ACUTE TREATMENT OF MIGRAINE

Stewart J. Tepper

ABSTRACT

The goals of acute treatment in migraine should be sustained pain-free response, which will reduce disability and optimally restore function with minimal adverse events and cost. A validated four-item tool, Migraine-ACT, can measure adequacy of acute treatment.

The strategy for picking the right acute treatment initially should be one of stratified care, matching patient need to migraine characteristics. Disability is a surrogate marker for disease severity, allowing for the decision as to when to use migraine-specific treatment versus nonspecific treatment in the absence of vascular disease.

The evidence for efficacy of nonspecific treatments in migraine is mixed, due to variabilities in study designs, but they can be effective for moderate level migraine with low disability. Most studies for acute treatment with oral opioids have been poorly designed or negative. No randomized controlled trials have shown benefit for butalbital mixtures in the acute treatment of migraine.

Migraine-specific treatments include triptans and ergots. Triptans are divided into groups by speed of onset and formulation. When possible, patients should be instructed to take these medications early in the migraine attack to make a sustained pain-free response more likely. Ergot use is limited by poor oral absorption and adverse events.

HISTORICAL VIEW

Initially, the acute treatment of migraine involved alleviation of pain with non-specific treatment, opioids, aspirin, or mixed analgesics. Opioids reduced pain, but often with the burden of sedation and nausea, both of which prevented return to function. Aspirin was unhelpful for severe, disabling headache.

Wolff’s pathophysiological model of migraine envisaged migraine pain as caused by vasodilation, and aura by vasoconstriction. The acute treatment of migraine would thus involve use of a vasoconstrictive agent, such as an ergot, to reverse the vascular cause of the headache (Wolff, 1963). Other vasoconstrictive agents include isomethoheptene mucate (one of the active ingredients in Midrin/Duradrin), caffeine, triptans, and serotonin itself.

Intravenous serotonin (5-hydroxytryptamine [HT]) relieves migraine but causes significant adverse effects, including blood pressure change, nausea, and diaphoresis (Kimball et al, 1960). Both ergots and triptans are 5-HT1 agonists, and their action in migraine may be due to both their serotonergic activity and vasoconstriction. The serotonin-agonist effect may inhibit neurogenic inflammation peripherally around extracerebral intracranial vessels and most likely also inhibits nociceptive afferent input centrally. The vasoconstriction reverses peripheral meningeal vasodilation. It is by no means certain which mechanism is most important in acute migraine pain and its treatment, but it is clear that these medications are migraine specific.
The clinical questions that have evolved and are critical in acute treatment for migraine are: Which patients should receive specific treatment for migraine? When in the attack should patients be instructed to take specific treatment?

GOALS OF ACUTE TREATMENT

The US Headache Consortium published a list of goals for acute migraine treatment in 2000 in *Neurology* (Silberstein, 2000). The goals are:

- Treat attacks rapidly and consistently without recurrence.
- Restore the patient’s ability to function.
- Minimize the use of back-up and rescue medications.
- Optimize self-care and reduce subsequent use of resources.
- Be cost effective for overall management.
- Have minimal or no adverse events.

These goals are clearly what physicians set out to accomplish in the acute treatment of migraine. But are they what patients want from acute treatment?

Over the last 15 years, a number of clinical end points have been used in the evaluation of acute migraine medications. The International Headache Society (IHS) has utilized a 4-point scale from 0 to 3, where 1 is mild pain, 2 is moderate pain, and 3 is severe pain. The end point in a roundtable discussion underwritten by pharmaceutical researchers in conjunction with headache specialists was “headache response,” also referred to as “headache relief” or “pain relief,” depending on the study, and meaning that a patient moves from moderate to severe pain (2, 3) to mild pain or no pain (1, 0) at a particular point in time after treatment.

The IHS has suggested a more rigorous end point, pain free, which means moving from 2 or 3 to 0 after treatment. The advantage of this end point is a lower placebo rate, but the disadvantage is that it raises the bar for treatment and may discourage patients and doctors alike when they find that treatment of a moderate to severe headache results in only a 30% to 40% or lower likelihood of pain freedom at 2 hours.

All of the triptan regulatory trials used an artificial model in which patients were told to wait until they had at least moderate to severe–level pain before treating. This was to assure that they really had a migraine, which by one of the IHS criteria requires moderate to severe pain for diagnosis. However, this does not mean that this approach is the correct clinical technique to maximize benefit from an acute medication. By allowing the migraine to reach a moderate to severe level, the diagnosis becomes clearer, but the treatment may be more difficult. This will be discussed further below.

Several studies have asked patients what is most important to them in an acute migraine medication. While this is not the same as asking what goals a physician should set in acute treatment, it is important to bear in mind the patient’s perspective when providing acute treatment.

Lipton and Stewart (1999) found that the three attributes most important to patients in an acute migraine medication are, in order: (1) complete pain relief (pain free), (2) no recurrence of headache, and (3) rapid onset of pain relief.

The IHS has suggested incorporation of these three features into an even more rigorous single clinical end point with which to evaluate acute migraine medications called sustained pain free, which consists of a patient with a migraine reaching a pain-free state within a specific time after taking acute medication and then having no recurrent migraine or use of rescue medication for the next 24 hours.
Thus, to optimize acute treatment, clinicians should correctly select patients for specific acute migraine treatment and then use these specific medications in such a way as to reach the sustained pain-free state, the patient’s first goal and the new standard of the IHS.

Dowson and colleagues (2004) tested 27 items in four domains to evaluate patient satisfaction and adequacy of acute treatment. The domains were headache impact, global assessment of relief, consistency of response, and emotional response. The four most sensitive and specific questions to ask patients for adequacy of acute treatment constitute the Migraine Assessment of Current Therapy (Migraine-ACT) and are as follows:

- **Consistency of response:** Does your migraine medication work consistently, in the majority of your attacks?
- **Global assessment of relief:** Does the headache pain disappear within 2 hours?
- **Impact:** Are you able to function normally within 2 hours?
- **Emotional response:** Are you comfortable enough with your medication to be able to plan your daily activities?

Scoring the questionnaire is by adding the number of “yes” scores (range: 0 to 4). A score of 2 or less indicates that a change in the acute medication is warranted, and a score of 1 or less may indicate a change is mandated.

Evaluation of the effectiveness of acute treatment for reaching treatment goals can be as simple as asking if the patient has a sustained pain-free response or using Migraine-ACT (Dowson et al, 2004) (Tepper et al, 2005) (Case 5-1).

**STRATEGIES FOR SELECTING ACUTE MIGRAINE MEDICATION**

The significant clinical question facing the neurologist after diagnosing migraine in the office is whether to initially select a nonspecific treatment or a migraine-specific treatment for acute management.

Lipton and colleagues (2000b), after surveying various approaches to acute migraine treatment, described three strategies for treating diagnosed acute migraine, which they called step care across attacks, step care within attacks (also called staged care), and stratified care. Lipton and colleagues’ prospective study in 2000 showed that the stratified care approach yields optimal clinical outcome (Lipton et al, 2000b), and post hoc analysis suggested lower costs with stratified care when compared with the other approaches (Sculpher et al, 2002).

**Step Care Across Attacks**

In this approach after a diagnosis of migraine, the least expensive nonspecific

---

**Case 5-1**

Patient A takes a triptan early in three migraine attacks and is not pain free at 2 hours in two of the three attacks. She cannot go back to work during any of the three attacks even though she gets headache relief, and she is very anxious about her next menstrual attack since she gets menstrually related migraine. She takes the Migraine-ACT and scores 0.

**Comment.** It is mandatory to switch acute medications in this patient. Her description of only partial relief and her very low Migraine-ACT score should compel the clinician to make a change.
medication is selected by the physician for the patient to use first. If this medication fails, the physician will then “step up” to the next drug, until finally reaching a specific, more effective medication.

**Step Care Within Attacks (Staged Care)**

This approach involves starting with a nonspecific, less expensive medication first and then if it fails, having the patient take the specific medication at that point. The specific drug would be used during an attack only if the lower-level medicine had failed. The specific medication would in fact be used as a rescue. Patients often take the staged-care approach themselves. Patients reason that since insurance companies will pay for only a limited number of triptan tablets each month, they should only use the triptan when “things are really bad.” They will start with nonsteroidal anti-inflammatory drugs (NSAIDs) and over-the-counter medication or prescribed nonspecific medication and step up to the triptan during the attack only if the lower-level medication fails. They will hoard their expensive, specific medication.

**Stratified Care**

The third strategy is stratified care, defined as matching treatment to a patient’s characteristics or the characteristics of the disease. Two types of stratified care have been described.

The first would be to evaluate the characteristics of the attack itself. This would involve establishing the following:

- The severity of the peak intensity of the attack
- The time to peak intensity, ie, the rate at which the attack proceeds
- How much time is available to achieve adequate treatment before the patient is disabled?
- Presence of associated symptoms, eg, nausea, vomiting, phonophobia, and photophobia
- Time to associated symptoms

The second type of stratified care is that which is based on disability or impact of the migraine on the patient over time, rather than evaluation of the character of multiple attacks. In this form of stratified care, a disability or impact assessment tool is used, usually the Migraine Disability Assessment Scale (MIDAS), developed by Lipton and colleagues (2000a), or the Headache Impact Test (HIT)-6 (Ware et al, 2000).

MIDAS uses five questions to assess disability, which can be condensed into a single question (not validated as such): “How many days in the last 3 months were you at least 50% disabled at work, home, school, or recreational activities?” Each day of at least 50% disability is given one point, and a score of greater than 10 suggests moderate to severe level of disability (Table 5-1). HIT-6 uses six questions in six domains to assess headache impact and disability, and scores greater than 60 suggest severe impact (Ware et al, 2000).

The Disability in Strategies of Care (DISC) study is the only randomized prospective comparison of step care within attacks, step care across attacks (staged care), and stratified care (Lipton et al, 2000b). Patients with episodic migraine were treated with either 900-mg aspirin (ASA) and 10-mg metoclopramide (MCP) as nonspecific medication, or zolmitriptan as the specific triptan.

The patients were randomly assigned by the strategy with which to treat them. In Group I, the step-care-across-attacks group, subjects received ASA/MCP to abort migraine for three attacks, and if this was not successful, the patients were allowed to “step up” to zolmitriptan for the fourth attack and thereafter.
In Group II, step care within attacks, subjects were given ASA/MCP for three attacks, and if it was not successful within each attack, they were given zolmitriptan to use at 2 hours.

In Group III, the stratified-care group, subjects were stratified to a low treatment–need group (MIDAS score less than 11, or fewer than 11 days of at least 50% disability in the previous 3 months), to receive ASA/MCP, or to a moderate to high treatment–need group (MIDAS score greater than 10) to receive zolmitriptan from the beginning. If after six attacks, the subjects receiving ASA/MCP wished to switch to zolmitriptan, they were then allowed to do so.

The primary end points were the 2-hour headache response rate over six attacks and the disability time per attack. Note that the study was not meant to see which worked better, low-level, nonspecific treatment or specific treatment with triptans. Rather this was a study to determine which strategy for selecting an acute-care medication would work better for patients. The idea was to find out when to use which treatment in which patient (ie, how to get to the right treatment the first time).

All primary end points were superior for stratified care as the strategy for treatment, as opposed to the step-care strategies. Even in the patients who

---

**TABLE 5-1**

**MIDAS Questionnaire**

1. On how many days in the last 3 months did you miss work or school because of your headaches? _____ days

2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.) _____ days

3. On how many days in the last 3 months did you not do household work because of your headaches? _____ days

4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.) _____ days

5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? _____ days

Your rating: TOTAL: _____ days

A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.) _____ days

B. On a scale of 0–10, on average how painful were these headaches? (Where 0 = no pain at all, and 10 = pain as bad as it can be.) _____ days

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Minimal or infrequent disability</td>
<td>0–5</td>
</tr>
<tr>
<td>II</td>
<td>Mild or infrequent disability</td>
<td>6–10</td>
</tr>
<tr>
<td>III</td>
<td>Moderate disability</td>
<td>11–20</td>
</tr>
<tr>
<td>IV</td>
<td>Severe disability</td>
<td>21+</td>
</tr>
</tbody>
</table>

were stratified to ASA/MCP in the stratified-care group because of low disability scores, 56% chose to move up to zolmitriptan after six attacks treated with ASA/MCP. This suggests that even in the low treatment–need group, patients felt a need for stronger or specific medication more often than not.

Disability time was also consistently less for stratified care, suggesting pharmacoeconomic benefit for choosing a stratified-care strategy for patients. Three post-hoc analyses have been conducted since the primary end points were calculated. All found lower costs with the stratified-care model (Rapoport et al, 2000a; Rapoport et al, 2000b; Sculpher et al, 2002; Tepper and Meddis, 2000).

Thus, the DISC study has yielded clear, prospective evidence in favor of matching disability to treatment. Patients with episodic migraine with more than 10 days of at least 50% disability in the last 3 months by MIDAS score and no medical contraindication should be given triptan therapy at the outset as their first medication for acute treatment, and not be given a lower-level medication and stepped-up care across attacks or in the same attack.

**NONSPECIFIC TREATMENT**

Nonspecific treatments for migraine include NSAIDs; ASA; acetaminophen (APAP); combinations of ASA, APAP, and aspirin/amphetamine/caffeine (AAC); neuroleptics; antiepilepsy drugs (AEDs); γ-aminobutyric (GABA) agonists, such as baclofen; antihistamines; mild vasoconstrictor/sedative/APAP mixtures (isometheptene/dichloralphanzone/APAP); barbiturate mixtures (butalbital/caffeine with either ASA or APAP); and opioids. Some of these are available over-the-counter and some require prescriptions, but all are used for cost reasons and to avoid significant vasoconstrictive effects of migraine-specific treatment.

The evidence for effectiveness of these medications is mixed. There is evidence that 1000 mg of ASA is as effective as 1000 mg of APAP in treatment of migraine (Tfelt-Hansen and Olesen, 1980).

In a placebo-controlled study of AAC, 172 subjects with IHS migraine but no vomiting for more than 20% of their attacks and no incapacitating disability (requiring bed rest for more than 50% of their attacks) on presentation were included. Thus they were preselected in a nonrandomized way. Eighty-nine subjects were randomly assigned to AAC and 83 to placebo. The end points of pain intensity, functional disability, nausea, vomiting, photophobia, and phonophobia were rated at baseline and after 30 minutes, 1, 2, 3, 4, and 6 hours postdose. From 1 hour and continuing through 6 hours postdose, the proportion of responders was significantly greater (P < .01) for AAC than placebo. These patients took two tablets of AAC, each containing 250-mg APAP, 250-mg ASA, and 65-mg caffeine. Other studies have confirmed AAC effectiveness in preselected patient groups with lower-level migraines (Goldstein et al, 1999; Lipton et al, 1998). A subsequent factorial analysis found that two tablets of a German AAC combination of ASA 250 mg, APAP 400 mg, and caffeine 50 mg was more effective than its individual single and dual combinations (Diener et al, 2005), suggesting that caffeine can be a useful adjuvant in nonspecific medications.

For the acute treatment of migraine attacks with NSAIDs, most of the anthranilic class (eg, tolfenamic acid) and propionic acid class (eg, naproxen) have been proven effective in randomized controlled studies (Limmroth and Przywara et al, 2000). Diclofenac, an NSAID derivative of acetic acid, was tested in migraine attacks and shown to be superior to placebo and APAP.
Solubilized ibuprofen is also effective in migraine compared with placebo (Kellstein et al, 2000). The US Headache Consortium guidelines have suggested that NSAIDs or AAC can be effective for moderate-level migraine (Silberstein, 2000). However, as noted above, the studies on ibuprofen and AAC over-the-counter medications for acute migraine treatment are not as strong methodologically as those suggesting effectiveness for triptans because in the US over-the-counter studies, patients were selected who had reduced frequency of vomiting or bedrest with their migraine, ie, less severe attacks, while in the triptan studies, all patients with episodic migraine of any intensity were included (Lipton et al, 2000b; Sculpher et al, 2002). Therefore, the evidence for effectiveness in the acute treatment of migraine is not equivalent for the non-specific medications and the triptans.

Most studies for acute treatment with oral opioids have been poorly designed or negative (Boureau et al, 1994; Carasso and Yehuda, 1984; Gawel et al, 1990; General Practitioner Research Group, 1973; Silberstein and McCrory, 2000; Snow et al, 2002; Uzogara et al, 1986). After considering the data on oral and nonoral opioids, the following recommendations were made by the US Headache Consortium (Silberstein, 2000; Snow et al, 2002):

Nasal butorphanol is a treatment option when other medications can’t be used or as a rescue medication when severe sedation is not a critical issue for the patient. Oral opioid combinations may be considered when sedation will not put the patient at risk and/or the risk for abuse has been addressed. Parenteral opioids may be considered a choice only in a supervised setting and again when sedation will not put the patient at risk and/or the risk for abuse has been addressed.

One prospective study suggests that after migraine progresses to a state manifested by allodynia, sumatriptan subcutaneous plus parenteral NSAIDs such as ketorolac may make patients pain free. However, those patients previously exposed to opioids did not benefit from the intravenous ketorolac, suggesting that (1) NSAIDs may reverse central sensitization in migraine, but (2) opioids may worsen central sensitization and should be avoided for acute treatment (Jakubowski et al, 2005). No randomized controlled trials have shown benefit for butalbital mixtures in the acute treatment of migraine. Most countries, including the entire European Union, have elected to remove butalbital from the market because of the lack of evidence for efficacy and the high rates of habituation and dependence with its use. Butalbital is also not available in Latin America or Asia, leaving the United States as one of the only countries left in the world with this pernicious medication available for prescription (Case 5-2).

**SPECIFIC MEDICATIONS: TRIPTANS**

Oral triptans can be divided into two clinical groups. Group I consists of those triptans with fast onset, relatively high headache response, and pain-free rates at 2 hours (Tables 5-2, 5-4, 5-5, and 5-6).

Group II triptans have slower onset and lower efficacy rates. Their efficacy numbers at 4 hours are similar to the Group I triptans at 2 hours (see Tables 5-3, 5-4, 5-5, and 5-6). The similarities among the Group I oral triptans are greater than the differences, and the population differences are less important than individual patient preferences. Robert Kaniecki,

**KEY POINTS:**
- For the acute treatment of migraine attacks with NSAIDs, most of the anthranilic class (eg, tolfenamic acid) and propionic acid class (eg, naproxen) have been proven effective in randomized controlled studies.
- The US Headache Consortium guidelines have suggested that NSAIDs or aspirin/amphetamine/caffeine can be effective for moderate-level migraine.
- The evidence for effectiveness in the acute treatment of migraine is not equivalent for the nonspecific medications and the triptans.
- Data suggest that after migraine progresses to a state manifested by allodynia, sumatriptan subcutaneous plus parenteral NSAIDs such as ketorolac may make patients pain free.
in public lectures, has described the decision as to which triptan to choose a spick in ga mon geth e r e three F’s: fast versus slow, formulation, and formulary availability.

Two brief cases of young patients without vascular risk factors will illustrate this decision process (Cases 5-3 and 5-4).

The orally dissolvable tablets available with rizatriptan (Maxalt MLT) and zolmitriptan (Zomig ZMT) do not have buccal or sublingual absorption. Rather, they are oral tablets that taste better than conventional tablets and so do not represent truly different formulations that would meet patient need in the setting of vomiting, such as in patient C in Case 5-3. Finally, once the group of triptans is selected and the need for formulation is established, a triptan can be selected based on formulary tier status. In the United States, triptans are either Tier 2 or Tier 3, with average copays of $25 and $50 respectively. Patients greatly appreciate a preferred formulary status in Tier 2 for cost reasons.

Having decided which patients in whom to use triptans, the next question is how to use the triptans to best achieve a sustained pain-free response. Burstein and colleagues published evidence that as migraine progresses, cutaneous allodynia is manifested, and they have suggested that earlier treatment might avoid this process. They have shown that in patients who develop allodynia, treatment with sumatriptan before allodynia develops is far more likely to result in a pain-free response (Burstein et al, 2004; Burstein et al, 2000; Burstein and Jakubowski, 2004). If the migraine is allowed to proceed, multiple non-nociceptive stimuli—sensitivity to light, noise, smell, movement, and possibly to the effects of medication—become painful. Treating early would abort this.

Reviewing the naratriptan database for evidence that early treatment would be associated with lower recurrence, Sheftell and colleagues (1994)

### TABLE 5-2

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Imitrex, Imigran</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig, AscoTop, Zomigon</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Axert, Almogran</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax</td>
</tr>
</tbody>
</table>
found that patients who were treated in the first 90 minutes of an attack were less likely to experience recurrence than those who were treated after 2 hours. They speculated that achieving a pain-free response might be tied to reduced recurrence rate.

Early intervention resulting in greater likelihood of a sustained pain-free effect appears to be a triptan class effect. The preponderance of evidence suggests that early intervention is the best way to use triptans to achieve optimal results in terms of both patient outcome and pharmacoconomics, since a sustained pain-free result means fewer tablets per attack because there is no recurrence.

To summarize, selection of patients for specific migraine treatment involves stratifying the patient according to disability or characteristics of the migraine attack. In the absence of medical contraindications, if an episodic migraineur has had greater than 10 days of at least 50% disability in the last 3 months, initial acute treatment should be with a triptan (although more than half of the patients stratified to nonspecific treatment in the DISC study requested a triptan later). Furthermore, if the patient has been stratified to use a triptan, the patient should be instructed not to step up medication in an attack or delay treatment, but rather to treat with the triptan at the mild level of

**TABLE 5-3** Group II Triptans: Slower Onset

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naratriptan</td>
<td>Amerge, Naramig</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova</td>
</tr>
</tbody>
</table>

**TABLE 5-4** Triptan Medications

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Formulations</th>
<th>Doses</th>
<th>Maximum Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Imitrex</td>
<td>Tablets</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>200 mg (US)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasal spray</td>
<td>5 mg, 20 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous injection</td>
<td>4 mg, 6 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suppositories (EU)</td>
<td>25 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Zomig</td>
<td>Tablets</td>
<td>2.5 mg, 5.0 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td></td>
<td>Zomig-ZMT</td>
<td>Orally disintegrating tablets</td>
<td>2.5 mg, 5.0 mg</td>
<td>10 mg (US)</td>
</tr>
<tr>
<td></td>
<td>Zomig</td>
<td>Nasal spray</td>
<td>5.0 mg</td>
<td>10 mg (US)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Maxalt</td>
<td>Tablets</td>
<td>5 mg, 10 mg</td>
<td>30 mg (US)</td>
</tr>
<tr>
<td></td>
<td>Maxalt-MLT</td>
<td>Orally disintegrating tablet</td>
<td>5 mg, 10 mg</td>
<td>30 mg (15 mg if on concomitant propranolol)</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Amerge</td>
<td>Tablets</td>
<td>1.0 mg, 2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Axert</td>
<td>Tablets</td>
<td>12.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Frova</td>
<td>Tablets</td>
<td>12.5 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Relpax</td>
<td>Tablets</td>
<td>20 mg, 40 mg</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

US = United States; EU = European Union.

**KEY POINTS:**

- Patients who are treated in the first 90 minutes of an attack are less likely to experience recurrence than those who are treated after 2 hours.
- The preponderance of evidence suggests that early intervention is the best way to use triptans to achieve optimal results in terms of both patient outcome and pharmacoconomics, since a sustained pain-free result means fewer tablets per attack because there is no recurrence.
pain to avoid incomplete response, recurrence, and disability.

**ERGOTS—THE OTHER MIGRAINE-SPECIFIC TREATMENTS**

The ergot alkaloids were the first specific antimigraine therapy available. Their use in the treatment of migraines has declined, and their role is less clear now in the triptan era.

The ergot alkaloids interact with multiple receptors. The two used for acute treatment of migraine, dihydroergotamine (DHE) and ergotamine (ET), can cause vasoconstriction by stimulating α-adrenergic and 5-HT receptors, although ET is a more potent vasoconstrictor (Tables 5-7 and 5-8). Both can inhibit the actions of norepinephrine (NE) and 5-HT and are venoconstrictors (Müller-Schweinitzer, 1984; Silberstein, 1997). ET and DHE bind to 5-HT\textsubscript{1A}, 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D}, 5-HT\textsubscript{1F}, 5-HT\textsubscript{2A} (D), 5-HT\textsubscript{2C}, and 5-HT\textsubscript{3} (M) receptor sub-types (Müller-Schweinitzer

<table>
<thead>
<tr>
<th>Drug</th>
<th>T\textsubscript{max} (h)</th>
<th>T\textsubscript{1/2} (h)</th>
<th>Bioavailability (%)</th>
<th>Elimination Route/ Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>2</td>
<td>2</td>
<td>14</td>
<td>Hepatic; MAO-A; 60% renal</td>
</tr>
<tr>
<td>50-mg tablet</td>
<td>2.5</td>
<td>2</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>20-mg spray</td>
<td>1</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-mg subcutaneous</td>
<td>0.2</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2</td>
<td>2.5–3.0</td>
<td>40–48</td>
<td>Hepatic (1 active and 2 inactive metabolites; CYP/MAO-A</td>
</tr>
<tr>
<td>2.5-mg tablet</td>
<td>2</td>
<td>2.5–3.0</td>
<td>40–48</td>
<td></td>
</tr>
<tr>
<td>2.5-mg ZMT</td>
<td>3.3</td>
<td>2.5–3.0</td>
<td>40–48</td>
<td></td>
</tr>
<tr>
<td>2.5-mg nasal</td>
<td>2</td>
<td>2.0–3.0</td>
<td>45</td>
<td>Hepatic MAO-A; 30% excreted renally unchanged</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>1.2 (Tablet)</td>
<td>2.0–3.0</td>
<td>40</td>
<td>Hepatic; CYP/MAO-A; 15% active N-demethyl metabolite; 26%–35% excreted renally unchanged</td>
</tr>
<tr>
<td></td>
<td>1.6–2.5 (MLT)</td>
<td>2.0–3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td>2.0–3.0</td>
<td>5.0–6.3</td>
<td>63 (men), 74 (women)</td>
<td>70% excreted renally unchanged; CYP; not MAO-A</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>1.4–3.8</td>
<td>3.2–3.7</td>
<td>80</td>
<td>Hepatic; CYP/MAO-A; 15% active N-demethyl metabolite; not MAO-A</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>1.0–2.0</td>
<td>3.6–5.5</td>
<td>50</td>
<td>Hepatic; CYP3A4; 15% active N-demethyl metabolite; not MAO-A</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.0–4.0</td>
<td>25</td>
<td>24–30</td>
<td>Hepatic; CYP/MAO-A; 26%–35% excreted renally unchanged</td>
</tr>
</tbody>
</table>

T\textsubscript{max} = time to peak plasma concentration.; T\textsubscript{1/2} = half-life; MAO-A = monoamine oxidase-A; CYP = cytochrome P450.

and Weidmann, 1978). Triptans bind only to 5-HT\textsubscript{1B}, 5-HT\textsubscript{1D}, and 5-HT\textsubscript{F} receptors.

Clinically, ergots are difficult to use. The oral bioavailability of ET is less than 1% (Little et al, 1982). Because most of the drug is metabolized during the first pass through the liver (Iversen et al, 1990), use of ET suppositories is more likely to give clinical benefit than the oral formulation.

Oral ET is appropriate for patients with slowly evolving migraine without early-onset nausea. The patient should take one 1-mg tablet at the start of an attack, with a maximum total dose of 6 mg per attack. Even this 1-mg dose, the smallest available in the United States, is often nauseating.

Nausea may indicate that the dose is too high, but the ET currently available in the United States is neither scored nor breakable into smaller doses, further limiting clinical usefulness. Taking the ET early, before migraine nausea has begun with its associated symptoms, may be more effective.

### Case 5-3

**Patient C with no vascular risk factors has episodic migraines with severe peak intensity, a short time to vomiting, and a short time to peak intensity.**

**Comment.** A nonoral triptan will be necessary. The only two triptans with multiple formulations are sumatriptan with oral, nasal, and subcutaneous (SC) formulations, and zolmitriptan with oral and nasal formulations. With severe vomiting and prostration, injectable sumatriptan will be necessary.
gastric stasis, is critical for using the oral formulation.

Even more important than limiting total dosage is restricting ET use to no more than 2 days per week with an interval of at least 4 days in between usage days to prevent drug-induced headache (Saper, 1987; Silberstein and Young, 1995), which is extremely common with frequent ET usage.

The suppository, which is useful in patients with severe nausea and vomiting, yields higher plasma levels of ET and has greater efficacy than oral tablets. According to Raskin (1988) and Mathew (1997), the likelihood of drug-associated nausea, a frequent side effect of ET, can be reduced through determination of a subnauseating dose of ET suppository. The patients are instructed to cut the suppositories, and subnauseating doses may range from one-half suppository (1.0 mg) down to as little as one-eighth suppository (0.25 mg) (Mathew, 1991). When an attack develops, the patient should administer the subnauseating dose at the start of the attack. Once again, limiting to no more than 1 to 2 days of usage per week is critical to avoiding habituation, rebound, and daily headache.

There is no doubt that DHE represents an advance over ET in treating migraine with or without aura, status migrainosus, and chronic daily headache (transformed or chronic migraine). Side effects are fewer, and habituation is rare.

Oral DHE has even lower bioavailability than ET, due to incomplete drug passage across the gastrointestinal tract.

### TABLE 5-7 Ergotamine and Dihydroergotamine Receptor Profile

<table>
<thead>
<tr>
<th>Adrenergic Receptors</th>
<th>Dopaminergic Receptors</th>
<th>Serotonergic Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha&lt;sub&gt;1&lt;/sub&gt;</td>
<td>DA&lt;sub&gt;1&lt;/sub&gt;</td>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
</tr>
<tr>
<td>Alpha&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DA&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td>5-HT&lt;sub&gt;1F&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-HT&lt;sub&gt;2A&lt;/sub&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-HT&lt;sub&gt;2C&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

*<sup>Alpha<sub>1</sub> > Alpha<sub>2</sub> > Beta.</sup><br>DA<sub>2</sub> > DA<sub>1</sub>.

mucosa and a high first-pass metabolism, in contrast to the absolute bioavailability of intramuscular (IM) DHE (100%) (Little et al, 1982). The absolute bioavailability of DHE following intranasal (IN) administration is approximately 40% (Bigal and Tepper, 2003). Peak plasma levels occur approximately 1 to 2 minutes after intravenous (IV) administration, 24 minutes after IM administration, and 30 to 60 minutes after IN administration. IN administration of DHE avoids first-pass hepatic metabolism (Ziegler et al, 1994). Both IN and parenteral administration of DHE are reasonable.

Studies published in the 1990s have shown comparable efficacy between SC and IM administrations (Winner et al, 1993). Anecdotally, clinicians advise patients to mix DHE with 0.25 mL to 0.50 mL of 1% to 2% lidocaine in the same syringe (they are miscible) to reduce injection-site burning. The patient will need training to self-administer DHE by IM or SC injection, starting with a single injection of DHE 1 mg, which may be repeated, if needed, after 60 minutes. Once again, titration to a subnauseating dose is important. Maximum dosing is 3 mg/d, 21 mg per week. Dosing of IN DHE is one spray (0.5 mg) into each nostril (without sniffing) at the first sign of migraine, followed 15 minutes later by an additional spray into each nostril. Thus, the total dose administered is 2 mg in four sprays. The maximum recommended dose is 4 mg per attack (Raskin, 1988). The utility of DHE nasal spray is limited clinically by relatively low efficacy and high frequency of prolonged nasal stuffiness. The advantage of ergots is that once headache relief is established, recurrence of migraine is low.

In randomized clinical trials, oral ET was found superior to placebo but inferior to oral sumatriptan 100 mg (Tfelt-Hansen, 2001; Tfelt-Hansen et al, 2000). IN DHE was found superior to placebo but less effective than SC and IN sumatriptan, at least for initial response. Recurrence was lower.

<table>
<thead>
<tr>
<th>Safety/Efficacy Measure</th>
<th>Dihydroergotamine Mesylate</th>
<th>Ergotamine Tartrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-hydroxytryptamine 1 (5-HT1) activity</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Arterial vasoconstriction</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Venoconstriction</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>α-Adrenergic antagonist activity</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Uterotonic effects</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Pain relief</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Headache recurrence</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Rebound headache</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

0 indicates none; + mild; ++ moderate; +++ prominent.

with IN DHE than with sumatriptan (Winner et al, 1996).

In summary, the issues for use of ergots are as follows: (1) They cannot be mixed with each other or triptans. (2) They are difficult to use, requiring titration of dose. (3) ET is highly associated with medication overuse.

### TABLE 5-9
**Parenteral Acute Treatments for Migraine for Use in Clinic or Emergency Department**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Other Facts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dihydroergotamine</td>
<td>1-mg or maximum subnauseating dose</td>
<td>SC, IM, IV</td>
<td>May be mixed with lidocaine in SC or IM dosing; recurrence is low; non-sedating; contraindicated with vascular disease</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>6 mg</td>
<td>SC</td>
<td>Non-sedating; contraindicated with vascular disease</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg</td>
<td>IV</td>
<td>Risk of extrapyramidal effects and mild sedation</td>
</tr>
<tr>
<td>Promethazine</td>
<td>25 mg to 50 mg</td>
<td>IM, IV</td>
<td>Risk of extrapyramidal effects and sedation</td>
</tr>
<tr>
<td>Prochlorperazone</td>
<td>10 mg</td>
<td>IV</td>
<td>Risk of extrapyramidal effects and sedation</td>
</tr>
<tr>
<td>Droperidol</td>
<td>2.5 mg to 5.0 mg</td>
<td>IV</td>
<td>Risk of QT prolongation, extrapyramidal effects and sedation</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg to 8 mg</td>
<td>IV</td>
<td>Non-sedating antinauseant</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>30-mg IV, 60-mg IM</td>
<td>IM, IV</td>
<td>Non-sedating</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>4 mg to 10 mg</td>
<td>IM, IV</td>
<td>Non-sedating</td>
</tr>
<tr>
<td>Valproate</td>
<td>500 mg to 1000 mg</td>
<td>IV</td>
<td>Non-sedating</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1 g</td>
<td>IV</td>
<td>Non-sedating; works best for patients with migraine with aura</td>
</tr>
</tbody>
</table>

SC = subcutaneous; IM = intramuscular; IV = intravenous.

---

**Case 5-5**

Patient E wakes up with a vomiting migraine, takes a 100-mg sumatriptan tablet, and only partially holds it down. She calls and says she needs a rescue medication. What options does she have to avoid a trip to the emergency department?

**Comment.** The easiest rescue would be sumatriptan SC, since forms of sumatriptan can be mixed. This can be supplemented with a neuroleptic suppository, since she is vomiting. If she comes to the office, parenteral ketorolac, steroids, or valproate can also be used.
headache (Saper, 1987). (4) Adverse events can be significant. (5) They are not clearly superior to the more convenient triptans, except with respect to IV DHE.

Both triptans and ergots are contraindicated in the setting of vascular disease, and when vascular risk factors are present, a functional workup should be undertaken prior to administering the first dose in the office. As noted, both triptans and ergots are vasoconstrictive. Also, both triptans and ergots are contraindicated in hemiplegic and basilar-type migraine within 24 hours of each other.

RESCUE AND EMERGENCY TREATMENT

As noted above in the section on opioids, the use of narcotics as rescue treatment for status migrainosus should be avoided. In an outpatient setting, when a migraine appears to spiral out of control due to late or inadequate treatment, this author recommends use of SC sumatriptan, repetitive DHE nasal spray, or a brief several-day course of steroids, such as dexamethasone (Case 5-5).

In the clinic or emergency department, a variety of IM or IV treatments can be used together or separately, with the only contraindication that of mixing triptans and ergots in the same day, and that of avoiding triptans and ergots in patients with vascular disease. Rescue treatments are listed with doses in Table 5-9.

CONCLUSIONS

Acute treatment of migraine involves stratified care and preferential use of migraine-specific medications for those with disabling migraines. Nonspecific treatment is probably less effective for severe migraine, and ergots are more difficult to use. Rescue can involve medications from multiple classes, including triptans or ergots, neuroleptics, steroids, nonsteroidal anti-inflammatories, valproate, and magnesium.

REFERENCES


The above three articles by Burstein and colleagues form a trio of seminal research and hypothesis pieces on understanding allodynia, migraine pathophysiology, and the link to acute treatment.


A typical well-controlled nonsteroidal anti-inflammatory drug (NSAID) trial for acute treatment.


A superb factorial study in which the components of aspirin/amphetamine/caffeine (AAC) are compared with the combination and placebo.


The validation study on Migraine Assessment of Current Therapy (Migraine-ACT).


A thoughtful guide to analgesic treatment in headache.


Regulatory trial for the indication of AAC in the acute treatment of migraine.


Winner of the Wolff award for best headache research of 2005, this is a must-read study describing the effects of NSAIDs on central sensitization and of the deleterious effects of opioids in treating acute migraine.


The regulatory trial for the indication of ibuprofen in the acute treatment of migraine.

Early description of serotonin effects.


Introduction of the Migraine Disability Assessment Scale (MIDAS).


Establishes sustained pain free as the appropriate clinical goal in acute treatment.


Regulatory trial for the indication of AAC in the acute treatment of migraine.


A must-read study of the requirement for disability assessment in the decision on acute migraine treatment.


Post-hoc pharmacoeconomic analysis of the Disability in Strategies of Care (DISC) study.
Post-hoc pharmaceconomic analysis of the DISC study.


Classic review.

The largest and best post-hoc pharmaceconomic analysis of the DISC study.

Onset study for the RT sumatriptan tablets.

First study to note decreased effectiveness of sumatriptan late in attacks.

The American Academy of Neurology (AAN)/American Headache Society/ US Headache Consortium Guidelines with links to federally funded technical reports on prophylaxis, acute treatment, imaging, and nonpharmacological treatments.


A must-read, the professional guideline recommendations on ergots of the AAN.

More of the US Headache Consortium Guidelines, this time published in the internal medicine literature.


A review with the personal point of view of the author about the current uses and problems of ergotamine and dihydroergotamine.


Presents the European consensus regarding the treatment of migraine with ergotamine.


Provides the Headache Impact Test, another validated disability assessment tool.


Study on outpatient use of dihydroergotamine.


The classic text.


Regulatory trial for indication of nasal dihydroergotamine for acute migraine treatment.