Review

Diagnosis and Treatment of Migraine

ROGER CADY, MD, AND DAVID W. DODICK, MD

Despite recent advances in understanding the pathophysiology and treatment of migraine, considerable uncertainty remains surrounding the diagnosis and treatment of this disorder. This uncertainty is reflected in studies that show both underdiagnosis and undertreatment of migraine. While the diagnosis can be assisted by criteria from the International Headache Society, other approaches may be useful in clinical practice. Treatment of migraine must be based on an individualized patient strategy that integrates education, patient participation, and effective use of pharmacological interventions. Many patients, despite self-treatment with simple analgesics, continue to suffer considerable disability associated with their migraines. Triptans, which are more effective at relieving migraine symptoms and maintaining patient function than are nonspecific therapies, are used in only a minority of patients with migraine. Treatment goals of rapid, complete relief with no recurrence and minimal adverse effects can be achieved when effective therapy is matched to individual patient goals. For prophylaxis, anticonvulsant drugs emerging as effective options are being added to the armamentarium with traditional compounds such as tricyclic antidepressants and β-blockers.

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5-HT$_1$ = serotonin (5-hydroxytryptamine$_1$); IHS = International Headache Society; NSAID = nonsteroidal anti-inflammatory drug

Considerable inroads have been made in recent decades in the understanding and treatment of migraine.[1-3] The introduction of effective serotonin (5-hydroxytryptamine$_1$ [5-HT$_1$]) agonists, along with new prophylactic strategies, offers more treatment options than available previously. Despite these advances, appreciable uncertainty surrounding the management of migraine remains, which is reflected in studies that show both underdiagnosis and undertreatment.[4-6] The yearly prevalence of migraine has been estimated to range from 17.6% to 33% in women and 5.7% to 13% in men.[5,6] In a 1993 survey, only 38% of patients who fulfilled diagnostic criteria for severe migraine had received a physician diagnosis.[4] Although a follow-up study almost a decade later showed improvement in diagnosis, migraines remain undiagnosed in more than 50% of patients.[7] Reasons for this low rate of diagnosis are complex but are in part due to patient underreporting of migraine to physicians and lack of a simplified diagnostic test. Higher rates of diagnosis have been reported for patients with annual household income greater than $45,000[4]; however, the prevalence is actually inversely proportional to income. Because of the high prevalence of migraine, virtually all clinicians see patients with migraine, and the vast majority of patients who seek medical attention present initially to a family physician.[4] The diagnosis of and treatment options for migraine are reviewed with an emphasis on the appropriate role of 5-HT$_1$ agonist therapy.

From the Headache Care Center, Primary Care Network, Springfield, Mo (R.C.); and Department of Neurology, Mayo Clinic, Scottsdale, Ariz (D.W.D.).

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Address reprint requests and correspondence to Roger Cady, MD, Primary Care Network, 1230 E Kingsley, Springfield, MO 65804 (e-mail: rcady@primarycarenet.org).

DIFFERENTIAL DIAGNOSIS OF MIGRAINE

In 1988, the International Headache Society (IHS) developed criteria for headache and facial pain disorders, including migraine (Table 1).[8] These guidelines have proved invaluable in organizing headache research, and they form the basis for the category of headache in the International Classification of Diseases.[9] Many primary care clinicians are unfamiliar with or do not implement these criteria and may prefer assessment tools more applicable to clinical practice.

Primary vs Secondary Headaches

Headache can be broadly categorized into primary headaches and secondary headaches due to an underlying medical condition. The diagnosis of a primary headache is a proactive process that necessitates a thorough history and physical examination, including a focused neurologic ex-

Table 1. **Categories of the International Headache Society Classification System***

1. Migraine
2. Tension-type headache
3. Cluster headache and chronic paroxysmal hemicrania
4. Miscellaneous headache not associated with structural lesions
5. Headache associated with head trauma
6. Headache associated with vascular disorders
7. Headache associated with nonvascular intracranial disorder
8. Headache associated with substance use or withdrawal
9. Headache associated with noncephalic infection
10. Headache associated with metabolic disorders
11. Headache or facial pain associated with disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure
12. Cranial neuralgias, nerve trunk pain, and deafferentation pain
13. Headache not classifiable

*Data from Headache Classification Committee of the International Headache Society.[8]

amination. The diagnosis of migraine is not simply ruling out a secondary organic process but is effectively accomplished by understanding the clinical features and pattern of migraine. Also essential is a review of current medications for both potential headache triggers (ie, vasodilators) and signs of analgesic overuse.

Several historical factors can suggest primary headache, including onset in adolescence or early adulthood, stable pattern of similar headaches over a period of more than 6 months, family history, menstrual association, and variable site of headache from attack to attack or within the same attack. In addition, several "red flags" can increase the index of suspicion for secondary headache disorders: headache that begins suddenly, onset after age 40 years, onset of new headache type, new level of pain ("worst headache ever"), accelerating headache intensity or frequency (gradual or acute), headache initiated with exertion or Valsalva maneuver, headache associated with neurologic changes, headache in patients with a history of human immunodeficiency virus or an underlying malignancy, and history of headache that interrupts sleep (also reported in patients with migraine and cluster headache).[9-11] In patients with nonacute headache, neuroimaging studies should be considered in those with abnormal neurologic examination findings of unknown etiology and in patients with additional risk factors warranting imaging (eg, postural headache).[9]

Spectrum of Headaches

Primary headache conditions include migraine and tension-type headache, the latter being the most common headache experienced by the general population but not necessarily in patients seeking medical evaluation. Individuals are unlikely to seek medical attention for episodic tension-type headache or other mild nondisabling headache conditions. Usually, these types of headaches are effectively managed with lifestyle modifications or nonprescription analgesics.

Patients with clinically relevant migraine often experience several different clinical presentations of headache, including migraine, migrainous headache (not meeting all IHS criteria for migraine), and tension-type headache. This entire spectrum of headache activity responds equally well to migraine-specific (eg, triptans) medications, suggesting that these different clinical presentations of headaches in patients with migraine have a similar underlying biology.[12] This factor implies that headaches experienced by migraine sufferers differ more in degree than in type. In other words, the biological underpinning of headaches in migraineurs that phenotypically resemble tension-type headache is similar to headaches that fulfill IHS criteria for migraine. Thus, the academic headache community no longer supports the concepts or use of the terms *mixed headache disorder*, *tension-vascular headaches*, *vascular headaches*, or *muscle-contraction headaches*. These terms imply different headache types with a different pathophysiological basis, and they are incompatible with the current construct of migraine as a paroxysmal neurologic disorder that is initiated within the central nervous system rather than a disorder of cerebral blood vessels.

Based on IHS criteria, the diagnosis of migraine without aura (formerly termed *common migraine*) requires that patients fulfill certain criteria (Table 2).[8] For migraine with aura (formerly termed *classic migraine*), additional characteristics for the aura must be met (Table 2). These IHS criteria have not been widely adopted into clinical practice for various reasons, including a lack of awareness of their existence, the need for accurate and complete reporting of symptoms by patients, and the dilemma of patients who have some migraine symptoms but not enough to fulfill all the diagnostic criteria.

MEASURES OF EFFECT OF HEADACHES ON DAILY FUNCTION

Headaches that interfere with daily living warrant medical attention and effective treatment. To address this issue, work has focused on measures of migraine disability, specifically the Migraine Disability Assessment,[13] the Headache Intensity Test,[14] and the Headache Disability Inventory.[15] The Migraine Disability Assessment is a 5-item questionnaire designed to assess headache-related disability for use in routine clinical practice. Scores are divided into grades I through IV with I indicating little disability over the past 3 months associated with low treatment need. Grade II indicates mild disability and moderate treatment

need. Grades III (scores 11-20) and IV (scores ≥21) identify moderate to severe disability and high treatment need.

The Headache Impact Test is available both as an online (www.headachetest.com) and as a paper-based questionnaire that consists of 6 questions. Scores of 60 or more indicate very severe impact. This tool was developed to measure the impact of headache on individuals' lives and facilitate communication between patient and health care provider.

The Headache Disability Inventory, developed at Henry Ford Hospital, has 25 items that probe the functional and emotional effects of headache on everyday life. Each item may be answered with either "yes" (4 points), "sometimes" (2 points), or "no" (0 points). A maximum score of 100 points rates the individual as having severe self-perceived headache disability. These measures assist the physician in determining the medical relevance of patients' headaches.

Headache frequency of more than 2 days per week strongly suggests the need for prophylactic therapy and directs exploration of the possibility of analgesic-rebound headache and the evolution of episodic migraine into chronic daily headache.[16] Treatment efficacy assesses patient expectations of treatment and reviews current and past treatment successes and failures. The "clinical pearl" is that a patient with a recurrent, severe, and stereotyped pattern of headache of more than 6 months' duration has migraine until proved otherwise.

APPROACHES TO TREATMENT

Migraine treatment begins with the patient's headache history. The history not only provides valuable information about severity, duration, premonitory symptoms, and possible precipitating factors but also involves patients in the management of their condition. Understanding the pattern of headache activity is essential to determining treatment needs. This understanding can be facilitated with use of a headache diary. Sample diaries are readily available from various sources, including the National Headache Foundation and the American Council for Headache Education.[17] The patient records the time, date, duration, and treatment efforts. This documentation allows the clinician and the patient to view the pattern and degree of headache control being obtained. In addition, risk factors associated with headaches, such as menses, weather, foods, medication, or life circumstances, can be studied in the context of the headaches. Patients can see which behaviors or foods should be avoided in managing their headache, and they can articulate goals and assess the outcome of therapy.

Models of Care

Several models of care have been proposed for the management of migraine, including step care (Figure 1),[18] staged care, stratified care (Figure 2),[18] and patient-centered stratified care (Figure 3).[16] Step care is initiating symptomatic (acute) headache therapy with inexpensive low-end medications and establishing failure before using more specific treatment. Typically, the patient starts with a trial of over-the-counter products; if these drugs fail to diminish migraine attacks, the patient tries nonsteroidal anti-inflammatory drugs (NSAIDs). If NSAIDs fail, the patient tries combination analgesics, etc, until treatment is effective.

The second model is staged or step care within attack care. Patients take low-end medication at the beginning of a migraine attack and if the intervention is ineffective advance to another more effective compound. This approach

Table 2. **International Headache Society Diagnostic Criteria for Migraine With and Without Aura***

Without aura
At least 5 attacks fulfilling the following
Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)
Headache has at least 2 of the following characteristics
Unilateral site
Pulsating quality
Moderate or severe intensity (inhibits or prohibits daily activities)
Aggravation by routine physical activity, such as walking stairs
During headache, at least 1 of the following
Nausea and/or vomiting
Photophobia and phonophobia
At least 1 of the following
History, physical and neurologic examinations do not suggest secondary headache
History and/or physical examination suggests such a disorder, but it is ruled out by appropriate investigations
Such disorder is present, but migraine attacks do not occur for the first time in close temporal relationship to the disorder
With aura†
At least 2 attacks with at least 3 of the 4 following characteristics
One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brainstem dysfunction
At least 1 aura symptom develops gradually over more than 4 minutes or 2 or more symptoms occur in succession
No aura symptom lasts more than 60 minutes; if more than 1 aura symptom is present, accepted duration is proportionally increased
Headache follows aura with a pain-free interval of fewer than 60 minutes (headache may also begin before or simultaneously with the aura)

*Data from Headache Classification Committee of the International Headache Society.[8]

†Typical aura symptoms are described as homonymous visual disturbances, unilateral paresthesias and/or numbness, unilateral weakness, aphasia or unclassifiable speech difficulty.

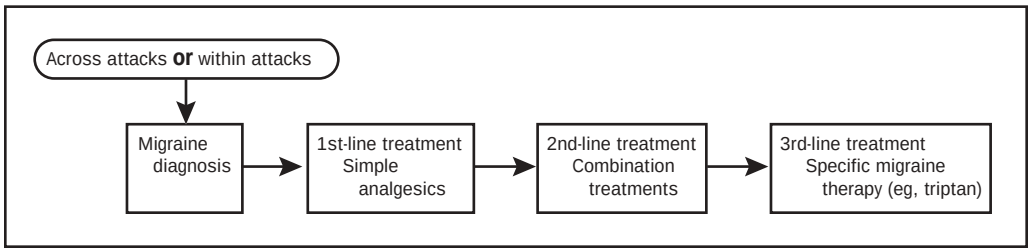

Figure 1. With the step care approach, treatment is initiated with first-line agents with progressive steps to second- and third-line therapy if the response is inadequate. Adapted from Lipton[18] with permission.

can be beneficial while the headache is mild in patients with slow to develop migraine, and a change in medication can be initiated before the pain becomes moderate to severe and associated migraine symptoms develop fully.

Stratified care determines treatment need based on patient characteristics, especially headache-related disability. High-end therapy is provided for patients with pronounced migraine-related disability, whereas those with less severe symptoms are prescribed low-end therapy. Once failure is established for low-end therapy, patients take high-end therapy. This approach has the advantage of rapidly providing effective therapy to migraineurs with the greatest need. However, it does not readily escalate the treatment needs of those with infrequent disabling migraine and assumes that an individual patient has migraine attacks of similar severity and disability.

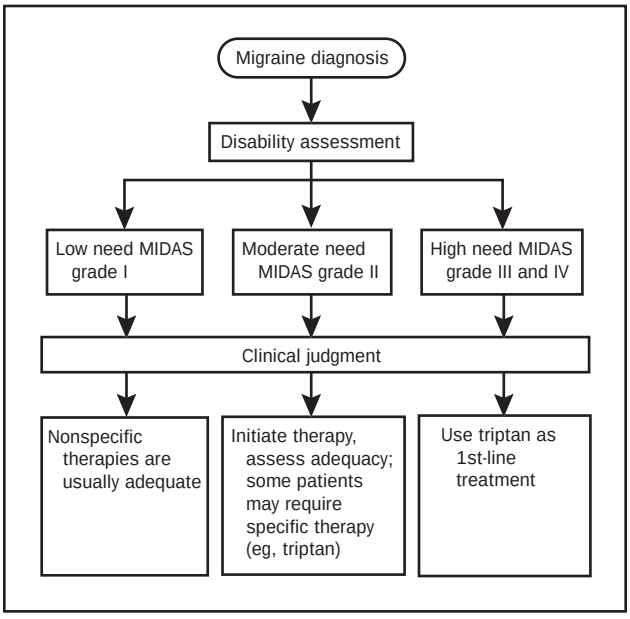

Figure 2. With the stratified care approach, the most appropriate treatment is based on the patient's disability. MIDAS = Migraine Disability Assessment. Adapted from Lipton[18] with permission.

Patient-centered stratified care relies on educating migraineurs such that they determine treatment need based on the characteristics of individual headache attacks. Thus, some headaches may require high-end therapy as the initial intervention, whereas others may be treated in a staged-care model. The physician's role is to provide education and the range of appropriate therapeutic modalities required to control each headache. Guidelines for use and frequency of medication are established, and patients are followed up over time to ensure efficacy and safety of the treatment plan.[16]

Abortive Treatment

Most migraineurs self-treat their headaches with nonprescription analgesics.[4] Recently, several nonprescription NSAIDs were approved by the Food and Drug Administration for treatment of mild to moderate migraine. Although these drugs can be beneficial in treating some migraine attacks, they rarely can be relied on as sole therapy for the spectrum of treatment needs required in patients who experience moderate and severe attacks. Most patients seeking medical care for migraine have used nonprescription analgesics before consulting a medical provider. If these compounds were effective, patients would have little need to pursue medical consultation.

Highly selective 5-HT_1 agonists have emerged as the "gold standard" for acute migraine therapy. These drugs are thought to act predominantly as agonists at the 5-$HT_{1B/D}$ receptor, although binding at other subtypes, including the 5-HT_{1A} and 5-HT_{1F} receptor, has also been observed. Stimulation of the 5-$HT_{1B/D}$ receptors by triptans has several important pharmacological consequences. During a migraine attack, triptans, through stimulation of the 5-HT_{1B} receptor on cranial blood vessels, cause vasoconstriction that is relatively selective for cerebral blood vessels since vasoconstriction in the peripheral circulation is mediated predominantly by 5-HT_2 receptors. In addition, triptans activate 5-HT_{1D} receptors located on first- and second-order neurons of the trigeminal nerve, effectively decreasing the release of neuropeptides responsible for vasodila-

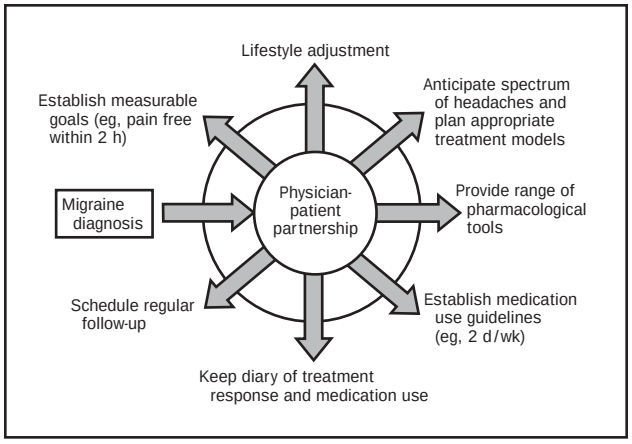

Figure 3. With patient-centered strategies, a partnership is established between the physician and patient, and factors that are important to each in managing migraine are considered. From Advisory Committee of Primary Care Network.[16]

tion and the activity of pain-signaling neurons within the trigeminal nucleus. Ergot derivatives used for the treatment of migraine also have activity at the 5-$HT_{1B/D}$ receptors, but they are limited by adverse effects due to binding at non-5-HT_1 receptors, as well as at dopaminergic and adrenergic receptors. Sumatriptan was the first of the triptans to be marketed; however, all the current 5-HT_1 receptor agonists are thought to act by the same mechanism. The few comparative trials conducted have focused predominantly on sumatriptan.[19,20]

The recently developed triptans, although acting on the same receptor complexes, differ somewhat from sumatriptan with respect to their pharmacological profiles. These changes may translate into attributes that address treatment characteristics deemed desirable by patients and clinicians. Patients rank complete pain relief as their highest treatment priority, followed by speed of pain relief, lack of migraine recurrence, lack of adverse effects, relief of associated symptoms, and desirability of routes of administration.[21,22] Pharmacokinetic profiles of almotriptan,[22] naratriptan, rizatriptan, orally and subcutaneously administered sumatriptan, and zolmitriptan are shown in Table 3. Drugs with a longer half-life were developed with the expectation of having a lower rate of headache recurrence (return of a moderate to severe headache within 24 hours after initial relief). Consistency of response and speed of onset are thought to correspond to bioavailability and T_{max}, respectively. Whether these attributes translate into clinically meaningful differences is debatable. Interestingly, the extent of pain relief is the only therapy goal not reflected in the pharmacological profile. All the newer triptans appear to be comparable to sumatriptan in the degree of pain relief.

Adverse event rates are similar for all triptans and include facial flushing, tingling, and chest discomfort. Although triptans are relatively selective vasoconstrictors for cranial arteries, they have been observed to have a minor vasoconstrictive effect on coronary vessels. Data from extensive clinical trial programs, coupled with information from nearly 10 years of postmarketing clinical experience, show that when sumatriptan is used properly, it is generally well tolerated with an acceptable risk-benefit ratio.[23] Severe cardiovascular and neurologic events are rare but have been observed.[23] Thus, appropriate patient selection and adherence to the prescribing recommendations for every member of this class of medications are necessary. The prescribing information for these medications indicates that they are not to be administered to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes.

The relationships among the 5-HT_1 agonists and the treatment characteristics most desirable for patients (complete pain relief, no recurrence, speed of pain relief, and lack of adverse effects) are summarized in Table 4.[20,24] However, more studies are needed for a direct comparison of the 5-HT_1 agonists.

A growing body of evidence suggests that early intervention during mild headache with triptans can abort head-

Table 3. **Pharmacokinetic Characteristics of 5-HT_1 Receptor Agonists***

Drug	Time to peak levels (h)	Elimination half-life (h)	Primary elimination routes
Almotriptan[22]	1.5-2.0	3.5	Hepatic and renal, C P-450†
Naratriptan	2-3	6	Hepatic, C P-450 and renal
Rizatriptan	1-1.5	2	Hepatic and renal
Sumatriptan			
Oral	2-3	2	Hepatic, MAOA
Subcutaneous	12 min	1.9	Hepatic, MAOA
Zolmitriptan	1-1.5	2.5	Hepatic, MAOA

*C P-450 = cytochrome P-450; MAOA = monoamine oxidase A.
†12% of dose metabolized by C P-450–mediated oxidation (CYP3A4 and CYP2D6).

Table 4. **Relationship of Preferred Treatment Characteristics and the 5-HT$_1$ Agonists*†**

Drug	Dose (mg)	Complete pain relief‡	Recurrence rate§	Speed of pain relief§	Adverse effects//
Almotriptan	12.5	36 (32-39)	26 (22-30)	35 (31-38)	Nausea (2%)[25]
Naratriptan	2.5	23 (20-26)	25 (22-29)	24 (21-26)	Nausea (5%), paresthesia (2%), drowsiness (2%), malaise/fatigue (2%), dizziness (2%), throat/neck pain/pressure (2%)[26]
Rizatriptan	10	40 (38-42)	37 (34-39)	43 (41-45)	Nausea (6%), dizziness (9%), somnolence (8%), asthenia/fatigue (7%), paresthesia (4%), dry mouth (3%)[27]
Sumatriptan	50	28 (23-32)	34 (27-40)	38 (33-42)	Warm/cold sensation (5%), paresthesia (5%), malaise/fatigue (2%), chest pain/tightness/heaviness (2%), neck/throat/jaw pain/tightness/pressure (2%)[28]
Zolmitriptan	2.5	25 (21-29)	31 (26-37)	39 (36-41)	Nausea (9%), dizziness (8%), paresthesia (7%), somnolence (6%), warm/cold sensation (5%), chest pain/tightness/heaviness (3%), dry mouth (3%), asthenia (3%), neck/throat/jaw pain/tightness/pressure (2%), pain-specified (2%), other heaviness (2%), other pressure/tightness (2%)[29]

*Data from Ferrari et al[20] and Roon et al.[24]
†Values are percentage (range) unless indicated otherwise.
‡Percentage of patients pain free at 2 hours.
§Percentage of patients experiencing pain response at 1 hour.
//Adverse effects that occurred in at least 2% of patients.

aches in 80% to 90% of patients within 2 to 4 hours, with lower headache recurrence, less disability, and possibly fewer adverse events.[30-33] NSAIDs, nonnarcotic analgesics, and isometheptene combinations may be effective in selected patients if used early in the migraine process, but no clinical trials have investigated this assumption. Narcotic and butalbital-containing products are not recommended for early intervention strategies. If a patient provides a history of satisfactory response to nonspecific therapies with no escalation to disabling headaches, these interventions should be encouraged. If attacks escalate to moderate or severe levels, migraine-specific therapies (triptans) should be implemented.

In addition to NSAIDs and ergot-containing products, acute treatment of migraine also includes opiate analgesics and butalbital-containing products. However, the last 2 drugs have a high potential for habituation.[9] These drugs are not encouraged as first-line interventions except in patients who are poor candidates for 5-HT$_1$–agonist therapy (ie, those with high cardiovascular risk or those who are pregnant). In patients with severe nausea, parenteral therapies or combinations of triptans with antiemetics, such as prochlorperazine or metoclopramide, should be considered.

PROPHYLAXIS

Although intermittent therapy for acute migraine episodes can be effective in many patients, some are candidates for prophylaxis. Patients requiring acute therapy more than 2 days per week should be considered for prophylaxis. In addition, if patients are having 2 or more migraines a month that cannot be adequately controlled with abortive medication, prophylaxis may be necessary. When headaches interfere substantially with a patient's ability to function; when acute medications are contraindicated, ineffective, or not tolerated; or when it is a patient's preference, preventative medications should be considered. Response rates with most prophylactic agents studied are approximately 40% to 50%, with success being defined as a reduction in migraine frequency of more than 50%.[34] Patients should be reminded that it may take up to 4 weeks before a meaningful clinical response is observed and up to 12 weeks before the maximal effect is realized. Although patients may expect that prophylaxis will eliminate their migraines, reduction in headache frequency or duration is a more likely outcome.

The drug classes with the longest clinical history of use for prophylaxis are β-blockers and tricyclic antidepressants, particularly propranolol and amitriptyline. Nondihydropyridine calcium channel blockers (ie, verapamil) and selective serotonin reuptake inhibitors have also been tested in clinical trials, with equivocal lackluster results that mirror their low efficacy in clinical practice.[35] Valproic acid was the first anticonvulsant to be approved for migraine prophylaxis.[36,37] Since then, several new antiepileptic medications have been evaluated for the prophylaxis of migraine, including gabapentin and topiramate, and have shown preliminary evidence of efficacy.[38]

CONCLUSION

Recent decades have seen considerable advances in the understanding and treatment of migraine, although this disorder remains underdiagnosed and undertreated. More efficient recognition schemes for migraine are emerging

that will facilitate identification of patients with medically relevant headaches. Triptans with models of early intervention are redefining treatment opportunities and establishing treatment outcomes that can meet patient desires.

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