

Menstrual migraine: a clinical review

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Overview

Migraine attacks are often associated with menstruation in many, but not all, women with migraine. To date, no hormonal abnormalities have been identified in these women and it appears that normal hormonal fluctuations are associated with an abnormal central nervous system response. Diagnosis of migraine and confirmation of menstrual association is clinical, based on headache history and review of diary cards. Tests of hormone levels are rarely useful. Standard drugs to treat the acute symptoms suffice for the majority of women with monthly attacks. If acute therapy alone is inadequate, pre-emptive treatment of the expected menstrual headache with perimenstrual estradiol, triptans or non-steroidal anti-inflammatory drugs (NSAIDs) may be effective. Suppression of the menstrual cycle with anovulatory contraceptive agents is an additional option, particularly for women who also require contraception. A variety of other treatments have been studied, but the quality of evidence for their use is generally poor.

Search strategy

Data for this review were identified by a MEDLINE search using the following search terms: estrogen, estradiol, menstruation, menstrual cycle, menstrual migraine, menstrually related migraine, menstrually associated migraine, migraine and progesterone. The resultant search identified 554 publications. The Cochrane search strategy for identifying reports of randomised controlled trials was run on this database.¹ The search strategy identified 103 publications, which were scrutinised for relevancy to this review.

In addition, references from the author's own files, a hand search of the journals *Cephalalgia* and *Headache*, and peer-reviewed presentations at international congresses were considered.

How common is migraine?

The two most frequently encountered types of migraine differ only in their presence or absence of 'aura' (Box 1).² About 70–80% of migraineurs experience attacks of migraine without aura (formerly known as common or simple migraine), 10% have migraine with aura (formerly known as classical or focal migraine) and 15–20% have both types of attacks. Less than 1% of attacks are of aura alone, with no ensuing headache.

Migraine is equally common in both sexes before puberty, with increased female prevalence following menarche.³ At puberty, the incidence of migraine without aura rises in females,⁴ with 10% to 20% of women reporting migraine with menarche.⁵ This sex difference becomes greater with increasing age, peaking during the early 40s and declining thereafter. The lifetime prevalence of migraine is around 25% in women compared to only 8% in men.^{6–8}

Box 1 International Headache Society classification of migraine without aura and migraine with aura²

1.1 Migraine without aura

Recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least five attacks¹ fulfilling criteria B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 1. Unilateral location
 2. Pulsating quality
 3. Moderate or severe pain intensity
 4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
- D. During headache at least one of the following:
 1. Nausea and/or vomiting
 2. Photophobia and phonophobia
- E. Not attributed to another disorder in the Appendix because of uncertainty over whether they should be regarded as separate entities

1.2.1 Typical aura with migraine headache

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than 1 hour, a mix of positive and negative features and complete reversibility characterise the aura, which is associated with a headache fulfilling criteria for '1.1 Migraine without aura'.

Diagnostic criteria:

- A. At least two attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
 1. Fully reversible visual symptoms including positive features (e.g. flickering lights, spots or lines) and/or negative features (i.e. loss of vision)
 2. Fully reversible sensory symptoms including positive features (i.e. pins and needles) and/or negative features (i.e. numbness)
 3. Fully reversible dysphasic speech disturbance
- C. At least two of the following:
 1. Homonymous visual symptoms¹ and/or unilateral sensory symptoms
 2. At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 3. Each symptom lasts ≥ 5 and < 60 minutes
- D. Headache fulfilling criteria B–D for '1.1 Migraine without aura' begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder

Who gets menstrual migraine?

More than 50% of women with migraine, both in the general population and presenting to specialist clinics, report an association between migraine and menstruation.^{9–14}

For most women with menstrual attacks, migraine also occurs at other times of the month ('menstrually related' migraine).^{2,13} Fewer than 10% of women report migraine exclusively with menstruation and at no other time of the month ('true' or 'pure' menstrual migraine).^{2,11–14}

Prognosis

Migraine is a fluctuating condition. A longitudinal study of 73 migraineurs over 40 years showed that attack frequency was variable with time, sometimes with long episodes of remission.¹⁵ Similarly, the association with menstruation is inconsistent with time. Although a few women report a constant association between migraine and menstruation since menarche, the majority report a gradual association between migraine and menstruation developing from their late 30s, with

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Box 2 International Headache Society classification of pure menstrual migraine and menstrually related migraine²**A1.1.1 Pure menstrual migraine without aura***Diagnostic criteria:*

- A. Attacks, in a menstruating woman, fulfilling criteria for '1.1 Migraine without aura'
- B. Attacks occur exclusively on Day 1 ± 2 (i.e. Days +2 to -3)¹ of menstruation² in at least two out of three menstrual cycles and at no other times of the cycle

Notes:

1. The first day of menstruation is Day 1 and the preceding day is Day -1; there is no Day 0.
2. 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.

A1.1.2 Menstrually-related migraine without aura*Diagnostic criteria:*

- A. Attacks, in a menstruating woman, fulfilling criteria for '1.1 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

Notes:

1. The first day of menstruation is Day 1 and the preceding day is Day -1; there is no Day 0.
2. 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.

increasing prevalence in the years leading to menopause. Following the menopause, migraine prevalence declines.¹⁶ However, the female preponderance still persists after menopause with a female:male ratio of 2:1 after 70 years of age.

Clinical characteristics**Definition**

The International Headache Society Classification of Headache Disorders (ICHD) includes specific definitions for pure menstrual migraine and menstrually related migraine (Box 2).²

Although some women report a link between their migraine attacks and ovulation, this has not been confirmed in epidemiological studies.^{13,17,18} A prospective study confirmed that the observed number of attacks associated with ovulation was not significantly different from the expected number of attacks.¹⁹

When do migraines occur?

The definitions for pure menstrual and menstrually related migraine were developed from numerous studies, all of which have shown that migraine is most likely to occur on or between 2 days before menstruation and the first 3 days of bleeding.^{13,18-26}

In the largest study to date of migraine and the natural menstrual cycle, 693 cycles from 155 women were reviewed.¹⁸ In the 5 days leading up to menstruation, women were 25% more likely to have a migraine attack [relative risk (RR) 1.25]. This increased to 71% in the 2 days before menstruation (RR 1.71). The chance of migraine was more than two-fold on the first day of menstruation and during the 5 days afterward (RR 2.19). The risk was highest on the first day of menstruation and the following 2 days (RR 2.50).

What is different about menstrual attacks?

Menstrual attacks are almost invariably *without* aura, even in women who have attacks *with* aura at other times of the cycle.^{13,22,26,27}

Of specific relevance to clinical practice is that attacks occurring at the time of menstruation are more severe and disabling, last longer and are less responsive to symptomatic medication.^{10,14,18,28-31} Within-woman analyses show that compared to migraine at other times of the cycle, migraine in the 2 days before menstruation was 2.1 times more likely to be severe; those occurring on the first 3 days of bleeding were 3.4 times more likely to be severe and almost 5 times more likely to be accompanied by vomiting.¹⁸ In women with menstrually related migraine referred to tertiary care centres, premenstrual (Days -2 and -1), menstrual (Days +1 and +2), and late menstrual (Days +3 to +7) attacks lasted longer than attacks at other times of the cycle.³² Premenstrual and menstrual attacks were also less responsive to acute treatment than attacks at other times of the cycle.

The resulting disability is important. Recent research by the World Health Organization has established migraine as a leading cause of years of life lived with a disabling condition: ranked twelfth for women compared to nineteenth for men.³³ Of 389 people with migraine, 85% reported substantial reductions in their ability to do household work and chores, 45% missed family social and leisure activities, and 32% avoided making plans for fear of cancellation due to headaches.³⁴ Work-related disability is more often reported for premenstrual migraines than for non-menstrual attacks ($p = 0.006$).³² Similarly, time spent at less than 50% productivity is greater for menstrual than non-menstrual attacks ($p = 0.01$).³⁵

Disability does not only affect the individual but extends to the family and work environment. In one study, 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%).¹⁴

Pathophysiology

Estrogen (oestrogen) and progesterone are the main hormones that have been investigated in relation to migraine. Studies comparing levels of these hormones in women with menstrual migraine versus controls have not found any convincing differences. Research has focused on 'withdrawal' of estrogen and progesterone/progestogens as occurs during the luteal phase of the menstrual cycle and during the hormone-free interval of combined hormonal contraception.³⁶⁻³⁹ Since women with migraine using combined hormonal contraceptives still experience migraine during the hormone-free interval, it would seem that ovulation is not a prerequisite for menstrual attacks.

Estrogen 'withdrawal'

Somerville undertook several studies in a small group of women who had a history of pure menstrual migraine. He noted that a period of estrogen 'priming' with several days of exposure to high estrogen levels is necessary for migraine to result from estrogen 'withdrawal', as occurs in the late luteal phase of the menstrual cycle.⁴⁰⁻⁴² This would explain why migraine is not associated with the transient estrogen surge at ovulation.

Several other studies support Somerville's estrogen withdrawal theory. Epstein *et al.* noted that the extent of decline from peak to trough estrogen was greater in all 14 women with migraine in their study compared to eight women in the control group who did not have migraine.⁴³ They concluded that variation in hormonal activity might be a potentially relevant factor in all women with migraine; factors additional to the hormonal environment could account for the development of 'menstrual' attacks. Lichten *et al.* studied 28 postmenopausal women challenged with

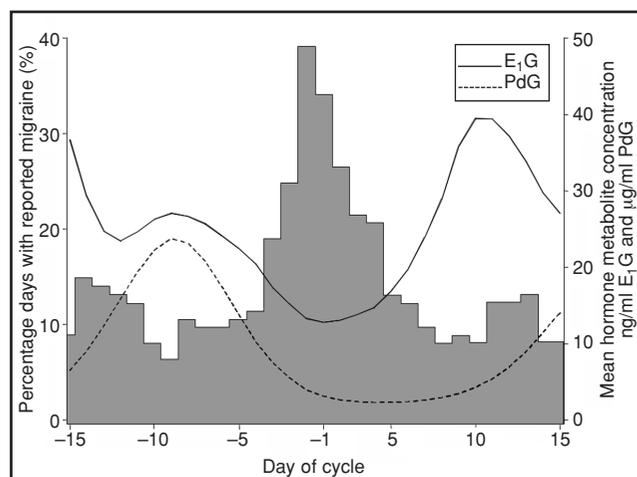


Figure 1 Incidence of migraine, urinary estrone-3-glucuronide (E₁G) and pregnanediol-3-glucuronide (PdG) levels on each day of the menstrual cycle in 120 cycles from 38 women. Figure reproduced with permission from MacGregor *et al.*¹⁹

estrogen, confirming that in women with a history of premenopausal menstrually related migraine a drop in serum estrogen could precipitate migraine and that a period of estrogen priming was a necessary prerequisite.³⁹

MacGregor *et al.* studied 38 women with pure menstrual or menstrually related migraine aged 29–49 (mean, 43) years. Urine was collected daily for assay over three menstrual cycles and analysed for luteinising hormone (LH), estrone-3-glucuronide (E₁G), pregnanediol-3-glucuronide (PdG) and follicle-stimulating hormone (FSH).¹⁹ Migraine was inversely associated with urinary estrogen levels across the menstrual cycle (Figure 1). Attacks were significantly more likely to occur in association with falling estrogen in the late luteal/early follicular phase of the menstrual cycle and significantly less likely to occur during the subsequent part of the follicular phase during which estrogen levels rose.

If the estrogen 'withdrawal' theory is correct, stabilising estrogen fluctuations by maintaining high, stable levels should prevent migraine. In support of this, Somerville showed that migraine could be postponed by maintaining high plasma estradiol levels with an intramuscular injection of long-acting estradiol valerate in oil; migraine subsequently occurred when the plasma estradiol fell.⁴⁰ This finding also supports the lack of effect of progesterone on migraine, since if progesterone was an important factor then the timing of menstrual attacks would have been unaffected by the use of estrogen supplements. Somerville further attempted to control estrogen fluctuations with oral estrogens and estrogen implants. Both of these routes of delivery failed to provide stable plasma levels of estradiol and so, not surprisingly, were of no benefit to migraine.⁴² The fact that administration of a short-acting estrogen did not produce the same results as the long-acting supplements confirms the hypothesis that prolonged estrogen exposure is necessary for 'withdrawal' to trigger migraine.

More recent trials using more stable routes of delivery have shown efficacy (Table 1). De Lignières *et al.* studied 18 women with strictly defined menstrual migraine who completed a double-blind placebo-controlled crossover trial using 1.5 mg estradiol gel, which allows a mean estradiol plasma level of 80 pg/ml to be reached, or placebo daily for 7 days during three consecutive cycles.⁴⁴ Only eight menstrual attacks occurred during the 26 estrogen-treated cycles compared with 26 attacks during the 27 placebo cycles. Furthermore, attacks during estrogen

treatment were considerably milder and shorter than those during placebo.

Eighteen women also completed a similar trial by Dennerstein *et al.* for four cycles.⁴⁵ The difference between estradiol gel and placebo was highly significant, favouring the estradiol gel, and less medication was used during active treatment. However, the results were not as impressive as the study by De Lignières *et al.* Dennerstein *et al.* comment that this might be because women in their study had menstrually related migraine rather than pure menstrual migraine and so migraine was only partially hormone dependent.

MacGregor *et al.* used 1.5 mg estradiol gel in a double-blind placebo-controlled study to prevent perimenstrual migraine attacks in 35 women with regular menstrual cycles and menstrual migraine or menstrually related migraine.⁴⁶ Each woman was treated for up to six menstrual cycles (three cycles estradiol, three placebo). Women used the Clearblue[®] Fertility Monitor (Unipath Ltd, Bedford, UK) to identify ovulation, conducting a test each day as requested by the monitor, using a sample of early morning urine. Estradiol gel or placebo was first applied on the tenth day following the first day that the monitor signified ovulation and continued daily until, and including, the second day of menstruation. Estradiol was associated with a significant reduction in the duration and severity of migraine. As Somerville had found, there was a significant increase in the migraine immediately following cessation of active gel compared to placebo. Possible reasons for this post-gel estrogen 'withdrawal' migraine may be that the dose of estradiol was inadequate; the duration of treatment was too short; or perhaps that exogenous estrogen prevents the normal secretion of endogenous estrogen.

Lower doses of estrogen have not been as effective.^{47–49} Patches containing 25 µg and 50 µg estradiol achieve serum estradiol levels of 25 pg/ml and 40 pg/ml, respectively. In contrast, the 100 µg patch effectively produces higher serum estradiol levels of 75 pg/ml, similar to levels attained with 1.5 mg estradiol gel.

A study of women with migraine during the pill-free interval of combined oral contraceptives also suggested that 50 µg patches are a suboptimal dose to prevent estrogen 'withdrawal' attacks associated with contraception.⁵⁰

How do estrogens act in migraine?

Migraine triggers are thought to activate specific centres in the brain stem in people with primed migrainous 'hyperexcitable' brains.⁵¹ This in turn alters the levels of brain chemicals such as serotonin, which has been strongly implicated in migraine, disrupting the normal function of the hypothalamus. Activation of the trigeminovascular system and release of vasoactive neuropeptides results in vasodilation and transduction of central nociceptive information.

Estrogen and progesterone are neurosteroids, which influence the pain processing networks and vascular endothelium involved in the pathophysiology of migraine. Estrogen has potent effects on the serotonergic system, increasing serotonergic tone. It also facilitates the glutaminergic system, potentially enhancing neural excitability. In contrast, progesterone appears to activate GABAergic (gamma-aminobutyric acid) systems, suppressing neuronal reactivity, and modulates the effects of estrogen on the central nervous system.⁵²

Estrogens also raise levels of endorphins and aberrant opioid control of the hypothalamic-pituitary-adrenal axis has been reported in menstrual migraine.^{53,54} Fluctuating

Table 1 Perimenstrual estrogen prophylaxis

Study	Study design	Sample size	Setting	Duration	Drugs	Outcome(s)	Results	Comments
MacGregor <i>et al.</i> (2006) ⁴⁶	RCT crossover	35	Single centre UK	6 treatment cycles Start 9 days following LH surge (approx. Day -5/-6); duration until second full day of bleeding (approx. 8 days)	Estradiol gel 1.5 mg vs PCB	Reduction in migraine days during treatment	22% (RR 0.78, 95% CI 0.62-0.99, $p = 0.04$)	Pure MM or MRM = attacks on Day -2 to +3 for at least 2/3 cycles ± attacks at other times 40% increase following Rx: estradiol vs placebo (RR 1.40, 95% CI 1.03-1.92, $p = 0.03$)
Pradaliar <i>et al.</i> (1994) ⁴⁹	Open parallel	24	Single centre France	1 baseline cycle; 2 treatment cycles Start Day -4; duration 8 days	Estradiol patches 25 µg vs 100 µg	Presence of MM in second cycle of treatment	Baseline 22/24; 25 µg 11/12; 100 µg 6/12	1 year history of MM confirmed by 2/12 diary MM = common migraine occurring not earlier than Day -2 and not later than the last day of menses
Smits <i>et al.</i> (1993) ⁴⁸	RCT crossover	20	Single centre Netherlands	3 treatment cycles Start Day -2; duration 8 days	Estradiol patches 50 µg vs PCB	Presence of MM	Estradiol 69%; PCB 59% (NS)	MM = common migraine exclusively occurring not earlier than Day -2 and not later than the last day of menses
Pfaffenrath (1993) ⁴⁷	RCT crossover	41	Single centre France	2 baseline cycles; 4 treatment cycles Start Day -2; duration not stated	Estradiol patches 50 µg vs PCB	Reduction in headache duration, intensity and impairment	No difference	MM = migraine attacks exclusively occurring between Day -2 and first day after onset of menses
Dennerstein <i>et al.</i> (1988) ⁴⁵	RCT crossover	18	Single centre Australia	2 baseline cycles; 4 treatment cycles; 1 follow-up cycle Start Day -2; duration 7 days	Estradiol percutaneous 1.5 mg vs PCB	Number of days moderate to severe intensity migraine during treatment	Estradiol vs PCB ($t = 3.96$, $p < 0.001$)	Women who reported regular migraine in the paramenstruum
de Lignières <i>et al.</i> (1986) ⁴⁴	RCT crossover	18	Single centre France	3 treatment cycles Start Day -2; duration 7 days	Estradiol percutaneous 1.5 mg vs PCB	Presence of MM	Estradiol 30.8% vs PCB 96.3% ($p < 0.01$)	MM = common migraine exclusively occurring not earlier than Day -2 and not later than the last day of menses

LH, luteinising hormone; MAM, menstrually associated migraine; MM, menstrually related migraine; MRM, menstrually associated migraine; NS, not significant; PCB, placebo; RCT, randomised controlled trial; RR, relative risk.

Table 2 Acute migraine treatment

Study	Study design	Sample size	Setting	Drug	Outcome(s)	Results ^a	Comments
Allais <i>et al.</i> (2006) ⁷³	RCT parallel	255	118 centres in nine European countries	Almotriptan 12.5 mg vs zolmitriptan 2.5 mg	2 h response; 2 h pain free; relapse 2-24 h; AE in 24 h	2 h pain response almoT 67.9%; zolmiT 68.6% 2 h pain free almoT 44.9%; zolmiT 41.2% Relapse almoT 32.8%; zolmiT 34.7% AEs almoT 19.8%; zolmiT 23.1%	Unselected population Retrospective analysis of menstrual data from an efficacy trial
Massiou <i>et al.</i> (2005) ⁷⁷	RCT parallel	229	Multicentre in France	Naratriptan 2.5 mg vs PCB	4 h pain free	4 h pain free naraT 58%; PCB 30% ($p < 0.001$)	MRM = Days -2 to +4 (6 days)
Dowson <i>et al.</i> (2005) ³⁰	RCT crossover	93	20 primary and secondary centres in the UK	Sumatriptan 100 mg vs PCB	4 h headache response for first treated MRM vs attacks at other times of the cycle	All women - MRM: sumaT 67% vs PCB 33% ($p = 0.007$); non-MRM sumaT 79% vs PCB 31% ($p < 0.001$) Women with confirmed MM and MRM - MRM: sumaT 56% vs PCB 23% ($p < 0.02$); non-MRM: sumaT 81% vs PCB 27% ($p < 0.001$)	Self-reported diagnosis of MM Prospective Diagnosis checked prospectively during the study: 11% had MM, 52% had MRM MM = Day -3 to +5 (8 days) MRM = $\geq 50\%$ attacks Day -3 to +5
Gross <i>et al.</i> (1995) ²⁸							
Loder <i>et al.</i> (2004) ⁷⁵	RCT parallel intensify-based treatment of three consecutive MAMs	Zolmitriptan, $n = 260$; PCB, $n = 251$	18 centres in North America	Zolmitriptan (1.25 mg, 2.5 mg, 5 mg) vs PCB	2 h response; 30 min and 1 h response; AE	2 h response: zolmiT 48%; PCB 27% ($p < 0.0001$) 30 min response: zolmiT 18%; PCB 14% ($p = 0.03$) 1 h response: zolmiT 33%; PCB 23% ($p < 0.001$) AEs zolmiT 16%; PCB 9%	Selected population of women who had 'experienced migraine with at least two-thirds of prior menstrual cycles' Prospective MAM = migraine that consistently occurred from 72 h before to 5 days after the onset of menses
Nett <i>et al.</i> (2003) ⁷⁹	RCT parallel Single attack	349	39 centres in North America and Puerto Rico	Sumatriptan (100 mg, 50 mg) vs PCB	2 h pain free AEs	2 h pain free; sumaT 100 mg 61%; sumaT 50 mg 51%; PCB 29% ($p < 0.001$) AEs sumaT 100 mg 16%; sumaT 50 mg 8%; PCB 7%	Selected population reporting 'regularly occurring menstrually associated migraines typically having mild pain phase' Prospective
Silberstein <i>et al.</i> (2000) ⁸¹	RCT	335 MAM 393 Non-MAM	107 centres in the USA	Rizatriptan (5 mg, 10 mg) vs PCB	2 h response	MAM 2 h response rizaT 10 mg 68%; rizaT 5 mg 70%; PCB 44% ($p < 0.05$) MAM vs non-MAM rizaT 10 mg 68% vs 69%; rizaT 5 mg 70% vs 66% (NS)	Unselected population Retrospective analysis of first treated attack in two RCTs of acute migraine Rx MAM = migraine that occurred within 3 days before or after the onset of the last menstrual period (7 days)
Silberstein <i>et al.</i> (1999) ⁸⁰	RCT Single attack	185 MAM 781 Non-MAM	Not stated	Acetaminophen, aspirin, plus caffeine (AAC) vs PCB	2 h response	MAM 2 h response AAC 61% vs PCB 29% ($p < 0.001$); 2 h pain free AAC 25% vs PCB 6% ($p < 0.001$) Non-MAM 2 h response AAC 58% vs PCB 33% ($p < 0.001$); 2 h pain free AAC 21% vs PCB 7% ($p < 0.001$) AEs MAM AAC 26% vs PCB 13% Non-MAM AAC 19% vs PCB 11%	Unselected population Retrospective analysis of three RCTs of acute migraine Rx MAM = not stated

^aResponse = a moderate/severe headache at the time of taking the drug has improved to mild/no headache by the 2-hour time point. Pain free = a moderate/severe headache at the time of treating has completely gone by 2 hours.

AE, adverse event; CT, controlled trial; MAM, menstrually associated migraine; MRM, menstrually related migraine; MRM, menstrually related migraine; PCB, placebo; RCT, randomised controlled trial.

Table 2 Acute migraine treatment (continued)

Study	Study design	Sample size	Setting	Drug	Outcome(s)	Results ^a	Comments
Facchinetti <i>et al.</i> (1995) ⁷⁴	CCT of two attacks Parallel	Attack 1: 179 Attack 2: 139	40 centres in six countries	Sumatriptan 6 mg vs PCB	2 h headache response; AEs	2 h response: attack one sumaT 73% vs PCB 31%; attack two sumaT 81% vs PCB 29% ($p < 0.001$) 2 h pain free: attack one sumaT 55% vs PCB 14%; attack two similar AEs sumaT 46% vs PCB 31%	Selected population Prospective study MM = Day -3 to +5 (8 days)
Solbach and Waymer (1993) ⁸³	RCT parallel	157 MAM vs 512 non-MAM	Not stated	Sumatriptan 6 mg sc vs PCB	1h response; AEs	1 h pain response MAM sumaT 80%; PCB 19% ($p < 0.001$) Non-MAM sumaT 70%; PCB 20% ($p < 0.001$)	Non-selected population Retrospective analysis of two RCTs of acute migraine Rx MAM = migraine beginning between 1 day before and 4 days after onset of menstrual flow (5 days)

^aResponse = a moderate/severe headache at the time of taking the drug has improved to mild/no headache by the 2-hour time point. Pain free = a moderate/severe headache at the time of treating has completely gone by 2 hours.

AE, adverse event; CCT, controlled trial; MAM, menstrually associated migraine; MM, menstrually related migraine; MRM, menstrually associated migraine; PCB, placebo; RCT, randomised controlled trial.

Table 3 Perimenstrual triptan prophylaxis

Study	Study design	Sample size	Setting	Duration	Drugs	Outcome(s)	Results	Comments
Tuchman <i>et al.</i> (2005) ¹⁰¹	RCT parallel	244	Multicentre	3 cycles Start Day -2; duration 7 days	Zolmitriptan 2.5 mg bd vs 2.5 mg tds vs PCB	$\geq 50\%$ reduction in MM attacks	zolmit tds 58.6%; bd 54.7%; PCB 37.8% ($p = 0.0007$ and $p = 0.002$)	MM = 75% of cycles associated with a migraine headache
Moschiano <i>et al.</i> (2005) ¹⁰⁰	CT open	59	10 centres in Italy	3 cycles Start Day -2; duration 6 days	Naratriptan 1 mg bd	Mean number of PMM attacks $\geq 50\%$ reduction in PMM	naraT 1.6 \pm 1.3; baseline 3.5 \pm 1.4 61.4%	PMM = three baseline cycles of migraine without aura Days -2 to +3 and at no other times of the cycle
Newman <i>et al.</i> (2001) ⁹⁸	RCT parallel	206	18 centres in the USA	4 cycles Start Day -2; duration 5 days	Naratriptan 1 mg bd vs 2.5 mg bd vs PCB	Percentage headache-free treatment periods per subject	naraT 1 mg 50%; PCB 25% ($p = 0.003$)	MAM = any patient identified migraine occurring during Days -2 to +4 (6 days)
Silberstein <i>et al.</i> (2004) ⁹⁹	RCT crossover	546	36 centres in the USA	3 cycles Start Day -2; duration 6 days	Frovatriptan 2.5 mg od vs 2.5 mg bd vs PCB	Mean number of MAMs during each treatment period	2.0 vs 4.0 ($p < 0.05$) frovaT bd 41%; od 52%; PCB 67% ($p < 0.001$)	naraT 2.5 mg no different to PCB MAM = Day -2 to +4 (6 days) Double dose on Day 1 of treatment
Newman (1998) ⁹⁷	CT open	20	Single centre in the USA	Up to 14 cycles (mean 6.3) Start Day -2 or -3; duration 5 days	Sumatriptan 25 mg tds	Proportion of treated cycles with no headache Proportion of treated cycles with $\geq 50\%$ reduction in severity of pain	52.4% 42%	MRM = patients reporting the association of migraine headache with each menstrual cycle at a predictable time relative to the onset of flow All patients sumatriptan responders

CT, controlled trial; MAM, menstrually associated migraine; MM, menstrually related migraine; MRM, menstrually associated migraine; PCB, placebo; PMM, pure menstrual migraine.

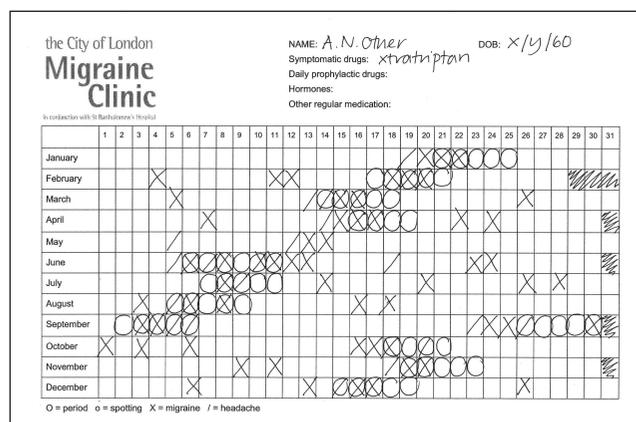


Figure 2 Diary card showing menstrually related migraine

estrogen levels are associated with impaired glucose tolerance in the luteal phase of the menstrual cycle.^{55,56} This leads to reactive hypoglycaemia at the start of menstruation, which could trigger migraine.⁵⁷

That estrogens do not affect all women with migraine might be explained by the intrinsic estrogen receptor sensitivity of the hypothalamic neurons. Limited data imply that this may have a genetic basis.⁵⁸ It has been suggested that when estrogen levels peak, increased neuronal excitability is balanced by homeostatic gene regulation in the brain cortex and nociceptive systems. As levels fall around menstruation, a mismatch in homeostatic gene regulation by estrogen unmasks non-nuclear mitogen-activated hyperexcitability of cell membranes, sensitising neurons to triggers that activate migraine attacks. At the trough of estrogen levels, the down-regulating effect on inflammatory genes is lost and peptide-modulated central sensitisation is increased, as is pain and disability of the migraine attack.⁵⁹

Other mechanisms

Other differences reported in menstrual migraine versus control groups include changes in aldosterone levels,⁶⁰ intracellular magnesium⁶¹ and platelet homeostasis.⁶²

Prostaglandins have also been implicated in menstrual migraine.⁶³ In particular, entry of prostaglandins into the systemic circulation can trigger throbbing headache, nausea and vomiting.⁶⁴ In the uterus prostaglandins are synthesised primarily by the endometrium. There is a three-fold increase in prostaglandin levels in the uterine endometrium from the follicular to the luteal phase, with a further increase during menstruation.⁶⁵ As a result of the 'withdrawal' of estrogen and progesterone the endometrium breaks down and prostaglandins are released. This causes vasoconstriction within the endometrium and disruption of endometrial cells, stimulating further prostaglandin synthesis. When an excessive amount of prostaglandins gain entrance to the circulation, other systemic symptoms occur that are characteristically associated with menorrhagia and/or dysmenorrhoea such as headache and nausea.^{66,67} Plasma taken during the premenstrual phase from women with dysmenorrhoea and re-infused post-menstruation into the same women resulted in premenstrual symptoms, including headache.⁶⁸ Thus prostaglandins may have a specific role in migraine associated with dysmenorrhoea and/or menorrhagia. In support of this, prostaglandin inhibitors are effective for the prevention of menstrual attacks of migraine.⁶⁹

Diagnosis

Relying on the history to confirm the diagnosis can be misleading.⁹ Contemporaneous headache diaries recording

menstrual periods and headache incidence should corroborate a history of migraine occurring around menstruation (Figure 2).⁷⁰ Headache occurring within -2 to +3 days of the onset of menstrual flow (counting the first day of bleeding as Day 1) in two out of three menstrual cycles is reasonable evidence of a clinically important link that might benefit from specific management strategies.

Investigations

Many women expect to have their migraine investigated, either with a hormone test or with a brain scan. Since no abnormalities of either have been identified in migraine or, more specifically, menstrual migraine there is no place for investigations other than those indicated to exclude suspected secondary headache resulting from underlying pathology.

Interventions

Once the diagnosis of migraine has been confirmed, a variety of management strategies are available, depending on individual symptoms and needs (Figure 3).

Identification of non-hormonal triggers

Assuming the concept of multiple factors acting in combination to trigger migraine, hormonal factors combine with non-hormonal triggers to increase the overall susceptibility to attacks at the time of menstruation.⁷¹ Therefore, every effort should be made to identify and eliminate non-hormonal triggers. In some cases, this may reduce the frequency and severity of all attacks. In others, non-hormonal attacks are eliminated while menstrual attacks persist.

Acute

The treatment of menstrual attacks of migraine is the same as for non-menstrual attacks. Acute treatment regimens usually include a combination of analgesics with or without prokinetic anti-emetics, NSAIDs, ergot derivatives and triptans (Table 2).⁷²

Studies with almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan suggest that they are effective for migraine attacks with menstruation.^{28,30,73-83}

Specific prophylaxis for menstrual migraine

Only a small percentage of women will have menstrual migraine and wish to consider specific prophylaxis. Although many patients favour non-drug approaches, non-drug prophylaxis of menstrual migraine appears to be ineffective.⁸⁴⁻⁸⁶

None of the drugs and hormones recommended below are licensed for management of menstrual migraine because although effective in clinical trials, evidence is limited. Given that there are no investigations to identify the most effective prophylactic, an empirical approach is necessary, prescribing on a 'named' patient basis. Because of the fluctuating nature of migraine, it is sensible to try a method for at least three cycles before considering alternative prophylaxis.

Non-steroidal anti-inflammatory drugs

NSAIDs are effective prostaglandin inhibitors. They should be tried as first-line agents for migraine attacks that start on the first to third day of bleeding, particularly in the presence of dysmenorrhoea and/or menorrhagia.^{66,87} Side effects of NSAIDs include gastrointestinal disturbance. Misoprostol 800 µg or omeprazole 20-40 mg daily may give some gastroduodenal protection.⁸⁸ Contraindications

include peptic ulcer and aspirin-induced allergy. Interactions include anticoagulants and antihypertensive agents.

Mefenamic acid is an effective migraine prophylactic and has been reported to be particularly helpful in reducing migraine associated with menorrhagia and/or dysmenorrhoea.^{87,89} A dose of 500 mg, three to four times daily, may be started 2–3 days before the expected onset of menstruation, but is often effective even when started on the first day of bleeding; this is useful if periods are irregular. Treatment is usually only necessary for the first 2–3 days of bleeding.

Naproxen has also been found to be effective in the management of headache associated with dysmenorrhoea. Studies using 550 mg once or twice daily perimenstrually have shown efficacy.^{90–92} Fenoprofen 600 mg has been tried, taken twice daily from 3 days before the onset of menstruation until the last day of bleeding.⁹³

Although an open-label study suggested that perimenstrual rofecoxib significantly reduced the frequency of perimenstrual migraine, there is no evidence that the new cyclo-oxygenase-2 (COX-2) inhibitors (rofecoxib, celecoxib, valdecoxib) are more effective than traditional NSAIDs.⁹⁴ They are more

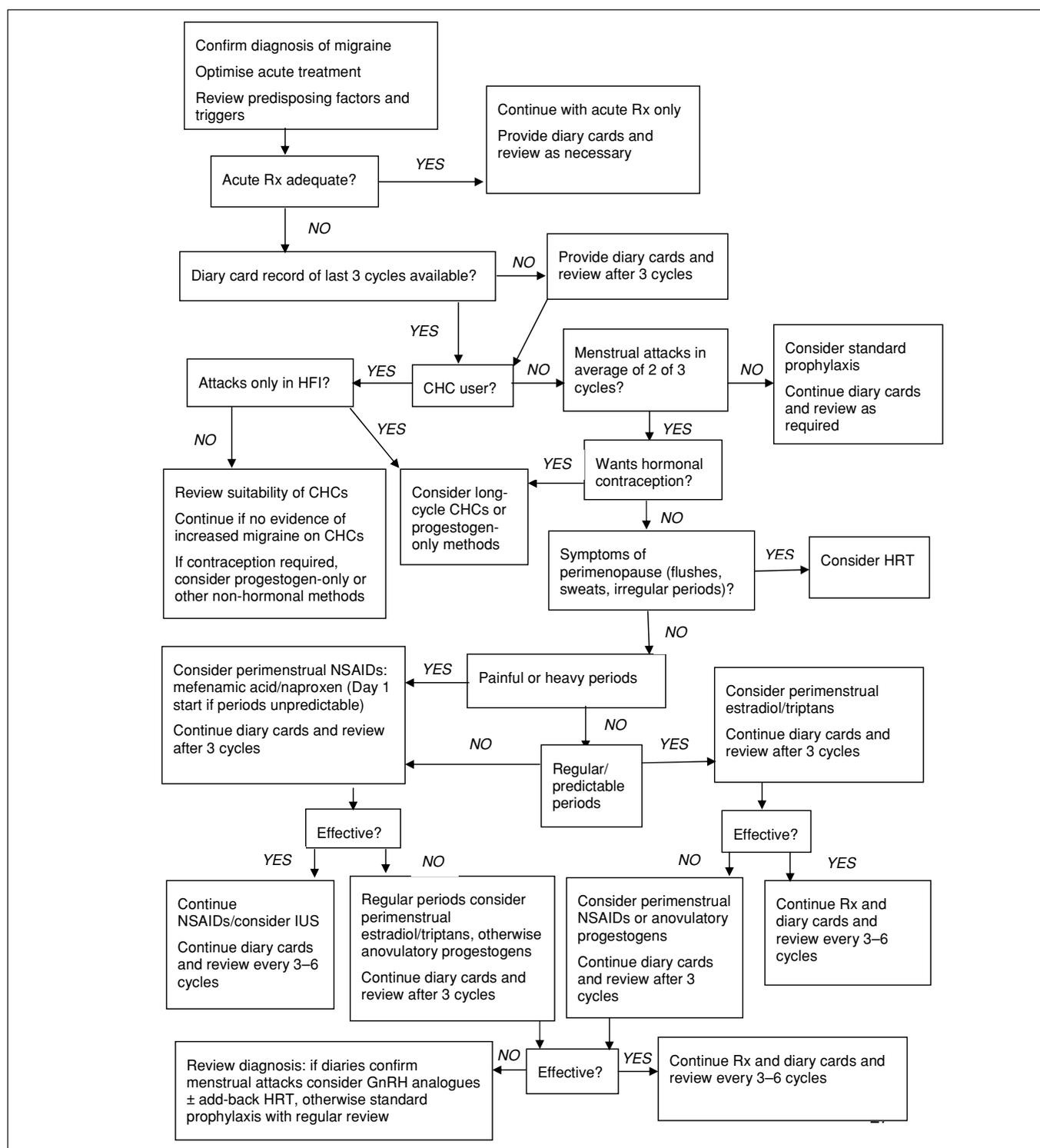


Figure 3 Algorithm for the management of menstrual attacks of migraine. CHC, combined hormonal contraceptives; GnRH, gonadotrophin-releasing hormone; HFI, hormone-free interval; HRT, hormone replacement therapy; IUS, intrauterine system; NSAIDs, non-steroidal anti-inflammatory drugs

costly but may provide a relative safety advantage for patients who need to use these agents for long periods of time and who are especially prone to gastrointestinal complications.

Perimenstrual estrogen supplements

Perimenstrual estrogen can be used only when menstruation is regular and predictable. If the woman has an intact uterus, no additional progestogens are necessary, provided that she is ovulating regularly. Ovulation can be confirmed using a home-use fertility monitor, which has the advantage of predicting menstruation.⁹⁵

Safety of estrogens is an important concern. Physiological doses of supplemental estrogens are well tolerated in clinical trials.⁴⁶ Furthermore, there is no evidence of increased risk of thrombosis or cancer in women already producing endogenous estrogen. However, supplemental estrogens are not recommended for women who have estrogen-dependent tumours or other estrogen-dependent conditions, including a history of venous thromboembolism.

The recommended strategy for perimenstrual prophylaxis is estradiol gel 1.5 mg applied daily from 2–3 days before expected menstruation for 7 days.⁹⁶ Alternatively, transdermal estrogen 100 µg can be used from 2–3 days before expected menstruation up to the fourth or fifth day of menstruation (i.e. two twice-weekly patches or one 7-day patch, although an additional patch may be necessary if menstruation is late).⁹⁶

There is evidence that some women responding to estrogen supplements experience delayed attacks when the supplements are discontinued.^{41,46} 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.

Perimenstrual triptans

Trials using frovatriptan, naratriptan, sumatriptan and zolmitriptan for perimenstrual prophylaxis have suggested efficacy (Table 3).^{97–101}

Triptan prophylaxis of menstrual migraine is costly and, to date, there are no trials that compare triptan prophylaxis of menstrual migraine with other lower-cost regimens. Furthermore, use of triptans for prophylaxis limits the choice for effective abortive therapy. Thus perimenstrual triptans should be considered for women with menstrual migraine in whom standard strategies fail.

Continuous contraceptive strategies

Continuous hormonal methods are particularly useful if cycles are irregular, or when the above strategies prove ineffective despite a convincing hormonal link.

Continuous combined hormonal contraceptives

Continuous hormones, in place of the usual regime of 3 weeks of active followed by 1 week of inactive pills or no therapy, has been recommended based on evidence that estrogen withdrawal provokes migraine in susceptible women. 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.¹⁰²

Combined hormonal contraceptives should not be used by women with migraine with aura because of the synergistic increased risk of ischaemic stroke.^{103,104}

Progestogen-only methods

Intramuscular depot medroxyprogesterone acetate (Depo-Provera[®]), subdermal etonorgestrel (Implanon[®]) and oral

desogestrel (Cerazette[®]) inhibit ovulation. However, even when ovulation is suppressed irregular bleeding can occur, often associated with migraine. Somerville hypothesised that since fluctuations in estrogen levels can occur even when ovulation is suppressed, estrogen withdrawal will still act as a migraine trigger.¹⁰⁵ Although irregular bleeding can occur in the early months of treatment, amenorrhoea is usual with continued use. It is therefore important to warn women who use this method that they should persevere until amenorrhoea is achieved.

The levonorgestrel intrauterine system (Mirena[®]) is highly effective at reducing menstrual bleeding and associated pain. It can be considered for migraine related to menorrhagia.¹⁰⁶ Systemic effects are usually minor but erratic bleeding and spotting is common in the early months of use. Most women are amenorrhoeic within 1 year. The treatment is not effective for women who are sensitive to estrogen withdrawal as a migraine trigger, as the majority of women still ovulate.

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.¹⁰⁷ In contrast, unlicensed higher doses of oral progestogen, sufficient to inhibit ovulation, have shown benefit.¹⁰⁸

Other therapies

Estradiol implants or patches

These are the most effective method of obtaining high stable estrogen levels, inhibiting ovulation. Magos *et al.* showed that implant doses large enough to suppress ovulation and produce constant plasma estrogen levels achieved a 96% response rate in 24 patients studied.¹⁰⁹ However, in unhysterectomised women, progestogen opposition is necessary to protect the endometrium, which can mimic premenstrual symptoms, including headache.¹¹⁰ Although there are no clinical trials for migraine, suppression of ovulation with 100 µg patches used continuously together with continuous progestogen are likely to be effective with fewer progestogenic side effects.¹¹¹

Gonadotrophin-releasing hormone analogues

Although effective, adverse effects of estrogen deficiency (e.g. hot flushes) restrict the use of gonadotrophin-releasing hormone (GnRH) analogues.¹¹² 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 estrogen and progestogen can be given to counter these difficulties.^{113,114} Given these limitations, in addition to increased cost, such treatment should be instigated only in specialist departments.

Magnesium

Magnesium prolidone carboxylic acid 360 mg decreased the duration and intensity of premenstrually occurring migraine in a placebo-controlled, double-blind study of 24 women with premenstrual syndrome and migraine.¹¹⁵ This study was principally aimed at identifying the effect of magnesium on a number of premenstrual problems, not just headache. The generalisability of the results to women whose menstrual headaches do not occur in association with other premenstrual symptoms is unclear. Diarrhoea is the major side effect and can sometimes be controlled by changing preparation. Magnesium oxide is widely available and the recommended dose is 300–600 mg daily.

Bromocriptine

Bromocriptine, a dopamine agonist, inhibits GnRH and LH. Its use can result in reduced peak luteal estradiol levels and consequent reduced premenstrual estrogen withdrawal. Two studies have suggested the efficacy of bromocriptine in migraine, although larger double-blind placebo-controlled studies are necessary before it can be recommended.^{116,117}

Anti-estrogens

Danazol has been used with some effect but adverse effects restrict its use.^{118,119} Tamoxifen has been associated with varying effect on migraine.¹²⁰⁻¹²²

Surgery

Migraine is more likely to deteriorate after surgical menopause with bilateral oophorectomy.^{54,123} If other medical problems require surgical menopause, the effects on migraine may be lessened with estrogen replacement therapy, as for natural and medical menopause.^{109,114}

What to do when nothing works

In most cases, menstrual migraine can be effectively controlled by following the strategies detailed in the preceding paragraphs. However, a few cases may be refractory, even to total suppression of the menstrual cycle. The usual reason for such treatment failure is incorrect diagnosis. Therefore, if migraine remains refractory despite trials of several different strategies given in an adequate dose for an adequate duration, reconsider the diagnosis.

A common cause for refractory migraine is medication overuse.² All symptomatic drugs including analgesics, triptans and ergots are effective provided that they are used intermittently and not regularly more often than 2 or 3 days a week. More frequent use can perpetuate headache rather than relieve it.¹²⁴

The exact mechanism of medication overuse headache is unknown but it is generally believed to involve a disturbance of central pain systems. Frequency of dosing is important: low daily dosing carries a greater risk than larger intermittent dosing. The only effective treatment is to stop the drugs, either immediately or by gradually reducing the amount over several weeks. Up to 60% of sufferers who are withdrawn from drugs improve, although it can take up to 3 months before full improvement is seen and the relapse rate is high.¹²⁴

Conclusions

Despite the high prevalence of menstrual attacks of migraine, limited recognition of this condition has resulted in unnecessary disability. Use of simple diary cards to establish the association between migraine and menstruation can enable the instigation of more effective treatment strategies and improve the quality of the lives of migraineurs and those around them.

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