trial. The nimodipine and placebo groups showed no significant differences in the frequency of attacks, severity or duration of headache, or gastrointestinal or other symptoms.

Ansell E, Fazzone T, Festenstein R, Johnson ES, Thavapalan M, Wilkinson M, et al. Nimodipine in migraine prophylaxis. Cephalalgia. 1988 Dec;8(4):269-72

Migraine triggers

Precipitants of individual migraine attacks were studied in 23 migraineurs. Patients were aware of 91 precipitants (average 4 per patient); by direct questioning we could add a further 127 (average 5.5 per patient) provoking factors for migraine episodes. Avoiding these stimuli reduced attacks from 2 to 1g per month in 19 of the 23 patients without prophylactic drugs. Lessened severity or better analgesic control was noted by some. In 4 of the 23 patients the frequency of attacks remained unchanged.

Blau JN, Thavapalan M. Preventing migraine: a study of precipitating factors. Headache 1988;28(7):481-3

Epilepsy and migraine

One hundred epileptic patients were questioned about their headaches. Post-ictal headaches occurred in 51 of these patients and most commonly lasted 6-72 hours. Major seizures were more often associated with post-epileptic headaches than minor attacks. Nine patients in this series of 100 also had migraine: in eight of these nine a typical, albeit a mild, migraine attack was provoked by fits. The post-ictal headache in the 40 epileptics who did not have migraine was accompanied by vomiting in 11 cases, photophobia in 14 cases and vomiting with photophobia in 4 cases. Furthermore, post-epileptic headache was accentuated by coughing, bending and sudden head movements and relieved by sleep. It is, therefore, clear that seizures provoke a syndrome similar to the headache phase of migraine in 50% of epileptics. It is proposed that post-epileptic headache arises intracranially and is related to the vasodilatation known to follow seizures. The relationship of post-epileptic headache to migraine is discussed in the light of current ideas on migraine pathogenesis, in particular the vasodilation which accompanies Leao's spreading cortical depression.

Schon F, Blau JN. Post-epileptic headache and migraine. J Neurol Neurosurg Psychiatry 1987;50(9):1148-52

Naproxen to treat migraine attacks

Seventy patients with classical or common migraine were treated during their attacks with either naproxen sodium or placebo in a randomised, double-blind parallel group study. The initial dose of naproxen sodium was 825 mg followed one hour later by a further 550 mg, if symptoms were the same or had improved. If the migraine symptoms had worsened, patients were offered an escape analgesic combination of 1000 mg paracetamol and 10 mg metoclopramide. Patients were assessed at monthly intervals for changes in the severity and duration of headache, premonitory symptoms (mainly visual disturbances) and photophobia, nausea and vomiting associated with migraine attacks that had occurred since the previous visit. Patients were studied for a maximum of ten attacks and significant

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improvement was observed in the severity and duration of headache when the patients were on naproxen sodium. Also the premonitory symptoms and photophobia improved significantly on naproxen sodium and significantly less rescue analgesics were required. Patients suffering from common migraine had less severe headaches and photophobia when taking naproxen sodium than when taking placebo and the headaches were shorter in duration and patients took less rescue analgesic. No significant difference was observed between the treatment groups in patients with classical migraine. Ten patients in the placebo group and six in the naproxen sodium group reported side-effects but these were possibly related to the use of rescue medication. Naproxen sodium proved safe and effective in common migraine attacks, but in this study efficacy was not established for classical migraine.

Johnson ES, Ratcliffe DM, Wilkinson M. Naproxen sodium in the treatment of migraine. Cephalalgia 1985;5(1):5-10

Senses and migraine

Osmophobia or hyperosmia featured in 25 of 50 migraineurs during the headache phase of their attacks. Pleasant or unpleasant odours could precipitate migraines in 11 patients in this series. Other sensory disturbances and precipitants were also studied. Neurological precipitation of attacks provides further support for a primary neural rather than a vascular pathogenesis of migraine.

Blau JN, Solomon F. Smell and other sensory disturbances in migraine. J Neurol 1985;232(5): 275-6

Ergotamine toxicity and migraine

Twenty-five migraine patients (9 males and 16 females) aged 22-71 who had used between 7 and 60 mg ergotamine tartrate per week for 1.5-30 y volunteered to participate in the study. Side-effects attributable to ergotamine were wide ranging and included daily headache and pain in the limbs. Wide variation in sensitivity to the drug was observed and side-effects were not always proportional to the dose of ergotamine. Random serum ergotamine concentrations were estimated in all patients and 10 of them volunteered to take a 2 mg oral challenge of ergotamine tartrate. Ergotamine was not detected in 44% of the random estimations even though all patients exhibited clinical signs of ergotamine tartrate overdose. The remaining 56% estimations all showed low drug concentrations. After the 2 mg oral challenge of ergotamine in the 10 patients, significantly higher concentrations, but still within therapeutic range, were detected in the sera when compared with mean concentrations achieved after the same oral dose of the drug in healthy, non-migrainous subjects.

Graham AN, Johnson ES, Persaud NP, Turner P, Wilkinson M. Ergotamine toxicity and serum concentrations of ergotamine in migraine patients. Hum Toxicol 1984;3(3):193-9

Migraine in children

Forty-seven migrainous children were examined medically, neurologically and psychiatrically and compared with matched controls from a dental clinic. One in six children suffered from more than one type of migraine. There was a wide variation in age of onset and the frequency and duration of attacks varied considerably. An "emotional upset" was the most frequently reported (86%) precipitating factor. Most children responded to simple therapeutic measures and detailed instructions about the timely use of medication. A significantly higher proportion of migrainous children than their controls showed signs of a neurotic disorder (mainly anxiety or depression) and had had a higher prevalence of neurotic disorder in the previous year. This increased prevalence was found to be



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associated with a disturbed parental relationship and certain factors related to their mothers (age, "malaise" score). A prospective study of an epidemiological sample based on systematic observation rather than recollections and opinions is likely to yield more conclusive results.

Maratos J, Wilkinson M. Migraine in children: a medical and psychiatric study. Cephalalgia 1982;2(4):179-87

Resolution of migraine attacks

A study of 50 migraineurs has confirmed previous observations that sleep is a common way of ending the headache phase. 14 subjects could shorten attacks by going to sleep during the day for an average of 2 1/2 hours. Different methods used by patients to aid falling asleep are described. 47 of the 50 subjects had symptoms after the headache had gone-- here called the recovery phase which can double the length of individual attacks. It is suggested that prodromata, some symptoms of the headache and recovery phases, as well as the therapeutic effect of sleep, indicate that migraine is primarily a neurological rather than a vascular disorder.

Blau JN. Resolution of migraine attacks: sleep and the recovery phase. J Neurol Neurosurg Psychiatry 1982;45(3):223-6

Site of origin of migraine pain

Fifty patients were examined during a migraine attack to seek the site of origin of the headache. There being no single specific test for an intra-or extracranial source of head pain, we employed a series of manoeuvres: coughing, rapid side-to-side head rotation, and breath-holding for 30 seconds--indicative of an intracranial component. Digital compression of the superficial temporal artery, and a blood pressure cuff round the head to occlude the scalp circulation, were used as evidence of an extracranial component. Patients were asked to comment on the effect each of these procedures had on their headache. The observations suggest that in 49/50 an intracranial factor was operative, and in 21 of these no extracranial component was apparent. In 28/49 there seemed to be both intra- and extracranial contributions to the headache. One patient did not respond to any test. The evidence presented seems to implicate intracranial structures in the pathogenesis of migraine headaches.

Blau JN, Dexter SL. The site of pain origin during migraine attacks. Cephalalgia 1981;1(3):143-7



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Complete migraine

Detailed questioning of 50 patients with uncomplicated migraine has shown that 17 had symptoms that preceded the headache phase by several hours. These prodromes consisted of changes in mood, behaviour, wakefulness, appetite, bowel activity, or fluid balance. The term "complete migraine" is proposed for attacks that include prodromal symptoms, whose occurrence implies an initial diffuse cerebral or hypothalamic disturbance.

Blau JN. Migraine prodromes separated from the aura: complete migraine. BMJ 1980;281(6241):658-60

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