

## CLINICAL THERAPEUTICS

## Triptan Therapy in Migraine

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*This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.*

An otherwise healthy 23-year-old woman presents to her internist with a report of headaches and associated symptoms that occur twice a month. A diagnosis of migraine without aura is made. The patient's headaches last up to a day and cause her to miss work. The headaches have not responded reliably to analgesics or to combinations of analgesics with caffeine. Her internist has previously recommended the combination of aspirin and metoclopramide, which usually diminishes but does not eliminate her headache pain. On one occasion, her headache progressed despite treatment, and the patient went to the emergency department. She received subcutaneous sumatriptan for a presumptive diagnosis of migraine. Her headache and nausea resolved, but she had a sensation of mild chest pressure for about 5 minutes, without associated symptoms. Her internist refers her to a headache specialist with the question of what therapy should be used to treat her headache episodes.

## THE CLINICAL PROBLEM

Migraine is a genetically influenced chronic brain condition marked by paroxysmal attacks of moderate-to-severe, throbbing headache with associated symptoms that may include nausea, vomiting, and photophobia or phonophobia. In up to a third of patients with migraine, the headaches are accompanied by focal neurologic symptoms (often visual) known as aura (Table 1).<sup>1</sup> The World Health Organization estimates that 324 million persons worldwide have migraines.<sup>2</sup>

Migraine is both more common and more severe in women than in men.<sup>3</sup> Symptoms generally begin in adolescence or early adulthood. Disease activity peaks during middle age, with a lifetime cumulative incidence of 43% in women and 18% in men.<sup>4</sup> Although migraine is not life-threatening, it is associated with an increased risk of other vascular complications, including ischemic stroke and preeclampsia.<sup>5,6</sup>

Almost a quarter of patients with migraines have more than 3 days of headache a month, and such headaches often interfere with work, social functioning, and overall quality of life.<sup>7</sup> Episodes of headache, the majority of which are migraine headaches, account for almost 3% of visits to the emergency department in the United States<sup>8,9</sup> and 1.3% of outpatient visits.<sup>10</sup> Health care expenses associated with migraine include direct costs of roughly \$11 billion among patients with health insurance and indirect costs of almost \$12 billion.<sup>11,12</sup>

## PATHOPHYSIOLOGY AND THE EFFECT OF THERAPY

The pathophysiology of migraine is not completely understood. There is considerable evidence that intracranial vasodilatation, long thought to be causal, in fact

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**Table 1. Diagnostic Criteria for Migraine.\*****Migraine without aura**

Criterion A — At least five attacks fulfilling criteria B through D

Criterion B — Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)

Criterion C — Headache having at least two of the following characteristics:

Unilateral location

Pulsating quality

Moderate or severe intensity (inhibiting or prohibiting daily activities)

Aggravation on using stairs or engaging in similar routine physical activity

Criterion D — Headache during which at least one of the following occurs:

Nausea or vomiting

Photophobia and phonophobia

Criterion E — At least one of the following criteria is met:

History and physical and neurologic examination do not suggest an organic disorder

History or physical or neurologic examination suggests an organic disorder that is ruled out after appropriate investigation

Organic disorder is present, but initial migraine attacks do not occur close to the time at which the organic disorder began

**Typical aura with migraine headache†**

Criterion A — At least two attacks fulfilling criteria B through D

Criterion B — Aura consisting of at least one of the following criteria but no motor weakness:

Fully reversible visual symptoms, including positive features (e.g., seeing flickering lights or spots or lines), negative features (e.g., loss of vision), or both

Fully reversible sensory symptoms, including positive features (e.g., feeling of pins and needles, usually in the arms and legs, the face, or on one side of the body), negative features (e.g., numbness), or both

Fully reversible dysphasic speech disturbance

Criterion C — At least two of the following criteria:

Visual symptoms on one or both sides of the visual field, or unilateral sensory symptoms

At least one symptom of aura develops gradually over the course of 5 minutes or more, or other symptoms of aura occur in succession over the course of 5 minutes or more

Each symptom lasts between 5 and 60 minutes

Criterion D — Headache fulfilling criteria B through D for migraine without aura; migraine without aura begins during the aura or follows the aura within 60 minutes

Criterion E — Symptoms cannot be attributed to another disorder

\* Adapted from the International Classification of Headache Disorders II (2004).<sup>1</sup> More information on the classification of headache disorders is available at the International Headache Society Web site at [www.i-h-s.org](http://www.i-h-s.org).

† Typical aura with migraine headache is the most common subform of migraine with aura.

occurs in response to the neurologic events of migraine.<sup>13</sup> The most widely accepted theory regarding the physiological mechanism of migraine proposes that early in an attack, vasoactive peptides are released from the primary

sensory nerve terminals that innervate meningeal blood vessels. These peptides activate perivascular trigeminal nerves and cause dilatation of arteries in the meninges as well as perivascular inflammation and extravasation of plasma proteins. First-order neurons terminate in the trigeminal nucleus caudalis in the brain stem. They activate second-order neurons that ascend to the thalamus, and from there, third-order neurons project to higher cortical centers. If uninterrupted, this process causes pain and can lead to hyperalgesia and allodynia, both hallmarks of prolonged migraine attacks.<sup>14</sup>

Activation of the sympathetic nervous system is the likely cause of nausea, vomiting, and other autonomic symptoms associated with migraine. Sensitivity to light, sound, and smell is theorized to result from abnormal brain-stem modulation of sensory information.<sup>15,16</sup> There is evidence that aura is caused by cortical spreading depression, a transient, spreading disturbance in cortical function. Cortical spreading depression is most easily triggered in the occipital cortex, possibly explaining the predominance of visual forms of aura.<sup>15</sup>

Triptans are serotonin (5-hydroxytryptamine, or 5-HT) agonists with high affinity for 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> receptors. Triptans were originally thought to provide relief from migraine by causing cranial vasoconstriction, most likely through action at postsynaptic 5-HT<sub>1B</sub> receptors on the smooth-muscle cells of blood vessels. It is now theorized that triptans also block the release of vasoactive peptides from the perivascular trigeminal neurons through their action at presynaptic 5-HT<sub>1D</sub> receptors on the nerve terminals. In addition, triptans bind to presynaptic 5-HT<sub>1D</sub> receptors in the dorsal horn, and this binding is thought to block the release of neurotransmitters that activate second-order neurons ascending to the thalamus.<sup>17</sup> Triptans may also facilitate descending pain inhibitory systems.<sup>18,19</sup>

#### CLINICAL EVIDENCE

Randomized, controlled trials have evaluated parenteral, oral, suppository, and nasal formulations of various triptans for short-term treatment of migraine. In these trials, the most widely used measure of benefit is a reduction in the severity of headache pain 2 hours after treatment, rated on a four-point scale (no pain, mild pain, moder-

ate pain, or severe pain). Headache “response” has traditionally been defined as a reduction from moderate or severe headache to mild or no headache 2 hours after administration of the medication. The “therapeutic gain” is the difference between the headache response with triptan therapy and the response with placebo.

In a review of 13 randomized trials, a 6-mg dose of a subcutaneous formulation of sumatriptan was shown to have a mean therapeutic gain of 51 percentage points (70% response with active treatment vs. 19% with placebo), which is the largest for all available triptans.<sup>20</sup> Most patients, however, prefer to use oral drugs to treat migraine. A meta-analysis by Ferrari et al. summarized 53 randomized, double-blind controlled trials, involving more than 24,000 patients, in which oral triptans were compared with placebo.<sup>21</sup> The 100-mg oral dose of sumatriptan was the reference dose, with a mean therapeutic gain at 2 hours of 29 percentage points (59% response rate with active treatment vs. 30% with placebo). Most of the other triptans evaluated had similar therapeutic gain when administered at doses recommended by the manufacturer. The exceptions were frovatriptan, which was significantly less effective, and naratriptan, which was marginally less effective.

Fewer trials have compared the effectiveness of triptans directly with that of nontriptan therapy. In a review of published trials in which oral triptans were used, Lipton et al. found that the data suggested a significantly greater benefit with triptans than with ergotamine compounds, but no significant difference was detected between the effect of triptans and that of nonsteroidal or other analgesics.<sup>22</sup> In one study of 733 patients, 54% of patients receiving 40 mg of oral eletriptan had relief from headache at 2 hours, as compared with 33% of those receiving a combination of 1 mg of ergotamine and 100 mg of caffeine ( $P < 0.001$ ).<sup>23</sup> In another study, involving 666 patients, which defined efficacy as a headache response in three of three migraine attacks, the efficacy was 33.4% with 2.5 mg of oral zolmitriptan as compared with 32.9% with 900 mg of acetylsalicylic acid plus 10 mg of metoclopramide ( $P = 0.72$ ).<sup>24</sup>

Recently, new information has become available about unpublished comparative randomized trials of oral sumatriptan.<sup>25</sup> The results of these trials did not especially favor sumatriptan. It is

unclear whether additional unpublished comparative trials of other triptans have been conducted. This makes it difficult to draw definite conclusions about the overall place of orally administered triptans in the treatment of acute migraine.

#### CLINICAL USE

Triptans are first-line therapies for individual attacks of migraine in patients whose attacks do not reliably respond to simple or combination analgesics.<sup>26</sup> Alternatives include ergot derivatives, opioids, and barbiturate-containing medications. A key advantage of triptans over most of these alternatives is their more favorable side-effect profile and more specific mechanism of action. Triptan therapy is most effective when provided rapidly in adequate doses and when used early, while headache pain is still mild.<sup>27</sup>

Seven triptans are approved by the Food and Drug Administration (FDA) for the treatment of acute migraine in adults (Table 2). The decision about which triptan and which formulation to use depends on the patient's preference, the characteristics of the headache, convenience, and cost. Only sumatriptan is available for parenteral administration.

Most patients have a strong preference for oral treatment of migraine. Oral triptans are appropriate when nausea and vomiting are mild or absent at the time of treatment. Naratriptan and frovatriptan are generally less effective in relieving headache at 2 hours than the other agents, although their longer half-lives may prove useful in some situations. The onset of action of most oral triptans is within 20 to 60 minutes.<sup>20</sup> If necessary, patients can take another dose of most oral triptans after 2 or 4 hours. The usual initial dose and maximum daily dose for each agent are listed in Table 2. For patients who are very sensitive to side effects of triptans, the dose may need to be lowered.

Subcutaneous sumatriptan has the fastest onset of action of all available triptans (approximately 10 minutes) and is also the most effective,<sup>20</sup> making it the best choice for rapidly developing or well-established migraines or for patients with prominent early nausea or vomiting. It is commonly used in the emergency department, but it can also be self-administered in the thigh or deltoid region with a reusable auto-

**Table 2.** Characteristics of Triptans Commercially Available in the United States.\*

Drug	Available Formulations and Recommended Doses	Commonly Prescribed Initial Dose	Half-Life <i>hr</i>	Selected Drug Interactions	Minimum Interval before Repeating Dose <i>hr</i>	Highest Approved Dose per 24 Hr
Almotriptan (Axert)	Tablet: 6.25 and 12.5 mg	12.5 mg	3–4	Contains a sulfa group — contraindicated in patients with sulfonamide allergies; dose reduction to 6.25 mg suggested when used with potent CYP3A4 inhibitor, such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, rifonavir, or nelfinavir	2	25 mg
Eletriptan (Relpax)	Tablet: 20 and 40 mg	40 mg	4	Metabolized by CYP3A4 enzyme — should not be used within 3 days after potent CYP3A4 inhibitor, such as ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, or nelfinavir	2	80 mg
Frovatriptan (Frova)	Tablet: 2.5 mg	2.5 mg	26		2	7.5 mg
Naratriptan (Amerge)	Tablet: 1 and 2.5 mg	2.5 mg	6		4	5 mg
Rizatriptan (Maxalt)	Tablet: 5 and 10 mg Orally dissolving wafer: 5 and 10 mg	Tablet: 10 mg Wafer: 10 mg	2–3	Dose reduction to 5 mg recommended in patients taking propranolol; should not be used within 2 wk after monoamine oxidase inhibitor	Tablet: 2	30 mg (15 mg for cases in which initial dose must be reduced to 5 mg)
Sumatriptan (Imitrex)	Tablet: 25, 50, and 100 mg Nasal spray: 5 and 20 mg Single-dose vial: 6 mg/0.5 ml of solution for subcutaneous injection Cartridges used in reusable autoinjector device: 4 and 6 mg Needlefree, single-use device for subcutaneous administration: 6 mg Fixed-dose combination tablet: 85 mg of sumatriptan with 500 mg of naproxen sodium	Tablet: 50 or 100 mg Nasal spray: 20 mg Subcutaneous injection cartridge: 6 mg	2.5	Should not be used within 2 wk after monoamine oxidase inhibitor	Tablet: 2 Nasal spray: 2 Subcutaneous injection: 1 Sumatriptan–naproxen tablet: 2	200 mg 40 mg 12 mg 2 tablets
Zolmitriptan (Zomig)	Tablet: 2.5 and 5 mg Orally dissolving wafer: 2.5 and 5 mg Nasal spray: 5 mg	Tablet: 5 mg Wafer: 5 mg Nasal spray: 5 mg	3	Should not be used within 2 wk after monoamine oxidase inhibitor	Tablet or wafer: 2 Nasal spray: 2	10 mg 10 mg

\* Information on dosing is from package inserts.

injector device into which medication cartridges are inserted. A needlefree, disposable device is also available; it uses a blast of air to create a small hole in the skin through which medication passes into the subcutaneous tissues.<sup>28</sup>

Rectal formulations (available in Europe and Asia) and intranasal or orally dissolving tablet formulations of triptans offer clinically meaningful advantages in some situations. Orally dissolving wafers, intranasal triptans, and rectal formulations can be taken without water and may be useful for patients who have difficulty swallowing tablets. However, the acceptability of rectal formulations to patients is low, and triptan nasal sprays and orally dissolving tablets have a bitter taste.

Triptan monotherapy does not provide relief from headache in about one third of patients.<sup>21</sup> If the initial dose is ineffective, the dose should be increased within the approved limits (Table 2). If an appropriate dose of a triptan is ineffective for two headache attacks, or has unacceptable side effects, a switch to a different triptan or triptan formulation should be considered.<sup>29</sup> In particular, patients with headache that does not respond to an oral triptan should be encouraged to consider subcutaneous sumatriptan. If triptan monotherapy remains ineffective, triptans should be tried in combination with other drugs, especially antiemetics or nonsteroidal antiinflammatory drugs (NSAIDs).<sup>23,30</sup> Return of headache after initial treatment success (recurrence) occurs in about one third of triptan-treated attacks.

Triptans are contraindicated in patients with poorly controlled hypertension, severe hepatic or renal impairment, or basilar or hemiplegic migraine (uncommon forms of migraine with aura). Patients with known vasospastic or ischemic coronary artery disease should not use triptans. Triptans also should be avoided in patients who are at high risk for coronary artery disease on the basis of risk-factor stratification. If the use of triptans is contemplated despite the presence of substantial coronary risk factors, cardiac evaluation is recommended before use.<sup>31</sup>

Because the majority of patients using triptans are women of childbearing age, their safety in pregnancy is an important consideration. The available data are sufficient to rule out a large increase in the overall risk of birth defects from exposure to sumatriptan during the first trimester, but they are not adequate to rule out small

or moderate increases in the risk of a particular birth defect.<sup>32-34</sup> The risks of exposure are probably very low, but because evidence is incomplete, triptans should not be used routinely during pregnancy. For some women whose severe headaches do not respond to other treatments, the benefits of use may outweigh potential harms.

When prescribing triptans, clinicians should be aware of several drug interactions (Table 2). Triptans should not be used within 24 hours after receipt of ergotamine or ergot-type medications. A 2006 FDA advisory alerted prescribers to the possible development of the serotonin syndrome when triptans are used in combination with selective serotonin-reuptake inhibitors or selective norepinephrine-reuptake inhibitors.<sup>35</sup> Migraine is often present in patients with affective disorders, so it is not uncommon for patients to require treatment for both conditions.

After several months of use, patients beginning to take a triptan should be seen for a follow-up visit to evaluate the frequency of headaches and the completeness, duration, and consistency of the response to the drug. To avoid causing medication-overuse headache, treatment of migraine should generally be limited to an average of about 2 days per week.<sup>26</sup> Triptans should be combined with preventive treatment in patients with frequent headache. In most cases treatment results are best monitored with the use of a headache diary, which can also be used to track possible migraine triggers.<sup>36</sup> A template for a simple headache diary is available at the Web site of the American Headache Society at [www.americanheadachesociety.org](http://www.americanheadachesociety.org).

Most triptans are expensive as compared with alternative migraine treatments. The average wholesale price for a single brand-name triptan tablet is in the range of \$23 to \$31.<sup>37</sup> However, a generic formulation of sumatriptan is now available, and the average wholesale price of generic sumatriptan is as low as \$2.55 per tablet.<sup>37</sup> Several triptans are available without a prescription in some countries, but not the United States.

#### ADVERSE EFFECTS

Certain minor adverse events — including paresthesias, flushing, and mild, transient neck tightness or chest pressure — occur commonly



enough with the use of triptans that they are known as triptan sensations.<sup>38</sup> In one study, these sensations were reported by almost half of patients who received subcutaneous sumatriptan and in about a quarter of those who took oral formulations. These side effects may be more common in women and in younger people. They can sometimes be mitigated by switching to a different triptan or another route of administration. Some other mild adverse events, particularly central nervous system effects such as somnolence or asthenia, can be features of the underlying migraine attack that become apparent after successful treatment of the headache.<sup>39</sup>

Neck or chest tightness occurring in association with triptan use may alarm patients and doctors. When evaluated, most patients with triptan-induced neck or chest pain do not have electrocardiographic or other evidence of decreased myocardial perfusion. Thus, in most cases triptan-associated chest pain is not caused by coronary vasoconstriction.

However, serious cardiovascular events, some resulting in death, have been reported in association with triptan use. Among the patients who died almost all those in whom a causal link was likely had cardiac risk factors and were found to have coronary artery disease on postmortem examination. The authors of one study estimated that the rate of serious cardiovascular events was lower than 1 event per 4 million uses.<sup>40</sup> In a cohort study of almost 64,000 patients with migraine who were receiving triptans as used in general practice, there was no observed association between triptan use and coronary events.<sup>41</sup> A consensus statement issued by an expert panel of the American Headache Society concluded that chest symptoms related to triptan use were “generally nonserious and are not explained by ischemia” and noted that “the incidence of serious cardiovascular events with triptans in both clinical trials and clinical practice appears to be extremely low.”<sup>31</sup>

#### AREAS OF UNCERTAINTY

As with other drugs used for the treatment of acute migraine, triptans have been associated with the development of headache caused by medication overuse, in which frequent use of medication leads to a cycle of increased headache and medication use. Most experts thus recommend a

conservative limit on use to about 2 days per week. However, many patients seen in specialty practice continue to have numerous, disabling headaches, despite aggressive preventive treatment. More frequent use of triptans may be appropriate in these circumstances, since good evidence is lacking with regard to individual susceptibility and medication thresholds for the development of medication-overuse headache.<sup>42,43</sup> Triptans do not seem to lead to progression of migraine in those with relatively infrequent headache.<sup>44</sup>

Triptans do not prolong aura in the roughly 30% of patients with migraine who are subject to it, but it is uncertain whether efficacy is reduced or absent when the drug is given during the aura. Thus, the optimal timing of triptan use in relation to aura is in doubt.<sup>45,46</sup> In the absence of firm evidence, patients with aura who take triptans should experiment with the timing of use to find the timing that works for them.

There has been interest in using triptans preventively. A number of studies have investigated the use of daily, scheduled doses of triptans for the prevention of highly predictable attacks of migraine, such as those occurring in association with menstruation.<sup>47,48</sup> These studies have attributed modest benefits to triptans as compared with placebo, but the long-term ratio of harm to benefit is not well established. No triptan has been approved by the FDA for preventive use.

#### GUIDELINES

The 2000 U.S. Headache Consortium Guidelines consider triptans an appropriate initial choice for the treatment of acute migraine in patients with moderate-to-severe headaches and in patients with milder headaches that have previously failed to respond to nonspecific treatment. The guidelines propose that NSAIDs or combination analgesics with caffeine are reasonable choices for the treatment of less severe headaches that have previously responded to such drugs.<sup>26</sup>

In contrast, guidelines from the American College of Physicians and American Academy of Family Practice published in 2002 (which have since expired) endorsed NSAIDs as first-line therapy for most patients and recommended the use of an antiemetic in patients with nausea and vomiting. Triptans were recognized as an alternative treatment for attacks that failed to respond to NSAIDs.<sup>49</sup>

Guidelines from the European Federation of Neurological Societies published in 2009 recommend either triptans or NSAIDs for the treatment of acute migraine and suggest that treatment be preceded by the use of metoclopramide or domperidone (not available in the United States). The use of intravenous acetylsalicylic acid or subcutaneous sumatriptan is recommended for very severe attacks.<sup>50</sup>

## RECOMMENDATIONS

For the patient described in the vignette, it is reasonable to recommend the use of an oral triptan. She has not had a consistent benefit from NSAIDs or combination analgesics but obtained complete relief of headache and associated nausea with subcutaneous sumatriptan. There is a good chance that her headaches will also respond to an oral triptan. The chest symptoms she reported are entirely consistent with nonserious triptan sensations and will be less likely to occur with an oral

formulation. In young, healthy patients who are at low risk for cardiovascular disease according to risk-factor stratification, there is no need to perform baseline cardiovascular testing before prescribing triptans.

Because it is the least expensive option, I would prescribe a dose of 50 mg or 100 mg of generic oral sumatriptan and advise the patient to take it early in the course of a headache, before the pain becomes severe. I would ask her to limit use of the medication to 2 days a week and to keep a diary of headache frequency, characteristics, and response to treatment. I would see the patient in a follow-up visit several months later to assess treatment results. If sumatriptan causes unpleasant side effects or is not helpful, I would consider trying a different triptan.

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