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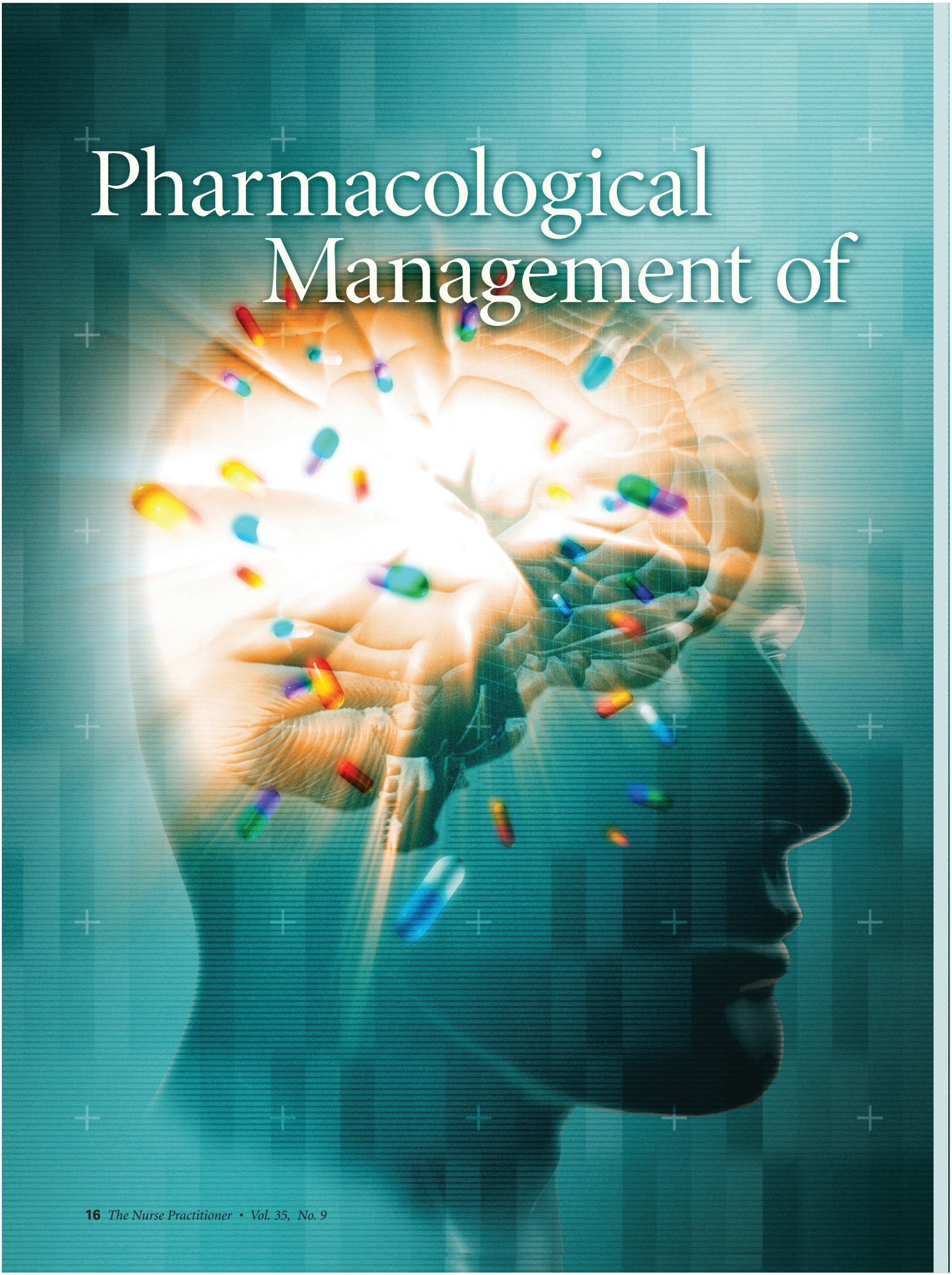

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Migraine Headaches

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Migraine is one of the top 20 causes of disability worldwide, occurring in 17.6% of women and 5.7% of men;[1] the incidence of migraine has remained stable over the past 15 years. Although migraine reduces quality of life and increases work absenteeism, many are not aware that there are effective prescription medications, and only about half of migraine sufferers are correctly diagnosed and/or receive appropriate treatment.[2] A 2007 study found that about 71% of patients who experienced migraines were treating them with over-the-counter (OTC) medications and only 8% were using preventive medication. Some 53% had never used any preventive medications.[3]

NPs must establish a relationship with patients who experience migraines as a bridge to ensure patient participation in treatment. Patient participation in treatment is crucial, as they need to record how often headaches occur and whether there were any trigger events that preceded the migraine, as well as discuss any quality-of-life issues. For NPs to manage migraine therapy successfully, they need to understand trigger patterns, headache, and patient goals, and be able to counsel patients appropriately about their condition to offer the most effective treatment.

Pathophysiology

Migraine is one of the most common primary headaches.[2] Primary headaches are typically diagnosed by patient history as there should be no abnormal findings with physical examination or laboratory testing. If an abnormality is found during testing, the clinician should consider the possibility that the headache is caused by an underlying condition or disease.

Previously, psychological factors, such as stress, or vascular factors had been thought to cause migraines; however, it is now known that migraine is primarily a genetically transmitted neurovascular condition.[4] Stimulation of the trigeminovascular system (blood vessels and neural connections) is believed to initiate the physiological cascade that causes a migraine. Neurotransmitters, such as substance P and calcitonin gene-related peptide, are secreted and cause inflammation and dilatation of affected cranial blood vessels.

The result is headache pain and the migraine may be accompanied by other symptoms. Individuals can experience photophobia; phonophobia; nausea, vomiting, and other gastrointestinal (GI) symptoms; fatigue; allodynia (painful response to a stimulus that does not normally elicit pain); or cognitive changes. Some individuals have "triggers" that can cause a migraine to occur. About 60% of women who experience migraines associate them with their menstrual cycles; other triggers may include stress, changes in weather or barometric pressure, and changes in schedule.[5]

Although 94% of patients who present with a chief complaint of headache are experiencing migraines, NPs must examine patient claims of new or different headaches or systemic symptoms for headaches thoroughly, as well as headaches that have positive lab or exam findings (see *International Headache Society criteria for migraine without aura; typical aura with migraine*).[6]

Approaches to pharmacologic management

Considerations in making medication choices for migraines include patient history, treatment goals, how to collaborate with the patient in medication management, and whether to use abortive (acute care) medication, preventive medication, or both. Unfortunately, due to cost and other reasons, patients often wait until pain and accompanying symptoms are severe before taking abortive medication.[7]

Ascertaining the frequency and severity of headaches is crucial. If most headaches are mild and relieved by OTC

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medication, prescription medication may not be indicated initially. Understanding headache patterns and individual triggers is also important. A daily diary of headache and symptoms kept for several months can help identify triggers (sample diaries are available online).[8] Because migraines can last up to 3 days, both the number of headache days per month and the number of headaches should be noted. Clinicians need to consider the presence of other health conditions such as hypertension and depression, since medications used for these conditions may help diminish or prevent migraines also. Other health conditions should be reviewed, as they may be comorbid with migraines, and some medications may be effective for both conditions. It's also important to assess current and previous treatments for migraines, including dosage and duration of the medications and the perceived effectiveness of the treatment. An adequate trial for effectiveness is more likely when medication is used for several different headache episodes.

Optimal treatment outcomes usually address rapid and complete relief of pain and preventing recurrence after initial treatment. Two hours to complete relief is considered the standard for medication effectiveness, as is nonrecurrence within 24 hours.[9] Many individuals wish to maintain their usual activities and responsibilities, and this includes relief of accompanying migraine symptoms and few or no adverse effects from medication.[7,10] Being knowledgeable about the patient's past experience with pain relief and headache recurrence facilitates the understanding of the effectiveness of current treatment and improves the ability to make appropriate decisions about new treatment.

Migraine is similar to other chronic conditions in that it requires patient participation regarding self-care. The condition is complex, and it requires the knowledge and insight of individuals to self-identify and then recognize triggers, identify premonitory and accompanying symptoms, and make appropriate decisions regarding when to take medications and what to take for a specific headache episode. Research indicates that patients with migraines value relationships with clinicians who are committed to a joint decision-making process and offer patients treatment choices by providing educational information.[11,12]

There are two general decisions for the clinician: how to treat acute migraine and whether to use preventive medication. It is most effective to tailor an individual's medication using a stratified approach. Instead of using stepwise care where all patients begin with mild pain relievers such as ibuprofen, the level of treatment is guided by severity of the patient's headache and accompanying symptoms.[13] For example, patients with mild-to-moderate pain that is usually relieved by OTC medication can remain on that regimen. Patients with severe headaches unrelieved by OTC medication, with headaches recurring the same day or severe accompanying symptoms like nausea and/or vomiting, need more effective medication as a first-line measure.

International Headache Society diagnostic criteria for migraine without aura[2]

A. At least five attacks fulfilling criteria B through D

B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)

C. Headache with 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 (for example, 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

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International Headache Society criteria for typical aura with migraine[2]

A. At least two attacks fulfilling criteria B-D:

B. Aura consisting of at least one of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (for example, flickering lights, spots, or lines) and/or negative features (that is, loss of vision)
2. fully reversible sensory symptoms including positive features (that is, pins and needles) and/or negative features (that is, 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 1 aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
3. each symptom lasts ≥5 minutes and ≤60 minutes

D. Headache fulfilling criteria for migraine without aura begins during the aura or follows aura within 60 minutes

E. Headache not attributed to another disorder

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Acute treatment of mild-to-moderate migraines

Medications to treat mild-to-moderate migraines include nonsteroidal anti-inflammatory drugs (NSAIDs) and isometheptene/dichloralphenazone/acetaminophen.

NSAIDs (naproxen, ibuprofen) are extremely effective for the treatment of mild-to-moderately severe migraines. They may be used alone or with acetaminophen and caffeine. They act by inhibiting cyclooxygenase and prostaglandin synthesis in inflammatory response pathways and are rapidly absorbed by the GI tract, distributed to all body tissues, and highly protein-bound. For many women with menstrual migraines, beginning NSAIDs before anticipated headaches can prevent or diminish migraines.[14] Although NSAIDs may be used during the first and second trimesters of pregnancy, they are contraindicated in the third trimester.[15] NSAIDs are also contraindicated with anticoagulant or antiplatelet drugs, or when there is active bleeding, bleeding risk, or gastric ulcer. They should be used cautiously in patients with impaired kidney and liver function; they also have an FDA black-box warning for increased risk of myocardial infarction and stroke.[16] Patients need to know the risks versus benefits of NSAIDs; they may be prescribed for a migraine patient at low risk for adverse effects from NSAIDS. If the patient is at risk for the most common adverse effects of NSAIDS, then the patient should not receive an NSAID. Isometheptene/dichloralphenazone/acetaminophen (Midrin) is a combination product used to treat tension-type and migraine headaches. Isometheptene works as a vasoconstrictor, dichloralphenazone as a sedative, and acetaminophen is an analgesic. It is taken orally at headache onset and can be repeated for a maximum of five capsules in 12 hours for migraine, or eight capsules in 24 hours for tension headache. Isometheptene is contraindicated in patients with glaucoma, severe kidney disease, hypertension, and organic heart disease, or those using monoamine oxidase inhibitors.

Medications for moderate-to-severe migraines

Medications to treat moderate-to-severe migraines include serotonin 5-$HT_{1B/1D}$ receptor agonists (triptans), ergotamines (also called ergots), antiemetics, and opioids and butalbital-containing medications. Although ergots were the first drugs prescribed to treat moderate-to-severe migraines, they are now seldom prescribed because triptans are safer than ergots and more effective than opioids.

Triptans were formulated in the early 1980s—the first, sumatriptan, was approved by the FDA in 1991—and have revolutionized migraine treatment (see *Triptans*). They are prescribed in nasal spray, oral tablet, oral quick-dissolve tablet, and injectable formulation. The efficacy of triptans varies when timing to headache onset or time to symptom relief is taken into account, as well as by half-life. Different triptans work for different patients as the form and dosage depend on the rapidity of headache onset and usual headache length; varying routes can be used for patients with nausea and/or vomiting. Because triptans have a small but significant risk of coronary vasoconstriction they are contraindicated in patients with ischemic disease, including coronary artery disease, peripheral vascular disease, and uncontrolled hypertension. Although most people tolerate triptans well, possible adverse effects include paresthesias, neck/jaw tightness, chest tightness, dizziness, and difficulty with concentration.[17] Other adverse effects are route-specific, including discomfort at injection site or bad taste and/or GI symptoms with nasal spray. Although there are no studies of triptan use in pregnancy, there are few reports of adverse effects during pregnancy. However, it cannot be assumed that triptans are safe, and they are currently rated category C.[15]

Triptans may be used in combination with NSAIDs, as they are more effective together than either alone.[18] One formulation, sumatriptan 85 mg with naproxen 500 mg (Treximet), contains both. However, triptans should not be taken within 24 hours of taking ergots, and different triptans should not be used together. The use of triptans, especially in conjunction with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), carries a small risk of serotonin syndrome.[19,20] Although most patients have no adverse events associated when taking a triptan and an SSRI or SSNRI, they should understand that symptoms of serotonin syndrome—including tremor, musculoskeletal stiffness,

Triptans

Generic name	Brand	Peak*	Half-life*
Almotriptan	Axert	1-3 hours	3-4 hours
Eletriptan	Relpax	1.5-2 hours	4 hours
Frovatriptan	Frova	2-4 hours	26 hours
Naratriptan	Amerge	2-3 hours	6 hours
Rizatriptan	Maxalt, Maxalt MLT	1-1.5 hours	2-3 hours
Sumatriptan	Imitrex	1.5 hours	2 hours
Zolmitriptan	Zomig, Zomig ZMT	2 hours	3 hours

*Peak and half-life hours are for oral formulations.

palpitations, flushing, hypertension, and agitation—require immediate evaluation. Overall, triptans have an excellent safety record.[21]

For years, primary treatment for acute migraine were ergots. These drugs include dihydroergotamine mesylate (D.H.E. 45, Migranal), and ergotamine tartrate. These are inexpensive and available as injectable formulation (D.H.E.), nasal spray (Migranal), and oral sublingual tablets (Ergomar). They are serotonin receptor agonists, as are triptans; however, triptans have a more selective pharmacology with a vasoconstrictive mechanism of action directed toward the headache, unlike the more general vasoconstrictive action of ergots. The vasoconstrictive effect of triptans resolves quickly, while that of ergots persists. Ergots have many potential adverse effects, including burning and rhinitis with nasal spray and dizziness, nausea, vomiting, and taste disturbance with oral and injectable routes. They are contraindicated in those with ischemic disease, should not be used in conjunction with triptans, and are not recommended for routine use. They are pregnancy category X, and women of childbearing age should be counseled on reliable methods of contraception. Nausea and vomiting sometimes accompany migraine, and patients can be prescribed an antiemetic medication as needed.

Triptans have largely replaced the ergotamines, especially ergotamine tartrate, as abortive medication because of their better safety profile and more targeted action. However, DHE is used intravenously for status migrainosis in acute care settings. DHE formulations may also be appropriate for patients who do not achieve optimal response with triptans.

Opioids and butalbitals are less effective for routine treatment of migraines than other medications such as triptans and NSAIDs. They should not be used routinely in primary care settings because of adverse effects and potential for addiction, unless the patient has contraindications to other medications.[22] The most common prescriptions are combinations of butalbital with acetaminophen and caffeine (Dolgic Plus, Esgic-Plus, or Fioricet) or butalbital with aspirin and caffeine (Fiorinal); sometimes codeine is added (Fioricet with codeine or Fiorinal with codeine). These are available only in oral form, are potentially sedating, and are contraindicated with alcohol use or liver disease. Patients should be educated about the possibility of sedation, dizziness, constipation, and addiction as well as implications of taking the drug with alcohol or other central nervous system (CNS)-sedating drugs. Opioids should be used for short periods only and in the lowest dose possible; an opioid agreement should be signed and kept in the patient's chart.

Prophylactic pharmacotherapy

Sometimes people with migraines experience an increase in the number of headaches. When the number of headache days reaches 15 or more per month, the headaches are considered to have reached a level sometimes known as "chronic daily headache" or "transformed migraine." This may be related to overuse of abortive medications, as any prescription or OTC abortive medication can cause "overuse headaches" even when the medication is being used for something else (for example, daily use of NSAIDs for chronic back pain can cause increase in number and/or severity of headaches). It is wise to consider preventive migraine medication if a patient is experiencing two or more headache days per week, particularly if the number of headache days is increasing. In other cases, if a significant number of headaches result in disability or if headaches interfere with activities and responsibilities, it may also be important to use daily preventive medications.

In most cases, drug doses needed for migraine prevention are lower than for other conditions. They should be started at low doses and titrated up over several weeks or months. It may take several months for improvement; asking the patient to record daily progress in a headache diary may be helpful.

There are a number of preventive medications that are up to 60% effective in decreasing the number and severity of headaches. These include tricyclic antidepressants (TCAs), SSRIs, beta-adrenergic blockers, calcium-channel blockers (CCB), antiepileptic drugs, and NSAIDs. Botulinum toxin type A (Botox) is also used preventively in specific cases.

Selection of medication is based on patient's age, comorbid conditions, and adverse effect profile of the preventive drug. For example, an SSRI or tricyclic antidepressant would be appropriate for a patient who also has an anxiety disorder or depression, and a CCB could be used for a patient who has hypertension. Although various drugs in these classes are used for headache prevention, some are more effective than others and only a few are FDA-approved.

Nonprescription preventive mineral and vitamin supplements such as magnesium and riboflavin (B_2) are effective in reducing number and frequency of headaches.[23] Riboflavin is well tolerated, although magnesium can cause diarrhea and gastric irritation. Magnesium and riboflavin can be purchased together in a single supplement that includes the herb, feverfew. Coenzyme Q-10 can be effective and has few adverse effects, as is petasites hybridus root (Butterbur).[24,25] The herb, butterbur contains pyrrolizidine alkaloids (PAs), which can cause hepatotoxicity; thus raw butterbur should be avoided. Only butterbur products labeled "PA-free," should be used. Butterbur is contraindicated in patients

with liver disease. Prescription preventive medications include antihypertensives, specifically beta-adrenergic blockers and CCBs; antidepressants; and antiepileptics.

Beta-adrenergic blockers propranolol (Inderal) and timolol (Blocadren), are FDA-approved for migraine prevention. It is thought that they block beta-receptors in the vascular smooth muscle and prevent arterial dilation; they also affect the central catecholaminergic system as well as the brain's serotonin receptors.[26] Starting doses should be low and titrated up; monitoring for signs and symptoms of bradycardia and/or hypotension is also crucial.[27]

Verapamil (Calan) is a CCB that is widely used and considered effective, however it is not FDA-approved for migraine prevention. It is thought to inhibit vasospasm of cerebral arteries, preventing cerebral hypoxia during migraines.[26] As with beta-adrenergic blockers, baseline pulse and BP should be obtained and then monitored. Patients should be counseled that CCB can cause constipation, lethargy, weight gain, and depression.[27]

Amitriptyline, and other tricyclic antidepressants to a lesser extent, are often used off-label with varying effectiveness in migraine prevention. It affects serotonin receptor function and also modulates neurotransmitters.[26] Much lower doses are needed for migraine treatment than for depression—as a result, adverse anticholinergic effects such as drowsiness, sedation, dry mouth, constipation, weight gain, and orthostatic hypotension are usually better tolerated, especially if the drug is taken at bedtime.[27]

Topiramate (Topamax), an antiepileptic that is FDA-approved for migraine prevention, has demonstrated fewer migraine days and fewer sick days, is well tolerated by patients, and is cost-effective.[28] Its mechanism of action for migraines is thought to be reduction of neuron firing in the trigeminocervical complex.[29] A common adverse effect is weight loss, which often encourages longer use than other preventive medications; however, topiramate should not be used by individuals with eating disorders. Other adverse effects include paresthesias, upper respiratory tract infection, fatigue, and nausea. The most common CNS adverse effects are somnolence; insomnia; difficulty with memory, language, and concentration; mood problems; and anxiety.[28] It should be used with caution in patients with hepatic, renal, or respiratory impairment. Divalproex (Depakote) is also an antiepileptic that is FDA-approved for migraine prevention. Because of risks of liver failure, increased bleeding time, hepatic toxicity, and thrombocytopenia, clinical monitoring for divalproex requires monitoring of drug serum levels, as well as regular liver function, platelet count, and bleeding time.[27] Divalproex should not be used in pregnancy (category D) as there is a risk of neural tube defects.

The botulinum toxin product, onabotulinumtoxinA is sometimes used off-label for preventive treatment of chronic daily headaches, for migraine patients who do not respond to other therapy, or for those who have contraindications to other drugs.[30,31] OnabotulinumtoxinA (Botox) blocks neuromuscular transmission by binding to sites on motor nerve terminals and inhibits the release of acetylcholine. Research results are mixed, although studies suggest that results in patients with chronic daily headaches are comparable with those obtained with topiramate.[32]

Conclusion

As with all medication management, one of the primary roles of the NP is that of educator. Achieving an effective migraine therapy that includes the alleviation of symptoms, pain, and disability, requires an accurate understanding of headache and trigger patterns as well as patient goals, subsequent appropriate patient education, and a successful NP–patient relationship. Choices regarding drug therapy are guided by headache characteristics, individual health history, and patient goals. Therapy should be tailored and evaluated on a regular basis. Involving the patient as a member of the treatment team can be time-consuming and complicated; however, the benefit to the patient is undeniable. The patient who is educated with regard to drug choices, use, and timing of drugs, as well as potential adverse effects, and who is a full partner in the decision-making process, will most likely experience an improved outcome. NP

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