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EXPERT REVIEW

Progress in the Pharmacotherapy of Menstrual Migraine

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Abstract: Menstrual migraine is a common neurological condition reported to affect up to 60% of women with migraine. Most women manage migraine adequately with symptomatic treatment alone. However, in women with menstrual migraine, menstrual attacks are recognised to be more severe, last longer, and are less responsive to treatment compared with attacks at other times of the menstrual cycle. In these situations, prophylactic treatment may be necessary. Short-term perimenstrual and continuous prophylactic treatments have shown efficacy in clinical trials but none are licensed for menstrual migraine. This article reviews the evidence for acute and prophylactic drugs in the management of this condition and considers future therapeutic options.

Keywords: menstrual migraine, estrogen, estradiol, acute treatment, prophylaxis

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Introduction

Migraine is prevalent neurological disorder, affecting four of every 10 women and two of every 10 men, mostly before age 35 years.[1] By age 30 years migraine is 3-fold more prevalent in women than in men with the peak periods for migraine risk in women being at age 25 ± 8.6 years and 50 ± 15.8 years.[2] Diagnostic features accompanying headache include photophobia, nausea and limitation of usual daily activities.[3] Recent research by the World Health Organization has established migraine as a leading cause of years of life lived with a disabling condition—12th for women, compared to 19th for men.[4]

The two most frequently encountered types of migraine differ only in their presence or absence of 'aura'[5] Table 1. Menstruation is a significant risk factor for migraine *without* aura, even in women who have attacks *with* aura at other times of the cycle.[6–10] In population and clinic-based studies, between 20% and 60% of women with migraine report an association with menstruation.[9,11–16] Attacks are most likely to occur on or between two days before menstruation and the first three days of bleeding.[5,7–9,17–22] Although long-recognised as a clinical entity, the research definitions for menstrual.

Fewer than 10% of women report migraine exclusively with menstruation and at no other time of the month ("pure" menstrual migraine) Table 2.[5,9,11,14–16] The majority of women with regular menstrual attacks also experience migraine at other times of the month ("menstrually-related" migraine).[5,9] The term "menstrual migraine" is often used to encompass both conditions. Although some women report a link between their migraine attacks and ovulation, this has not been confirmed in epidemiologic studies.[9,20,23] A prospective study confirmed that the observed number of attacks associated with ovulation was not significantly different from the expected number of attacks.[21]

Menstrual attacks are more severe and disabling, last longer, and are less responsive to symptomatic medication compared to attacks at other times of the cycle.[13,16,20,24–29] Menstrual migraine is also associated with increased menstrual distress and disability.[30–33]

The timing of menstrual attacks is consistent with the natural fall in estrogen during the late luteal phase of the menstrual cycle Figuer 1. This 'estrogen-withdrawal' trigger is consistent with increased risk of migraine during the hormone-free interval of combined hormonal contraceptives and during puberty and the perimenopause, times of fluctuating hormone levels.[2,21,34] Stable low, high, or rising hormone levels, such as during pregnancy and postmenopause are associated with reduced risk of migraine.

Treatment Options

All treatments licensed for migraine can be used to treat menstrual migraine. Summaries of Product Characteristics provide information on the licensed indications. However, if the posology and method of administration of a drug used to treat or prevent menstrual migraine is different from the license, the drug must be prescribed 'off-license'. This is particularly the case for prophylaxis of menstrual migraine.

Lifestyle Recommendations

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.[35] Therefore, every effort should be made to identify and cope with non-hormonal triggers.[36] A case-control study of 85 women with migraine compared with 85 controls identified a significant relationship between diet, eating habits, resting and sleeping patterns.[37] Of the migraine group 37.6%, did not have a regular diet program, compared with 17.6% of the control group ($P = 0.004$); 37.6% of the migraine group, compared with 23.5% of the control group, did not eat meals on a regular schedule ($P = 0.046$), and 29.4% of the migraine and 9.4% of the control groups had less than 3 meals per day ($P = 0.001$). Study findings related to the sleep and rest patterns showed that 50.6% of migraineurs and 29.4% of the control group did not have regular sleep hours ($P = 0.005$). Further, 23.5% of the migraine and 4.7% of the control subjects slept less than 6 hours per night, while 28.2% of the migraine and 25.9% of the control group subjects slept more than 8 hours per night ($P = 0.001$). In some cases, attention to modifiable lifestyle factors may reduce the frequency and severity of all attacks. In others, non-hormonal

Table I. Diagnostic criteria for migraine without aura and migraine with aura (adapted from[5]).

Migraine without aura
A. At least 5 attacks 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 (eg, 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

Migraine with aura
Typical aura consists of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterize the aura which is associated with a headache fulfilling criteria for Migraine without aura.
A. At least 2 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 (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
   2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
   3. fully reversible dysphasic speech disturbance
C. At least two of the following:
   1. homonymous visual symptoms 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 Migraine without aura-begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

attacks are eliminated while menstrual attacks persist and may require specific management.

Acute Treatment

A variety of non-prescription and prescription drugs are available for the acute treatment of migraine.[38] A number of open-label studies Table 3, post-hoc analyses Table 4 and prospective randomized controlled trials Table 5 have been undertaken to assess comparative efficacy and tolerability of menstrual versus non-menstrual attacks. There is considerable variation in the definition of menstrual attacks as well as in the diagnosis of menstrual migraine. An evidence-based systematic review and meta-analysis concluded that, based on trial quality, evidence supported grade B recommendations for use of sumatriptan 50 and 100 mg,

Table 2. Diagnostic criteria for pure menstrual migraine and menstrually-related migraine (adapted from[5]).

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

Pure menstrual migraine without aura
A. Attacks, in a menstruating woman, fulfilling IHS criteria for migraine without aura
B. Attacks occur on day 1 ± 2 (ie, days –2 to +3)[a] of menstruation[b] in at least two out of three menstrual cycles and additionally at other times of the cycle

Notes: [a]The first day of menstruation is day 1 and the preceding day is day –1; there is no day 0; [b]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.

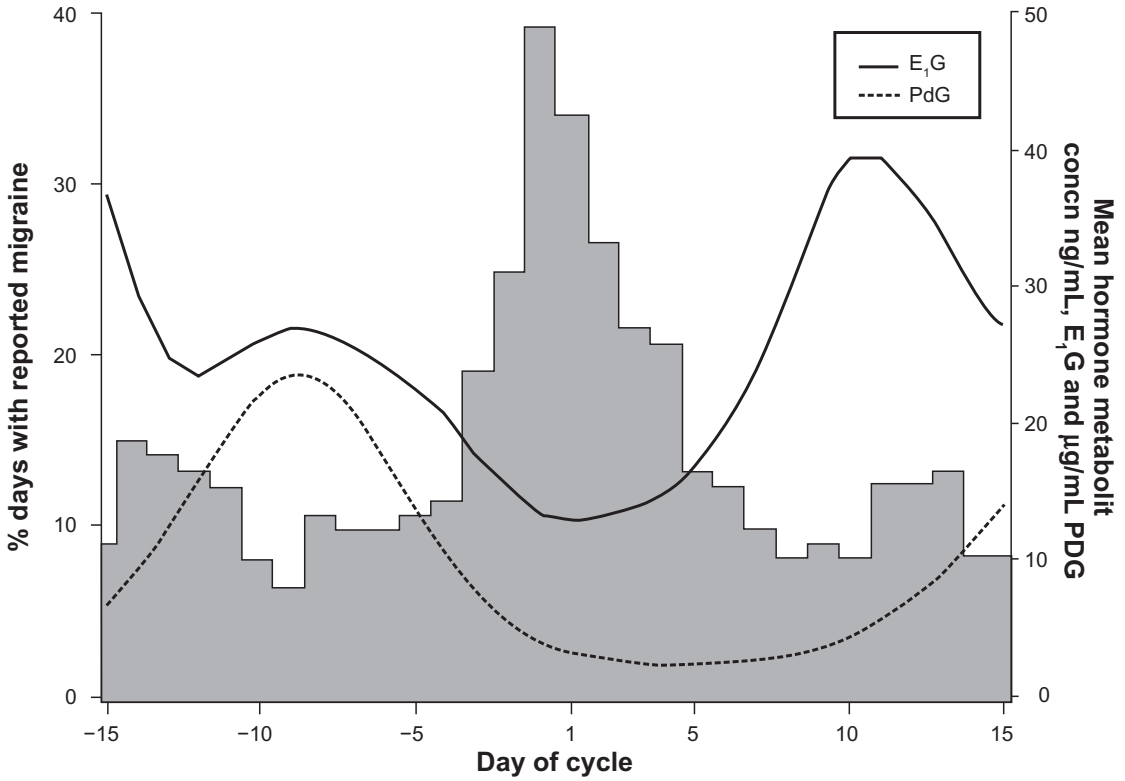

Figure 1. Incidence of migraine, urinary estrone-3-glucuronide (E1G) and pregnanediol-3-glucuronide (PdG) levels on each day of the menstrual cycle in 120 cycles from 38 women.
Reproduced with permission from.[21]

mefenamic acid 500 mg, and rizatriptan 10 mg for acute treatment of menstrual migraine.[39] Trial quality also supports grade B recommendations (good evidence of efficacy; benefits outweigh harms; improves important health outcomes) for the combination sumatriptan 85 mg-naproxen 500 mg.[40]

In all studies, treatment was well tolerated with adverse events similar to those reported throughout the clinical trial programmes for each drug. The most frequent triptan-related adverse events include tingling, paresthesias, and warm sensations in the head, neck, chest, and limbs; less frequent are dizziness, flushing, and neck pain or stiffness.[41]

While these studies confirm efficacy of acute treatments for menstrual and non-menstrual attacks of migraine, there are differences between results of analyses of attacks diagnosed as menstrual and results from clinical trials in women diagnosed with menstrual migraine at baseline. While the former suggest no difference in efficacy, the latter confirm the clinical impression that in women with menstrually related migraine, menstrual attacks do not respond as well to acute treatment as nonmenstrual attacks.[24,27]

Prophylaxis

Most women with pure menstrual migraine manage their condition with acute treatment. Prophylaxis should be considered for women who have inadequate relief from the usual forms of acute therapy or who are troubled by headache recurrence and require multiple doses of acute migraine medications. Diary evidence to confirm the diagnosis should be a prerequisite before prescribing prophylaxis for menstrual migraine as the patient history of a menstrual association can be unreliable.[12,27]

Prophylaxis of menstrual migraine using non-drug approaches such as relaxation biofeedback, person-centered insight therapy or acupuncture appears to be ineffective.[42–44] For women with frequent non-menstrual attacks in addition to menstrual migraine, standard prophylactic agents are recommended. These include tricyclic anti depressives, beta-blockers and anti-epileptics.[38,45] A post-hoc analysis suggests that to piramate reduces the frequency, but not severity or duration, of perimenstrual migraines in women with menstrually-related migraine.[46] No prophylaxis prevents all attacks but they can reduce the frequency

Table 3. Open-label trials for acute treatment of menstrual migraine.

Trial	Trial design	n	Treatment	Results	Safety/tolerability	Definition of menstrual attacks
Triptans						
Frovatriptan						
Newman et al[126]	Post hoc sub analysis of an open-label post marketing surveillance study of 3 attacks	MM 1931; non-MM 2080	2.5 mg frovatriptan	Subjective rating of good or very good efficacy 92.7%; 90.9%	Tolerability of previous therapy rated as good (MM, 37.2%, n = 673 of 1809; non-MM, 36.2%, n = 717 of 1980) or very good (MM, 6.5%, n = 117 of 1809; non-MM, 6.5%, n = 128 of 1980) Tolerability of frovatriptan rated as good (MM, 35.2%, n = 669 of 1902; non-MM, 35.3%, n = 725 of 2056) or very good (MM, 61.5%, n = 1169 of 1902; non-MM, 61.0%, n = 1254 of 2056)	At least 1 of the 3 attacks treated with a positive response to patients' self-report that migraine occurred ±2 days of menses start
Allais et al[127]	Open label treatment of 1 attack	20	2.5 mg frovatriptan for migraine in the pill-free-week of combined oral contraceptives	2 h response: 55% 2 h pain free: 10% 4 h response: 75% 4 h pain free: 35% 24 h response: 75% ($P = 0.135$) 24 h pain free: 60% ($P = 0.003$)	Not reported	6-month history of pure OCMM, with attacks appearing exclusively in the pill-free week, irrespective of the day of onset of bleeding
Sumatriptan						
Schreiber et al[128]	Open label study of previously undiagnosed menstrual migraine	31	100 mg sumatriptan during moderate or severe attacks	2 h response: 70% 2 h pain free: 41% 4 h response: 86% 4 h pain free: 61%	Not reported	Menstrual headache occurring in at least 3 of 4 menstrual cycles

Notes: 2 h/4 h/24 h response, reduction in headache pain from moderate or severe at baseline to mild or no headache 2 h/4 h/24 h after treatment; 2 h/4 h/24 h pain free, reduction in headache pain from moderate or severe at baseline to no headache 2 h/4 h/24 h after treatment.
Abbreviations: MM, menstrual migraine; OCMM, oral contraceptive menstrual migraine.

Table 4. Post hoc analyses of menstrual attacks in clinical trials for acute treatment of migraine.

Trial	n	Treatment	Results menstrual; *non-menstrual*	Safety/tolerability	Definition of menstrual attacks
Acetaminophen, aspirin, plus caffeine (AAC)					
Silberstein et al[129]	185 menstrual attacks; 393 non-menstrual attacks	500 mg acetaminophen, 500 mg aspirin, 130 mg caffeine po vs. placebo during moderate or severe pain	2 h response: 61% vs. placebo 29% ($P < 0.001$); 58% vs. placebo 33% ($P < 0.001$) 2 h pain free: 25% vs. placebo 6% ($P < 0.001$); 21% vs. placebo 7% ($P < 0.001$)	Nausea (menstrual attacks AAC 10.3%, placebo 1.0%, $P = 0.006$; nonmenstrual AAC 3.8%, placebo 2.5%, NS) Dizziness (menstrual attacks AAC 1.1% placebo 1.0%, NS; nonmenstrual AAC 4.1%, placebo 1.5%, $P = 0.030$) Nervousness (menstrual attacks AAC 8.0% placebo 0%, $P = 0.004$; nonmenstrual AAC 4.3%, placebo 0.7%, $P = 0.001$)	Attacks occurring during menstrual period
Triptans					
Almotriptan					
Diamond et al[130]	42 menstrual attacks; 248 non-menstrual attacks	12.5 mg almotriptan po vs. placebo during mild, moderate or severe pain within one hour of onset (placebo data not reported)	2 h response: 77.4% vs. 68.3% 2 h pain free: 35.4% vs. 35.9% 24 h sustained pain free: 22.9% vs. 23.8%	Patients experiencing ≥1 drug-related (within 24 hours of drug dosing) almotriptan vs. placeobo: 9.8% vs. 6.4% Drug-related AEs almotriptan vs. placebo: somnolence 1.1% vs. 2.3%, nausea 1.1% vs. 1.7%, vomiting 1.1% vs. 0.6%, and fatigue 1.1% vs. 0%	Attacks which occurred ±2 days of the first day of menstrual flow
Allais et al[131]	136 menstrual attacks	12.5 mg almotriptan po during moderate or severe pain of menstrual attack only	2 h response: 67.9% 2 h pain free: 44.9% 24 h sustained pain free: 29.3%	Triptan-related AEs in the 24 h after dosing reported by 13.2%	Attacks occurring 2 days before to 4 days after the onset of menstruation
Eletriptan					
Massiou et al[132]	698 women	40 mg and 80 mg eletriptan po during moderate or severe pain	40 mg eletriptan 2 h response: 64% 80 mg eletriptan 2 h response: 68% Placebo 26% ($P < 0.001$)	Not reported	Attacks occurring from 1 day before to 4 days after onset of menses
Frovatriptan					
MacGregor et al[133]	659 menstrual attacks; 1780 non-menstrual attacks	Up to three 2.5 mg frovatriptan po in 24 hours	Migraine relief within 24 h: 82%; 87% Time to overall relief: 5.5 h; 3.6 h	Not reported	Attacks occurring from 3 days before to 4 days after onset of menses
Rizatriptan					
Silberstein et al[134]	421 menstrual attacks; 1418 non-menstrual attacks	10 mg rizatriptan po during moderate or severe pain	2 hr response: 78% vs. 78% 2 hr pain free: 48% vs. 52% 24 h sustained pain free: 32% vs. 37%	Not reported	Attacks which occurred ±2 days of the first day of menstrual flow

Silberstein et al[135]	5 mg rizatriptan: 115 menstrual attacks; 391 non-menstrual attacks; 10 mg rizatriptan: 139 menstrual attacks; 393 non-menstrual attacks	5 mg and 10 mg rizatriptan po vs. placebo during moderate or severe pain	5 mg rizatriptan 2 hr response: 70% vs. 66% 2 hr pain free: 33% vs. 31% 10 mg rizatriptan 2 hr response: 68% vs. 69% 2 hr pain free: 42% vs. 37%	Not reported	Attacks that occurred within 3 days before or after the onset of any recorded menstrual period for a given patient
Sumatriptan					
Solbach and Waymer[136]	157 menstrual; 512 non-menstrual attacks	6 mg sumatriptan sc vs. placebo during moderate or severe pain	1 h response: 80% vs. 70%	Triptan-related AEs similar in menstrual vs. non-menstrual groups	Attacks beginning between 1 day before and 4 days after the onset of menstrual flow
Zolmitriptan					
Allais et al[131]	119 menstrual attacks	2.5 mg zolmitriptan po during moderate or severe pain	2 h response: 68.6% 2 h pain free: 41.2% 24 h sustained pain free: 27.1%	Triptan-related AEs in the 24 h after dosing reported by 17.6%	Attacks occurring 2 days before to 4 days after the onset of menstruation

Notes: 1 h/2 h/24 h response, reduction in headache pain from moderate or severe at baseline to mild or no headache 1 h/2 h/24 h after treatment; 1 h/2 h/24 h pain free, reduction in headache pain from moderate or severe at baseline to no headache 1 h/2 h/24 h after treatment; 24 h sustained pain free, pain free at 2 h with no recurrence and no rescue medication through 24 h.
Abbreviations: AEs, adverse events; ICHD, International Classification of Headache Disorders; po, oral; sc, subcutaneous.

and severity of attacks and improve response to acute treatment.

Specific management strategies have been studied but none are licensed specifically for management of menstrual migraine. Given that there are no investigations to identify the most effective prophylactic, an empirical approach is necessary, considering the individual needs and wishes of each woman. In order adquately to assess efficacy, each method should be tried for at least three cycles before considering alternative prophylaxis.

Perimenstrual (Short-term/Intermittent Prevention)

Short-term prevention strategies have the advantage that treatment is only used at the time of need, thus avoiding continuous exposure to active drug and the potential for adverse events associated with daily prophylaxis.[47] However, many studies are open label Table 6 and results from randomized controlled trials are limited Table 7. None of the drugs and hormones recommended below is licensed for management of menstrual migraine.

Women using perimenstrual prophylaxis must have regular periods and a predictable relationship between migraine and menstruation as treatment is typically started a few days before expected onset of menstruation or the anticipated menstrual attack. A home-use fertility monitor can be used to predict menstruation accurately.[48]

Non-steroidal anti-inflammatory drugs

Prostaglandins have been implicated in the pathophysiology of menstrual migraine.[49] In particular, entry of prostaglandins into the systemic circulation can trigger throbbing headache, nausea and vomiting.[50] 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.[51] 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

Table 5. Randomized controlled trials for acute treatment of menstrual attacks of migraine.

Trial	Trial design	n	Treatment	Results menstrual attacks; non-menstrual	Safety/tolerability	Definition of menstrual attacks
Mefenamic acid						
Al-Waili[137]	Crossover	24	500 mg mefenamic acid po vs. placebo tds from onset of menstrual migraine until end of bleeding	2 h pain response: mefenamic acid 79.1% vs. placebo 16.4% ($P < 0.05$)	Two patients experienced mild epigastric pain with mefenamic acid	Attacks on or between days ±2 relative to the start of menstruation
Triptans						
Almotriptan						
Allais et al[138]	Crossover	147	12.5 mg almotriptan po vs. 2.5 mg zolmitriptan po during moderate or severe pain	2 h pain free: RR 1.81; $P = 0.0008$ 24 h sustained pain free: RR = 1.99; $P = 0.0022$ 24 h sustained pain free with adverse events (RR = 1.94; $P = 0.0061$)	Drug-related AEs: almotriptan 6.1% vs. placebo 6.1% No serious AEs, deaths or changes in vital signs or laboratory tests occurred	Six-month history of regularly occurring ICHD-II MRM (migraine attacks without aura, occurring on days –2 to +3 of menstruation in at least two of three menstrual cycles, with or without additional attacks at other times of the cycle)
Naratriptan						
Massiou et al[139]	Single attack	229	2.5 mg naratriptanpo vs. placebo during mild, moderate or severe pain	2 h pain free: 2.5 mg naratriptan 43% vs. placebo 25%; ($P = 0.0.004$) 4 h pain free: 2.5 mg naratriptan 58% vs. placebo 30% ($P < 0.001$)	Drug-related AEs: naratriptan, three (2%) cases (thoracic symptoms, fatigue, and vertigo); placebo, one (<1%) case (paresthesia)	Single attack occurring on or between days –2 and +4 relative to the start of menstruation
Rizatriptan						
Martin et al[140]	Prospective subgroup analysis	94	10 mg rizatriptan vs. placebo during mild pain	2 h pain free: 63.5%; 57.5% ($P = 0.454$) 24 h sustained pain free: 41%; 44%	AEs that occurred in >5% of patients: dry mouth (5%), dizziness (8%) in the rizatriptan group Drug-related AEs: rizatriptan 9 cases (14.3%); placebo 1 case (3.2%)	Based patient recall of attacks fulfilling ICHD-II criteria and headache treated in the study within 2 days before to 3 days after the onset of menses. Patients were identified as experiencing menstrual migraine if attacks occurred

						during the perimenstrual time period in 2 of 3 menstrual cycles (ICHD-II MRM)
Nett et al[141] Mannix et al[142]	2 single attack RCTs	707	10 mg rizatriptan po vs. placebo during moderate or severe pain	Study 1 2 h response: 10 mg rizatriptan 70% vs. placebo 53% ($P = 0.001$) Study 2 2 h response: 10 mg rizatriptan 73% vs. placebo 50% ($P < 0.001$) Pooled data ICHD pure menstrual migraine 2 h response: 10 mg rizatriptan 73% vs. placebo 50% ($P = 0.006$) 2 h pain free: 10 mg rizatriptan 42% vs. placebo 12% (P not assessed) 24 h sustained pain free: 10 mg rizatriptan 23% vs. placebo 10% (P not assessed) Pooled data ICHD menstrually-related migraine 2 h response: 10 mg rizatriptan 71% vs. placebo 52% ($P < 0.001$) 2 h pain free: 10 mg rizatriptan 36% vs. placebo 19% (P not assessed) 24 h sustained pain free: 10 mg rizatriptan 24% vs. placebo 14% (P not assessed)	Drug-related AEs: rizatriptan 15.6%, placebo 4.0% AEs in ≥2% of patients in the rizatriptan group vs. placebo: palpitations (3.1% vs. 0%), dry mouth (4.2% vs. 2.0%), fatigue (2.1% vs. 0%), joint stiffness (2.1% vs. 0%), dizziness (3.1% vs. 0%), somnolence (5.2% vs. 0%) For menstrually-related migraine, AEs occurring in ≥2% of patients in the rizatriptan group: fatigue (2.1% vs. 1.1%), dizziness (2.9% vs. 0.6%)	A recent history of migraine within 2 days before to 3 days after the onset of menses in at least 2 of the most recent 3 menstrual periods
Sumatriptan						
Facchinetti et al[143]	Crossover	135 MRM; 97 OCMM	25 mg sumatriptan pr; 50 mg sumatriptan po	MRM: 2 h response: suppository 72% vs. oral 66% 2 h pain free: suppository 24% vs. oral 27% 4 h response: suppository 85% vs. oral 81% 4 h pain free: suppository 52% vs. oral 53% OCMM: 2 h response: suppository 55% vs. oral 46% 2 h pain free: suppository 27% vs. oral 18%	Both formulations well tolerated. Three patients with rectal treatment and one with oral treatment reported mild adverse effects	MRM diagnosis based on attacks occurring on or between 2 days before, to 3 days after the onset of menstrual flow who had no more than 3 non-menstrual attacks per month during the 6 months previous to inclusion in the study and at least 1 predictable

(*Continued*)

Table 5. (*Continued*)

Trial	Trial design	n	Treatment	Results menstrual attacks; non-menstrual	Safety/tolerability	Definition of menstrual attacks
				4 h response: suppository 71% vs. oral 64% 4 h pain free: suppository 49% vs. oral 38%		menstrual migraine attack per month during the same period OCMM: attacks exclusively during the pill-free week of contraceptive pills—regardless of whether menstrual flow had begun or not occurring at least once during the previous 6 months and no attacks on contraceptive pill taking days
Dowson et al[27]	Crossover All attacks for 4 months (2 months sumatriptan; 2 months placebo)	93	100 mg sumatriptan po vs. placebo during moderate or severe pain	4 h response: 67% vs. placebo 33% ($P = 0.0072$); 79% vs. placebo 31% ($P < 0.00010$) 4 h pain free: 49% vs. placebo 10% ($P = 0.0001$); 60% vs. placebo 9% ($P < 0.0001$)	AEs reported: sumatriptan 64% vs. placebo 44% Most common AEs were associated with the nervous and digestive systems Eight patients (7%) withdrew due to adverse events	MRM diagnosis based on patient recall of having experienced a migraine on or between 3 days before, to 5 days after the onset of menstrual flow in two of their last three menstrual cycles and >80% of their attacks falling within the menstrual window in the previous 6 months
Landy et al;[144] Nett et al[145]	2 single attack RCTs	752	50 mg sumatriptan po vs. 100 mg sumatriptan po vs. placebo during mild, moderate and severe pain	Study 1: 2 h pain free: 50 mg sumatriptan 51% vs.100 mg sumatriptan 58% vs. placebo 22% ($P < 0.001$) 24 h sustained pain free: 50 mg sumatriptan 30% vs.100 mg sumatriptan 35% vs. placebo 8% ($P < 0.001$)	AEs reported in >2% of patients in any treatment group: nausea, paresthesia, dizziness and malaise/fatigue Incidence of these AEs was slightly higher for sumatriptan vs. placebo No serious AEs reported	At least a 6-month history of menstrually associated migraine (a new migraine attack beginning from 2 days before through 4 days after the day of onset of menstrual flow), with migraine attacks during two

				Study 2: 2 h pain free: 50 mg sumatriptan 51% vs.100 mg sumatriptan 61% vs. placebo 29% ($P < 0.001$) 24 h sustained pain free: 50 mg sumatriptan 30% vs.100 mg sumatriptan 31% vs. placebo 14% ($P < 0.05$)		of the last three menstrual periods prior to screening for the studies, and a history of moderate to severe menstrually associated migraines typically preceded by a mild-pain phase
Facchinetti et al[146]	Parallel	179	6 mg sumatriptan sc vs. placebo during moderate or severe pain	Attack 1: 1 h response: sumatriptan 71% vs. placebo 22% ($P < 0.001$) 2 h response: sumatriptan 73% vs. placebo 31% ($P < 0.001$) 2 h pain free: sumatriptan 55% vs. placebo 14% Attack 2: 1 h response: sumatriptan 70% vs. placebo 24% ($P < 0.001$) 2 h response: sumatriptan 81% vs. placebo 29% ($P < 0.001$) 2 h pain free: sumatriptan 55% vs. placebo 14%	Drug-related AEs: sumatriptan 53 cases (46%), placebo 28 cases (25%) Withdrawn because of AEs: sumatriptan 3 cases (3%), placebo 2 cases (2%) Most common AEs (sumatriptan vs. placebo): dizziness/vertigo (10% vs. 5%), nausea/vomiting (9% vs. 5%), paresthesia (9% vs. 3%), tingling (7% vs. 3%), warm/hot sensation (7% vs. <1%), throat symptoms (6% vs. <1%), neck pain/ stiffness (4% vs. 2%), sweating (4% vs. 0%)	Attacks occurring −3 to +5 days relative to the first day of menstruation
Sumatriptan-naproxen						
Mannix et al[40]	2 single attack RCTs	621	85 mg sumatriptan, 500 mg naproxen po vs. placebo during mild pain	Study 1: 2 h pain free: sumatriptan-naproxen 42% vs. placebo 23% ($P < 0.001$) 48 h sustained pain free: sumatriptan- naproxen 26% vs. placebo 17% ($P = 0.04$) Study 2: 2 h pain free: sumatriptan-naproxen 52% vs. placebo 22% ($P < 0.001$) 48 h sustained pain free: sumatriptan-naproxen 28% vs. placebo 8% ($P < 0.001$)	Most commonly reported AEs: nausea, dizziness, and dry mouth No serious AEs or withdrawals due to AEs occurred	Attacks occurring 2 days before to 3 days after the onset of menses

(*Continued*)

Table 5. (*Continued*)

Trial	Trial design	n	Treatment	Results menstrual attacks; non-menstrual	Safety/tolerability	Definition of menstrual attacks
Zolmitriptan						
Tuchman et al[147]	Single attack RCT	334	2.5 mg zolmitriptan po vs. placebo during moderate or severe pain	2 h response: 2.5 mg zolmitriptan 65.7% vs. placebo 32.8% ($P < 0.0001$)	AEs: zolmitriptan 110 reports (62.9%), placebo 43 reports (26.7%) Most common AEs (zolmitriptan vs placebo): dizziness (15% vs 4%), chest tightness (11% vs 0), nausea (10% vs 3%), paresthesia (9% vs 3%), somnolence (9% vs 2%), dry mouth (7% vs 4%), asthenia (6% vs 4%), pain (6% vs 0), vasodilatation (6% vs 4%)	Attacks occurring exclusively within 2 days before the expected onset of menses through to 5 days after onset of menses, but not at other times of the menstrual cycle
Loder et al[148]	Parallel	597	1.25 mg, (for mild pain) 2.5 mg (for moderate pain), 5 mg (for severe pain) zolmitriptan po vs. placebo	2 h response: 2.5 mg zolmitriptan 48% vs. placebo 27% ($P < 0.0001$)	Drug-related AEs: zolmitriptan 41 cases (16%), placebo 23 cases (9%) Most common AEs (zolmitriptan vs. placebo): asthenia (2% vs. <1%), tightness (3% vs. 2%), dizziness (3% vs. 2%), paresthesia (4% vs. 2%), somnolence (4% vs. 2%)	Attacks occurring from 3 days before to 5 days after the onset of menses

Notes: 1 h/2 h/4 h response, reduction in headache pain from moderate or severe at baseline to mild or no headache 1 h/2 h/4 h after treatment; 2 h/4 h pain free, reduction in headache pain from moderate or severe at baseline to no headache 2 h/4 h after treatment; 24 h/48 h sustained pain free, pain free at 2 h with no recurrence and no rescue medication through 24 h/48 h.
Abbreviations: ICHD, International Classification of Headache Disorders; MRM, menstrually related migraine; OCMM, oral contraceptive menstrual migraine; po, by mouth; pr, rectal suppository; RCT, randomized clinical trial; RR, risk ratio; sc, subcutaneous; tds, three times daily.

Table 6. Open label trials of perimenstrual migraine prophylaxis.

Trial	n	Dose	No. of cycles	Treatment timing	Results	Safety/tolerability
Non-steroidal anti-inflammatory drugs						
Naproxen						
Guidotti et al[59]	14	500 mg po od	Baseline untreated cycle followed by one treated cycle	2 days before anticipated menstrual migraine Duration 6 days	Median score of headache severity: Baseline 4.3 During treatment 3.9	Not reported
Allais et al[60]	20	550 mg po od	Baseline untreated cycle followed by six treated cycles	cycles 2–4: days −7 to +7; cycles 5–7: days −5 to +5	Baseline no. of attacks: 1.7 ± 0.11 End of month 3 1.2 ± 0.10 ($P < 0.001$) End of month 6 1.1 ± 0.07 ($P < 0.0001$)	AEs: 2 gastric pain, 1 allergic skin reaction All 3 cases discontinued treatment
Rofecoxib						
Von Seggern et al[61]	14	25 mg or 50 mg po od	Baseline untreated cycle followed by two treated cycles	Days −2 to +4	Mean migraine frequency decreased from 5.6 to 2.6 migraines per menstrual cycle ($P = 0.005$) 57% reported ≥50% reduction in headache frequency	No drug-related AEs reported
Triptans						
Eletriptan						
Marcus et al[88]	61	20 mg po tds	Three baseline untreated cycles followed by three treated cycles	2 days before anticipated menstrual migraine Duration 6 days	Overall 46% decrease in headache activity Mean percentage of treated menses without migraine occurring during the 6 days of treatment was 71% Percentage of women with 1, 2, and 3 migraine-free menstrual periods (no migraines occurring 2 days before menses through the first 3 days of menstruation) were 14%, 19%, and 53%	Most common AEs: headache (40 reports 22%), fatigue (22 reports, 12%), dizziness/light-headedness (16 reports, 9%), nausea (13 reports, 7%)
Frovatriptan						
Guidotti et al[59]	14	2.5 mg po od	Baseline untreated cycle followed by one treated cycle	2 days before anticipated menstrual migraine Duration 6 days	Median score of headache severity: baseline 4.6; during treatment 2.5 ($P = 0.049$ vs. estradiol or naproxen)	Not reported

(*Continued*)

Table 6. (*Continued*)

Trial	n	Dose	No. of cycles	Treatment timing	Results	Safety/tolerability
Naratriptan						
Moschiano et al[85]	59	1 mg po bd	Baseline untreated three cycles followed by three treated cycles	Days –2 to +4	Baseline no. of attacks: 3.5 ± 1.4 per 3 months End of month 3 1.6 ± 1.3 per 3 months 61.4% reported ≥50% reduction in mean no. of attacks	Most common AEs: pharyngitis/flu 11%, dizziness 8%, headache 3%, sleepiness 3% AEs were generally of mild to moderate intensity and spontaneously remitted. Two AEs, scored as severe, were pharingitis and depressed mood. No serious AEs occurred
Sumatriptan						
Newman et al[89]	20	25 mg po tds	Baseline untreated two cycles followed by up to 14 treated cycles	2–3 days before anticipated menstrual migraine Duration 5 days	52.4% treated cycles with no headache 42% treated cycles with ≥50% reduction in severity of pain	Not reported
Estrogens						
Estradiol						
Guidotti et al[59]	10	0.025 mg transdermal patch	Baseline untreated cycle followed by one treated cycle	2 days before anticipated menstrual migraine Duration 6 days	Median score of headache severity: Baseline 4.2 During treatment 3.0	Not reported
Pradalier et al[75]	24	0.025 mg or 0.1 mg transdermal patch	Baseline untreated cycle followed by two treated cycles	Days –4 to +4	Presence of menstrual migraine in baseline cycle 22/24; in 2nd treated cycle: estradiol 0.025 mg 11/12; estradiol 0.1 mg 6/12	Not reported
Phyto-estrogens						
Ferrante et al[93]	11	56 mg genisteine and 20 mg diadzeine po od	Baseline untreated 3 cycles followed by 3 treated cycles	Days –7 to +3	Reduction in number of days of headache Baseline 5.7 days per month End of month 3 2.2 days per month ($P < 0.005$)	No severe or serious AEs AEs: delay in one menstrual cycle (n = 1), mild and transient abdominal pain (n = 1) One case withdrew because of lack of efficacy

Ergot alkaloids						
Ergonovine						
Gallagher[97]	40	0.2 mg tds-qds during menses	6 months		After 3 months: 60% reported less severe attacks and 25% reported less frequent attacks After 6 months: 50% reported less severe attacks and 5% reported less frequent attacks	AEs: 6 cases (3 leg cramps, 2 nausea, 1 dry mouth). AEs mild and did not require cessation of treatment medication
Dihydroergotamine						
D'Alessandro et al[96]	20	1.5 mg immediate release and 3.5 mg over 12 hours po bd	Baseline untreated cycle followed by five treated cycles	Days –2 to +5	Mean Headache Index Baseline: 69.12; end of month 5: 28.00 ($P < 0.001$) Hours of headache Baseline: 28.56; end of month 5: 17.18 ($P < 0.01$)	Four cases withdrew: 3 lack of efficacy, 1 parasthesia in the hands

Abbreviations: bd, twice daily; GnRH-a, gonadotropin releasing hormone agonist; im, intramuscular; od, once daily; po, oral; qds, four times daily; sc, subcutaneous; tds, three times daily.

associated with menorrhagia and/or dysmenorrhoea such as headache and nausea.[52,53] Plasma taken during the premenstrual phase from women with dysmenorrhoea and reinfused postmenstruation into the same women resulted in premenstrual symptoms, including headache.[54] 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.[55]

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.[52,56,57] Side effects of NSAIDs include gastro-intestinal disturbance. Misoprostol 800 µg or omeprazole 20 to 40 mg daily may give some gastroduodenal protection.[58] NSAIDs may cause fluid retention, leading to edema and elevated blood pressure. Kidney failure can also occur. Contraindications include peptic ulcer, aspirin-induced allergy, severe hepatic, renal and cardiac failure. Interactions include anticoagulants, diuretics and antihypertensive agents.

Open-label studies using perimenstrual naproxen 500–550 mg once daily suggest efficacy of this approach for menstrual migraine.[59,60] Rofecoxib was not associated with gastrointestinal symptoms in an open-label study.[61] However, the drug has since been withdrawn because of cardiovascular safety concerns with high-dosage long-term use.

Randomized studies using naproxen 550 mg twice daily perimenstrually have confirmed efficacy with good tolerability.[62,63] Sances et al, noted that 25% of women taking naproxen reported mild or moderate nausea and epigastric distress but all continued treatment.[62] Limited data from a single randomized placebo-controlled trial suggest nimesulide may be an effective alternative.[64]

Estradiol

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.[65–68]

The rationale for perimenstrualestrogen supplementation is based on evidence that the natural decline

Table 7. Randomized placebo-controlled trials of perimenstrual migraine prophylaxis.

Trial	Trial design	n	Dose	No. of cycles	Treatment timing	Results	Safety/tolerability
Non-steroidal anti-inflammatory drugs							
Naproxen							
Sances et al[62]	Parallel	35	550 mg po bd	Baseline untreated 2 cycles followed by 3 treated cycles (then 3 open-label cycles)	Days −7 to +6	No significant difference in Pain Total Index = no. of attacks + (duration X severity) 16.7% patients in 1st treatment month with naproxen and 33% in 2nd and 3rd month reported absence of migraine vs. 0% placebo	AEs: 25% taking naproxen reported mild or moderate nausea and epigastric distress. None discontinued treatment
Szekely et al[63]	Crossover	22	550 mg po bd	Baseline untreated 2 cycles followed by 4 treated cycles	Treatment started 8 days after ovulatory temperature rise (day −2/−3) to Day +8	Frequency reduced with both naproxen and placebo. Reduction in frequency by naproxen greater than placebo ($P = 0.02$) Reduction in HI > 44%: naproxen 68% vs. placebo 36% ($P = 0.03$)	No AEs reported
Nimesulide							
Giacovazzo et al[64]	Parallel	30	100 mg po tds	2 cycles	1st day of menstrual migraine Duration 10 days	Pain intensity and duration reduced during treatment with nimesulide vs. placebo ($P = 0.0001$)	Not reported
Triptans							
Frovatriptan							
Silberstein et al[81] (Post-hoc subgroup analysis of Silberstein et al[86])	Crossover	179	2.5 mg po bd 2.5 mg po od	3 cycles	2 days before anticipated menstrual migraine Duration 6 days	ICHD Pure menstrual migraine Migraine incidence 37.7% during bd treatment, 51.3% during od treatment ($P = 0.002$), 67.1% with placebo	AEs reported more frequency with frovatriptan twice daily: nausea 8%, dizziness 5.7%, fatigue 4.6%, upper respiratory chest infection 4.6%, back pain 4%, chest pain 2.9%, paresthesia 2.9%. AEs reported more frequently with placebo: headache 7.5%, dyspepsia 3.2%, nasopharygitis 4.3%, dysmenorrhea 4.3%

Brandes et al[82]	Parallel	410	2.5 mg po bd 2.5 mg po od	3 cycles	2 days before anticipated menstrual migraine Duration 6 days	Headache-free treatment periods 0.92 during bd treatment, 0.69 during od treatment, 0.42 with placebo ($P < 0.001$ and $P < 0.02$ vs. placebo)	Drug-related AEs: frovatriptan bd 24%, frovatriptan od 32%, placebo 19%. Most common AEs: migraine (frovatriptan bd 8%, frovatriptan od 4%, placebo 4%), headache (frovatriptan bd 7%, frovatriptan od 4%, placebo 3%), nausea (frovatriptan bd 12%, frovatriptan od 8%, placebo 6%) No drug-related severe AEs
Silberstein et al[86]	Crossover	546	2.5 mg po bd 2.5 mg po od	3 cycles	2 days before anticipated menstrual migraine Duration 6 days	Migraine incidence 43% during bd treatment, 52% during od treatment, 69% with placebo ($P < 0.0001$ vs. placebo)	Most common AEs: nausea (frovatriptan bd 6.8% [$P = 0.028$], frovatriptan od 4.8%, placebo 3.4%), dizziness (frovatriptan bd 4.8%, frovatriptan od 3.6%, placebo 2.6%), nasopharyngitis (frovatriptan bd 3.4%, frovatriptan od 3.2%, placebo 2.4%), headache (frovatriptan bd 4.2% [$P = 0.011$], frovatriptan od 4.6%, placebo 6.3%), dysmenorrhea (frovatriptan bd 1.8%, frovatriptan od 2.2%, placebo 3.0%)
Naratriptan							
Mannix et al[84]	Parallel	Study 1: 287 Study 2: 346	1 mg po bd	4 cycles	3 days before anticipated menstrual migraine Duration 6 days	Study 1: Mean 40% of treatment periods without migraine per patient with naratriptan vs. 27% with placebo ($P < 0.05$) Study 2: Mean 37% of treatment periods without migraine per patient with naratriptan vs. 24% with placebo ($P < 0.05$)	Drug-related AEs infrequently reported in both treatment groups. No individual drug-related AE was reported in more than 2% of patients. Three naratriptan drug-related AEs lead to withdrawal: 1 case parasthesia, 1 case vertigo, 1 case gastritis

(*Continued*)

Table 7. (*Continued*)

Trial	Trial design	n	Dose	No. of cycles	Treatment timing	Results	Safety/tolerability
Newman et al[87]	Parallel	206	1 mg po bd 2.5 mg po bd	4 cycles	Days –2 to +3	50% headache-free treatment periods per patient with 1 mg bd vs. 25% with placebo ($P = 0.003$) Mean no. of migraines 2.0 with 1 mg bd vs. 4.0 with placebo ($P < 0.05$) No significant different with 2.5 mg bd	Drug-related AEs naratriptan 2.5 mg vs. placebo: 17% vs. 13%; dizziness: 4% vs. 1%; chest symptoms: 3% vs. 3%; malaise and fatigue: 3% vs. 3%; parasthesia: 3% vs. 0%; burning/stinging sensation: 3% vs. 0%. No serious AEs, pregnancies, or drug-related changes in vital signs or laboratory tests were reported during the study period.
Zolmitriptan							
Tuchman et al[83]	Parallel	244	2.5 mg po bd 2.5 mg po tds	3 cycles	Days –2 to +5	58.6% reduction in migraine with 2.5 mg tds vs. 54.7% with 2.5 mg tds and 37.8% with placebo ($P = 0.0007$ and $P = 0.002$) vs. placebo	Most common AEs: asthenia (zolmitriptan tds 10.7%, zolmitriptan bd 8.8%, placebo 9.8%), headache (zolmtriptan tds 8.3%, zolmitriptan bd 3.8%, placebo 2.4%), dizziness (zolmitriptan tds 7.1%, zolmitriptan bd 6.3%, placebo 4.9%), nausea (zolmitriptan tds 7.1%, zolmitriptan bd 6.3%, placebo 1.2%), somnolence (zolmitriptan tds 7.1%, zolmitriptan bd 6.3%, placebo 3.7%), tightness (zolmitriptan tds 7.1%, zolmitriptan bd 5.0%, placebo 2.4%), dry mouth (zolmitriptan tds 6.0%, zolmitriptan bd 1.3%, placebo 1.2%) Seven patients withdrew due to adverse events (zolmitriptan tds n = 3, 3.6%; zolmitriptan bd n = 3, 3.8%; placebo n = 1, 1.2%) No serious drug-related AEs

Estrogens							
Estradiol							
MacGregor et al[73]	Crossover	35	1.5 mg gel	Baseline untreated 3 cycles followed by 6 treated cycles	Treatment started 9 days after luteinizing hormone surge (day –5/–6) to Day +2	22% reduction in migraine days during estradiol treated cycles compared to placebo RR 0.78, 95% CI 0.62–0.99 ($P = 0.04$)	No adverse events reported
Smits et al[74]	Crossover	20	0.5 mg patch	3 cycles	Days –2 to +6	No significant difference in percentage of treatment periods with migraine	No difference in bleeding pattern changes and breast tension with Estraderm TTS treatment vs. placebo Itching in the area of patch was reported in 9% estradiol treated cycles 0% placebo
Pfaffenrath[76]	Crossover	41	0.5 mg patch	Baseline 2 untreated cycles followed by 4 treated cycles	2 days before anticipated menstrual migraine Duration not stated	No significant difference in reduction in headache duration, intensity and impairment	Not reported
Dennerstein et al[77]	Crossover	22	1.5 mg gel	Baseline 2 untreated cycles followed by 4 treated cycles	2 days before anticipated menstrual migraine Duration 7 days	Days of moderate to severe migraine during treatment: estradiol 47 vs. placebo 86 ($P < 0.001$)	Four women with drew: 2 lack of improvement (1 placebo, 1 estradiol), 1 skin rash (placebo), 1 severe ache in upper thigh (estradiol). AEs: 3 missed menses (2 oestradiol, 1 pre-treatment)
De Lignieres et al[78]	Crossover	18	1.5 mg gel	3 cycles	2 days before anticipated menstrual migraine Duration 7 days	Migraine in 30.8% estradiol treated cycles vs. 96.3% with placebo ($P < 0.01$)	No adverse events reported
Magnesium							
Facchinetti et al[149]	Parallel	20	360 mg po od	Baseline untreated 2 cycles followed by 2 treated cycles (then 2 open-label cycles)	Day +15 to Day +1 of next cycle	Pain Total Index decreased in both treated and placebo groups (NS) Menstrual Distress Questionnaire decreased in treated group vs. placebo ($P < 0.01$)	Two patients withdrew: one diarrhea on magnesium, one continuous headache on placebo

(*Continued*)

Table 7. (*Continued*)

Trial	Trial design	n	Dose	No. of cycles	Treatment timing	Results	Safety/tolerability
Vitamin E							
Ziaei et al[95]	Crossover	67	400IU	2 placebo cycles followed 1 untreated then 2 treated cycles	Days −2 to +3	Median Pain Severity [IQR]/day: vitamin E 1[1–2] vs. placebo 2[2–3] ($P < 0.001$) Median Functional Disability [IQR]/ day: vitamin E 1[1–2] vs. placebo 2[2–3] ($P < 0.001$) Mean ± SD Ibuprofen consumption dose (mg): vitamin E 219 ± 195 vs. placebo 388 ± 220 ($P < 0.001$) Mean ± SD Duration of pain (hours): vitamin E 6.4 ± 4.8 vs. placebo 8.9 ± 6.1 ($P < 0.001$)	Not reported

Abbreviations: bd, twice daily; ICHD, International Classification of Headache Disorders; IQR, inter quartile range; od, once daily; po, oral; RR, relative risk; SD, standard deviation; SEM, standard error of the mean; tds, three times daily.

in estrogen in the late luteal phase of the menstrual cycle, just prior to menstruation, is associated with increased risk of migraine.[69] Somerville 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.[70–72] This would explain why migraine is not associated with the transient estrogen surge at ovulation. Since women using combined hormonal contraceptives still experience migraine occurring during the hormone-free interval, it would seem that ovulation is not a prerequisite for menstrual attacks.

Somerville showed that migraine could be postponed by maintaining high plasma estradiol levels with an intramuscular injection of long-acting estradiolvalerate in oil; migraine subsequently occurred when the plasma estradiol fell.[70] 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.[72] This supports the hypothesis that prolonged estrogen exposure is necessary for 'withdrawal' to trigger migraine.

Several trials have confirmed the efficacy of transcutaneous estradiol for menstrual migraine prophylaxis.[73–78] Transdermal administration is preferred since it provides more stable serum levels than oral estrogen. The recommended strategy is estradiol gel 1.5 mg applied daily from two to three days before expected menstruation for seven days.[79] Alternatively transdermal estrogen 0.1 mg can be used from two to three days before expected menstruation or menstrual migraine up to the fourth or fifth day of menstruation, ie, two twice-weekly patches or one seven-day patch, although an additional patch may be necessary if menstruation is late.[79] Lower doses of 0.025 mg and 0.05 mg estradiolare not effective.[59,74–76]

Estradiol is well tolerated although post-treatment migraine can occur. Somerville noted that migraine estradiol treatment delayed migraine between three and nine days in all 6 women studied.[70] De Lignières reported that 1 of 20 women had migraine three days after stopping estradiol treatment.[78] MacGregor found an increase in migraine occurrence in the 5 days immediately following estradiol use compared to placebo, relative risk [RR] 1.40 (95% CI 1.03 to 1.92, $P = 0.03$).[73] Possible reasons for this posttreatment 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. 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 two days.

Menstrual irregularity can occur, probably due to suppression of endogenous estrogen during treatment.[73] There is no evidence that estradiol supplements increase the risks of cancer or thrombosis in premenopausal women.[80]

Triptans

Randomized placebo-controlled trials and open-label studies of frovatriptan, naratriptan, and zolmitriptan for perimenstrual prophylaxis have suggested efficacy although direct comparison of the results is limited by the different endpoints used.[59,81–87] Only results from single open-label studies are available for eletriptan and sumatriptan.[88,89] Although the definitions of menstrual migraine appear similar, only one trial required review of documented diary data as confirmation for inclusion.[82] Only two studies required confirmation of menstrual migraine as a specific diagnosis.[82,85]

Perimenstrualtriptan prophylaxis is well tolerated and the incidence and type of adverse events reported is consistent with those reported in trials of acute treatment. The high completion rates in the clinical trials are notable. However, there is potential concern that treatment may defer attacks or result in 'rebound' migraine following treatment. This has been noted with naratriptan, with the percentage of patients reporting migraine during the immediate post-treatment period being higher in those treated with naratriptan compared to patients receiving placebo.[84] Increased migraine post-treatment has been reported not to occur following perimenstrual frovatriptan.[82]

Specific analyses of safety and tolerability have been undertaken on long-term trials of frovatriptan and naratriptan. During treatment of up to 12 perimenstrual periods over a 12- to 15-month period, adverse events with frovatriptan were generally mild or moderate in severity and were similar to

that observed with acute use of triptans.[90] Results of subgroup analyses of women whose medical histories included comorbidities that might suggest increased cardiovascular risk but were not themselves contraindications to frovatriptan, provide preliminary evidence of safety of frovatriptan in this population.[91]

Patients completing 6- to 12-months perimenstrual prophylaxis with naratriptan noted that no specific adverse event considered at least possibly to be related to study medication occurred in more than 2% of patients. No serious drug-related adverse events were reported and no patient experienced clinically relevant drug-related changes in 12-lead ECGs, vital signs, or clinical laboratory tests.[92]

Other treatments used for perimenstrual prophylaxis

In an open-label of 10 women with pure menstrual migraine taking phyto-estrogensgenistein 56 mg and daidzeine 20 mg daily, 10 days per month (starting 7 days before the predicted onset of menses) for three cycles, the average number of days with migraine during the baseline period decreased significantly after 3 months of therapy ($P < 0.005$).[93]

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.[94] This study was principally aimed at identifying the effect of magnesium on a number of premenstrual problems, not just headache. The generalizability of the results to women whose menstrual headaches do not occur in association with other premenstrual symptoms is unclear. Diarrhea was reported by one woman during treatment with magnesium.

A trial of vitamin E 400IU, an anti prostaglandin agent, given perimenstrually in a cross-over study of two menstrual cycles showed limited effect as a prophylactic, although headache pain and associated symptoms were reduced compared to placebo.[95] Tolerability was not reported.

The ergot alkaloids ergonovine and dihydroergotamine have shown efficacy in open-label studies of menstrual migraine prophylaxis but there are no data from randomized controlled trials to support their use.[96,97]

Continuous Prophylaxis

For women who are unable to predict menstruation, several continuous prophylactic strategies specifically for women with menstrual migraine have been studied Table 8.

Estradiol

Estradiol implants are the most effective method of obtaining high stable estrogen levels. In an open-label study estradiol implant given in doses large enough to suppress ovulation and produce constant plasma estrogen levels achieved an 96% response rate in 24 women with menstrual migraine treated for up to five years, with 46% of women becoming completely headache free.[98] Treatment was well tolerated.

In unhysterectomised women, progestogen opposition is necessary to protect the endometrium, as unopposed oestrogens increase the risk of endometrial cancer. However, cyclical progestogen can mimic premenstrual symptoms, including headache.[99] 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.[100]

Dietary estrogens

Phyto-estrogens are estrogen-like molecules derived from soy, which have gained interest as a "natural" alternative to prescription estrogens. They have estrogenic effects in some tissues, without stimulation of the endometrium. Theoretically, this confers greater long-term safety than with estradiol treatment, although this has yet to be established. Black cohosh (*Cimicifugaracemosa*) contains several compounds with estrogen receptor activity similar to soy isoflavones. Dong quai (*Angelica polymorpha*), known as Chinese Angelica, also has estrogen-like effects. In a randomized placebo-controlled trial, a combination of 60 mg soy isoflavones, 100 mg dong quai, and 50 mg black cohosh the average frequency of menstrual attacks in women treated with the phytoestrogen preparation was 4.7 ± 1.8 (mean ± SEM) during weeks 9–24 compared with 10.3 ± 2.4 in placebo treated patients ($P < 0.01$).[101]

Gonadotropin-releasing hormone analogues

These drugs inhibit ovulation, reducing levels of estrogen. Although effective, adverse effects of estrogen

Table 8. Continuous prophylaxis for menstrual migraine.

Trial	n	Trial design	Dose	Duration of study	Results	Safety/tolerability
Estrogens						
Estradiol						
Magos et al[98]	24	Open-label	50–100 mg estradiol sc	Mean 2.5 years (range 0.5–5)	83% became completely or almost completely headache free	One patient withdrew because of lack of improvement. No other AEs reported
Dietary estrogens						
Burke et al[101]	49	Parallel RCT	60 mg soy isoflavones, 100 mg dong quai, and 50 mg black cohosh po od	24 weeks	Average frequency of menstrual attacks during weeks 9 ± 24 (mean ± SEM) Phyto-estrogen 4.7 ± 1.8 vs. placebo 10.3 ± 2.4 ($P < 0.01$)	Five AEs: placebo group 3 cases diarrhea; phytoestrogen group 1 case nausea, 1 case pruritis which resolved after the third day on study medication. All patients completed the study except the woman with the nausea.
GnRH agonist						
Murray and Muse[103]	5	Open-label	3.75 mg imleuprolideacetate monthly. Additional estradiol 0.1 mg transdermal patch and medroxyprogester one acetate 2.5 mg po daily from treatment month 5	Baseline untreated 2 months followed by 10 treated months	Headache scores per month mean ± SEM: Control months 15.3 ± 2.4 GnRH-a treatment months 4.0 ± 1.5 GnRH-a and "add-back" treatment months 3.1 ± 0.7	GnRH agonist: 1st month associated with a variable amount of unpredictable bleeding (0 to 21 days). Next 3 months associated with almost complete amenorrhea Add-back therapy was associated with erratic light but often prolonged bleeding; mean number of days of bleeding was 7.8 ± 1.3 per month which reduced with continued treatment. Four of five patients reported hot flushes. No other significant side effects were noted
Bromocriptine						
Herzog[105]	21	Open-label	2.5 mg tds	One treated year compared to prior untreated year	72% overall reduction in migraine frequency ($P < 0.01$)	Three women did not tolerate bromocriptine because of light-headedness or nausea
Hockaday et al[104]	7	Open-label	1 mg tds at 4-day intervals	15 menstrual cycles	1 migraine attack occurred in 12 treated cycles	AEs: nausea (n = 4); dizziness or light headed ness (n = 4), cramps or aching in the legs (n = 2), stomach ache and diarrhea (n = 1), flatus and constipation (n = 1) Two patients withdrew because of drug-related AEs

Abbreviations: bd, twice daily; GnRH-a, gonadotropin releasing hormone agonist; im, intramuscular; od, once daily; po, oral; qds, four times daily; sc, subcutaneous; tds, three times daily.

deficiency, eg, hot flushes, restrict their use.[102] The hormones are also associated with a marked reduction in bone density and should not usually be used for longer than six months without regular monitoring and bone densitometry. 'Add-back' continuous combined estrogen and progestogen can be given to counter these unwanted effects.[103]

Bromocriptine

This dopamine agonist inhibits gonadotrophin releasing hormone and luteinizing hormone, reducing estrogen levels. Two studies have suggested efficacy of bromocriptine in migraine although larger double-blind placebo controlled studies are necessary before it can be recommended.[104,105] Although generally well-tolerated, adverse events related to treatment included light-headedness or nausea.

Anti-estrogens

There is some limited evidence of efficacy for danazoland tamoxifen but symptoms of estrogen deficiency such as hot flushes, menstrual irregularity, fatigue and joint pains, restrict their use.[106–110]

Contraceptive Strategies

Combined hormonal contraceptives minimize the hormonal fluctuations associated with migraine and are particularly useful when a woman also requires contraception.[111] They have additional non-contraceptive benefits on premenstrual syndrome, menorrhagia and dysmenorrhoea. International guidelines for safe prescribing are available. In particular, contraceptive doses of synthetic estrogens should not be used by women who also have with migraine with aura because of the synergistic increased risk of ischemic stroke.[112]

Most licensed combined hormonal contraceptives include a hormone-free interval during which a withdrawal bleed occurs. However, this withdrawal of hormones is associated with increased risk of migraine.[113–115]

Supplementing estrogen during the hormone-free interval can minimize this risk of migraine. In a small open-label study, 11 women with menstrual migraine were treated with a 28-day cycle of 0.02 mg ethinylestradiol oral contraceptive for 21 days followed by 0.9 mg conjugated equine estrogen daily for 7 days. All women achieved at least a 50% reduction in number of headache days per cycle (mean 77.9% reduction).[116] Transdermal estrogen in an alternative option. A study using 0.05 mg estradiolpatches during this time suggested that this dose is suboptimal for prophylaxis although post-trial treatment with 0.1 mg doses was effective.[114]

Continuous use of combined hormonal contraceptives is a more simple strategy to prevent 'estrogen-withdrawal' migraine. This regime is well tolerated, although unscheduled bleeding is a common reason for withdrawal from clinical trials in the first 6-months of treatment. Continued use induces amenorrhea in 80% to 100% of women by 10 to 12 months of treatment.[117] For women who experience migraine during the seven-day hormone-free interval of standard regimes, data from an open-label study suggest that continuous use of combined hormonal contraceptives is effective.[118]

To date, larger trials have only assessed headaches in the hormone-free interval and not specifically migraine. A trial of 102 women taking 3 mg of drospirenone and 0.03 mg ethinylestradiol continuously showed that, compared to 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.[119] Similarly, an extended 84-day regimen of a transdermal contraceptive reduced the total incidence of mean headache days compared to a 21/7-day regimen.[120]

Progestogen-only contraceptives

In general, standard contraceptive oral progestogens have little place in the management of menstrual migraine since most are associated with a disrupted menstrual cycle.[121] In contrast, unlicensed higher doses of oral progestogen, sufficient to suppress oestrogen fluctuations and achieve amenorrhoea, have shown benefit.[122,123] Depot medroxyprogesterone acetate should, in theory, provide stable low levels of oestrogen to prevent menstrual migraine but there are no studies to support or refute this.

Future Therapeutic Approaches

While trial data can support the efficacy, safety and tolerability of treatments, data on patient satisfaction and compliance in clinical practice are much needed.

A new therapeutic approach being studied is with the calcitonin-gene related peptide antagonist telcagepant. Results are awaited from a six-month phase 2/3, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety, tolerability, and efficacy of telcagepant for prevention of menstrually-related migraine in 4500 female patients with episodic migraine (NCT01125774). In this study, women were randomized to 140 mg telcagepant or placebo once daily at bedtime for 7 days, beginning at onset of menses, for 6 menstrual cycles.

Genetic research is also underway, with the hope of identifying genes that will enable an objective method of diagnosing menstrual migraine. Studies investigating the role of the estrogen receptor 1 (ESR1) gene in migraine show a significant association of the A allele of the G594A SNP and the progesterone receptor (PGR) PROGINS insert with migraine.[124,125] 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.

Accurate diagnosis of menstrual migraine can aid the selection of currently available treatments and could ultimately lead to the development of more specific treatments, targeted to the affected genes.

Conclusions

The majority of women with menstrual migraine need only to optimize symptomatic treatment. Trial data to support grade B recommendations (good evidence of efficacy; benefits outweigh harms; improves important health outcomes) are available for sumatriptan 50 and 100 mg, mefenamic acid 500 mg, rizatriptan 10 mg and the combination sumatriptan 85 mg-naproxen 500 mg.[39]

If acute treatment is insufficient for effective control, perimenstrual prophylaxis is usually considered in addition to symptomatic medication. A number of different treatment strategies have been studied for the prevention of menstrual migraine in randomized placebo-controlled trials and open-label studies. Choice of prophylaxis depends on the regularity of the menstrual cycle, timing of attack in relation to bleeding, presence of dysmenorrhoea and/or menorrhagia, and the need for contraception. Each prophylactic should be tried for a minimum of three menstrual cycles before considering an alternative option, using diary cards to record outcomes. Trial data to support grade B recommendations exist for use of transcutaneous estradiol 1.5 mg, frovatriptan 2.5 mg twice daily, and naratriptan 1 mg twice daily for perimenstrual prophylaxis.[39]

Contraceptive approaches should be considered for women with menstrual migraine who also wish to prevent pregnancy. Continuous combined hormonal contraception has limited evidence of efficacy but should not be used by women with migraine with aura.

Results from a prophylactic trial of telcagepant, a calcitonin-gene-related peptide antagonis are awaited. Research to identify relevant genes has the potential to improve diagnosis and enable targeted management.

Disclosures

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