Acute and Preventive Treatment of Migraine

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Relationship Disclosure: Dr Rizzoli served on a Zogenix, Inc., advisory board in 2010 and has performed legal record review in expert testimony.

Unlabeled Use of Products/Investigational Use Disclosure: Dr Rizzoli discusses the unlabeled use of medications in the acute and preventive treatment of migraine. Unlabeled use of these medications is disclosed in the article.

ABSTRACT

Purpose of Review: Migraine remains underdiagnosed and undertreated despite advances in the understanding of its pathophysiology and management. This article focuses on acute and preventive treatment of migraine, including the mechanisms of action, dosing and side effects of medications, and strategies for the most effective care.

Recent Findings: Best practice suggests that acute migraine treatment should be stratified based on the severity of the individual event, with a goal of returning the patient to full function within 2 hours of treatment. Migraine prevention strategies continue to be underused in the United States. More than 1 in 4 patients with migraines may be candidates for preventive therapy. To obtain the best results from preventive therapy, slow titration to an adequate dose for an adequate timeframe with good documentation of the results is recommended.

Summary: This article reviews several options for managing acute attacks, including information on expected efficacy, dosing, and adverse effects. Strategies for effective application of acute therapies are discussed. Prevention can be added to acute therapy depending on headache characteristics such as frequency, severity, disability, and the presence of comorbid conditions. The mechanisms of action of preventive medications and strategies for their most effective use are discussed.

Continuum Lifelong Learning Neurol 2012;18(4):764–782.

INTRODUCTION

Migraine has been described as ''a chronic disorder that afflicts many millions, pursues a highly variable and unpredictable clinical course, is quite likely polygenetic and susceptible to epigenetic factors, and is accompanied by a plethora of comorbid conditions that may influence its clinical expression and complicate its treatment.''[1] Despite the need for therapy for this common and disabling condition, migraine in the United States remains both underdiagnosed and undertreated.[2] The American Migraine Prevalence and Prevention Study found that just over half of questionnaire-diagnosed severe migraine patients in the United States had ever received a formal diagnosis.[2] Although most were using some form of abortive therapy, only 12% were on dedicated preventive management.

Diagnostic information and reassurance are rarely all that the patient is seeking from a clinical evaluation of headache; most are seeking some sort of relief. Goals of treatment include restoration of function, reduction of disability and suffering, and, possibly, reduction in disease progression and future expression. Treatment often centers on pharmacotherapy, but it can include a host of medication, nonmedication, alternative, and interventional therapies and their combinations.

The ideal acute medication treatment would quickly restore the patient to normal functioning in a safe, side

effect–free, cost-effective manner that would minimize the need for additional medication exposure or resource use.[3] The ideal preventive therapy would reduce the frequency, duration, and severity of individual events and possibly also reduce the progression of the disease.

ACUTE TREATMENT

History

Initially, acute migraine-specific management was based on the vascular model of headache advanced by Wolff and Graham after their seminal article in 1938 linking migraine to vasoconstriction; thus, vasoconstricting agents were sought that could terminate an attack. As a result, ergot preparations were developed and were efficacious, but with significant side effects. The 1990s saw a major advance with the introduction of sumatriptan. This serotonin receptor 5-hydroxytryptamine 1 (5-HT_1) agonist was as effective as ergots but generally produced fewer concerning side effects. Presently, there are seven triptans (**Table 2-1**).[4] Their exact mechanism of action in migraine is unclear. They may inhibit neurogenic inflammation peripherally, inhibit nociceptive inputs to the central pain system, or act as peripheral vasoconstrictors. Further migraine-specific agents are in development.

Many less specific or nonspecific agents continue to be used in acute migraine management. Over-the-counter agents, usually containing acetylsalicylic acid, acetaminophen, ibuprofen, or naproxen, are widely used, with mixed benefit. Butalbital-containing combination products remain in use in the United States, but they are controversial because they often induce medication-overuse headache and have been poorly studied in migraine. Opioids are generally reserved for rescue therapy. Neuroleptics are used in both acute management and rescue therapy.

Principles of Acute Treatment

Currently, stratified care is the preferred acute management strategy; the patient treats his or her migraine based on the challenges presented by the specific event, with management depending on the threatened disruption or disability caused by the event.[5]

One measure of success is the frequency with which the patient returns to a headache-free, fully functional state within 2 hours of treatment, with no recurrence within 24 hours.[6]

Hu and colleagues[7] showed that early treatment of an acute attack was associated with an overall reduced migraine burden for the event, and early treatment is commonly emphasized in clinical recommendations. Early management requires diligence and can be challenging. Migraine may not always begin as pain, but instead may present as a prodrome of mood change, fatigue, muscle tension, yawning, cognitive dysfunction, or other vague symptoms.[6] Further, acute stratified management implies that the patient will be able to assess and choose appropriately among available agents while experiencing a headache. Evidence suggests that many people with migraine are reluctant to treat early. In one study of the timing of acute treatment, almost 50% of respondents delayed initial treatment in order to see if the presentation really represented a migraine.[8] Other respondents wished to avoid medication unless they could determine that it was a severe attack. Lastly, patients with frequent attacks may limit acute medication for cost or supply reasons, or in fear of overuse.

The patient should treat early in the attack, use an adequate dose and formulation of a medication appropriate to the circumstances, maintain hydration, and seek rest if necessary. Ideally, acute therapy should be restricted to no more

KEY POINT

- Acute migraine treatment by the patient at home should be stratified based on the severity of the individual event with the goal of returning the patient to full function within 2 hours of treatment and with no recurrence.

TABLE 2-1 Triptan Characteristics[a]

Drug	Dose/Formulation	Half-Life (Hours)	Selected Drug Interactions	Maximum Daily Dose
Group 1 Fast-Onset Triptans				
Almotriptan	6.25-mg and 12.5-mg tablets	3 to 4	Contains a sulfa group Dose reduction to 6.25 mg suggested when used with potent CYP3A4 inhibitors[b]	25 mg
Eletriptan	20-mg and 40-mg tablets	4	Avoid with potent CYP3A4 inhibitors[b]	80 mg
Rizatriptan	5-mg and 10-mg tablets 5-mg and 10-mg orally dissolving wafers	2 to 3	Dose reduction to 5 mg recommended in patients using propranolol Do not use within 2 weeks of a monamine oxidase inhibitor (MAOI)	30 mg (15 mg if on propranolol)
Sumatriptan	25-mg, 50-mg, and 100-mg tablets 5 mg and 20 mg intranasal Single dose vial, 6 mg/0.5 mL for subcutaneous injection 4-mg and 6-mg cartridges for autoinjector 6-mg needle-free single-use devices for subcutaneous injection Fixed-dose combination tablet of 85-mg sumatriptan with 500-mg naproxen sodium	3	Do not use within 2 weeks of an MAOI	200 mg oral 40 mg intranasal 12 mg subcutaneous
Zolmitriptan	2.5-mg and 5-mg tablets 2.5-mg and 5-mg orally dissolving wafers 5 mg intranasal	3	Do not use within 2 weeks of an MAOI	Two tablets or 10-mg maximum oral daily dose Two sprays or 10 mg intranasal
Group 2 Slower-Onset Triptans				
Frovatriptan	2.5-mg tablet	26		7.5 mg
Naratriptan	1-mg and 2.5-mg tablets	6		5 mg

[a] Adapted from Loder E, N Engl J Med.[4] © 2010, with permission from the Massachusetts Medical Society. *www.nejm.org/doi/full/10.1056/NEJMct0910887.*
[b] Such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir.

than 2 to 3 days per week to avoid medication overuse. In many cases non-oral formulations of medications should be available for use when headache is accompanied by significant nausea and vomiting. In addition, specific pharmacologic advantages may be realized with non-oral routes of administration; eg,

injectable sumatriptan is more effective than oral sumatriptan because of its increased bioavailability.[9] Avoiding an emergency department (ED) visit for treatment is a worthy secondary goal for a number of reasons, including timeliness of treatment, patient inconvenience, and efficient resource use.[3]

Nonspecific Acute Treatment

Nonsteroidal anti-inflammatory drugs/acetaminophen. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as acetylsalicylic acid (ASA), ibuprofen, naproxen sodium, indomethacin, diclofenac, and ketoprofen, have long been used alone or in combination with other agents for the acute treatment of migraine. Good quality evidence supports this practice.[10,11]

NSAIDs are less costly and more readily available than triptans. A 2008 review suggests that the efficacy of oral NSAIDs, at times studied with concomitant administration of antiemetic agents, is comparable to that of the oral triptans.[12] Acetaminophen is considered less potent than the NSAIDs but is well tolerated. Multiple NSAIDs with multiple delivery systems are available (**Table 2-2**). Recently a powdered form of diclofenac potassium for oral solution was shown to be effective for the acute management of migraine.[13] Ketorolac is often used by IV injection in ED management of migraine. Dosing is limited because of concern for renal toxicity.

Neuroleptics/antiemetics. Dopamine D2 receptor antagonists, used alone or in combination, may treat headache pain in addition to migraine-associated nausea.[14,15] These agents may be used parenterally in the ED or at home in a tablet or suppository form (**Table 2-3**). Dopamine antagonists are probably underused in outpatient migraine management due to the lack of familiarity

TABLE 2-2 Nonsteroidal Anti-Inflammatory Drugs for Outpatient Acute Migraine Treatment[a]

Medication	Formulation	Dose for Migraine
Aspirin	Tablet, oral solution	650 mg to 1000 mg
Ibuprofen	Tablet, oral suspension, capsule	400 mg to 800 mg Maximum initial dose of 1 g
Ketorolac[b]	Tablet	10 mg
Naproxen	Tablet, oral suspension	125 mg to 550 mg
Naproxen controlled release	Tablet	750 mg Maximum initial dose of 825 mg
Meclofenamate	Capsule	50 mg, 100 mg
Diclofenac potassium	Tablet, powder pack	50 mg
Etodolac	Tablet, capsule	200 mg to 500 mg
Ketoprofen	Capsule	50 mg to 75 mg
Ketoprofen extended release	Capsule	200 mg

[a] Nonsteroidal anti-inflammatory drugs carry US Food and Drug Administration Black Box warnings for gastrointestinal risk, cardiovascular risk, and bleeding.
[b] Renal toxicity is a concern with the use of ketorolac.

with their migraine efficacy, concern over potential extrapyramidal side effects, and concern over potentially permanent tardive dyskinesia.

Prochlorperazine, available in 5-mg or 10-mg tablets and 25-mg suppositories, may be effective in acute migraine, alone or in combination with triptans or NSAIDs. Parenteral administration is generally more effective. Metoclopramide (10 mg) is effective early in the management of associated gastroparesis, allowing for better absorption of other oral agents, but also may be effective for headache pain. In combination with aspirin or acetaminophen, its efficacy may be equal to that of 100 mg of sumatriptan.[16] Chlorpromazine (25 mg to 100 mg) is probably effective in both oral and parenteral forms.[17] Side effects include sedation and orthostatic hypotension.

Promethazine, an antihistamine, is commonly used to treat nausea-associated migraine with little evidence of an effect on migraine pain.

Ondansetron, a serotonin 5-hydroxytryptamine 3 (5-HT_3) antagonist available in 4 mg and 8 mg orally dissolving tablets, is used primarily as an antiemetic but can be used in combination with other acute treatments in patients who are unable to tolerate the dopamine antagonists.

Corticosteroids. Anecdotal evidence suggests that a brief course of oral steroids (eg, methylprednisolone dose pack) is frequently used to treat a prolonged migraine. One small study suggests benefit from a single oral dose of dexamethasone to prevent headache recurrence after initial treatment with a triptan and NSAID.[18] In another study, short-course prednisone therapy is advocated as adjunctive therapy for withdrawal headache associated with medication overuse.[19] Other trial results have been conflicting; however, a 2008 meta-analysis did support single-dose parenteral dexamethasone (10 mg to 24 mg) along with usual abortive care in the acute management of migraine.[20]

Osteonecrosis is occasionally reported, even with use of short-term or "pulsed" steroids for migraine. One study suggests that migraine itself might be a risk factor for osteonecrosis.[21]

TABLE 2-3 Neuroleptics/Antiemetics for Acute Migraine Treatment

Medication	Formulation	Dose for Migraine
Dopamine antagonists		
Prochlorperazine[a]	Tablet	5 mg to 10 mg
	Suppository	25 mg
Metoclopramide	Tablet, oral suspension	10 mg
Chlorpromazine[b]	Tablet	10 mg to 25 mg
Antihistamine		
Promethazine	Tablet	25 mg to 50 mg
	Suppository	25 mg
Serotonin (5-hydroxytryptamine 3) antagonist		
Ondansetron	Tablet	4 mg
	Orally disintegrating tablet	8 mg

[a] Side effects may include akathisia.
[b] Side effects may include sedation and orthostatic hypotension.

Specific Acute Treatment

Triptans. Triptans are selective serotonin 5-hydroxytryptamine 1B and 1D (5-HT_{1B}, 5-HT_{1D}) receptor agonists[22] with three postulated mechanisms of action: intracranial vessel vasoconstriction (5-HT_{1B}), peripheral neuronal inhibition (5-HT_{1D}), and presynaptic dorsal horn stimulation (5-HT_{1D}) producing second-order brainstem neuronal inhibition. Triptans may also enhance descending inhibitory pain pathways and influence the function of 5-hydroxytryptamine 1F (5-HT_{1F}) receptors. Efficacy has been demonstrated in multiple randomized controlled trials (RCTs) measuring reduction in headache pain severity at 2 hours.[4] The 6-mg subcutaneous injection of sumatriptan appears to be the most efficacious dosage formulation; however, patients often prefer oral formulations. Current evidence outlined by Loder[4] suggests nearly equivalent efficacy among the oral formulations, except for frovatriptan which is less efficacious but has a longer duration of action. Clinically the choice of agent may often be determined by which is best covered by a patient's insurance. In addition, patients may prefer one triptan over another, so it can be useful to try several different triptans in order to find the best fit for a particular patient.

Oral triptans are somewhat less efficacious than the parenteral versions and, in some studies, are comparable in efficacy to nonsteroidal agents or other analgesics. Thus, clinicians should discuss with patients the potential benefits of a non-oral acute treatment for use when oral medications are ineffective.

The triptans (**Table 2-1**) are considered first-line treatment for the acute management of moderate to severe migraine pain. Best results are achieved by taking an adequate dose early in the attack. Oral triptans take effect within 20 to 60 minutes and, if needed, the dose may be repeated in 2 to 4 hours. Recurrence of headache after initial response does seem to occur frequently, in as many as one-third of patients.[4] Triptans may be combined with NSAIDs or antiemetic drugs.

The risk of serotonin toxicity with the use of triptans in combination with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors is the subject of a US Food and Drug Administration (FDA) alert.[23] There is little clinical or theoretical evidence of this interaction,[23,24] and these agents are commonly used in combination.[23] Triptans are contraindicated in patients with known fixed or spastic coronary artery disease or with risk factors for coronary artery disease. In the absence of clear guidelines, some degree of cardiac evaluation may be warranted in patients considered possibly at risk for coronary disease prior to initiation of therapy. Other ischemic complications, such as ischemic colitis, have been reported but appear to be rare. Minor symptoms of neck or chest tightness are frequently reported and may resolve with a switch to another oral triptan.

Ergots. Clinicians continue to prescribe ergot alkaloids in the acute treatment of migraine and some patients find them more efficacious than triptans. Ergots are less specific than triptans in their serotonin receptor agonism and interact with multiple other receptors, possibly explaining their more robust side-effect profile.[25] Side effects, primarily vasoconstrictive in nature, as well as nausea, may limit their use. Pretreatment with antiemetics may be needed. The contraindications for their use include any form of vascular disease, hypertension, renal or hepatic failure, and pregnancy. Caution is advised with ergot use in migraine associated with complex symptomatology.

KEY POINTS

- Parenteral sumatriptan should not be overlooked in acute treatment planning because it is very effective.
- Very little evidence links serotonin toxicity and the use of triptans with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.

Dihydroergotamine (DHE) is currently the only widely available ergot alkaloid. Available preparations include DHE nasal spray (1 puff [0.5 mg] in each nostril, repeat in 15 minutes, 2-mg maximum daily dose) and injection. The nasal spray is cumbersome to use but is efficacious and preferred by some patients.

Injected DHE (0.5 mg to 1 mg, repeat in 1 hour, 3-mg maximum daily dose) is usually administered in the ED or inpatient setting but can be self-administered at home and has well-documented efficacy.[26] Repetitive IV administration of DHE over several days (eg, Raskin and other protocols[27]) is considered safe and effective, and can be helpful for managing a refractory attack or status migraine. This type of administration typically requires an inpatient admission.

Rescue and Emergency Treatment

Rescue treatment. Acute migraine management is unsuccessful on occasion. A checklist of solutions to improve management (**Table 2-4**)[28] can be a useful reference.

In addition to adjustment of acute therapy, the addition of rescue therapy may be warranted. Effective rescue treatment may avoid more invasive, expensive, and time-consuming emergency treatment and may return the patient to a functional state more rapidly. Many patients ask what to do during an attack should all else fail. In some patients, anticipatory anxiety about being unable to control the next attack can be crippling and foster unrealistic requests for multiple and stronger medication options. This anxiety could promote medication overuse and dependence, and should be addressed openly. It is common for patients to ask for specific medication, which can signal possible abuse and dependency issues.

Combination analgesics for rescue. Analgesic formulations containing butalbital with caffeine and ASA or acetaminophen are widely used in the United States. Introduced before current FDA approval practices, no RCTs have established their efficacy, although there is a clinical impression of benefit. Overuse with resulting worsening of headache control is well described. Advise patients to limit use to less than 15 doses per month.

Opioids for rescue. Opioids comprise both synthetic and naturally occurring derivatives of opium and include codeine, hydrocodone, meperidine, oxycodone, butorphanol, and the more potent hydromorphone and morphine. Most are orally self-administered and

TABLE 2-4 Options If Acute Treatment Is Inadequate

- Change dose or formulation
- Treat early when headache is mild
- Add adjunctive therapy (eg, nonsteroidal anti-inflammatory drug)
- Consider dihydroergotamine (nasal spray, injection)
- Add preventive therapy
- Screen for caffeine or other acute medication overuse
- Screen for prescription medications that promote headache (eg, nitroglycerin)

Data from Tepper S, Tepper D.[28] *www.americanheadachesociety.org/assets/1/7/How_I_Do_It_Acute_Treatment.pdf.*

are often given in combination with acetaminophen or ASA, although rectal, intranasal, and transdermal formulations are available and can be used at home. Opioids are ideally limited to short-term intermittent use. All opioids can produce tolerance, dependence, and addiction.

Overuse of opioids may worsen the overall primary headache disorder and predispose patients to the development of a chronic or transformed migraine pattern.[29] Currently, the recommendation is to limit the use of these agents to a maximum of 2 days per week.[30] Intranasal butorphanol is associated with high levels of dependence and addiction.

Emergency department management. Should ED management be required, approaches to treatment are inconsistent. Many factors, including prior training and local practice patterns, influence which medications are chosen as initial treatment.

Migraine-specific treatments are available in the ED (**Table 2-5**),[31] but they appear to be used infrequently. A review published in 2008 showed that opioids continue to be the most frequent treatment given for all acute headaches in the ED and that migraine-specific agents are used in only a small number of patients.[32]

PREVENTIVE TREATMENT

History

The notion of preventing headaches began with the introduction of methysergide in the 1960s. Except for methysergide, which is mentioned for historical reasons, agents unavailable in the United States are not included in this article. The prophylactic use of methysergide constitutes one of the most important breakthroughs in headache management.[33] Preventive treatment not only changed the management of migraine it also caused a paradigm shift toward viewing migraine as a biological rather than a psychiatric entity. To date, no medication other than methysergide has been introduced exclusively for migraine prevention.

Given the large number of classes of preventive agents (**Table 2-6**), no single unified mechanistic theory of action has been advanced. Possible therapeutic mechanisms include stabilization of reactive nervous system centers, enhancement of antinociceptive pathways, inhibition of central and peripheral

TABLE 2-5 Migraine-Specific Emergency Department Treatment Options

- **Sumatriptan 4 mg to 6 mg subcutaneously**
- **Antiemetics plus dihydroergotamine (0.5 mg to 1 mg IV, repeat in 1 hour)**
- **Neuroleptics**
  Chlorpromazine (0.1 mg/kg) 12.5 mg to 37.5 mg IV/IM
  Prochlorperazine 5 mg to 10 mg IM, 25 mg per rectum
  Haloperidol 5 mg IV in 500 mg normal saline over 20 to 30 minutes
- **Ketorolac 30 mg to 60 mg IM; may treat cutaneous allodynia if not complicated by opioid use**
- **Magnesium 1 g to 2 g IV; limited evidence; may treat photophobia/phonophobia**
- **Valproate 300 mg to 500 mg IV; open-label trials**
- **Corticosteroids (eg, dexamethasone 10 mg to 24 mg IV)**
- **Metoclopramide 20 mg IV; may repeat**

Data from Acute Migraine Treatment.[31] *www.americanheadachesociety.org/assets/1/7/INAP_for_Web_-_Acute_Treatment_of_Migraine.pdf.*

KEY POINT

- More than one in four people with migraine may be candidates for preventive therapy.

TABLE 2-6 Classes of Migraine Preventives

- Antiepileptic drugs
- Antidepressants
- Beta-adrenergic blockers
- Calcium channel antagonists
- Nonsteroidal anti-inflammatory drugs
- Serotonin (5-hydroxytryptamine) antagonists
- Neurotoxins (eg, onabotulinumtoxinA)
- Other/miscellaneous

sensitization, and inhibition of cortical spreading depression. Inhibition of cortical excitation and restoration of central nociceptive dysmodulation as potential mechanisms of action were investigated in two 2007 reviews.[34,35] Another review suggests that delaying the development of tolerance to the analgesic effects of opioids might, in part, underlie the therapeutic mechanism of some preventive agents.[36]

Preventive therapy is used to reduce headache frequency, severity, and duration. In addition, some evidence suggests that preventive treatment results in improved responsiveness to acute therapy and reduced resource use.[37] It has also been suggested that prevention might slow migraine progression[38]; however, more recent limited information posits that preventive therapy in migraine may predispose patients to the development of tolerance and even possible disease progression.[39]

Migraine prevention medication appears to be underused according to the authors of the 2007 American Migraine Prevalence and Prevention (AMPP) Study.[2] By their criteria (**Table 2-7**)[2,3] almost 40% of people with migraines should be offered or at least considered for treatment with a preventive agent. Yet at the time of their study only 12% of patients with migraines were taking a specific migraine preventive agent.

The goals of prevention are to reduce attack frequency and severity, reduce associated disability, return the patient to normal function, and improve response to treatment of future acute attacks. Guideline principles (**Table 2-8**)[3] suggest starting with low doses of medication and increasing slowly. My routine is to increase doses about every 2 weeks, allowing time for assessment between increases. A slow titration can help patients adjust to the effects of a new medication. An

TABLE 2-7 When to Use Migraine Prevention[a,b]

- Three or more headache episodes per month
- Significant interference of headache with daily activity
- Acute medications ineffective, contraindicated, or overused
- Adverse effects from acute medications
- Patient preference for prevention
- Special circumstances: elderly, pregnant, and pediatric populations

[a] Data from Lipton RB, et al, Neurology.[2] *www.neurology.org/content/68/5/343.long.*
[b] Data from Silberstein SD, Neurology.[3] *www.neurology.org/content/55/6/754.long.*

TABLE 2-8 General Principles of Preventive Treatment[a]

- ▶ Start with a low dose and increase slowly
- ▶ Use an adequate trial of 2 to 3 months
- ▶ Avoid medication interactions/contraindications
- ▶ Monitor with calendar or diary
- ▶ Monitor for medication overuse
- ▶ Consider comorbid conditions
- ▶ Consider preventive medication combinations in refractory patients
- ▶ Taper when headaches are controlled

[a] Data from Silberstein SD, Neurology.[3] *www.neurology.org/content/55/6/754.long.*

KEY POINT

■ Slow titration to an adequate dose for an adequate timeframe with good documentation of the results is recommended to obtain the best results from migraine preventive therapy.

adequate trial duration of 2 to 3 months is often necessary to determine efficacy. Patients should monitor headache response with a calendar or diary. Reviewing all medications and doses with patients at follow-up visits can help prevent medication interactions. Tapering the preventive treatment after a 6-month period of headache control is often feasible.[40]

Comorbid conditions, such as stroke and other vascular conditions, epilepsy, and affective disorders, can influence preventive treatment decisions in migraine.[41] When practical, an agent can be selected that treats two comorbid conditions, such as migraine and hypertension (**Case 2-1**). Alternatively, avoiding agents that could worsen a comorbid condition is also important, as is monitoring for medication interactions. Pregnancy issues can add another layer of complexity to appropriate medication selection.

Although combining medications in the treatment of refractory cases can be useful (**Case 2-1** and **Case 2-2**), it has not been studied rigorously. Peterlin and colleagues[42] review various possible combination therapies and their rationales in refractory migraine.

Migraine Prevention Guidelines

An AAN practice parameter[3] on migraine prevention was published in 2000. An updated guideline, published jointly by

Case 2-1

A 59-year-old man presented with what he said was a debilitating headache. He reported lifelong rare (2 to 3 events per year) episodes of migraine with visual aura, but his headache frequency had progressed slowly to one event per week at the time of the visit. The patient had been previously diagnosed with and treated for hypertension, diabetes, and obstructive pulmonary disease. Treatment for migraine included 10 to 12 doses of 100 mg sumatriptan per month, and oxycodone. Preventive treatment with 25 mg of atenolol was ineffective, and he was unable to tolerate 30 mg of nortriptyline although it was beneficial. Cardiac catheterization, done because of an abnormal stress test, showed minimal disease. On 25 mg to 50 mg of topiramate and 50 mg to 75 mg of atenolol his migraines were better controlled and he was able to reduce the use of the triptan and opioid by 50%.

Comment. Headache may progress instead of recede with age, and treatment can be a challenge in the setting of multiple medical comorbidities.

Case 2-2

A 45-year-old female executive with childhood onset of episodic migraine without aura reported increased headache frequency after a pregnancy. She also developed new migraine with aura that was responsive to verapamil, although she was unable to tolerate the medication even at a low dose. Preventive therapy with 50 mg of topiramate caused sedation and cognitive changes but was helpful. A 150-mg dose of venlafaxine was also helpful but caused weight gain. A stimulant was added to counteract the sedation, and this combination provided good headache control of one episode every 6 months until she was promoted to a new, more stressful job. At the same time, the stimulant was discontinued because of a minor blood-pressure elevation, and her sleep was disrupted because of health issues in the family. Her prior topiramate adverse effects returned, and she was unable to function or remain awake at work. She was unable to taper the preventive medications because of an increase in both headache patterns. Reintroduction of the stimulant resulted in panic and increased headache.

Comment. This case exemplifies a common constellation of features in patients with migraine. When first seen, the patient had left work on disability because of these issues. She feared reducing the current preventive medications although they produced significant side effects; however, with a very slow taper over 3 to 4 months, she was able to remove them. Because of the potential for side effects, amitriptyline had originally been dismissed, but she was able to tolerate it at low doses of 2.5 mg to 5 mg and obtained good control of her migraines.

the American Headache Society (AHS) and the AAN and containing information from studies published since 1999, was published in April of 2012.[43] New information along with a change in the analytic methodology has resulted in some changes in medication recommendations. Whereas the 2000 guideline was based on a combination of clinical trial evidence, clinical judgment, and assessment of side effects, the updated guideline included only published clinical trial evidence. Studies published between June 1999 and May 2009 were reviewed, rated, and analyzed to determine which preventive agents could be considered of established efficacy (Level A), probable efficacy (Level B), or possible efficacy (Level C). Other medications were given the designation Level U, meaning the data were considered inadequate or conflicting. Summaries of these guidelines are included in **Appendix A** and **Appendix B**. Level A medications for long-term prevention of episodic migraine included divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol. Compared with the 2000 guideline, metoprolol and topiramate have been moved to the top category and amitriptyline, which has a strong clinical impression of efficacy but few recent studies, has been moved to the probably effective (Level B) category. The probable efficacy (Level B) category has seen considerable revision since 2000. Gabapentin, verapamil, and fluoxetine, previously considered probably effective, have been moved to Level U. Conversely, venlafaxine has been moved up to the Level B category. Other changes have been made as well. Relevant notations are made below in the discussion of specific agents.

Comparison of this updated guideline to recent European and Canadian

guidelines[44] shows a fair degree of consistency, especially for the highest rated drugs. Among prescription agents for migraine prevention, there is divergence of opinion regarding some medications, notably gabapentin and venlafaxine as mentioned, that may relate to the differing methodologies used in the classifications. For example, a system that incorporates medication adverse effects in its analysis may favor gabapentin because of its relatively low rate of serious side effects. Thus, it is important to be aware of the methodology used to construct a guideline and to view guidelines as one of many tools useful in the construction of a patient's headache management program.

Specific Migraine Preventive Agents

Specific examples from different medication categories are discussed below and in **Table 2-9**.

Antiepileptic drugs. Some antiepileptic drugs (AEDs) are useful for migraine prophylaxis. Valproate and topiramate are FDA approved for prophylaxis and carry strong evidence of efficacy. When used as preventive therapy for migraine, valproate/divalproex sodium is used in doses comparable to or lower than those used when treating epilepsy. Valproate is contraindicated in pregnancy because of associated neural tube defects and should be avoided in women likely to become pregnant. Side effects, which include nausea, weight gain, tremor, and alopecia, are common. Valproate has also been associated with encephalopathy, elevation of liver enzymes, hepatitis, pancreatitis, and agranulocytosis. Appropriate laboratory testing is suggested in order to detect potential liver and blood abnormalities early in treatment. Despite these limitations, valproate is an effective preventive agent, and special circumstances, eg, a migraine patient with coexisting bipolar disorder, might favor its use.[42]

Topiramate was originally introduced as an anticonvulsant but is FDA approved for the prophylaxis of migraine. Doses between 100 mg and 200 mg are commonly used. Titrating slowly from an initial daily dose of 15 mg or 25 mg may improve tolerability, and advising patients to expect initial paresthesia of the extremities or change in taste may prevent unwarranted discontinuation. These side effects often improve or disappear with continued treatment.

Cognitive side effects, such as slowing of cognitive processing and delayed word retrieval, may complicate use. Introducing the medication at a low dose and increasing slowly may avoid or blunt this effect. In some patients, maintaining the current dose can allow tolerance to the cognitive problems to develop. Topiramate has recently been reclassified as category D in pregnancy because of concern of oral cleft development.

An idiosyncratic syndrome of myopia with secondary angle-closure glaucoma is an extremely rare but potentially severe complication that typically occurs early in therapy and can develop in patients of any age. Management involves immediate discontinuation of the medication and emergency ophthalmic care.

Topiramate has been studied in chronic migraine prevention. One study shows a reduction in migraine or migrainous headache days with treatment but no clear benefit for preventing transformation to a chronic pattern.[45] Another study, however, suggests possible benefit in reduction of risk of conversion from episodic to chronic migraine.[36] Gabapentin and valproate have also been studied in chronic migraine prevention.[46] Research on the various forms of chronic headache continues and may eventually provide clarification

TABLE 2-9 Specific Migraine Preventive Drugs

Medication	Usual Daily Dose	Evidence Group (2000)[a]	Evidence Level (2012)[b]
Beta-adrenergic Blockers			
Atenolol	50 mg to 100 mg	2	B
Metoprolol succinate or tartrate	50 mg to 150 mg	2	A
Nadolol	20 mg to 160 mg	2	B
Propranolol[c]	80 mg to 240 mg	1	A
Timolol maleate[c]	10 mg to 20 mg	1	A
Calcium Channel Antagonists			
Amlodipine besylate	10 mg to 20 mg	Not included in evidence review	Not included in evidence review
Diltiazem	80 mg to 240 mg	3a	Not included in evidence review
Nimodipine	60 mg to 120 mg	2	U
Verapamil	180 mg to 480 mg	2	U
Antiepileptic Drugs			
Divalproex sodium[c]	250 mg to 1500 mg	1	A
Gabapentin	300 mg to 1800 mg	2	U
Pregabalin	50 mg to 200 mg	Not available in 2000	Not included in evidence review
Topiramate[c]	25 mg to 150 mg	3 (Randomized clinical trials and US Food and Drug Administration indication after 2000)	A
Zonisamide	100 mg to 200 mg	Not included in evidence review	Not included in evidence review
Antidepressants			
Amitriptyline	25 mg to 150 mg	1	B
Citalopram	20 mg to 60 mg	Not included in evidence review	Not included in evidence review
Desipramine	25 mg to 100 mg	Not included in evidence review	Not included in evidence review
Doxepin	25 mg to 150 mg	3a	Not included in evidence review
Duloxetine	30 mg to 90 mg	Not available in the United States in 2000	Not included in evidence review
Fluoxetine	20 mg to 60 mg	2	U
Nortriptyline	25 mg to 100 mg	3a	Not included in evidence review
Phenelzine	15 mg to 45 mg	3b	Not included in evidence review
Protriptyline	5 mg to 10 mg	3a	Not included in evidence review
Sertraline	50 mg to 150 mg	3a	Not included in evidence review
Venlafaxine	37.5 mg to 150 mg	3a	B
Nonsteroidal Anti-inflammatory Drugs			
Celecoxib	200 mg to 400 mg	Not included in evidence review	Not included in evidence review

Continued on next page

TABLE 2-9 *Continued*

Medication	Usual Daily Dose	Evidence Group (2000)[a]	Evidence Level (2012)[b]
Flurbiprofen	100 mg to 200 mg	2	Not included in evidence review
Indomethacin	75 mg to 150 mg	5 (But used for indomethacin-responsive headache syndromes)	Not included in evidence review
Naproxen sodium	500 mg to 1000 mg	2	Not included in evidence review
Serotonin Agonists			
Methysergide maleate	50 mg to 150 mg	Not available in the United States	Not included in evidence review
Methylergonovine (methergine)	0.2 mg		Not included in evidence review
Antiserotonin/Antihistamine			
Cyproheptadine	2 mg to 8 mg	3a	C
Neurotoxins			
OnabotulinumtoxinA[d]	155 units IM		Not included in evidence review
Other/Miscellaneous			
α-Agonists			
Clonidine	0.075 mg to 0.15 mg daily	5	C
Guanfacine	1 mg daily	2	C
Tizanidine	Up to 24 mg/d in divided doses, 3 times a day		Not included in evidence review
Angiotensin-converting enzyme inhibitors			
Lisinopril	10 mg daily		C
Candesartan	16 mg daily		C

[a] Evidence group data outlined in AAN practice parameter[3]:
Group 1: Proven high efficacy and mild to moderate adverse events
Group 2: Lower efficacy and mild to moderate adverse events
Group 3: Evidence based on opinion, not randomized controlled trials
3a: Low to moderate adverse events
3b: Frequent or severe adverse events
Group 4: Proven efficacy but frequent or severe adverse events
Group 5: Limited or no efficacy
[b] Evidence level data outlined in AAN evidence-based guideline[43]:
Level A: Medications with established efficacy
Level B: Medications that are probably effective
Level C: Medications that are possibly effective
Level U: Inadequate or conflicting data to support or refute medication use
[c] US Food and Drug Administration (FDA) indication.
[d] First agent FDA approved for chronic migraine.

of this notion of disease modification or prevention of progression.

Other AEDs (**Table 2-9**) used with limited or mixed evidence in migraine prophylaxis include carbamazepine, gabapentin, pregabalin, levetiracetam, and zonisamide. Of these, gabapentin is probably the most commonly used. Study doses showing efficacy ranged from 1800 mg/d to 2400 mg/d, although doses of around 900 mg daily may be more clinically common. The evidence for gabapentin in migraine prophylaxis has been called into serious question. A 2008 report[47] showed that outcomes were unreported or changed

KEY POINTS

- Beta-blockers are no longer the most recommended migraine prevention medications for a variety of reasons and should be considered with some caution in migraine prophylaxis.
- Amitriptyline continues to be widely used in migraine prophylaxis with a good level of supportive evidence for migraine prevention.

in several studies. Internal company reports for unpublished studies were also located in the course of US government legal action against the company for off-label promotion. This information challenges published positive trial results. Gabapentin is generally well tolerated with somnolence being the most commonly reported adverse effect.[48]

Beta-adrenergic blockers. Two beta-blockers, propranolol and timolol, are FDA approved for the prevention of migraine and are recommended as first-line migraine therapy in many guidelines.

As a group, beta-blockers have generally been viewed as safe and inexpensive, and many studies over the years have documented their efficacy. Some studies have recommended them preferentially for use in patients with migraine and hypertension.

A review by Evans and colleagues[49] highlights some problems with the use of beta-blockers to prevent migraine. Beta-blockers may no longer be considered first-line therapy for hypertension because of lack of evidence that they prevent the complications of hypertension. Case reports of prolonged aura and possible ischemic stroke in patients with migraine with aura on beta-blockers have caused concern for their use as a first-choice treatment of migraine with aura. This review reported that other studies have linked the use of beta-blockers with weight gain and increased risk of type 2 diabetes mellitus. Consideration should be given to avoiding beta-blockers in patients with elevated body mass index, diabetes or a family history of diabetes, and migraine with aura.

Antidepressants. Of the multiple antidepressants (**Table 2-9**) used in migraine prophylaxis, the best evidence is for the tricyclic antidepressant amitriptyline. Several small but controlled studies also show amitriptyline efficacy in several chronic forms of headache. Doses in most studies are low, 10 mg to 25 mg, and this continues to be the most common dosage range for initial preventive use. Also, evidence outlined by the AAN practice parameter (**Table 2-9**) lists amitriptyline in evidence group 1.[3] The more recent AHS/AAN guideline downgraded amitriptyline to the ''probably effective'' category because of a change in methodology.

Amitriptyline blocks neuronal uptake of both serotonin and norepinephrine with multiple resulting putative antinociceptive effects, as reviewed by Buchanan and colleagues.[50]

Anecdotal evidence (**Case 2-2**) suggests that amitriptyline can be helpful in migraine patients with associated sleep disruption, often described as a fragmented, discontinuous sleep pattern, because it can stabilize sleep. On the other hand, prolonged morning sedation is the major adverse effect, so patients should take this medication early in the evening, not at the hour of sleep, in order to avoid sedation and be more likely to wake refreshed. Some patients may tolerate and respond to remarkably small doses, eg, 2.5 mg to 5 mg daily, when more standard doses are not tolerated. This obviates the need to discontinue what may have otherwise been a helpful agent.

Calcium channel antagonists. Multiple trials have shown some efficacy of this heterogeneous group in migraine prevention, although this conclusion has now been questioned, with a resulting downgrade in the level of efficacy in the updated AHS/AAN guideline, as noted above. The exact mechanism of action of calcium channel antagonists is uncertain and may be complex. It has been proposed that they work either by blocking serotonin release or by interfering with neurovascular inflammation or cortical spreading depression. Other

mechanisms may relate to their ability to potentiate opioid and acetaminophen-induced analgesia or their inhibition of calcitonin gene-related peptide release.[50]

The L-type calcium channel blocker verapamil has perhaps been the most commonly used of the group. Dosing is typically between 120 mg and 480 mg daily after titration. Limiting side effects may include constipation, dizziness, hypotension, and, at higher doses, cardiac conduction blocks. Higher doses may be effective in the management of cluster headache, and ECGs may be necessary to assess the medication's effect on cardiac conduction. A slow upward titration is suggested, and the beneficial effect of verapamil may be delayed. Constipation can be managed in a number of ways, but the addition of oral magnesium may offset constipation and provide some additional migraine prevention. In addition to managing cluster headaches, verapamil may be specifically considered in patients with hypertension, those unable to take beta-adrenergic blockers, and possibly those with prolonged aura or vestibular migraine.

Nonsteroidal anti-inflammatory drugs. Multiple trials and meta-analyses show the efficacy of NSAIDs (**Table 2-2**) in migraine prevention. Naproxen is probably backed by the most evidence, with overall efficacy similar to the beta-adrenergic blockers.[3] Adverse effects, such as gastrointestinal upset, peptic ulcer disease, and renal toxicity, are experienced by 13% to 26% of patients. There is concern about an increased risk of cardiovascular disease with prolonged treatment. Because of this risk and adverse effects, NSAIDs are more suitable for intermittent use, such as monthly use for menstrual-related migraine.[50]

Serotonin antagonists. These antagonists generally block serotonin and norepinephrine reuptake. The methysergide-like drugs, methylergonovine and cyproheptadine, are used infrequently in migraine. Cyproheptadine shows RCT evidence of efficacy and is used more commonly in childhood migraine.[50] Side effects include weight gain and drowsiness. Methylergonovine is used to prevent migraine based on anecdotal evidence.

Neurotoxins. OnabotulinumtoxinA is the sole agent to receive FDA approval for chronic migraine, defined as 15 or more headache days per month, with 4 or more headache hours per day. Pooled results from two RCTs[51] show the efficacy of onabotulinumtoxinA compared with placebo for the primary end point of reduced headache episodes and also for multiple secondary end points.[52] A recent review[53] suggests a variety of mechanisms may underlie its clinical benefit (**Case 2-3**). Cost and insurance coverage issues remain potential barriers to its use.

Patients should be advised that the clinical effect of onabotulinumtoxinA may be delayed or transient after the first set of injections and that a second set of injections is warranted before concluding that the therapy is unhelpful. Repeat injection sets, initially every 3 months, are usually required to maintain benefit.

Other Preventive Agents

α-Adrenergic agonists. The centrally acting α_2-adrenergic agonists clonidine (used in hypertension and other conditions), guanfacine (used in attention deficit disorder), and tizanidine (used as a muscle relaxant) have been used in migraine prophylaxis but with variable evidence and generally small clinical benefit. These received a Level C rating in the updated AHS/AAN guideline.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. Evidence supports

KEY POINT

- OnabotulinumtoxinA, the first agent to receive US Food and Drug Administration approval for chronic migraine, is likely safe and well tolerated.

Case 2-3

A 27-year-old woman with childhood-onset episodic migraine developed progression of her headache syndrome in her late teens. Amitriptyline provided adequate control and was discontinued in her early twenties because of infrequent symptoms. When headaches returned several years later, she had become intolerant to amitriptyline at the prior dosage and received no benefit from propranolol. Topiramate produced paresthesia. She progressed to chronic migraine, a daily level 6/10 right retro-orbital sharp headache with associated nausea, photophobia, and phonophobia. Her sleep pattern was fragmented and she reported excessive daytime somnolence. She was able to maintain her activity level despite this pattern. She improved early into a 9-month course of onabotulinumtoxinA therapy and reported no headache for days to weeks at a time. Those that did occur responded to over-the-counter agents. Amitriptyline was restarted, primarily for sleep, at a low dose of 2.5 mg, and was tolerated and beneficial.

Comment. This case exemplifies a fairly typical response to onabotulinumtoxinA therapy. After a latency period, the prior headache pattern is diminished to the point where previous preventive medication dosages can be reduced, response to abortive medications improves, and functional level improves.

the use of the antihypertensive medications lisinopril (10 mg twice daily) and candesartan (16 mg once daily) in the prevention of migraine.[50,54] These received a Level C rating in the updated AHS/AAN guideline. Adverse effects for lisinopril include cough, hypotension, and fatigue. Candesartan may cause back pain, upper respiratory infection, pharyngitis, and dizziness. The antimigraine mechanism of these agents is unclear, but specific potential may exist for their use in patients with the angiotensin-converting enzyme (ACE) DD gene, which codes for a higher ACE activity and may be associated with migraine with aura.[50]

CONCLUSION

Available choices of medications for acute and preventive treatment of migraine have grown in response to advances in our understanding of migraine pathophysiology. Many experts agree, however, that there is still an urgent need for more specific and more potent agents, along with further investigation into the best methods for applying, managing, and withdrawing these therapies to obtain the best level of control while minimizing side effects. Expanding interest in and funding for headache research and clinical training should help realize these goals.

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