REVIEW ARTICLE

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Acute Treatment of Migraine

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Dr Vargas has received personal compensation for serving on the advisory boards of Alder BioPharmaceuticals, Inc; Allergan; Amgen Inc; Avanir Pharmaceuticals, Inc; Eli Lilly and Company; Pernix Therapeutics; Teva Pharmaceutical Industries Ltd; and Upsher-Smith Laboratories, LLC; for serving on the speaker's bureau of Amgen Inc and Avanir Pharmaceuticals, Inc; and has received travel compensation for serving as an editor for *Neurology Today*.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Vargas discusses the unlabeled/investigational use acetaminophen, acetylsalicylic acid, dexketoprofen, diclofenac, dipyrone, droperidol, haloperidol, ibuprofen, ketorolac, lasmiditan, metoclopramide, naproxen, peripheral nerve block, prochlorperazine, and valproate for the acute treatment of migraine.

ABSTRACT

PURPOSE OF REVIEW: **This article provides a framework to help providers formulate a plan for the acute treatment of migraine. Topics covered include the cost-effective patient-centered approach known as stratified care and a summary of evidence-based treatment options that are currently available. Strategies for improving treatment response, troubleshooting suboptimal results, and addressing the needs of special populations are also reviewed.**

RECENT FINDINGS: **Both the American Headache Society and the Canadian Headache Society have released evidence-based assessments and reviews of acute treatments for migraine that can be used to help guide treatment decisions. Although several older medications have been re-released with new formulations or new delivery systems, several new medications have also become available or are in the final phases of study, further increasing the number of options available for patients.**

SUMMARY: **The acute management of migraine should incorporate a stratified care model in concert with evidence-based treatment options. The response to treatment should be monitored regularly, and measures should be taken to identify suboptimal tolerability or efficacy.**

INTRODUCTION

One of the cornerstones of migraine management is establishing an effective acute and rescue treatment plan. Unfortunately, many times the treatment plan does not reflect patient preferences nor does it address patients' unique individual needs based on their migraine characteristics. The fact that up to 40% of patients are dissatisfied with their acute treatment suggests that health care providers should be mindful of the myriad factors that can contribute to treatment success, including medication selection, dosing, route of administration, timing of administration, safety, tolerability, and whether the treatment addresses the patient's definition of effectiveness.[1] Despite a number of advances in diagnosis and treatment, only 22% of patients with migraine use a migraine-specific medication, and a nearly equivalent percentage use barbiturates or opioids for their attacks.[2] This is especially important as inadequate acute treatment exerts a significant socioeconomic burden[3] and has also been associated with transition from an episodic to a chronic pattern of migraine.[4]

Although the American Headache Society (AHS) and the Canadian Headache Society (CHS) have released evidence-based assessments and reviews of various acute treatments for migraine,[5,6] the subsequent release of literature providing guidance on how to properly use these guidelines and how to assess efficacy and patient satisfaction suggests that selecting the best individualized treatment is far more nuanced than simply selecting a medication from a list of evidence-based options.

This article serves to highlight acute treatment options in the context of their level of evidence but also serves to provide guidance on factors to consider while making treatment selections.

MODELS OF ACUTE TREATMENT

A plan for acute and rescue treatment should be provided to every patient with migraine. The plan should be individualized and address the issues and treatment barriers that are specific to each patient and each attack, including the presence of associated nausea or vomiting and the time to peak severity. Treatment approaches frequently follow one of three models of care including step care across attacks, step care within attacks, and stratified care.[7]

In step care across attacks, the patient is usually prescribed an inexpensive, nonspecific analgesic medication and, if unsuccessful, will return to their provider for consideration of a different medication along a stepwise pattern of treatment that eventually incorporates more migraine-specific options. A significant drawback to this model is that when unsuccessful, it may lead to suboptimal and delayed treatment as patients must frequently wait for follow-up visits from their providers for the next step in their care.[7]

In step care within attacks, the patient is counseled to initiate treatment with a low-cost nonspecific analgesic medication and, if unsuccessful, can advance themselves after several hours to more migraine-specific treatment options along a stepwise pattern within each individual attack. One of the drawbacks, however, is that this can lead to suboptimal efficacy of treatment as many migraine-specific treatments, including triptans, are best taken early in the attack rather than several hours after an initial failed treatment.[7]

In stratified care, the patient is entrusted with determining which attacks will respond to various treatments and is given the autonomy to make the appropriate treatment decision based on his or her personal experiences and preferences. Of these three models of care, it is stratified care that best considers individual variance in headache severity and associated features such as nausea or vomiting; this also allows the patient the ability to make his or her own treatment decisions based on their unique needs. Stratified care is equated with higher patient satisfaction and also with decreased health care costs (CASE 4-1).[7]

FIRST-LINE TREATMENT

In 2015, the AHS published a detailed evidence assessment of acute migraine therapies and in 2016 published subsequent guidance on how to interpret and apply the evidence assessment to the clinical setting.[5,8] The CHS published a similar review of acute treatments for migraine in 2013, which addressed the quality of evidence alongside practical recommendations, taking into account factors such as side effect profile and potential for abuse or misuse.[6] These recommendations are summarized in TABLE 4-1. Acute treatments with the highest level of evidence include all triptans as well as nonspecific analgesics

KEY POINTS

- Inadequate acute treatment of migraine exerts a significant socioeconomic burden and has also been associated with transition from an episodic to a chronic pattern of migraine.
- Stratified care considers individual variance in headache severity and associated features such as nausea or vomiting and allows patients the ability to make their own treatment decisions based on their unique needs.
- Stratified care of patients with migraine is equated with higher patient satisfaction but also with decreased health care costs.
- Acute treatments of migraine with the highest level of evidence include all triptans as well as nonspecific analgesics including acetaminophen and certain nonsteroidal anti-inflammatory drugs.

including acetaminophen and certain nonsteroidal anti-inflammatory drugs (NSAIDs). Conflicting opinions exist on the strength of evidence for intranasal dihydroergotamine; however, both groups include it as a first-line option, with the CHS assigning it a weak recommendation. Conflicting opinions on strength of evidence were reported for the opioid medication butorphanol, with the CHS making strong recommendations against its use despite Level A evidence cited by the AHS. The following medication summaries highlight only medications with both the highest level of evidence from AHS and strongest recommendations from CHS.

Triptan Monotherapy

A recent systematic review and meta-analysis demonstrated equivalent or slightly better effectiveness of triptans as a group when compared to NSAIDs, acetaminophen, and acetylsalicylic acid.[9] All triptans and triptan combination medications have strong evidence for effectiveness for acute treatment of migraine at standard doses, with 42% to 76% of patients experiencing pain relief at 2 hours (compared to only 27% of patients treated with placebo), but demonstrated slightly less efficacy than those treated with triptan combination medications such as triptan/acetaminophen and triptan/naproxen (with 2-hour pain relief responses of 80% and 62%, respectively). All standard-dose triptans and triptan combinations also demonstrated superiority with regard to 24-hour headache relief, ranging from 29% to 50% (versus placebo at only 17%), but again triptans in monotherapy performed slightly less well than triptan/acetaminophen and triptan/naproxen, with 24-hour headache relief responses of 50% and 46%, respectively. Triptans also demonstrate superiority to placebo using end points of 2-hour freedom from pain (18% to 50% versus 11%) and 24-hour sustained pain-free periods (18% to 33% versus 10%). Of note, the two orally disintegrating formulations (rizatriptan and zolmitriptan) do not convey

CASE 4-1

A 45-year-old man presented for evaluation of frequently occurring episodic migraine. He reported 6 headache days per month, and on average, two of his attacks were severe, incapacitating, and responsive to a triptan. His headache severity on the other 4 days was typically mild to moderate, and he was usually able to complete his workday with mild impairment in his ability to function. On these mild to moderate days, he felt his triptan was "overkill," and he found nonsteroidal anti-inflammatory drugs to be effective on the rare occasions that he had attempted treatment with them.

COMMENT

This patient was able to make a distinction between attacks that were severe enough to require treatment with a triptan and those that were responsive to over-the-counter nonsteroidal anti-inflammatory drugs. He should be encouraged to treat each of his headaches with a medication commensurate to his attack severity and degree of disability. He should be monitored for overuse, and a prophylactic medication should be considered. This is an example of stratified care.

any significant benefit compared to the standard tablets with regard to their pharmacokinetics but appeared to convey the largest benefit among all oral triptan monotherapies.[9]

Triptan Combination Medications

Several studies have shown the combination of sumatriptan and naproxen (85 mg/500 mg) to be effective for the acute treatment of migraine compared to placebo, with some studies also showing statistical superiority to sumatriptan or naproxen monotherapy. Brandes and colleagues[10] reported the results of two replicate, multicenter, randomized, double-blind, placebo-controlled studies showing that 65% and 57% of subjects reported 2-hour headache relief with the sumatriptan/naproxen combination for both studies compared to placebo (28% and 29%, respectively). In both studies, statistically significant improvement compared to placebo was also demonstrated at 2 hours for resolution of photophobia and phonophobia but not for nausea.

Another study by Mathew and colleagues[11] investigated the sumatriptan/naproxen combination in a population of patients with migraine who had previously discontinued an average of 3.3 triptans because of intolerance or inefficacy. In this population of subjects designated as triptan nonresponders, two randomized, multicenter, double-blind, placebo-controlled studies demonstrated statistical superiority of sumatriptan/naproxen over two attacks for a 2-hour to 24-hour pain-free response in both studies (26% and 31%, respectively) over placebo (8% and 8%, respectively) and a 2-hour pain-free response for both studies of 40% and 44% versus placebo (17% and 14%, respectively).[11]

Of note, taking sumatriptan 50 mg and naproxen 500 mg as two separate tablets for acute treatment also seems to convey some benefit over taking either of the two medications in monotherapy. Effectiveness of this combination was supported with a large, multicenter, randomized, double-blind, double-dummy, placebo-controlled, four-arm study with 46% of subjects taking the active two-tablet combination achieving a statistically superior 24-hour sustained pain-free response versus sumatriptan monotherapy (29%), naproxen monotherapy (25%), or placebo (17%).[12]

Triptan Contraindications and Updates

Triptans are contraindicated in individuals with a history of stroke, heart attack, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease. Rizatriptan, zolmitriptan, and sumatriptan should be avoided within 14 days of using a monoamine oxidase inhibitor.[8]

New developments since the publication of the AHS and CHS guidelines include the addition of a breath-powered device for the delivery of intranasal sumatriptan 22 mg in a powdered versus nasal spray formulation and the voluntary withdrawal of the sumatriptan 6.5 mg iontophoretic patch because of concerns of site irritation, scarring, and burns.[13]

Nonspecific Analgesics

Several nonspecific analgesics have been shown to be efficacious when compared to placebo in the acute treatment of migraine. These include acetylsalicylic acid, acetaminophen, ibuprofen, naproxen, and diclofenac, with both the AHS and CHS ascribing to them the highest level of evidence and with the CHS review

KEY POINTS

- Triptans are contraindicated in individuals with a history of stroke, heart attack, coronary artery disease, hemiplegic migraine, uncontrolled hypertension, migraine with brainstem aura, and peripheral vascular disease.
- A number of nonspecific analgesics have been shown to be efficacious when compared to placebo in the acute treatment of migraine.

TABLE 4-1 **Summary of American and Canadian Headache Societies' Evidence-Based Assessments, Reviews, and Recommendations for Acute Migraine Treatment[a]**

Medication and Dose	American Headache Society Evidence Assessment[b]	Canadian Headache Society Quality of Evidence	Canadian Headache Society Recommendation
		Recommendation for Use in Episodic Migraine	
Analgesics			
Acetaminophen 1000 mg	Level A	High	Strong
Nonsteroidal anti-inflammatory drugs			
Acetylsalicylic acid 500 mg	Level A	High	Strong
Diclofenac 50 mg, 100 mg	Level A	High	Strong
Ibuprofen 200 mg, 400 mg	Level A	High	Strong
Naproxen 500 mg, 550 mg	Level A	High	Strong
Triptans			
Almotriptan 12.5 mg	Level A	High	Strong
Eletriptan 20 mg, 40 mg, 80 mg	Level A	High	Strong
Frovatriptan 2.5 mg	Level A	High	Strong
Naratriptan 1 mg, 2.5 mg	Level A	High	Strong
Rizatriptan 5 mg, 10 mg	Level A	High	Strong
Sumatriptan (oral) 25 mg, 50 mg, 100 mg	Level A	High	Strong
Sumatriptan (intranasal) 10 mg, 20 mg	Level A	High	Strong
Sumatriptan (subcutaneous) 4 mg, 6 mg	Level A	High	Strong
Zolmitriptan (oral) 2.5 mg, 5 mg	Level A	High	Strong
Zolmitriptan (subcutaneous) 2.5 mg, 5 mg	Level A	High	Strong
Ergots			
Dihydroergotamine (intranasal) 2 mg	Level A	Moderate	Weak
Dihydroergotamine (subcutaneous) 1 mg	Level B	Moderate	Weak
Dihydroergotamine (IV, IM) 1 mg	Level B	N/A	N/A
Combinations			
Sumatriptan/naproxen 85 mg/500 mg	Level A	High	Strong
Acetaminophen/acetylsalicylic acid/caffeine 500 mg/500 mg/130 mg	Level A	N/A	N/A

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Medication and Dose	American Headache Society Evidence Assessment[b]	Canadian Headache Society Quality of Evidence	Canadian Headache Society Recommendation
		Recommendation for Nonroutine Use in Episodic Migraine	
Oral opioid and tramadol combinations			
Tramadol/acetaminophen 75 mg/650 mg	Level B	Moderate	Weak
Codeine/acetaminophen 25 mg/400 mg	Level B	Low	Weak
Codeine 30 mg	Level C	Low	Weak
Ergots			
Ergotamine 1-2 mg	Level C	Moderate	Weak
		Recommendation Against Use in Episodic Migraine Except Under Unusual Circumstances	
Opioids			
Butorphanol (intranasal) 1 mg	Level A	Low	Strong
Butalbital-containing medications			
Butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg	Level C	Low	Strong
Butalbital/acetaminophen/caffeine/codeine 50 mg/325 mg/40 mg/30 mg	Level C	Low	Strong

IM = intramuscular; IV = intravenous; N/A = not applicable.
[a] Data from Marmura MJ, et al, Headache,[5] and Worthington I, et al, Can J Neurol Sci.[6]
[b] Level A = medications are established as effective for acute migraine treatment based on available evidence; Level B = medications are probably effective based on available evidence; Level C= medications are possibly effective based on available evidence.

adding a strong recommendation for first-line use.[5,6] In general, most of the medications in this class performed only slightly less effectively than triptans when compared to placebo, are generally well tolerated, and are potentially useful options for treating mild to moderate headache (taking into account the model of stratified care). For some patients, nonspecific analgesics are also useful as the primary acute treatment for more severe pain.

NAPROXEN. In a meta-analysis that included four randomized, double-blind, placebo-controlled studies, naproxen sodium was found to be superior to placebo for the acute treatment of migraine with regard to 2-hour pain relief (pooled relative risk ratio of 1.58), 2-hour pain freedom (pooled relative risk ratio of 2.22), and with 2-hour relief of associated nausea (78%), photophobia (73%), and phonophobia (68%).[14]

ACETYLSALICYLIC ACID. Acetylsalicylic acid at doses of 1000 mg has been shown to have similar efficacy to sumatriptan with a high level of supportive evidence, including a Cochrane Review,[15] that it is more effective than placebo for treating acute migraine attacks. Acetylsalicylic acid has also received a strong recommendation by the CHS as a first-line treatment option.[6] In a study by Lipton and colleagues,[16] 2-hour headache relief (52%) and pain-free responses (20%) were superior to placebo (34% and 6%, respectively). When combined with metoclopramide 10 mg, 2-hour headache relief (57%) and 2-hour pain-free responses (18%) are superior to placebo (26% and 7%, respectively); metoclopramide is an excellent and potentially effective option, especially if nausea is a complicating factor.[15]

Effervescent acetylsalicylic acid 1000 mg is another effective option, with a meta-analysis of three studies showing 2-hour headache relief (52%) and 2-hour pain-free responses (27.1%) better than placebo (34% and 15%, respectively). Effervescent acetylsalicylic acid is the active ingredient in some over-the-counter antacids, typically in dosages of 325 mg per tablet.[17]

ACETAMINOPHEN. In a randomized, double-blind, placebo-controlled study of 351 subjects, Lipton and colleagues[18] demonstrated that oral acetaminophen 1000 mg is more effective than placebo for the acute treatment of migraine, including resolution of migraine-related symptoms of photophobia, phonophobia, and functional disability. Although 2-hour response rates and 2-hour pain-free rates for acetaminophen were statistically superior to placebo (57.8% versus 38.7% and 22.4% versus 11.3%), this study excluded patients with severe attacks that limited daily activity or required bed rest more than 50% of the time and excluded subjects with nausea in more than 20% of their attacks. A subsequent Cochrane Review supported the finding that acetaminophen is effective for the acute treatment of migraine occurring without a severe level of disability.[19]

IBUPROFEN. One large, multicenter, double-blind, placebo-controlled study of 660 subjects demonstrated that ibuprofen 200 mg and 400 mg is effective for treatment of acute migraine not requiring bed rest in more than 50% of attacks or with associated nausea more than 20% of the time.[20] Both the 200 mg and 400 mg doses of ibuprofen resulted in improvement of either mild or no pain at 2 hours (41.7% and 40.8%) compared to placebo (28.1%). For 2-hour reduction of severe pain to mild or no pain, the 400 mg dose proved to be more efficacious

than placebo (36.9% versus 21.6%); however, the 200 mg dose did not demonstrate statistically significant improvement. Of note, 280 (42.4%) of the subjects enrolled eventually withdrew from the study; 272 of which withdrew because of the need for rescue medication. Subsequent meta-analysis and a Cochrane Review yielded similar conclusions that low-dose ibuprofen is safe, well tolerated, and effective at relieving acute attacks of migraine and that the 400 mg dose outperformed the 200 mg dose.[21,22]

DICLOFENAC. Several randomized, double-blind, placebo-controlled studies and a Cochrane Review have shown efficacy of diclofenac for the acute treatment of migraine when compared to placebo.[5,6,23] Diclofenac can be administered orally both in a tablet formulation and also in a buffered, water-soluble, powder formulation that can be dissolved in approximately 2 oz of water. In one crossover study, subjects were significantly more likely to report 2-hour headache freedom with the 50 mg diclofenac powder in oral solution than with 50 mg diclofenac tablets (24.7% versus 18.5%) or placebo (24.7% versus 11.7%). Although somewhat less effective than diclofenac oral solution in this particular study, subjects taking 50 mg tablets were still significantly more likely to report being headache free at 2 hours than subjects taking placebo (18.5% versus 11.7%).[24] Another double-blind, placebo-controlled study investigating diclofenac powder in oral solution for a single moderate to severe migraine attack also showed statistical superiority versus placebo for 2-hour pain-free response (25% versus 10%) as well as an onset of pain relief in 30 minutes, outperforming placebo up to the 24-hour end point.[25]

Nonoral Treatments

In situations where standard evidence-based oral medications are ineffective, poorly tolerated, or contraindicated, it may be necessary to consider any of the several other nonoral treatment options.

PARENTERAL MEDICATIONS. With respect to parenteral options, the AHS has not identified any medications as having Level A evidence or that have a strong recommendation from the CHS for treating acute migraine attacks.[5,26] However, a number of parenteral medications have Level B evidence, including chlorpromazine 12.5 mg, droperidol 2.75 mg, metoclopramide 10 mg, prochlorperazine 10 mg (can also be given IM), dihydroergotamine 1 mg (can also be given IM/subcutaneously), ketorolac 30 mg to 60 mg (can also be given IM), and magnesium sulfate 1 g to 2 g (for migraine with aura). Options with Level C evidence include valproate 400 mg to 1000 mg, tramadol 100 mg, and dexamethasone 4 mg to 16 mg.[5] Parenteral options can be useful considerations for rescue therapy in the emergency department, an outpatient infusion center, or for those who are hospitalized. A separate AHS evidence assessment of parenteral therapies for acute treatment in the emergency department used levels of evidence to stratify various treatments into the following categories:

- **Should offer (Level B)**
  - **Metoclopramide**
  - **Prochlorperazine**
  - **Sumatriptan**

KEY POINT

- **In situations where standard evidence-based oral medications are ineffective, poorly tolerated, or contraindicated, it may be necessary to consider nonoral treatment options for migraine.**

- May offer (Level C)
  - Acetaminophen
  - Acetylsalicylic acid
  - Chlorpromazine
  - Dexketoprofen (not available in the United States)
  - Diclofenac
  - Dipyrone (not available in the United States)
  - Droperidol
  - Haloperidol
  - Ketorolac
  - Valproate

As with other evidence assessments, it was recommended based on Level C evidence that opioids "may be avoided" along with lidocaine, octreotide, and diphenhydramine. There is inadequate evidence (Level U) and no recommendation for acute parenteral treatment with dexamethasone, dihydroergotamine, ergotamine, magnesium (except for migraine with aura), propofol, ketamine, tramadol, promethazine, trimethobenzamide, meperidine, nalbuphine, and lysine clonixinate.[26] It is noted that the AHS evidence for some parenteral treatments in the emergency department differs slightly from the AHS acute treatment assessments.

NERVE BLOCKS

Although expert consensus recommendations from the AHS Special Interest Section for Peripheral Nerve Blocks and Other Interventional Procedures identified a lack of high-level evidence for peripheral nerve blocks in the acute treatment of migraine, a number of retrospective and noncontrolled prospective studies demonstrated efficacy for greater occipital, supratrochlear, and supraorbital nerve blocks.[27] Despite the short duration of local anesthesia, peripheral nerve blocks have been reported to provide long-term improvement lasting weeks as well as resolution of allodynia.[28] Despite a relative lack of evidence, peripheral nerve blocks are easily performed in the outpatient setting, are generally accepted as safe and well tolerated,[28] and continue to be a commonly employed treatment for acute migraine, with 69% of headache practitioners surveyed by the AHS Special Interest Section for Peripheral Nerve Blocks and Other Interventional Procedures consensus incorporating them into their practice.[27] Additional well-designed studies will be necessary to better delineate the efficacy and cost-effectiveness of these treatments in migraine populations.

NEUROSTIMULATION

Devices for external neurostimulation are emerging as effective strategies for the acute treatment of migraine. Specifically, transcutaneous supraorbital nerve stimulation was recently investigated in an open-label trial of 30 subjects using 1 hour of stimulation for an acute migraine attack. After 1 hour of treatment, pain intensity was reduced by 57.1% (−3.22 ± 2.40), and at 2 hours, pain was reduced by 52.8% (−2.98 ± 2.31); however, 36.4% of subjects required rescue medication within 24 hours of stimulation.[29]

One open-label study of 20 patients investigated noninvasive vagal nerve stimulation and demonstrated the effectiveness of both the prevention and acute treatment of episodic and chronic migraine.[30] Two additional open-label studies enrolled a total of 80 patients and specifically investigated noninvasive vagal nerve stimulation for the acute treatment of migraine attacks—one study for episodic migraine and the other for both episodic and chronic migraine. In the episodic study, 2-hour pain freedom for the first attack was reported by 21%, and 2-hour pain improvement was reported by 47% for treatment of moderate to severe pain. Of those treating mild pain, 63% reported 2-hour pain freedom.[31] In the study investigating acute treatment in episodic and chronic migraine, 56.3% of subjects reported improvement of 50% or more in headache severity at 1 hour (35.4% of whom reported pain freedom), and 64.6% reported improvement of 50% or more at 2 hours (39.6% of whom reported that they were pain free). In all studies, noninvasive vagal nerve stimulation was found to be safe and well tolerated. In January 2018, noninvasive vagus nerve stimulation obtained US Food and Drug Administration (FDA) approval for treatment of migraine pain.

In 2014, the FDA approved single-pulse transcranial magnetic stimulation for the acute treatment of migraine with aura. A randomized, double-blind, parallel-group, two-phase, sham-controlled study conducted by Lipton and colleagues[32] demonstrated efficacy of single-pulse transcranial magnetic stimulation versus placebo in subjects treating up to three attacks occurring with aura over 3 months. Pain-free response at 2 hours was 39% for single-pulse transcranial magnetic stimulation versus 22% for sham stimulation for a therapeutic gain of 17% with a sustained pain-free response versus placebo at 24 hours (29% versus 16%) and 48 hours (27% versus 13%).[32]

CALCITONIN GENE-RELATED PEPTIDE ANTAGONISTS

A large body of research supports the significant role of calcitonin gene-related peptide (CGRP) in the pathophysiology of migraine, which has led to the development of a new class of CGRP antagonists. Several CGRP antagonists are under development, including both small molecules and monoclonal antibodies directed at either the CGRP receptor or the peptide itself. A number of CGRP antagonists were shown to be effective acutely and are also being studied for migraine prevention; however, ubrogepant is the only medication in this class that is currently in phase 3 studies for acute treatment.[33] Phase 2b data showed that ubrogepant 100 mg was superior to placebo for the 2-hour pain-free end point (25.5% versus 8.9%) and was safe and well tolerated.[34] CGRP is a vasodilator, and its antagonism does not produce vasoconstriction,[35] suggesting that it might be a viable treatment option in patients with cardiovascular risk factors who are unable to take other migraine-specific medications such as triptans or ergotamines.

5-HT_{1F} AGONISTS

In early studies, agonism of the 5-HT_{1F} (serotonin) receptor has been shown to be effective for acute treatment of migraine, has anti-inflammatory effects, and does not produce vasoconstriction, making it a possible future treatment option in patients with cardiovascular risk factors.[35] One medication in this class, lasmiditan, has now been shown in phase 3 studies to be superior to placebo with regard to 2-hour pain-free response at a dose of 200 mg (32.2% versus 15.3%).[35]

KEY POINTS

- Despite a relative lack of evidence, peripheral nerve blocks are easily performed in the outpatient setting, are generally accepted as safe and well tolerated, and continue to be a commonly employed treatment for acute migraine.
- A large body of research supports the significant role of calcitonin gene-related peptide in the pathophysiology of migraine, which has led to the development of a new class of calcitonin gene-related peptide antagonists.

While the concept behind this class of medications is promising, clearly further research is warranted.

CONSIDERATIONS IN PATIENTS WHO ARE PREGNANT OR BREAST-FEEDING

Acute treatment of migraine in women who are either pregnant or breast-feeding presents a unique challenge; however, several observational studies and registry data have provided some guidance on medications that are considered to be among the safest options.

Among many providers, acetaminophen remains the first-line medication of choice and is the most commonly used medication for treatment of pain in pregnant women.[36] Although acetaminophen is generally considered to be safe, some studies have indicated a possible increased risk of hyperkinetic disorders, attention deficit hyperactivity disorder, and attention deficit hyperactivity disorder–like behavioral problems.[37–39] Acetaminophen is considered by the CHS to be the safest first-line medication for pregnant women.[40]

For many years, opioids had also been considered among the safer options for pregnant and breast-feeding women; however, many studies have demonstrated associations with congenital malformations and developmental defects.[41] A 2017 systematic review of opioid use in pregnancy conducted by Lind and colleauges[41] noted that while several retrospective and observational studies identified significant associations with congenital malformations, a number of important limitations in the quality of these studies influence their interpretation. This review did not provide a definitive recommendation against the use of opioids but rather suggested a judicious approach, taking into account risks and benefits. Additionally, codeine use in the third trimester has been associated with a higher risk of heart malformations, acute cesarean deliveries, and postpartum hemorrhage.[41,42] The additional risks of overuse and dependence in the mother suggest that this class of medications should be avoided if possible.

Caution has been advised regarding the use of triptans in pregnant women especially given the presence of 5-$HT_{1B/1D}$ receptors in the brain and the umbilical cord artery of the fetus.[43] Although numerous studies and registry data seem to indicate no increased risk for congenital malformations, developmental delay, behavioral, or motor problems,[44] some studies suggest that triptan use may result in a small increased risk for preeclampsia and, if used later in pregnancy, preterm delivery.[45] The use of sumatriptan in lactation has been determined to be safe according to the American Academy of Pediatrics, and minimal drug concentrations of eletriptan have been found in infants after breast-feeding. Similar studies on other triptans in humans have not been conducted.[46,47]

Evidence exists suggesting that NSAIDs may result in an increased risk of adverse fetal outcomes if taken in either the first or third trimesters. Specifically, a higher risk of miscarriage in the first weeks of pregnancy, a risk of cleft lip and palate, premature closure of the patent ductus arteriosus, and bleeding risks such as neonatal intraventricular hemorrhage appear to be present if used after the 32nd week of pregnancy.[43,46]

Metoclopramide is frequently used for nausea in pregnancy and also has some evidence for utility in acute treatment of migraine. It is generally considered to be

safe and is considered the preferred antiemetic for pregnant women with migraine according to the CHS.[40] A paucity of similar safety data exist for other antiemetics in pregnancy including domperidone (not available in the United States), ondansetron, and prochlorperazine.[40,43,46]

Ergots remain contraindicated with a high risk of adverse fetal outcomes in pregnancy and can result in decreased milk production and numerous potential adverse effects to the breast-fed infant.

Ultimately, no well-designed or definitive studies demonstrate the safety of any acute migraine medication in pregnant[48] or breast-feeding women. Nonetheless, providers should weigh the risks of using any medication in pregnant women versus the potentially detrimental effects of inadequately addressing headache and associated disability in the mother.[46] Treatment decisions should take into account other risk factors for poor fetal outcomes, headache characteristics (including frequency and degree of disability), and should also include input from the patient's obstetrician and pediatrician.[47] Whenever possible, nonpharmacologic options should be considered. For more information, refer to the article "Headache in Pregnancy" by Matthew S. Robbins, MD, FAAN, FAHS,[49] in this issue of *Continuum*.

TRIPTANS IN COMBINATION WITH SEROTONIN REUPTAKE INHIBITORS

When prescribing the combination of triptans and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), it is common for providers to receive alerts or warnings from pharmacies or the electronic medical record. These alerts are based on a 2006 FDA report concerning the risk of serotonin syndrome associated with the combination of triptans and either SSRIs or SNRIs and was based on 29 reported cases of serotonin syndrome in patients using one of these combinations. Evans and colleagues[50] conducted an in-depth review, which was reported as an evidence-based recommendation and AHS position paper. Ultimately, it was found that of the 27 cases prompting the FDA alert, only 10 met criteria for either of two established criteria for serotonin syndrome.[50] Taking into account the high frequency of coadministration of SSRIs/SNRIs and triptans, the overall annual incidence of serotonin syndrome with these combinations was estimated at less than 0.03%, and the incidence of life-threatening events was estimated to be less than 0.002%, both of which are less than the annual incidence of serotonin syndrome in SSRI/SNRI monotherapy.[51] Based solely on Class IV evidence, a Level U recommendation was ultimately rendered regarding this warning, reflecting a determination that the existing data are conflicting or inadequate to support the concern that coadministration of triptans with SSRIs or SNRIs confer any additional risk of serotonin syndrome.[50]

WHAT PATIENTS EXPECT FROM ACUTE TREATMENT

Among the numerous considerations that can influence the selection of an acute treatment, patient preference is important and occasionally overlooked. As only 29% of patients with migraine report being very satisfied with their treatment, it is important to understand the preferred outcomes and treatment shortcomings identified by most patients. Regarding preferred treatment outcomes, 87% of patients want complete pain relief, 86% want no recurrence of pain, 83% want fast relief of pain, 79% want their medication to be well tolerated without side effects, and 76% want relief of migraine-associated symptoms.[52] Compared to

KEY POINTS

- **Existing data are conflicting or inadequate to support the concern that coadministration of triptans with selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors confer any additional risk of serotonin syndrome in patients treated for migraine.**
- **Some common causes of suboptimal treatment include (but are not limited to): inadequate dosing, delay in treatment, not repeating treatment, suboptimal route of administration, and headache with a rapid time to peak severity.**

the previous attributes, the route of administration is less important but is a significant factor for 53% of patients, with 73% preferring tablets or capsules, 15% preferring orally disintegrating tablets, 8.3% preferring nasal sprays, and 2.6% preferring injections.[52]

Five Tips for Successful Acute Treatment of Migraine

The following are five tips for the successful acute treatment of migraine.

ENSURE THE HEADACHE DISORDER IS CORRECTLY DIAGNOSED. Not all primary headache disorders respond to the same medications, and levels of evidence for commonly used headache medications may vary greatly from one headache disorder to the next. Incorrect diagnosis may be one important factor for a lack of response to medications that should be effective based on existing evidence.[53] The initial consultation should always aim to identify and eliminate secondary causes of headache and then make a diagnosis based on the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria.[54]

USE EVIDENCE-BASED RECOMMENDATIONS AS A GUIDE TO SELECT AN INDIVIDUALIZED TREATMENT. Although the AHS and CHS evidence assessments are useful as a guide, it is important to note that findings in study populations are not always generalizable to individual patients and that other factors can influence medication selection including cost, tolerability, contraindications,[8] and the patient preferences discussed above. Treatment decisions should also always be made after a thorough review of other medications taken and comorbid medical conditions, both of which may limit or eliminate some treatment options.

A stratified approach should be taken, which includes arming the patient with a plan for milder headaches (which may respond adequately to nonspecific analgesics), a plan for moderate to severe attacks or attacks with disabling associated symptoms (which may respond best to migraine-specific medications), and the autonomy to make the appropriate treatment decision based on the specific features of each attack. A plan for rescue treatment or attacks that are refractory to a patient's usual treatment is also recommended and may include a plan for administering parenteral or IM injections, or (in very rare or unique circumstances) medications including opioids, opioid combinations, corticosteroids, or barbiturate combinations, taking into account their lower strengths of evidence and risks if overused or misused.[5,6,8]

OPTIMIZE TREATMENT. Recognize that the efficacies reported in many studies reflect acute treatment in select populations or suboptimal situations including many NSAID studies conducted on mild to moderate minimally disabling pain without nausea, or triptan studies conducted on pain that is already moderate to severe. In many instances, clinical performance can exceed performance in clinical trials by optimizing how specific treatments are administered, when (in the headache phase) they are administered, and which doses are used.

Nausea, vomiting, and gastroparesis frequently complicate migraine treatment and can often be the underlying cause of treatment failure with oral medications (CASE 4-2).[55] In these situations, intranasal or injectable formulations may confer a significant degree of additional benefit. As treatment is typically more effective when taken early in the headache phase, the time to peak severity of attacks is another important detail that can guide treatment selection. It is generally accepted that treating attacks early equates to better

outcomes,[8] suggesting that fast-onset attacks should be treated with medications that have a faster onset of action and shorter time to maximum plasma concentration (T_{max}). TABLE 4-2 provides a useful guide to onset of action, T_{max}, half-life, and maximum daily dosage.

ASSESS RESPONSE TO TREATMENT. At follow-up visits, patients should be asked specific questions about efficacy and tolerability of acute medications. It is never adequate to only ask if their treatment is "working," as this open-ended question does not adequately address specific questions about patient satisfaction with speed of onset, degree of improvement, recurrence of headache, and tolerability. In fact, it is estimated that a significant number of patients are dissatisfied with or respond suboptimally to treatment, including 30% to 40% of triptan users.[52,56] The four-item Migraine Treatment Optimization Questionnaire (mTOQ-4) (TABLE 4-3) is a validated questionnaire that can help assess treatment optimization.[57] Taking a more detailed inventory of the patient's response to acute therapy is important as suboptimal treatment can influence patient compliance, and patients with "poor" or "very poor" treatment efficacy are significantly more likely to progress to chronic migraine within 1 year (CASE 4-3).[4]

TROUBLESHOOT SUBOPTIMAL RESPONSE TO TREATMENT. If a suboptimal response to acute treatment is identified, it is important to review underlying possibilities before changing medications or classes of medications. Some common causes of suboptimal treatment include (but are not limited to): inadequate dosing, delay in treatment, not repeating treatment, suboptimal route of administration, and headache with a rapid time to peak severity. TABLE 4-4 can be used as a troubleshooting guide for addressing any of the above issues and are generalizable to most classes of medications (CASE 4-4).

CONCLUSION

Despite a growing armamentarium of treatment options for migraine, many patients remain unsatisfied with their acute medications. A comprehensive

CASE 4-2

A 22-year-old woman presented for consultation regarding her episodic migraine. She had a 4-year history of episodic migraine without aura with a time to peak severity of under 1 hour and prominent nausea and vomiting with most attacks. She stated that her orally administered acute treatment was effective only if she took it immediately and only if she could avoid vomiting.

COMMENT

This patient faces at least two barriers to effective treatment: the rapid onset of maximal pain severity and difficulty in taking oral medications because of nausea and vomiting. She would likely benefit from a change to an intranasal or injectable medication, which typically has a faster onset of action and bypasses the gastrointestinal system.

TABLE 4-2 **Pharmacology of Commonly Used Acute Migraine Medications**

Treatment	Onset (Minutes)	T_{max} (Hours)[a]	Half-life (Hours)	Maximum Daily Dose
Triptans				
Almotriptan	30–120	1.4–3.8	3.2–3.7	25 mg
Eletriptan	30	1.0–2.0	3.6–5.5	80 mg
Frovatriptan	120–180	2.0–4.0	25	7.5 mg
Naratriptan	60–180	2.0–3.0	5.0–6.3	5 mg
Rizatriptan (tablet)	30–120	1.2	2.0–3.0	30 mg (15 mg if taking propranolol)
Rizatriptan (orally disintegrating tablet)	30–120	1.6–2.5	2.0–3.0	30 mg (15 mg if taking propranolol)
Sumatriptan (tablet)	20–30	2.5	2.0	200 mg
Sumatriptan (nasal spray)	15	1.0–1.5	2.0	40 mg
Sumatriptan (nasal powder)	15	0.75	3.0	44 mg
Sumatriptan (injection)	10–15	0.2	1.7–2.0	12 mg
Sumatriptan/naproxen	20–30	1.0 (sumatriptan)/5.0 (naproxen)	2.0 (sumatriptan)/19 (naproxen)	2 tablets
Zolmitriptan (tablet)	45	2.0	2.5–3.0	10 mg
Zolmitriptan (orally disintegrating tablet)	45	3.3	2.5–3.0	10 mg
Zolmitriptan (nasal spray)	15	3.0	3.0	10 mg
Ergots				
Dihydroergotamine (nasal spray)	30	0.75	10	4 mg (maximum weekly dose 12 mg)
Simple analgesics				
Acetaminophen	30	0.5–1.0	2.0	4000 mg
Acetylsalicylic acid (effervescent)		0.3–0.5	0.25	2600 mg
Acetylsalicylic acid (tablet)	30	1.0–2.0	2.0–4.5 (<250 mg) 15–30 (>4000 mg)	4000 mg
Ibuprofen (tablet)	60	1.0–2.0	2.0	2400 mg
Naproxen sodium	30	2.0	14	1375 mg
Diclofenac potassium (tablet)	60	<1.0	2.0	150 mg
Diclofenac potassium (powder)	15	0.25	2.0	Safety and efficacy of a second dose not established

[a] T_{max} refers to time to maximum plasma concentration.

Migraine Treatment Optimization Questionnaire (mTOQ-4) to Assess Response to Acute Treatment[a]

TABLE 4-3

Domain	Never/ Rarely	Less Than Half the Time	Half the Time or More
After taking your migraine medication, are you pain free within 2 hours of most attacks?	0	1	2
Does one dose of your migraine medication relieve your headache and keep it away for at least 24 hours?	0	1	2
Are you comfortable enough with your migraine medication to be able to plan your daily activities?	0	1	2
After taking your migraine medication, do you feel in control of your migraines enough so that you feel there will be no disruption to your daily activities?	0	1	2
Subtotal			
	Total of all columns[b]		

[a] Data from Lipton RB, et al, Cephalalgia.[57]

[b] Scoring is as follows: 0 = very poor treatment efficacy; 1–5 = poor treatment efficacy; 6–7 = moderate treatment efficacy; 8 = maximum treatment efficacy.

CASE 4-3

A 32-year-old woman with a history of episodic migraine with aura was seen for a 3-month follow-up visit. She had been started on a new medication at her last visit. On the current visit, she stated that her response to treatment had been "good." A more detailed inventory of her response indicated that, although she could fully abort each attack with her new medication when taken early, she frequently delayed treatment or avoided treatment altogether because of the presence of medication side effects including nausea and chest tightness, which impaired her ability to function at work. When she delayed treatment, she often noted that her acute attacks improved but did not fully resolve. She had a total score of 5 on the four-item Migraine Treatment Optimization Questionnaire (mTOQ-4) administered in clinic.

COMMENT

Although this patient initially seemed pleased with her response to treatment, her response to directed questions and her mTOQ-4 score indicated that her acute treatment efficacy was poor. A change to a better-tolerated medication that does not impair her ability to function at work or cause her to delay treatment should be considered.

treatment plan for every patient with migraine should include an individualized, evidence-based approach to acute treatment. A stratified approach allows the patient to make autonomous decisions regarding the appropriate treatment for specific types and severities of attacks under the guidance of providers who should help patients select treatments based on their unique needs.

Triptans, intranasal dihydroergotamine, and nonspecific analgesics remain the mainstays of first-line treatment. Factors that should be considered when selecting an optimal first-line treatment include onset of action, T_{max}, half-life, route of administration, time to peak severity, recurrence of headache, and patient preference. Response to treatment and patient satisfaction with treatment should be assessed regularly.

TABLE 4-4 **Troubleshooting Guide for Suboptimal Response to Acute Migraine Treatment**[a]

Patient Response	Treatment Considerations
No response	Increase dose, ensure treatment is early, consider a need to change route of administration, try a different medication after two adequate trials
Partial response	Increase dose, ensure treatment is early, ensure a second dose is taken
Recurrence	Ensure treatment is early, ensure a second dose is taken, consider a longer-acting medication (TABLE 4-2), consider adding a complementary medication such as a nonsteroidal anti-inflammatory drug or antiemetic
Inconsistent response	Increase dose, consider a need to change route of administration
Overuse	Establish use limits and plan of care with patient, limit number prescribed, add prophylactic treatment

[a] Courtesy of David W. Dodick, MD.

CASE 4-4

A 19-year-old man with a history of migraine without aura presented for evaluation of 3 years of inconsistent response to sumatriptan 25 mg, which had previously provided consistent and complete relief since age 10. No changes had occurred in his health or migraine history, and he continued to tolerate the medication well.

COMMENT

This patient tolerated the medication well and should attempt treatment with a standard adult dose of sumatriptan of 100 mg. His inconsistent response may reflect suboptimal dosing that may have previously been effective prior to adolescence.

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