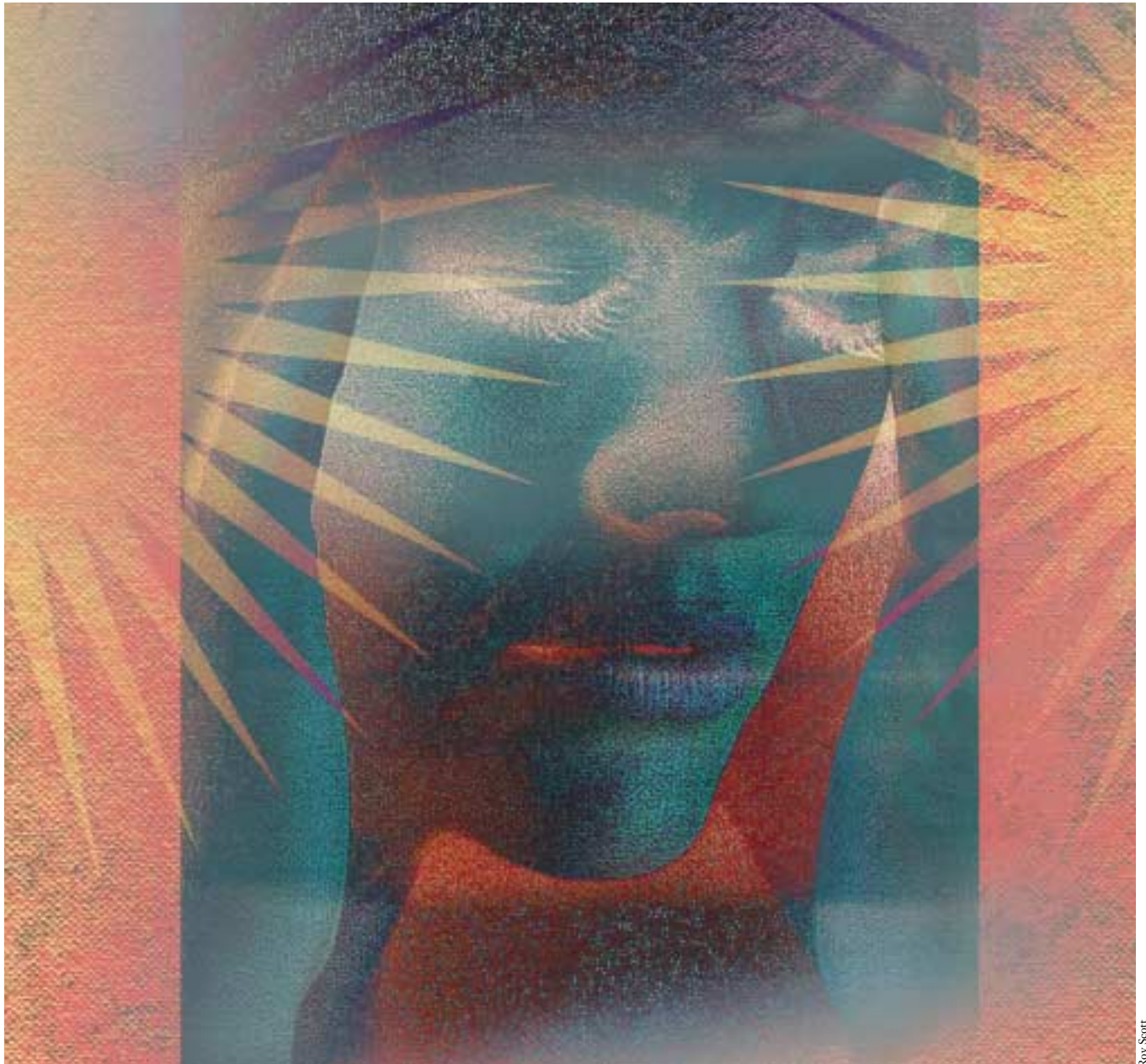

Migraine, Menopause, and Beyond

Miles J. Levy and Peter J. Goadsby



Roy Scott

Throughout their reproductive lives, women are three times more likely than men to experience migraine. Changing estrogen levels at menopause may be involved in exacerbations of migraine. Therefore, the clinician should be aware of the general principles of migraine management, as well as the need to individualize postmenopausal hormone therapy in their patients predisposed to migraine.

Introduction

Migraine is a common¹ and disabling² condition at all stages of life. As fluctuations in female hormones can have a profound effect on women who are susceptible to migraine,³ clinicians dealing with perimenopausal women's health problems often will see complaints of worsening headaches. This article will examine the relationship between migraine and menopause and offer selected potential solutions for women who experience headache during this time of their lives.

The link between fluctuations in female hormones and altered expression of migraine is well recognized. In children, the incidence of migraine is approximately equal in males and females. However, after menarche and throughout reproductive life, women are three times more likely to suffer from migraine than men.⁴ Cyclical changes in estrogen levels are thought to be key to triggering migraine, which explains why exacerbations in headache are particularly common perimenstrually during a woman's reproductive life.⁵

Women who experience hormonally sensitive migraine can be divided into two groups. The first group experiences worsening migraine during estrogen withdrawal—several days prior to menstruation or during the pill-free interval for those taking the combined oral contraceptive pill (COC). The second group of women experience worsening migraine when estrogen levels are increased, eg, after starting the COC or following the administration of postmenopausal hormone therapy.⁶ This hormonal sensitivity may explain why migraine worsens around the time of menopause, when estrogen levels decline, and why they often are sporadic and fluctuating as menopause approaches.

The prevalence of headache in postmenopausal women is reported to be 13.7%,⁷ although the figure is probably higher in perimenopausal women. The natural history of migraine after

menopause is unpredictable; two-thirds of women may notice an improvement, 10% experience worse headaches, and approximately 25% of women notice no change in symptoms.⁷ It is our experience that women who suffered from menstrually-associated migraine when they were younger are particularly susceptible to worsening migraine at menopause and perimenopause. This article will use the term “menstrually-associated migraine” to distinguish attacks that are more often than chance associated with menstruation. It is important to note that the prognosis for migraine frequency and severity is significantly worse if menopause is induced surgically rather than naturally, with two-thirds of these women experiencing an exacerbation in symptoms.⁷ Migraine itself is almost never an indication for hysterectomy.

In a similar manner to combined oral contraceptives during reproductive life, postmenopausal hormone therapy (estrogen and progesterone, [EPT]) can lead to either an exacerbation or improvement in migraine. There is no way of predicting which patients will respond positively or negatively to EPT, although patients who experienced worsening migraine with COCs may be more likely to experience a similar phenomenon with EPT. Often a trial-and-error approach to treatment is necessary; and there are means of addressing problems that are discovered.

Pathophysiology of Migraine

It is generally accepted that migraine is a brain and not a vascular disorder.⁸ The key feature of migraine is increased sensitivity to sensory input, pain, light, sound, smells, and head movement; therefore, it is a disorder of sensory modulation.

Imaging. Functional imaging studies have begun to elucidate the anatomical areas important in migraine. The dorsal mid-brain and pontine tegmentum are thought to be particularly important in migraine pathogenesis,⁹⁻¹¹ while the

hypothalamus may play a role in migraine expression.^{12,13}

Genetics. A strong familial component to migraine suggests that genetics play an important role in the disorder. The genetic abnormality in a rare sub-group of autosomal dominant migraine, familial hemiplegic migraine (FHM), has been identified in about 50% of cases to be a mutation in the $Ca_v2.1$ (α_1A) voltage sensitive subunit of the P/Q type calcium channel.¹⁴ It is likely that the genetic basis behind migraine is multi-factorial—and not the result of a single ‘migraine’ gene—given that there are at least three genes involved even for FHM.¹⁵

Triggers. Patients who are genetically predisposed to migraine are triggered when there is a change in the internal or external environment, eg, sleep alteration, stress, hunger, and changes in temperature. Alterations in female hormones are likely to provide a similar stimulus to migraine attacks. Estrogen and progesterone can profoundly alter the levels of dopamine, serotonin, and GABA activity in the brain, the latter neurotransmitters being important in the pathophysiology of migraine.¹⁶ Estrogen withdrawal also has been shown to alter the levels of prostaglandins,¹⁷ prolactin,¹⁸ opioids,¹⁹ and melatonin,²⁰ all of which are thought to play a role in central pain modulation. Therefore, it is not surprising that alterations in female hormones can trigger migraine in susceptible individuals.

Menopause. Another possible mechanism of menopause-related migraine involves the pathophysiology of menopause itself. Some believe that menopause is a result of an alteration in the circadian rhythmicity of the hypothalamus, specifically the suprachiasmatic nucleus,²¹ as opposed to ovarian failure. If the hypothalamus has a role in central pain modulation, it is understandable that an alteration in hypothalamic function also may cause a change in the expression of brain-determined headache syndromes, such as migraine.

Table 1.
Simplified diagnostic criteria for migraine³⁴

Episodic attacks of headache lasting 4-72 hours, without any other reasonable cause, and with the following features:

Two of:

- unilateral
- throbbing
- aggravated by movement
- moderate/severe intensity of pain

One of:

- nausea/vomiting
- photophobia and phonophobia

Management of Menopausal Migraine

Because of the close interaction between female hormones and migraine, it is useful to understand the general principles of migraine management, as well as the special aspects of female hormonal manipulation in perimenopausal migraineurs.

Diagnosis. Reliable diagnosis is the key starting point (Table 1). The majority of difficult headache problems that worsen in menopause will have a migrainous biology, but other primary and secondary headache syndromes are possible if the woman's symptoms do not suggest migraine. It is important to remember that while migraine is headache with other features, such as nausea, photophobia, or phonophobia, tension-type headache has no features at all. The presence of aura is not essential for the diagnosis of migraine; only approximately 15%-20% of migraineurs experience visual or sensory symptoms prior to a migraine attack.

Analgesia use. A common problem in patients with worsening migraine is that of analgesia overuse. Paracetamol, caffeine, and codeine-containing analgesics that are available over the counter are a particular problem. Using such compounds two or more days per week is probably sufficient to induce chronic daily headache (defined as 15 or more headache days/month),²² particularly in predisposed patients who seem to be largely migraineurs.^{23,24} Such patients report a significant worsening of their headache when the analgesics wear off

(ie, rebound headache). In this situation, the daily headache often is bilateral and less defined than in typical migraine, with exacerbations that have more common migrainous characteris-

Table 2.
Abortive treatments in migraine³⁵

Non-specific treatments

- Paracetamol 1 g
- Aspirin 900 mg
- Ibuprofen 400-800 mg
- Naproxen 500-1000 mg
- Tolfenamic acid 200 mg
- Diclofenac 50-75 mg

The efficacy of these agents is enhanced by concurrent use of prokinetics (eg, domperidone 10 mg or metoclopramide 10 mg)

Specific treatments

Triptans:

- Sumatriptan 50 mg or 100 mg orally; 20 mg nasal spray or 6 mg subcutaneous injection
- Rizatriptan 10 mg tablet or MLT wafer
- Zolmitriptan 2.5 mg tablet or rapidly dissolving wafer
- Naratriptan 2.5 mg
- Almotriptan 12.5 mg
- Eletriptan 40 mg or 80 mg
- Frovatriptan 2.5 mg

Ergot derivatives:

- Ergotamine 1-2 mg tablet or suppository
- Dihydroergotamine 0.5-1 mg nasal spray

tics (Table 1). As it is generally held that frequency intake by days used is the crucial determinant of medication overuse headache, the first step in the management of this problem is to encourage patients to limit their analgesia intake to no more than two days per week.²⁵ After stopping analgesics, such as paracetamol and codeine, it is useful to offer long-acting nonsteroidal anti-inflammatory agents, such as naproxen 500-1000 mg twice daily or ibuprofen 400-800 mg twice daily for short courses of 6-8 weeks to help patients through the initial period of medication withdrawal. However, it may be necessary to admit some patients to the hospital for medication withdrawal.

General Migraine Management, Acute and Preventive Treatment

Basic migraine management generally starts with advice on general lifestyle changes, followed by acute and preventative treatment. Lifestyle modifications generally involve attempts at regulating activities of daily life, including sleep patterns, meals, exercise, and avoidance of excess stress. Alcohol is a well-recognized trigger for migraine, with symptoms usually occurring on the day after ingestion; so abstinence from alcohol often is advised.

The acute treatments for migraine can be classified into non-migraine specific and migraine specific (Table 2). Triptans, serotonin 5-HT_{1B/1D} agonists,²⁶ are the mainstay of acute migraine-specific treatment for patients with disabling attacks.²⁷ The advent of these compounds has revolutionized the management of migraine in many respects. It is important to emphasize again that overuse of any acute migraine treatment (whether specific or non-specific) can lead to chronic daily headache or rebound headache, if these compounds are used on more than two days a week.

A patient with frequent headache requires a preventative treatment, not additional acute attack treatments.

Table 3.
Preventative treatments in migraine[§]

Drug	Dose	Selected side effects
Proven or very well accepted treatments		
<i>β-blockers</i>		
Propranolol	40mg – 120 mg BID	Reduced energy Tiredness
Metoprolol	100 – 200mg daily	Postural symptoms Contraindicated in asthma
<i>Tricyclics</i>		
Amitriptyline	25 mg – 75 mg nocte	Drowsiness note: some patients are very sensitive and may only need a total dose of 10 mg, although generally 1–1.5 mg/kg is required for a response
Dothiepin†		
Imipramine		
Pizotifen	0.5 – 3 mg daily	Drowsiness Weight gain
Sodium valproate	400 – 600 mg BID	Drowsiness Weight gain Tremor Hair loss Foetal abnormalities Haematological and liver abnormalities
Methysergide†	1 – 6 mg daily	Drowsiness Leg cramps Hair loss Retroperitoneal fibrosis (a one-month drug holiday is required every six months)
Widely used with poor evidence		
SSRIs	20 mg daily	
Promising		
Gabapentin	900 – 2400 mg daily	Tiredness Dizziness
Topiramate	25 – 200 mg daily	Confusion Parasthesiae Weight loss
Lisinopril	20 mg daily	Cough
Candesartan	16 mg daily	

†Not available in the United States

Preventative therapy means that medication should be taken on a daily basis, whether the patient experiences migraine or not. Preventative therapy, aimed at reducing the frequency and

severity of each attack, often is used in conjunction with acute treatments. Several classes of drugs can be used as migraine preventatives (Table 3). Physicians ideally should prescribe the med-

ication that they are comfortable with; and they should ensure that they understand dose titrations and potential side effects.

Hormone-specific Strategies

The contraindications for the use of EPT are identical for women with or without migraine. There is no evidence that women with migraine over age 45 are at increased risk of stroke, compared to women without migraine.²⁸ If a woman complains of classical menopausal symptoms as well as worsening migraine, it is reasonable to start EPT, although the patient should be advised that she may experience either an improvement or exacerbation in headache. When EPT significantly improves menopausal symptoms but causes worsening headache, it may be possible to resolve the situation through a step-wise alteration in the EPT preparation—instead of withdrawing EPT altogether (Table 4).

Estrogen. The estrogenic component of EPT should be considered first. Estrogen-induced migraine is thought to be dose-dependent, and a simple reduction in the estrogen dose may be sufficient to resolve the problem. However, if this fails, the estrogen type should be changed. There is evidence that converting from conjugated estrogen to pure estradiol and from synthetic estrogen to pure estrogen can significantly reduce headache.²⁹

Because estrogen withdrawal can exacerbate migraine, another strategy is to use continuous combined EPT (CCEPT) rather than cyclical EPT, even in the perimenopausal phase. This change from cyclical to continuous administration can improve headache by as much as approximately 60%.³⁰ Although not proven in a double-blind, placebo-controlled study, anecdotal evidence suggests that oral EPT preparations are more likely to induce headache than those administered parenterally. It is worth changing to a

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transdermal preparation of estrogen if a patient experiences worsening headache on an oral formulation.³¹ If these measures fail, Selective Estrogen Receptor Modulators (SERMs) can be used to good effect in estrogen-sensitive migraineurs. One study comparing raloxifene with EPT/placebo found that the incidence of headache was lower in the raloxifene group than with placebo.³²

Progestogen. In women who have a uterus, it is necessary to consider the progestogenic component of EPT, as headache may worsen with exogenous progestogen administration. If the suggested alterations in the estrogenic component of EPT have been unsuccessful in improving EPT-induced headache, it is useful to make similar alterations in the progestogenic component. Reducing the dose of progestogen may be very effective in reducing progestogen-induced CNS problems. For example, the rate of depression was significantly reduced in a group of women whose dose of medroxyprogesterone acetate was reduced from 7.5mg to 2.5mg.³³ An alternative strategy is to use locally applied preparations of progestogen to reduce its systemic effects. The advent of adhesive vaginal progestogen gels may provide a more targeted use of progestogen, enabling endometrial protection without the systemic adverse effects. In women who are perimenopausal, where contraception may still be an issue, the Mirena coil may be a useful way of providing contraception while reducing the risk of worsening migraine—without the vascular risks associated with estrogen-containing contraception.

Finally, there is a rare group of women who are extremely reliant on estrogen supplementation for a reasonable quality of life, but who also have headaches that become intolerably worse when progestogen is added to ET. For uterine-intact women with this problem, it may be necessary to switch

Table 4.
HRT-induced migraine: step-wise suggestions²⁹

Estrogen

- Reduce estrogen dose
- Change type of estrogen
- Change from cyclical to continuous regimen
- Change from oral to transdermal administration
- Switch to Selective Estrogen Receptor Modulator (SERM)

Progestogen

- Reduce progestogen dose
- Change type of progestogen
- Try local progestogen application
- Discontinue progestogen (with periodic endometrial biopsy or vaginal ultrasound)

to an estrogen-only regime in conjunction with annual endometrial biopsy or trans-vaginal ultrasound. However, this approach should be used only for those women with the severest of symptoms whose quality of life depends on the beneficial effects of estrogen.

Conclusion

There is a significant overlap between changes in female hormones and migraine. It is very helpful for physicians to have some understanding of the intricacies of female hormonal manipulation, whether they see migraine patients in a headache or menopause clinic. This is especially important as more challenging cases may lend themselves to a combined, multi-disciplinary approach to achieve the best outcome. ■

Dr. Goadsby is professor of clinical neurology at the Institute of Neurology, London. Dr. Levy is a Clinical Fellow at the Institute of Neurology, London.

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