Migraine is a highly prevalent disorder in women associated with significant disability. Yet it remains underdiagnosed and undertreated. Recent advances in our understanding of the pathophysiology of migraine, including the role of calcitonin gene-related peptide, has led to the development of new targeted migraine therapies. It is important for all healthcare professionals caring for women to be familiar with the diagnostic criteria for migraine and for them to follow a stepwise approach to management of acute and chronic migraine that comprises biobehavioral and pharmacologic management, particularly the more recently approved therapies.

Migraine is a chronic disorder affecting 18% of women worldwide—a prevalence rate three times that of men. Most reproductive-aged women who report episodic headache have migraine. Despite recent advances in our understanding of migraine pathophysiology and new FDA-approved targeted migraine therapies, migraine remains underdiagnosed and undertreated.

Pathophysiology and diagnostic criteria. Diagnosis of episodic migraine (EM) with or without aura requires a history of five unilateral, pulsating, moderate to severe headaches, lasting between 4 and 72 hours, that are worse with exercise and associated with nausea and vomiting or photophobia or phonophobia. Twenty-five percent of persons with EM have EM with aura—a constellation of visual, auditory, or somatosensory symptoms that precede the headache.

Migraine frequency in women is affected by reproductive hormone changes. The headaches often start at puberty, improve during pregnancy, worsen during perimenopause, and often improve after menopause. Seven percent of premenopausal women with migraine have pure menstrual migraine (PMM), and headaches occur only during the perimenstrual period. Seventy percent of women with EM have menstrual-related migraines (MRM), with headaches occurring not only around the menses but also at other times not associated with menses. It is the decline in estrogen levels that trigger migraine in women with PMM and MRM, and onset is typically 2 to 3 days before onset of menses through day 2 to day 3 of the menstrual cycle. Compared with EM, PMM and MRM are less associated with aura, tend to be more severe, last longer, and are more refractory to abortive treatment.
For decades, migraine was thought to be related to vascular dysregulation in the central nervous system (CNS). We now understand migraine through a model that involves the activation of the trigeminal vascular system (TGVS) in the CNS. In this model, a modulating trigger (such as lack of sleep or hormone changes) leads to activation of the TGVS and release of calcitonin gene-related peptide (CGRP), a 37 amino acid peptide with a half-life of 5 minutes that regulates pain transmission. Its levels increase during a migraine attack, and infusion of CGRP induces migraine.

**Acute treatment of migraine.** Early diagnosis of EM and treatment with specific therapies reduces disability by reducing headache duration, severity, and frequency, and it delays or prevents progression to chronic migraine. For all women with EM, first-line therapy includes identification of triggers and education regarding the importance of diet, sleep, and exercise. Pharmacologic therapy for acute migraine includes acetaminophen, nonsteroidal anti-inflammatory drugs, ergots, and triptans. Use of opioids or butalbital-containing products should be discouraged because of limited efficacy and potential for medication-overuse headaches, tolerance, and dependence. Triptans, the migraine specific 5-HT receptor agonists, presynaptically act on the TGVS, inhibit the release of CGRP, are highly effective, and are first-line pharmacologic therapy for most patients. There are now seven FDA-approved triptans, all with low-cost generic formulations, including oral, nasal, and subcutaneous preparations. All the short-acting triptans (sumatriptan, almotriptan, eletriptan, rizatriptan, and zolmitriptan) are similar in efficacy, speed of onset, and duration of action. Early treatment is key, and treatment failures are often because of late administration, incomplete absorption, or an inadequate dose. Contraindications to triptan use include coronary artery disease or hypertension, hemiplegic or basilar migraine, pregnancy, and use of ergots within 24 hours.

FDA has now approved three medications for acute migraine treatment that affect CGRP. Two of these medications, called gepants (remegepant and urogepant), are highly specific small-molecule CGRP antagonists that block the CGRP receptor. Both are effective and well tolerated and begin to reduce migraine pain within 60 minutes, although they appear to be less effective than triptans. The third, lasmitidant, is a 5-HT1F receptor agonist that selectively binds to 5-HT1F receptors on trigeminal neurons and inhibits pain pathways. All three medications can be used in patients with vascular disease. It is appropriate to consider one of the gepants or lasmitidant as abortive therapy for patients who fail or are intolerant of triptans.

**Menstrual migraine.** In women with PMM and EM with MRM, preventive interventions, including hormone manipulation, should be considered. In women with regular menstrual cycles and PMM or MRM, the long-acting triptan frovatriptan, with a half-life of 26 hours started 2 to 5 days and taken daily before menses, is often very effective. Continuous or extended-cycle oral contraceptives (COCs), with associated ovulatory suppression, may also be effective. It is important to note that migraine with aura is associated with an increased risk of stroke, and guidelines recommend against the use of COCs in smokers and in women with MRM with aura. Ultralow-dose COCs containing 10 µg or 20 µg ethinyl estradiol do not pose an increased risk of stroke in nonsmokers and are an excellent option for prevention. Progestin-
only contraceptive pills and intrauterine devices are unlikely to help with MRM because they do not reliably suppress ovulation.

Two FDA-cleared devices, a transcutaneous electrical neuromodulation device (Nerivio) and a transcutaneous electrical nerve stimulation device (Cefaly), are approved for acute treatment of migraine and are more effective than sham treatment in reducing pain.\textsuperscript{4} Supplements such as riboflavin, magnesium, feverfew (Tanacetum parthenium), butterbur (Petasites hybridus), and coenzyme Q10 have limited data but may be recommended.\textsuperscript{2} The benefit of acupuncture remains uncertain, but two recent studies suggest that it is superior to no treatment, sometimes superior to pharmacologic treatment, and occasionally superior to sham treatment.\textsuperscript{6}

**Migraine prevention.** Preventive options should be considered in persons with more than one migraine per week or more than four per month. Preventive therapies reduce the frequency, severity, and duration of migraine attacks; improve the efficacy of acute treatments; and decrease the progression to chronic migraine. All first-line FDA-approved preventive therapies, including beta blockers, antiepileptic medications (divalproex and topiramate), tricyclics, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, angiotensin-converting enzyme inhibitors, and botulinum toxin were originally approved for other indications. These options are not migraine-specific, lack efficacy, and are associated with poor adherence because of adverse events (AEs).

Four injectable CGRP monoclonal antibodies (mAbs) have been approved for migraine prevention. Eptinezumab, fremanezumab, and galcanezumab bind the CGRP ligand, and erenumab binds the CGRP receptor.\textsuperscript{7} All have been shown to be effective for migraine prevention, although there are no direct comparison data. The current American Headache Society guidelines recommend anti-CGRP mAbs to be used as third-line agents for prevention of migraine, after inadequate response or AEs with two other standard migraine-prevention treatments.

Recently, two small-molecule oral gepants (rimegepant and atogenpant) have been approved for migraine prevention. The efficacy and safety of these agents compared with the CGRP mAbs have not been studied.\textsuperscript{8}

**Pearls.** Early diagnosis of migraine is critical to reduce disability. Patients with migraine should be counseled to avoid migraine triggers, manage stress, practice good sleep hygiene, and exercise. Migraine-specific triptans should be first-line treatment unless contraindicated (pregnancy or cardiovascular disease), and patients should be educated on the benefit of early administration. If one triptan is not tolerated or is ineffective, a second triptan should be tried. If triptan use is limited by AEs or is contraindicated, rimegepant, urogepant, or lasmitidan may be considered. Migraine prevention should be considered for patients with PMM and EM with MRM and for those with two debilitating migraine headache days per month or more than four per month.\textsuperscript{7} Standard preventive therapies are first line, and one of the injectable CGRP-
targeted mAbs or oral gepants can be considered if standard options are ineffective or not tolerated.

References

Disclosures
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