Menstrual migraine: therapeutic approaches

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***Abstract*:** The development of diagnostic criteria has enabled greater recognition of menstrual migraine as a highly prevalent and disabling condition meriting specific treatment. Although few therapeutic trials have yet been undertaken in accordance with the criteria, the results of those published to date confirm the efficacy of acute migraine drugs for symptomatic treatment. If this approach is insufficient, the predictability of attacks provides the opportunity for perimenstrual prophylaxis. Continuous contraceptive strategies provide an additional option for management, although clinical trial data are limited. Future approaches to treatment could explore the genomic and nongenomic actions of sex steroids.

***Keywords*:** menstrual migraine, therapy, perimenstrual prophylaxis

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Incidence and prevalence of menstrual migraine

Four of every ten women and two of every ten men will contract migraine in their lifetime, most before age 35 years [Stewart *et al*. 2008]. More than 50% of women with migraine, both in the general population and presenting to specialist clinics, report an association between migraine and menstruation [MacGregor *et al*. 2004, 1997, 1990; Couturier *et al*. 2003; Dzoljic *et al*. 2002; Granella *et al*. 1993].

The peak incidence of migraine during the menstrual cycle occurs on the days directly before and after the first day of menstruation [MacGregor and Hackshaw, 2004; Dzoljic *et al*. 2002; Stewart *et al*. 2000; Johannes *et al*. 1995]. In a population-based study, Stewart *et al*. [2000] noted a significantly elevated risk of migraine without aura on the first two days of menstruation [odds ratio (OR) 2.04; 95% confidence interval (CI) 1.49–2.81]. The lowest risk for headache was around the expected time of ovulation [OR 0.44; 95% CI 0.27–0.72]. Headache duration appeared to be significantly longer for migraine headaches in the 3 to 7 day period before onset of menses [Stewart *et al*. 2000]. In a clinic-based study, MacGregor and Hackshaw [2004] noted that women were 25% (RR 1.25) more likely to have migraine in the five days leading up to menstruation increasing to 71% (RR 1.71; 95% CI 1.45–2.01 $p<0.0001$) in the two days before menstruation. The risk of migraine was highest on the first day of menstruation and the following two days (RR 2.50; 95% CI 2.24–2.77 $p<0.0001$). Similarly, in a population-based study, Wöber *et al*. [2007] found the highest risk of migraine on the first three days of menses (HR 1.96; $p<0.00001$). Menstrual migraine is also associated with increased menstrual distress and disability [Dowson *et al*. 2005; Kibler *et al*. 2005; Granella *et al*. 2004; MacGregor *et al*. 2004; Couturier *et al*. 2003; Beckham *et al*. 1992]. As a consequence of these findings, the International Headache Society developed diagnostic criteria for menstrual migraine (Box 1).

For most women with menstrual attacks, migraine also occurs at other times of the month ('menstrually-related' migraine) [Headache Classification Subcommittee of the International Headache Society (IHS), 2004; MacGregor *et al*. 1990]. Fewer than 10% of women report migraine exclusively with menstruation and at no other time of the month ('pure' menstrual migraine) [Headache Classification Subcommittee of the IHS, 2004; MacGregor *et al*. 2004; Dzoljic *et al*. 2002; Granella *et al*. 1993; MacGregor *et al*. 1990]. To confirm a diagnosis contemporaneous diary cards covering a minimum of three menstrual cycles should be reviewed.

Box 1. Diagnostic criteria for pure menstrual migraine and menstrually-related migraine [adapted from Headache Classification Subcommittee of the International Headache Society (IHS), 2004]. The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0. For the purposes of this classification, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the case of combined oral contraceptives and cyclical hormone replacement therapy.

Pure menstrual migraine
A. Attacks, in a menstruating woman, fulfilling criteria for migraine without aura
B. Attacks occur exclusively on day 1 ±2 (i.e. days −2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle
Menstrually-related migraine
A. Attacks, in a menstruating woman, fulfilling criteria for migraine without aura
B. Attacks occur on day 1 ±2 (i.e. days −2 to +3) of menstruation in at least two out of three menstrual cycles and additionally at other times of the cycle

Acute treatment

Acute treatment of menstrual migraine is the same as for nonmenstrual attacks and includes a combination of analgesics with or without prokinetic antiemetics, nonsteroidal anti-inflammatory drugs, ergot derivatives and triptans [Steiner *et al.* 2007]. The nonprescription combination of acetaminophen, aspirin, and caffeine (AAC; Excedrin Migraine, Bristol-Myers Squibb Company, New York) was assessed for the treatment of menstruation-associated migraine compared with migraine not associated with menses using data from three double-blind, randomized, placebo-controlled, single-dose trials [Silberstein *et al.* 1999]. Subjects with severe vomiting or disability were excluded. Menstruation-associated migraine was treated by 185 women and 781 women treated migraine not associated with menses. There was no statistically significant difference in pain response between menstruation-associated migraine and migraine not associated with menses.

Sumatriptan for the acute treatment of migraine occurring between day −2 and day +4 of the cycle was evaluated in a randomized, double-blind, placebo-controlled study [Nett *et al.* 2003]. A single headache was treated with oral sumatriptan 50 mg, sumatriptan 100 mg, or placebo taken within 1 hour of onset of a mild headache. At 2 hours, 51% and 61% of the sumatriptan 50 mg and 100 mg groups were pain-free compared with 29% of the placebo group ($p < 0.001$). Sustained pain-free response from 2 to 24 hours was reported by 30% of the sumatriptan 50 mg group ($p = 0.007$), 31% of the sumatriptan 100 mg group ($p = 0.004$), and 14% of the placebo group.

A prospective, multicentre, randomized, double-blind, placebo-controlled, two-group crossover study was carried out on patients who self-reported migraine during an 8 day window starting 3 days before the onset of menstruation in two of their last three menstrual cycles with >80% of their attacks falling within the window in the previous 6 months [Dowson *et al.* 2005]. Women treated all migraine attacks for 2 months with sumatriptan 100 mg and for 2 months with placebo. The primary endpoint was the proportion of patients reporting headache relief at 4 hours for the first treated attack. Significantly more women receiving sumatriptan than placebo reported headache relief for attacks occurring inside (67% *versus* 33%, $p = 0.007$) and outside (79% *versus* 31%, $p < 0.001$) the menstrual period.

In a randomized, placebo-controlled trial of acute treatment of migraine occurring between day −3 and day +5 of the menstrual cycle zolmitriptan 1.25 mg was used for mild pain, 2.5 mg for moderate pain, and 5 mg for severe headache pain [Loder *et al.* 2004]. Zolmitriptan (all doses) significantly increased 2-hour headache response compared with placebo (48% *versus* 27%, respectively; $p < 0.0001$). Pain relief was statistically superior ($p = 0.03$) with zolmitriptan treatment, as early as 30 minutes after dosing.

Naratriptan for the acute treatment of migraine occurring on day −2 to day +4 of the menstrual cycle was assessed in a randomized, double-blind, placebo-controlled trial [Massiou *et al.* 2005]. A significantly greater percentage of the naratriptan group were pain free at 4 hours compared with placebo (58% *versus* 30% with placebo; $p < 0.001$).

Almotriptan and zolmitriptan for acute treatment of menstrual migraine were evaluated in a double-blind, randomized trial of 255 women [Allais *et al.* 2006]. Pain-free response at 2 hours was achieved in 44.9% of patients receiving almotriptan and 41.2% of those receiving zolmitriptan. The 2-hour pain-free status was sustained for at least 24 hours in 29.3% and 27.1% of patients treated with almotriptan and zolmitriptan, respectively. In a *post hoc* analysis of the AXERT Early miGraine Intervention Study (AEGIS), 275 women treated 506 migraine attacks. Almotriptan treatment efficacy outcomes were not significantly different for menstrual and nonmenstrual attacks: 2-hour pain relief, 77.4% *versus* 68.3%; 2-hour pain free, 35.4% *versus* 35.9%; and sustained pain free, 22.9% *versus* 23.8% [Diamond *et al.* 2008].

Rizatriptan 10 mg was effective for the treatment of ICHD-II menstrual migraine in two prospective, randomised, double-blind, placebo-controlled trials, as measured by 2 hour pain relief and 24 hour sustained pain relief in 707 women [Nett *et al.* 2008]. In an early intervention model using rizatriptan 10 mg, 2 hour pain-free rates were comparable for 94 women treating menstrual and nonmenstrual migraine attacks [Martin *et al.* 2008].

Perimenstrual prophylaxis

When acute therapy is insufficient to reduce disability from menstrual migraine, there is the option for preventing attacks using perimenstrual or continuous prophylaxis. The choice depends on the individual woman's type of migraine, regularity of menstruation, other menstrual problems and need for contraception (Figure 1).

Short-term prophylactic strategies have the advantage that treatment is only used at the time of need, potentially reducing the risk of adverse events compared with continuous prophylaxis. However, results from RCTs are limited (Table 1). None of the drugs and hormones recommended for perimenstrual prophylaxis are licensed for management of menstrual migraine.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Studies using 550 mg naproxen once or twice daily perimenstrually have shown limited efficacy [Nattero *et al.* 1991; Sances *et al.* 1990; Szekely *et al.* 1989; Sargent *et al.* 1985]. A recent open-label study of perimenstrual naproxen 550 mg daily has shown efficacy for prevention of menstrual migraine [Allais *et al.* 2007]. NSAIDs are useful as first-line agents for migraine associated with dysmenorrhoea and/or menorrhagia.

Estradiol

Maintaining luteal phase oestrogen levels can prevent menstrual attacks [MacGregor *et al.* 2006; Somerville, 1975a, 1975b, 1972]. Doses equivalent to 1.5 mg estradiol gel allow a mean estradiol plasma level of 80 pg/ml to be reached. Lower doses of oestrogen are not effective [Smits *et al.* 1994; Pradalier *et al.* 1994; Pfaffenrath, 1993].

There is evidence that some women responding to oestrogen supplements experience delayed attacks when the supplements are discontinued [MacGregor *et al.* 2006] Oestrogen 'withdrawal' migraine may occur if treatment is not continued until the rise in endogenous oestrogen. Although there are no trial data, clinical practice suggests that for these women the duration of supplement use can be extended until day 7 of the cycle, tapering the dose over the last 2 days.

Triptans

Trials using frovatriptan, naratriptan, sumatriptan and zolmitriptan for perimenstrual prophylaxis have suggested efficacy [Tuchman *et al.* 2008; Moschiano *et al.* 2005; Silberstein *et al.* 2004; Newman *et al.* 2001, 1998].

Perimenstrual triptan prophylaxis is well tolerated and the high completion rates in the clinical trials are notable. Post-treatment migraine has been reported following naratriptan but not frovatriptan [Mannix *et al.* 2007; Brandes *et al.* (in press)]

A small pilot, open-label, nonrandomized, parallel group study assessed the efficacy of 2.5 mg frovatriptan against 25 µg transdermal oestrogen or 50 mg naproxen sodium each taken once daily for 6 days, beginning 2 days before the expected onset of menstrual headache [Guidotti *et al.* 2007]. The baseline median headache severity score severity was 4.6, 4.2 and 4.3 in the group subsequently treated with frovatriptan, transdermal oestrogen and naproxen sodium, respectively ($p = 0.819$) compared with scores of 2.5, 3.0 and 3.0 during treatment ($p = 0.049$). Although these results suggest that

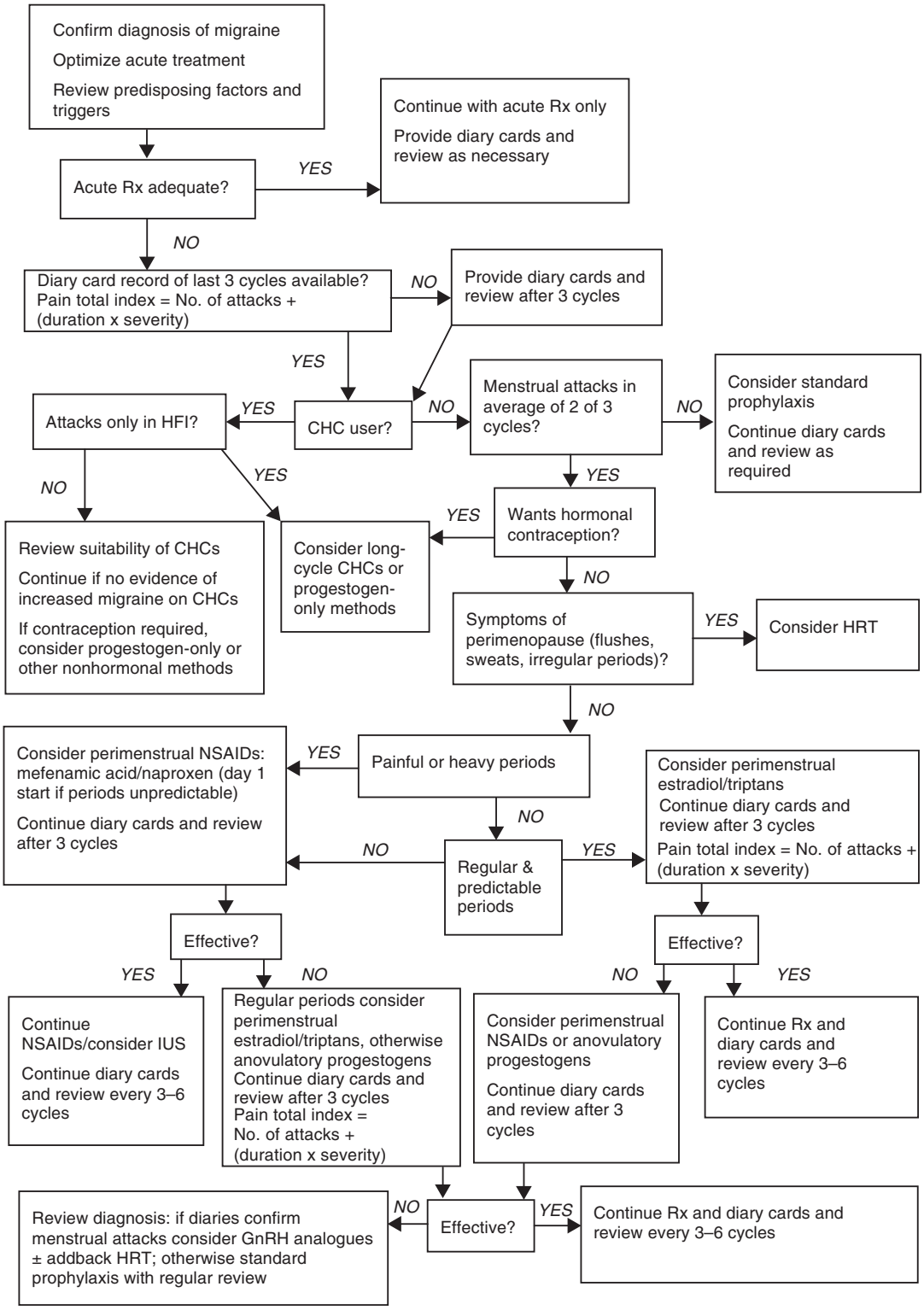

Figure 1. Management strategies for menstrual migraine. CHC, combined hormonal contraceptives; GnRH, gonadotrophin-releasing hormone analogue; HFI, hormone free interval; HRT, hormone replacement therapy; IUS, intrauterine system; NSAIDs, nonsteroidal anti-inflammatory drugs; Rx, treatment. Reproduced with permission from MacGregor, E.A. (2007) Menstrual migraine: a clinical review, *J Fam Plann Reprod Health Care* 33: 36–47.

Table 1. Randomized placebo-controlled trials of perimenstrual prophylaxis.

Trial	Study design	Sample size	Rx	No. of cycles	Treatment start	Primary endpoint	Results
Naproxen							
Sances *et al.* [1990]	Parallel	35	550 mg bd	3	7 days before expected menses through 6th day of menstrual flow	Pain Total Index = no. of attacks + (duration X severity)	NS
Estradiol							
De Lignieres *et al.* [1986]	Cross-over	18	1.5 mg	3	2 days before expected menses for 7 days	Presence of migraine	Estradiol 30.8% PCB 96.3% ($p<0.01$)
Dennerstein *et al.* [1988]	Cross-over	18	1.5 mg	4	2 days before expected migraine for 7 days	Days of moderate to severe migraine during treatment	Estradiol 47 days PCB 86 days ($p<0.001$)
Pfaffenrath [1993]	Cross-over	41	50 mcg	4	2 days before expected migraine Duration not stated	Reduction in headache duration, intensity and impairment	NS
Smits *et al.* [1994]	Cross-over	20	50 mcg	3	2 days before expected menses for 8 days	Percentage of treatment periods with migraine	NS
MacGregor *et al.* [2006]	Cross-over	35	1.5 mg	6	9 days after LH surge (approx day −5/−6) until 2nd full day of menses (approx 8 days)	Reduction in migraine days during treatment	22% RR0.78 95% CI 0.62–0.99 ($p=0.04$)
Frovatriptan							
Silberstein *et al.* [2004]	Cross-over	445	2.5 mg bd 2.5 mg od	3	2 days before expected migraine for 6 days	Incidence of migraine during each treatment period	bd 43% od 52% PCB 69% ($p<0.0001$) *vs* PCB
Brandes *et al.* [in press]	Parallel	410	2.5 mg bd 2.5 mg od	3	2 days before expected migraine for 6 days	No. of headache-free treatment periods	bd 0.92 od 0.69 PCB 0.42 (p<0.001 and p<0.02) *vs* PCB
Naratriptan							
Newman *et al.* [2001]	Parallel	206	1 mg bd 2.5 mg bd	4	2 days before expected menses for 5 days	Percentage headache-free treatment periods per patient Mean no. of migraines	1 mg bd 50% PCB 25% ($p=0.003$) 2.0 *vs* 4.0 ($p<0.05$) 2.5 mg NS

(Continued)

Table 1. Continued.

Trial	Study design	Sample size	Rx	No. of cycles	Treatment start	Primary endpoint	Results
Mannix *et al.* [2007]	Parallel	Study 1: 218 Study 2: 273	1 mg bd	4	3 days before expected menses for 6 days	Mean percentage of treatment periods without migraine per patient	Study 1: naratriptan 40% PCB 27% ($p<0.05$) Study 2: naratriptan 37% PCB 24% ($p<0.05$)
Zolmitriptan							
Tuchman *et al.* [2008]	Parallel	217	2.5mg bd 2.5mg tds	3	2 days before expected menses for 7 days	≥50% reduction in migraine	tds 58.6% bd 54.7% PCB 37.8% ($p=0.0007$ and $p=0.002$) *vs* PCB

bd, twice daily; NS, not sigficant *vs* placebo; od, once daily; PCB, placebo; RCT, randomized controlled trial; RR, relative risk; tds, three times daily.

short-term prophylaxis of menstrual migraine with frovatriptan may be more effective than transdermal oestrogen or naproxen sodium, the drug doses used in the study were suboptimal.

Continuous hormonal strategies

Combined hormonal contraceptives

Women with irregular periods or who require contraception may benefit from specific strategies that prevent migraine in the hormone-free interval of combined hormonal contraceptives, although to date evidence is currently based more on clinical practice than on robust clinical trial data [Calhoun and Ford, 2008; MacGregor, 2007].

Continuous hormones, in place of the usual regimen of 3 weeks of active followed by 1 week of inactive pills or no therapy, have been recommended based on evidence that oestrogen withdrawal provokes headache in susceptible women. Compared with the usual 21/7-day regimen of combined hormonal contraceptives, a 168-day extended placebo-free regimen led to a decrease in headache severity along with improvement in work productivity and involvement in activities [Sulak *et al.* 2007]. Similarly, an extended 84-day regimen of a transdermal contraceptive reduced the total incidence of mean headache days compared with a 21/7-day regimen [Laguardia *et al.* 2005]. No double-blind, placebo-controlled trials, or even open-label trials, of this strategy in menstrual migraine have been performed. However, there is increasing clinical experience of their use in this way [Edelman *et al.* 2006]. Combined hormonal contraceptives should not be used by women with migraine with aura because of the synergistic increased risk of ischaemic stroke [World Health Organization, 2004; MacGregor and Guillebaud, 1998].

Progestogen-only contraceptives

There are no studies assessing anovulatory progestogens such as the intramuscular depot medroxyprogesterone acetate, subdermal etonogestrel and oral desogestrel, which inhibit ovulation. In general, standard contraceptive oral progestogens have little place in the management of menstrual migraine since most do not inhibit ovulation and are associated with a disrupted menstrual cycle [Chumnijaraki *et al.* 1984]. In contrast, unlicensed higher doses of

oral progestogen, sufficient to inhibit ovulation, have shown benefit [Davies *et al.* 2003].

Gonadotrophin-releasing hormone analogues

Although effective, adverse effects of oestrogen deficiency; for example, hot flushes, restrict their use [Holdaway *et al.* 1991]. The hormones are also associated with a marked reduction in bone density and should not usually be used for longer than 6 months without regular monitoring and bone densitometry. 'Add-back' continuous combined oestrogen and progestogen can be given to counter these difficulties [Martin *et al.* 2003; Murray and Muse, 1997]. Given these limitations, in addition to increased cost, such treatment should be instigated only in specialist departments.

Future therapeutic approaches

The association between sex steroids and migraine warrants further investigation and has the potential to result in more targeted diagnosis and treatment. Sex steroid activity is not confined to reproductive tissues, having activity in both the peripheral and central nervous systems through genomic and nongenomic effects. Studies investigating the role of the oestrogen receptor 1 (ESR1) gene in migraine show a significant association of the A allele of the G594A SNP with migraine [Colson *et al.* 2004]. The progesterone receptor (PGR) PROGINS insert has also been implicated [Colson *et al.* 2005]. Women who carry a copy of both PR and ESR1 risk alleles were 3.2 times more likely to suffer from migraine, an effect that is greater than the independent effects of these genetic variants on disease susceptibility. It is anticipated that this association will be stronger in women with menstrual migraine, who have a strong hormonal trigger for attacks.

If the genes that play a role in this subtype of migraine can be identified, it should be possible to develop objective ways of testing for these genes as a diagnostic tool. Accurate diagnosis of menstrual migraine can aid the selection of currently available treatments. Further, identification of the genes involved could ultimately lead to the development of more effective treatments for this disabling condition, targeted to the specific genes.

Understanding how the genetics translates into a clinical outcome could also provide a more targeted therapeutic approach. Animal models suggest that abnormalities in how oestrogen modulates neuronal function in migraine are due to a mismatch between its gene-regulation and membrane effects [Welch *et al.* 2006]. The hypothesis is that during phases of high oestrogen levels, increased neuronal excitability is balanced by homeostatic gene regulation in brain cortex, and nociceptive systems. When oestrogen is 'withdrawn' around menstruation, mismatch in homeostatic gene regulation by oestrogen unmasks non-nuclear mitogen-activated hyperexcitability of cell membranes, sensitizing neurons to triggers that activate migraine attacks. At the trough of oestrogen levels, the downregulating effect on inflammatory genes is lost and peptide modulated central sensitization is increased as is pain and disability of the migraine attack.

Other potential lines of research could enable a better understanding of the interplay between oestrogen and serotonin. The mechanisms underlying the benefit of perimenstrual triptan prophylaxis are as yet unexplained. Sex steroids modulate neurotransmission in the brain, spinal cord and peripheral nerves, and influence receptor activity of other neurotransmitters, including the serotonergic system. Oestrogen is associated with increased production of serotonin, reduced serotonin reuptake and decreased serotonin degradation.

The role of progesterone also merits more research. Although oestrogen 'withdrawal' can trigger migraine in the absence of progesterone, the GABAergic actions of progestrogen are likely to modulate pain and pain perception.

Conflict of interest statement

Dr MacGregor has acted as a paid consultant to, and/or her department has received research funding from, Addex, AstraZeneca, BTG, Endo Pharmaceuticals, GlaxoSmithKline, Menarini, Merck and Pozen.

References

Allais, G., Acuto, G., Cabarrocas, X., Esbri, R., Benedetto, C. and Bussone, G. (2006) Efficacy and tolerability of almotriptan versus zolmitriptan for the acute treatment of menstrual migraine. *Neurol Sci* 27(Suppl. 2): S193–197.

Allais, G., Bussone, G., De Lorenzo, C., Castagnoli Gabellari, I., Zonca, M., Mana, O. *et al.* (2007) Naproxen sodium in short-term prophylaxis of pure menstrual migraine: pathophysiological and clinical considerations. *Neurol Sci* 28(Suppl. 2): S225–228.

Beckham, J.C., Krug, L.M., Penzien, D.B., Johnson, C.A., Mosley, T.H., Meeks, G.R. *et al.* (1992) The relationship of ovarian steroids, headache activity and menstrual distress: a pilot study with female migraineurs. *Headache* 32: 292–297.

Brandes, J.L., Poole, A.C., Kallela, M., Schreiber, C.P., MacGregor, E.A., Silberstein, S.D. *et al.* (2009) Short-term frovatriptan for the prevention of difficult-to-treat menstrual migraine attacks, *Cephalalgia* doi:10.1111/j.1468-2982.2009.01840.x.

Calhoun, A. and Ford, S. (2008) Elimination of menstrual-related migraine beneficially impacts chronification and medication overuse. *Headache* 48: 1186–1193.

Chumnijaraki, T., Sunyavivat, S., Onthuam, Y. and Udomprasetgurl, V. (1984) Study on the factors associated with contraception discontinuation in Bangkok. *Contraception* 29: 241–248.

Colson, N.J., Lea, R.A., Quinlan, S., Macmillan, J. and Griffiths, L.R. (2004) The estrogen receptor 1 G594a polymorphism is associated with migraine susceptibility in two independent case/control groups. *Neurogenetics* 5: 129–133.

Colson, N.J., Lea, R.A., Quinlan, S., Macmillan, J. and Griffiths, L.R. (2005) Investigation of hormone receptor genes in migraine. *Neurogenetics* 6: 17–23.

Couturier, E.G., Bomhof, M.A., Neven, A.K. and Van Duijn, N.P. (2003) Menstrual migraine in a representative Dutch population sample: prevalence, disability and treatment. *Cephalalgia* 23: 302–308.

Davies, P., Fursdon-Davies, C. and Rees, M.C. (2003) Progestogens for menstrual migraine. *J Br Menopause Soc* 9: 134.

Diamond, M.L., Cady, R.K., Mao, L., Biondi, D.M., Finlayson, G., Greenberg, S.J. *et al.* (2008) Characteristics of migraine attacks and responses to almotriptan treatment: a comparison of menstrually related and nonmenstrually related migraines. *Headache* 48: 248–258.

Dowson, A.J., Kilminster, S.G., Salt, R., Clark, M. and Bundy, M.J. (2005) Disability associated with headaches occurring inside and outside the menstrual period in those with migraine: a general practice study. *Headache* 45: 274–282.

Dowson, A.J., Massiou, H. and Aurora, S.K. (2005) Managing migraine headaches experienced by patients who self-report with menstrually related migraine: a prospective, placebo-controlled study with oral sumatriptan. *J Headache Pain* 6: 81–87.

Dzoljic, E., Sipetic, S., Vlajinac, H., Marinkovic, J., Brzakovic, B., Pokrajac, M. *et al.* (2002) Prevalence of menstrually related migraine and nonmigraine primary headache in female students of Belgrade university. *Headache* 42: 185–193.

Edelman, A., Gallo, M.F., Nichols, M.D., Jensen, J.T., Schulz, K.F. and Grimes, D.A. (2006) Continuous versus cyclic use of combined oral contraceptives for contraception: Systematic Cochrane Review of randomized controlled trials. *Hum Reprod* 21: 573–578.

Granella, F., Sances, G., Allais, G., Nappi, R.E., Tirelli, A., Benedetto, C. *et al.* (2004) Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. *Cephalalgia* 24: 707–716.

Granella, F., Sances, G., Zanferrari, C., Costa, A., Martignoni, E. and Manzoni, G.C. (1993) Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. *Headache* 33: 385–389.

Guidotti, M., Mauri, M., Barrila, C., Guidotti, F. and Belloni, C. (2007) Frovatriptan vs. transdermal oestrogens or naproxen sodium for the prophylaxis of menstrual migraine. *J Headache Pain* 8: 283–288.

Headache Classification Subcommittee of the International Headache Society (IHS). (2004) The International Classification of Headache Disorders (2nd Edition). *Cephalalgia* 24: 1–160.

Holdaway, I.M., Parr, C.E. and France, J. (1991) Treatment of a patient with severe menstrual migraine using the depot LHRH analogue zoladex. *Aust NZ J Obstet Gynaecol* 31: 164–165.

Johannes, C.B., Linet, M.S., Stewart, W.F., Celentano, D.D., Lipton, R.B. and Szklo, M. (1995) Relationship of headache to phase of the menstrual cycle among young women: a daily diary study. *Neurology* 45: 1076–1082.

Kibler, J.L., Rhudy, J.L., Penzien, D.B., Rains, J.C., Meeks, G.R., Bennett, W. *et al.* (2005) Hormones, menstrual distress, and migraine across the phases of the menstrual cycle. *Headache* 45: 1181–1189.

Laguardia, K.D., Fisher, A.C., Bainbridge, J.D., Lococo, J.M. and Friedman, A.J. (2005) Suppression of estrogen-withdrawal headache with extended transdermal contraception. *Fertil Steril* 83: 1875–1877.

Loder, E., Silberstein, S.D., Abu-Shakra, S., Mueller, L. and Smith, T. (2004) Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache* 44: 120–130.

MacGregor, E.A. (2007) Menstrual migraine: a clinical review. *J Fam Plann Reprod Health Care* 33: 36–47.

MacGregor, E.A., Brandes, J., Eikermann, A. and Giammarco, R. (2004) Impact of migraine on patients and their families: the migraine and zolmitriptan evaluation (MAZE) survey-phase III. *Curr Med Res Opin* 20: 1143–1150.

MacGregor, E.A., Chia, H., Vohrah, R.C. and Wilkinson, M. (1990) Migraine and menstruation: a pilot study. *Cephalalgia* 10: 305–310.

MacGregor, E.A., Frith, A., Ellis, J., Aspinall, L. and Hackshaw, A. (2006) Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology* 67: 2159–2163.

MacGregor, E.A. and Guillebaud, J. (1998) Combined oral contraceptives, migraine and ischaemic stroke. Clinical and Scientific Committee of the Faculty of Family Planning and Reproductive Health Care and the Family Planning Association. *Br J Fam Plann* 24: 55–60.

MacGregor, E.A. and Hackshaw, A. (2004) Prevalence of migraine on each day of the natural menstrual cycle. *Neurology* 63: 351–353.

MacGregor, E.A., Igarashi, H. and Wilkinson, M. (1997) Headaches and hormones: subjective versus objective assessment. *Headache Q* 8: 126–136.

Mannix, L.K., Savani, N., Landy, S., Valade, D., Shackelford, S., Ames, M.H. *et al.* (2007) Efficacy and tolerability of naratriptan for short-term prevention of menstrually related migraine: data from two randomized, double-blind, placebo-controlled studies. *Headache* 47: 1037–1049.

Martin, V., Cady, R., Mauskop, A., Seidman, L.S., Rodgers, A., Hustad, C.M. *et al.* (2008) Efficacy of rizatriptan for menstrual migraine in an early intervention model: a prospective subgroup analysis of the rizatriptan tame (treat a migraine early) studies. *Headache* 48: 226–235.

Martin, V., Wernke, S., Mandell, K., Zoma, W., Bean, J., Pinney, S. *et al.* (2003) Medical oophorectomy with and without estrogen add-back therapy in the prevention of migraine headache. *Headache* 43: 309–321.

Massiou, H., Jamin, C., Hinzelin, G. and Bidaut-Mazel, C. (2005) Efficacy of oral naratriptan in the treatment of menstrually related migraine. *Eur J Neurol* 12: 774–781.

Moschiano, F., Allais, G., Grazzi, L., Usai, S., Benedetto, C., D'Amico, D. *et al.* (2005) Naratriptan in the short-term prophylaxis of pure menstrual migraine. *Neurol Sci* 26(Suppl. 2): s162–166.

Murray, S.C. and Muse, K.N. (1997) Effective treatment of severe menstrual migraine headaches with gonadotropin-releasing hormone agonist and 'add-back' therapy. *Fertil Steril* 67: 390–393.

Nattero, G., Allais, G., De Lorenzo, C., Ferrando, M., Ferrari, P., Benedetto, C. *et al.* (1991) Biological and clinical effects of naproxen sodium in patients with menstrual migraine. *Cephalalgia* 11: 201–202.

Nett, R., Landy, S., Shackelford, S., Richardson, M.S., Ames, M. and Lener, M. (2003) Pain-free efficacy after treatment with sumatriptan in the mild pain phase of menstrually associated migraine. *Obstet Gynecol* 102: 835–842.

Nett, R., Mannix, L.K., Mueller, L., Rodgers, A., Hustad, C.M., Skobieranda, F. *et al.* (2008) Rizatriptan efficacy in ICHD-II pure menstrual migraine and menstrually related migraine. *Headache* 48: 1194–1201.

Newman, L., Mannix, L.K., Landy, S., Silberstein, S., Lipton, R.B., Putnam, D.G. *et al.* (2001) Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 41: 248–256.

Newman, L.C., Lipton, R.B., Lay, C.L. and Solomon, S. (1998) A pilot study of oral sumatriptan as intermittent prophylaxis of menstruation-related migraine. *Neurology* 51: 307–309.

Pfaffenrath, V. (1993) Efficacy and safety of percutaneous estradiol vs. placebo in menstrual migraine. *Cephalalgia* 13: 244.

Pradalier, A., Vincent, D., Beaulieu, P., Baudesson, G. and Launey, J.-M. (1994) Correlation between estradiol plasma level and therapeutic effect on menstrual migraine.. In Rose, F. (ed.), *New Advances in Headache Research*. London, Smith-Gordon.

Sances, G., Martignoni, E., Fioroni, L., Blandini, F., Facchinetti, F. and Nappi, G. (1990) Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache* 30: 705–709.

Sargent, J., Solbach, P., Damasio, H., Baumel, B., Corbett, J. and Al, E. (1985) A Comparison of naproxen sodium to propranolol hydrochloride and a placebo control for the prophylaxis of migraine headache. *Headache* 25: 320–324.

Silberstein, S.D., Armellino, J.J., Hoffman, H.D., Battikha, J.P., Hamelsky, S.W., Stewart, W.F. *et al.* (1999) Treatment of menstruation-associated migraine with the nonprescription combination of acetaminophen, aspirin, and caffeine: results from three randomized, placebo-controlled studies. *Clin Ther* 21: 475–491.

Silberstein, S.D., Elkind, A.H., Schreiber, C. and Keywood, C. (2004) A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology* 63: 261–269.

Smits, M.G., Van Der Meer, Y.G., Pfeil, J.P., Rijnierse, J.J. and Vos, A.J. (1994) Perimenstrual migraine: effect of estraderm TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. *Headache* 34: 103–106.

Somerville, B.W. (1972) The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology* 22: 355–365.

Somerville, B.W. (1975a) Estrogen-withdrawal migraine. I. Duration of exposure required and attempted prophylaxis by premenstrual estrogen administration. *Neurology* 25: 239–244.

Somerville, B.W. (1975b) Estrogen-withdrawal migraine II. Attempted prophylaxis by continuous estradiol administration. *Neurology* 25: 245–250.

Steiner, T.J., MacGregor, E.A. and Davies, P.T.G. (2007) Guidelines for All Healthcare Professional in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication Overuse Headache (3rd edition). Available at: http://216.225.288.243/upload/NS_BASH/BASH_guidelines_2007.pdf

Stewart, W.F., Lipton, R.B., Chee, E., Sawyer, J. and Silberstein, S.D. (2000) Menstrual cycle and headache in a population sample of migraineurs. *Neurology* 55: 1517–1523.

Stewart, W.F., Wood, C., Reed, M.L., Roy, J. and Lipton, R.B. (2008) Cumulative lifetime migraine incidence in women and men. *Cephalalgia* 28: 1170–1178.

Sulak, P., Willis, S., Kuehl, T., Coffee, A. and Clark, J. (2007) Headaches and oral contraceptives: impact of eliminating the standard 7-day placebo interval. *Headache* 47: 27–37.

Szekely, B., Meeryman, S. and Post, G. (1989) Prophylactic effects of naproxen sodium on perimenstrual headache: a double-blind, placebo-controlled study. *Cephalalgia* 9: 452–453.

Tuchman, M.M., Hee, A., Emeribe, U. and Silberstein, S. (2008) Oral zolmitriptan in the short-term prevention of menstrual migraine: a randomized, placebo-controlled study. *CNS Drugs* 22: 877–886.

Welch, K.M., Brandes, J.L. and Berman, N.E. (2006) Mismatch in how oestrogen modulates molecular and neuronal function may explain menstrual migraine. *Neurol Sci* 27(Suppl. 2): S190–192.

Wober, C., Brannath, W., Schmidt, K., Kapitan, M., Rudel, E., Wessely, P. *et al.* (2007) Prospective analysis of factors related to migraine attacks: the pamina study. *Cephalalgia* 27: 304–314.

World Health Organization (2004) *Medical Eligibility Criteria for Contraceptive Use*. Geneva, WHO.