Review of Treatment Strategies for Successful Migraine Management

Focus on Efficacy and Safety of Triptans

Sahar Swidan, PharmD, BCPS

Pain is the most common reason for consultation with primary care physicians, and the most common pain types evaluated are back pain and headaches. Migraine headache is a common complaint, with a higher incidence reported by females. It is estimated that 6% of men and 18% of women currently suffer from this disease. However, the prevalence of migraine headache is probably higher, according to the results of the American Migraine Study. Study results indicated that 71% of men and 59% of women were determined to have migraine headaches from self-reported symptoms but they never received a formal diagnosis.

An accurate estimate of the economic impact of migraine headaches has been difficult to obtain. However, most of the studies attribute the large economic burden to costs associated with disability, decreased functional status, and the consequent indirect costs to employers. A recent study by Stewart et al. indicated that the average number of migraine attacks per year was 34 for men and 37.4 for women, and 58% of patients needed some bed rest during the attack. Moreover, the study indicated that the annual treatment costs in the U.S. are over one billion health care dollars, 80% of which were spent treating female patients. Physician–office-related expenses accounted for 60% of the total cost and prescription drugs accounted for 30%. Notable is the low cost of emergency department treatment for migraine headache, which accounted for less than 1% of the total cost. The indirect cost to American employers was estimated at $13 billion annually. It is important to note that several components that were needed to calculate burden-of-disease estimates were missing from this study, such as the value of lost homeworker tasks; missing work to take care of a family member with a migraine; and decreased involvement in family, social, and leisure activities.

The aforementioned study and several others indicate that the cost of migraine headache to society is large and comparable to other costly chronic diseases, such as diabetes and asthma. Several treatment options are now available for migraine headache; however, effective management must incorporate a multidisciplinary approach and remains challenging. Evidence-based multispecialty consensus has been recently developed by the U.S. Headache Consortium in an effort to enhance the care of migraine patients. This article will provide an overview of the pharmacological agents used in migraine management, including the recommendations from the U.S. Headache Consortium, with a focus on the use and safety of the triptans in the acute management of migraine attacks.

Pathophysiology of Migraine Headaches

Thus far, no single theory can completely explain the etiology of migraine headaches, and probably most (if not all) current theories are interrelated. Neurotransmitters, including serotonin, adrenergic, dopamine, and histamine, have been implicated, and play an important role in the etiology of migraine. Serotonin (5-hydroxytryptamine, 5-HT) has been the center of interest for investigators; to date, seven classes of serotonin receptors have been identified. The 5-HT1A and 5-HT2A receptors are believed to be associated with migraine headache pathogenesis because activation of 5-HT1A receptors leads to effective symptomatic relief and because inhibition of 5-HT2A receptors results in prophylaxis of migraine attacks.

Based on our current understanding of the pathophysiology of migraine headache, there are at least three target mechanisms that can achieve efficacy and pain relief: (1) the reversal of cranial blood-vessel dilation, (2) inhibition of activated peripheral trigeminal nerve terminals, and (3) reduction in neuronal activity in central trigeminal neurons. The distribution and function of serotonin receptors throughout the body has been advanced by molecular biology and immunohistochemical research, which in part helped explain the efficacy and adverse effect profile observed with the 5-HT1D agonists. Wide 5-HT1D receptor expression has been located in the smooth muscle of meningeal blood vessels, which cause vasconstriction when stimulated. However, this receptor type has also been found in coronary arteries. The serotonin 5-HT1D subtype is expressed on both the peripheral and central terminals of the trigeminal nerve fibers arising from these cells. Moreover, this receptor subtype is extensively localized to the nucleus of the tractus solitarius, which mediates nausea and vomiting associated with central pain transmission.

The majority of current abortive therapies for migraine headache act primarily on serotonin receptors, including ergot derivatives and 5-HT1D agonists. Ergot derivatives, moreover, affect dopamine and α-adrenergic receptors. Other therapies, such as antihistamines and phenothiazines, have documented efficacy in the acute treatment of migraine headache through histamine blockade and actions at the dopamine receptors.

Principles of Treatment

General treatment principles of migraine management include establishing a diagnosis, establishing realistic patient expectations, encouraging the patient to identify and avoid triggers, and creating a formal, individualized management plan. A study conducted by Lipton and Stewart echoed the importance of creating a treatment plan after the physician gains insight into what the patient wants. If the patient’s and doctor’s expectations, treatment goals, and preferences are not mutually identified, then a lack of compliance can occur—possibly resulting in worse treatment outcomes.

Recently, the U.S. Headache Consortium, which is made up of a multidisciplinary panel of professional organizations, released evidence-based guidelines for migraine headache management (Table 1). The main goal was to establish treatment guidelines in four distinct areas of migraine management: diagnostic testing, pharmacologic management of acute attacks, preventive therapy, and behavioral and physical treatments of migraine.

NONPHARMACOLOGIC THERAPY

Nonpharmacologic treatment modalities, such as relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy, should be considered as treatment options. The U.S. Headache Consortium recommended the aforementioned treatment modalities as Grade A. Grade B recommendations, such as behavioral therapy, were also suggested in conjunction with preventive therapy. Evidence-based treatment for migraine with hypnosis, acupuncture, transcutaneous electrical nerve stimulation, chiropractic or osteopathic cervical manipulation, occlusal adjustment, and hyperbaric oxygen are not available and therefore are not recommended until further evidence is available. Nonpharmacologic treatment should always begin with lifestyle changes and avoidance of potential triggers.

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Patients should be advised to exercise regularly, avoid irregular sleeping habits, and quit smoking. Any unnecessary medications that could contribute to the headache should be discontinued. Once an attack occurs, resting in a dark, quiet environment will help in relieving the migraine-associated symptoms.  

**PHARMACOLOGIC THERAPY**

**Prophylactic Treatment**

The goals of preventive treatment are to decrease the severity, frequency, and duration of migraine attacks; improve outcomes of acute treatment medications; and improve function and reduce disability. Patients should also be started on preventive therapy if they have recurring migraines that interfere with their daily routine despite acute treatment. Furthermore, preventive therapy should be considered in patients who experience frequent headaches, who have contraindications or adverse events and/or who fail to gain relief from acute treatment medications, or who overuse acute therapy. Based on the U.S. Headache Consortium consensus panel recommendations, preventive therapy should also be used in patients with uncommon headache conditions, such as hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migraine with aura. 

If the decision is made to use preventive medications, therapy should be initiated with medications with the highest level of evidence-based efficacy. Therapy should be initiated at the lowest effective dose and the patient should remain on the medication for an adequate length of time (2-3 months to achieve maximum clinical benefit) to assess efficacy. The patient’s response to therapy should be monitored with a headache diary, and therapy should be reevaluated periodically. If the migraines are well controlled for three to six months, therapy should be tapered and discontinued. Many migraine patients have comorbid disease states that must be considered when selecting a preventive agent. Conditions that are more common in migraine patients include stroke, myocardial infarction, Raynaud’s phenomenon, epilepsy, and affective and anxiety disorders. Preferably, the preventive agent in question should treat the migraine and the comorbid illness without exacerbating the migraine. Preventive agents and their level of efficacy according to the U.S. Headache Consortium are listed in Table 2.

**Acute Treatment**

The goals of acute treatment are to decrease the severity or completely abolish the migraine and return the patient back to functionality as quickly as possible with the fewest adverse effects. Based on the patient preference surveys mentioned earlier, the ideal pharmacological agent should treat the attack rapidly and consistently, with minimal recurrence, and should minimize associated symptoms, such as nausea and vomiting. Furthermore, the agent should be easy to use and appropriate for self-care to decrease the use of resources, to be cost-effective, and to have a low adverse-effect profile. Currently, because of advances in research and enhanced understanding of the pathophysiology of migraine headache, we have a large array of pharmacologic agents from which to choose (Table 3). Nonetheless, agents that are available now still do not fulfill all of the ideal characteristics desired by patients, and so the search for the ideal agent is ongoing.

**TREATMENT STRATEGIES**

**Early Treatment of Migraine Attacks**

More recently, evidence indicates that early pharmacologic intervention during a migraine attack could provide higher levels of pain relief than later intervention. Retrospective post-hoc analysis of the Spectrum Study results was performed in patients with disabling headaches who were treated while the pain was mild. Results suggest that 50 mg of sumatriptan (Imitrex, Glaxo Wellcome Inc) was more effective than placebo for early treatment of migraine attacks. Moreover, pain-free rates were higher for attacks treated with a 50-mg sumatriptan tablet compared to placebo at two and four hours post-dose when pain was rated mild. Currently, no comparable, randomized, placebo-controlled trials support or refute this finding. This observation was not the primary endpoint of the study and, therefore, merits further investigation. Similar findings were reported by the International 311C90 Long-Term Study Group. Also of interest was the lower incidence of adverse effects reported in patients using 50-mg sumatriptan tablets when pain was mild as compared to patients who medicated when pain was moderate to severe. In part, this might be caused by a heightened sensory sensitivity during a migraine attack when pain is moderate to severe. Patients might have an improved tolerance to medications if they treat the migraine attack early, before the occurrence of heightened sensitivity; however, this needs further investigation.

**Stratified Care Versus Step Care**

Many treatment strategies exist in the medical community for dealing with the acute treatment of headache disorders. Strategies that have received a great deal of attention recently are the post-hoc analysis of the Spectrum Study, which was discussed earlier, and stratified versus step care. Stratified treatment of migraine attacks. Moreover, pain-free rates were higher for attacks treated with a 50-mg sumatriptan tablet compared to placebo at two and four hours post-dose when pain was rated mild. Currently, no comparable, randomized, placebo-controlled trials support or refute this finding. This observation was not the primary endpoint of the study and, therefore, merits further investigation. Similar findings were reported by the International 311C90 Long-Term Study Group. Also of interest was the lower incidence of adverse effects reported in patients using 50-mg sumatriptan tablets when pain was mild as compared to patients who medicated when pain was moderate to severe. In part, this might be caused by a heightened sensory sensitivity during a migraine attack when pain is moderate to severe. Patients might have an improved tolerance to medications if they treat the migraine attack early, before the occurrence of heightened sensitivity; however, this needs further investigation.

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Migraine Management: Focus on Triptans

Table 2 Preventive Agents and Their Level of Efficacy

<table>
<thead>
<tr>
<th>Group 1*</th>
<th>Group 2†</th>
<th>Group 3‡</th>
<th>Group 4§</th>
<th>Group 5¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>- Blockers</td>
<td>- Antidepressants</td>
<td>Methysergide</td>
<td>Acetebutol</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>Atenolol/metoprolol/nadolol</td>
<td>Doxepin</td>
<td>Carbamazepine</td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Propranolol/simolol</td>
<td>- Calcium channel blockers</td>
<td>Fluvoxamine</td>
<td>Clomipramine</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Nortriptyline</td>
<td>Imipramine</td>
<td>Clonazepam</td>
<td></td>
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<tr>
<td>Gabapentin</td>
<td>Ketoprofen</td>
<td>Tiagabine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Nortriptyline</td>
<td>Topiramate</td>
<td></td>
<td></td>
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<tr>
<td>Naproxen</td>
<td>Paroxetine</td>
<td>Methylergonovine</td>
<td></td>
<td></td>
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<tr>
<td>Naproxen sodium</td>
<td>Protriptyline</td>
<td>Phenereline</td>
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<td></td>
</tr>
<tr>
<td>- Other</td>
<td>Sertraline</td>
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<tr>
<td>Feverfew</td>
<td>Trazodone</td>
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<tr>
<td>Magnesium</td>
<td>Venlafaxine</td>
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<tr>
<td>Vitamin B2</td>
<td>Cyproheptadine</td>
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<tr>
<td></td>
<td>Diltiazem</td>
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<tr>
<td></td>
<td>Lidocaine</td>
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<td></td>
<td>Naproxen</td>
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<tr>
<td></td>
<td>Paroxetine</td>
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<td></td>
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<tr>
<td></td>
<td>Nicardipine</td>
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<td></td>
<td>Serotonin</td>
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<td></td>
<td>Trazodone</td>
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<tr>
<td></td>
<td>Diltiazem</td>
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<tr>
<td></td>
<td>Ibuprofen</td>
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<td></td>
<td>Ticlopidine</td>
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<tr>
<td></td>
<td>Topiramate</td>
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<tr>
<td></td>
<td>Methylergonovine</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Phenereline</td>
<td></td>
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</tbody>
</table>

*Medium-to-high efficacy, good strength of evidence, and mild-to-moderate adverse effects.
†Lower efficacy than those listed in first column, or limited strength of evidence, and mild-to-moderate adverse effects.
‡Clinically efficacious based on consensus and clinical experience, but no scientific evidence of efficacy.
§Medium-to-high efficacy, good strength, good strength of evidence, but with adverse effect concerns.
¶Evidence indicating no efficacy over placebo.

Adapted from the U.S. Headache Consortium Guidelines for Preventive Therapy.7

The triptans

5-HT1B/1D receptor agonists have been widely used for the treatment of moderate-to-severe migraine attacks. Sumatriptan was the first triptan that was available on the market; it was followed by zolmitriptan (Zomig, AstraZeneca), naratriptan (Amerge, Glaxo Wellcome Inc), rizatriptan (Maxalt, Merck), and almotriptan (Axert, Pharmacia), respectively. Eletriptan (Replax, Pfizer) is pending Food and Drug Administration (FDA) approval. Introduction of the 5-HT1B/1D agonists has revolutionized our understanding of the pathophysiology and treatment of migraine headache. 5-HT has long been suspected as a potential mediator in migraines, because its actions on vascular and gastrointestinal smooth muscle are compatible with the clinical features seen during a migraine attack. The addition of 5-HT to peripheral nerve tissue can induce pain. Modulating 5-HT receptors with a 5-HT antagonist, methysergide, results in effective migraine prophylaxis, whereas administering reboxetine, which releases 5-HT from nerve endings, often induces a migraine.33,34 Various studies reported that the intravenous administration of 5-HT often helps during migraine attacks, and it is likely that various 5-HT receptor subtypes exist.35 Vasodilation has been implicated in the pathogenesis of migraine, and stimulation of 5-HT receptors on blood vessels leads to vasoconstriction. 5-HT receptors on cerebral arteries are predominantly 5-HT1D; however, receptors on the temporal arteries tend to be 5-HT1A. Therefore, medications that cause vasoconstriction via modulation of 5-HT1D-type receptors should be effective pharmacologic agents in the acute treatment of migraine attacks.36

The pharmacokinetic profile of each 5-HT1B/1D agonist is slightly different, as shown in Table 4.37-41 Variability in the adverse-event profiles, onset of action, and patient preference in clinical practice can be partly explained by this variability; however, the clinical significance of such differences is not well delineated. Oral sumatriptan is poorly absorbed; it has an oral bioavailability of 15% and time to maximum concentration (tmax).
## Migraine Management: Focus on Triptans

### Table 3 Acute Treatment of Migraine Attacks

<table>
<thead>
<tr>
<th>Medication</th>
<th>Clinical Efficacy*</th>
<th>Dose per Attack</th>
<th>Common Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acetaminophen</td>
<td>+</td>
<td>500–1000 mg every 4–6 h</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Mild–Moderate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin and NSAIDs</td>
<td>++</td>
<td>Various</td>
<td>Occasional GI adverse effects</td>
</tr>
<tr>
<td>Isometheptene-containing compounds</td>
<td>++</td>
<td></td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Moderate–Severe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergot derivatives</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergotamine tartrate</td>
<td>+++</td>
<td>SL: 2 mg at onset, repeat every 30 min up to 6 mg/day PO: 1–2 tabs at onset; 1 tab every 30 min up to 6 tabs/day PR: 1 sup; may repeat after 1 h up to 2 sup/attack Max: 2 days/week or 10 mg/week</td>
<td>Nausea and vomiting are frequent. Can be associated with numbness, tingling sensation, chest pressure or tightness, ergotism, and rebound headache</td>
</tr>
<tr>
<td>Dihydroergotamine mesylate</td>
<td>+++</td>
<td>SC/IM/IV: 0.25–1 mg, may repeat q1h up to 3 mg/day IM, 2 mg/day IV, and 6 mg/wk IN: 1 spray in each nostril; must repeat in 15 min. Max: 4 sprays/day or 8 sprays/week</td>
<td>Occasional; including nausea, vomiting, dysphoria, flushing, restlessness, anxiety, and nasal congestion (intranasal)</td>
</tr>
<tr>
<td><strong>Triptans</strong></td>
<td></td>
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<tr>
<td>Sumatriptan</td>
<td>+++</td>
<td>SC: 6 mg; may repeat in 1 h. Max: 12 mg/day IN: 5–20 mg; may repeat in 2 h. Max: 40 mg/day PO: 25–50 mg; may repeat in 2 h. Max: 100 mg/dose, 300 mg/day</td>
<td>Usually mild and transient; including nausea, vomiting, malaise, dizziness, paresthesia, taste disturbance (intranasal), and chest tightness</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>+++</td>
<td>PO: 2.5–5 mg; may repeat in 2 h. Max: 5 mg/dose, 10 mg/day</td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td>++</td>
<td>2.5 mg; may repeat in 4 h. Max: 5 mg/day</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>+++</td>
<td>5 mg; may repeat in 2 h. Max: 30 mg/day</td>
<td></td>
</tr>
<tr>
<td>Almotriptan</td>
<td>+++</td>
<td>12.5 mg; may repeat in 2 h.</td>
<td>Incidence of treatment-related adverse events is less than 3%</td>
</tr>
<tr>
<td><strong>Opioid analgesics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>+++</td>
<td>IV: 0.5–2 mg q 3–4 h PRN IM: 1–4 mg q 3–4 h PRN IN: 1 spray in one nostril; repeat in 60 min</td>
<td>Dizziness, drowsiness, nausea, vomiting, blurred vision</td>
</tr>
<tr>
<td>Meperidine</td>
<td>++</td>
<td>50–150 mg/dose</td>
<td>Sedation, dizziness, nausea</td>
</tr>
<tr>
<td><strong>Adjunct Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>++</td>
<td>25–100 mg bid–tid up to 3 days per week</td>
<td>Sedation, extrapyramidal reactions</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>+++</td>
<td>3.5–10 mg IV</td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>+ – ++</td>
<td>10–15 mg tid up to 3 days per week</td>
<td>Sedation, restlessness, extrapyramidal reactions</td>
</tr>
</tbody>
</table>

*Adapted from the U.S. Headache Consortium Guidelines; Matcher et al.; and McEvoy.7, 21, 22

SL = sublingual; PO = oral; PR = rectal; SC = subcutaneous; IM = intramuscular; IV = intravenous; IN = intranasal; h = hours; bid = twice/day; tid = three times/day; PRN = as needed.

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of 1 to 1.5 hours, resulting in delayed onset of action compared to the intranasal and parenteral formulations. Zolmitriptan has better oral bioavailability than sumatriptan and a slightly faster onset, but a similar half-life (t1/2) and duration. Conversely, naratriptan is a longer-acting triptan with improved bioavailability and tolerability. However, its advantage is offset by a delayed onset of action. Rizatriptan has a faster onset of action because of its fast absorption, but it has a similar duration of action to sumatriptan and zolmitriptan. Almotriptan, which was recently approved by the FDA, is the latest 5-HT1D receptor agonist to be added to the triptans. Almotriptan has demonstrated high and specific affinity for human 5-HT receptors in vivo and in vitro. Like other triptans, almotriptan exhibits negligible affinity for histamine, α and β adrenergic receptors, and dopamine receptors. In addition, almotriptan has been shown to have a higher affinity for meningeal artery tissue than pulmonary or coronary artery tissue. The initial pharmacokinetic parameters of almotriptan were investigated in a study involving 24 volunteers. Almotriptan was well absorbed orally, with a bioavailability of approximately 70%. The time to peak plasma level was approximately 2.5 hours and was not affected by dose. The main route of elimination of almotriptan was renal; approximately 40% of the drug was excreted unchanged in the urine and 13%...
Migraine Management: Focus on Triptans

was excreted in feces. The elimination half-life did not vary with different doses and ranged from 3.19 to 3.69 hours. Unlike sumatriptan, the newer triptans are able to better penetrate the blood-brain barrier and access the central component of the trigeminal system; however, the clinical relevance of this effect has not been established. The triptans have different pathways of metabolism, resulting in different drug interaction profiles and contraindications. Sumatriptan, zolmitriptan, and rizatriptan are metabolized by monoamine oxidase–A to inactive compounds. Consequently, they interact with monoamine oxidase inhibitors (MAOIs); concomitant use and use within 14 days of stopping the MAOI is contraindicated. Until recently, naratriptan was the only triptan that did not interact with MAOIs, because it is mainly metabolized by cytochrome P-450 enzymes. Naratriptan is renally excreted and is contraindicated in patients with severe renal impairment; a lower dose should be considered in patients with mild-to-moderate renal impairment. Almotriptan is metabolized by monoamine oxygenase A and cytochrome P-450 3A4 and 2D6 isoenzymes to five inactive metabolites. However, no clinically relevant adverse events, compared with 27% in the placebo group. Dose–range-finding studies suggested that 10- and 20-mg intranasal sumatriptan, administered as a single dose in one nostril or as a divided dose in two nostrils, is safe and effective. The two-hour response rate ranged from 43% to 78% in the sumatriptan group compared to 29% to 42% in the placebo group. Significant improvement was reported as early as 30 minutes after treatment, and the response rate at two hours was comparable to the response rate of oral sumatriptan at four hours.

The administration of oral sumatriptan at the dose of 25 to 100 mg significantly reduced the severity of migraine headache from moderate or severe to mild or none two hours after drug administration. The response rate ranged from 50% to 57% at two hours and 63% to 78% at four hours, compared to the placebo response rate of 17% to 38%. Oral sumatriptan also improved associated symptoms (nausea, vomiting, photophobia, phonophobia) and clinical disability. Pfaffenrath et al. and Rederich et al. demonstrated that repeated use of oral sumatriptan was well-tolerated and provided consistent efficacy for up to 12 migraine attacks. Sumatriptan 100 mg seemed to be more effective but was associated with a higher incidence of adverse reactions compared to the 25-mg dose.

A dose–range-finding study demonstrated a clear dose–response relationship between efficacy and tolerability for zolmitriptan. The 2.5-mg dose of zolmitriptan was recommended as the optimal initial dose. However, the use of higher doses of zolmitriptan was associated with a slightly decreased rate of headache recurrence and a longer time to recurrence, but a higher incidence of adverse effects. Moreover, a long-term, open-label study in 2,068 patients demonstrated consistent efficacy and tolerability to zolmitriptan use over a period of one year.

Two multicenter, randomized, double-blind, placebo-controlled trials reported that the 1- and 2.5-mg naratriptan doses significantly relieved the severity of the migraine headache at four hours after administration in 50% to 57% and 60% to 68% of patients, respectively, and that response was maintained for at least 12 hours. Furthermore, only 27% to 28% of the 2.5-mg group had headache recurrence, compared with 33% to 39% of those in the 1-mg group and 36% to 38% in the placebo group.

Rizatriptan at the 5- and 10-mg doses was effective and well-tolerated. The 10-mg dose was preferred, however, because it was more efficacious and had a faster onset of action. The efficacy was consistent for long-term use up to one year. Rizatriptan is available as an oral tablet and an

Clandrical Efficacy

Sumatriptan is the prototype for the 5-HT_{1B/1D} agonists, and its therapeutic efficacy is well established (Table 5). In placebo-controlled, clinical trials, subcutaneous sumatriptan was significantly more effective than placebo in relieving migraine headache as well as associated symptoms of nausea, vomiting, photophobia, and phonophobia. All triptans interact with ergot derivatives and selective serotonin reuptake inhibitors (SSRIs). Concurrent use of triptans and ergot derivatives within a 24-hour period is contraindicated because of the increased risk of vasospasm. Finally, the concomitant use of SSRIs and triptans should be undertaken with great caution, as serotonin syndrome has been reported in patients using this combination.

Clinical Efficacy

Sumatriptan is the prototype for the 5-HT_{1B/1D} agonists, and its therapeutic efficacy is well established (Table 5). In placebo-controlled, clinical trials, subcutaneous sumatriptan was significantly more effective than placebo in relieving migraine headache as well as associated symptoms of nausea, vomiting, photophobia, and phonophobia. All triptans interact with ergot derivatives and selective serotonin reuptake inhibitors (SSRIs). Concurrent use of triptans and ergot derivatives within a 24-hour period is contraindicated because of the increased risk of vasospasm. Finally, the concomitant use of SSRIs and triptans should be undertaken with great caution, as serotonin syndrome has been reported in patients using this combination.

| Drug Route Onset t max t 1/2 Bioavailability Metabolism Drug Interactions |
|-----------------|-----------------|-----------------|------------------|---------------|-------------------|
| Sumatriptan (Imitrex) Subcutaneous 10–15 min 12 min 2 h 97% MAO Ergot-containing drugs, MAO-A inhibitors, SSRIs |
| Sumatriptan (Imitrex) Intranasal 15–20 min 1–1.5 h 2 h 17% MAO Ergot-containing drugs, MAO-A inhibitors, SSRIs |
| Sumatriptan (Imitrex) Oral 30–90 min 2.5 h 2 h 15% MAO Ergot-containing drugs, MAO-A inhibitors, SSRIs |
| Zolmitriptan (Zomig) Oral 1 h 2 h 3 h 40% CYP-450/MAO Ergot-containing drugs, MAO-A inhibitors, SSRIs, propranolol, cimetidine, oral contraceptives |
| Naratriptan (Amerge) Oral 1–3 h 3–4 h 6 h 70% Renal/P-450 Ergot-containing drugs, MAO-A inhibitors, SSRIs, oral contraceptives |
| Rizatriptan (Maxalt, Maxalt-MLT) Oral 0.5–2 h 1–1.5 h 2–3 h 45% CYP-450/MAO Ergot-containing drugs, MAO-A inhibitors, SSRIs, propranolol |
| Almotriptan (Axert) Oral 1–3 h 1.5–4 h 3–4 h 70% CYP-450/MAO Ergot-containing drugs |

MAO = monoamine oxidase; SSRIs = selective serotonin reuptake inhibitors; CYP-450 = cytochrome P-450; h = hours; min = minutes.
orally disintegrating tablet, which dissolves rapidly under the tongue or may be swallowed without liquid. The 10-mg wafer was shown to be superior to the 5-mg wafer and placebo in relieving the migraine headache and its associated symptoms, and therefore improving quality of life. The orally disintegrating tablet is not a sublingual formulation, so it does not have a quicker onset of action. The Almotriptan Study Group conducted a dose-finding, double-blind, parallel-group, multicenter, placebo-controlled study of oral almotriptan in the acute treatment of migraine. The doses tested were 2, 6.25, 12.5, and 25 mg of oral almotriptan in 742 evaluable patients. Migraine pain intensity was graded by patients in a self-assessment booklet using a four-point verbal scale (0 [no pain] to 3 [severe pain]). The primary efficacy endpoint of this study was headache relief at two hours after medication administration without the use of rescue medications. Headache relief at two hours was reported by 30%, 56%, 59%, and 67% of patients in the 2-, 6.25-, 12.5-, and 25-mg groups, respectively, compared with 33% in the placebo group. This study indicated that almotriptan 6.25 mg is the minimum effective treatment dose and that almotriptan 12.5 mg offers the maximum effective treatment dose and that almotriptan 12.5 mg offered the greatest improvement in migraine pain intensity and quality of life.

### Table 5 Clinical Trials for Comparison of 5-HT<sub>1B/1D</sub> Receptor Agonists<sup>50–55, 88</sup>

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Dose (mg) [sample size]</th>
<th>2-h Response</th>
<th>4-h Response</th>
<th>Headache recurrence</th>
<th>Other secondary outcomes</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral sumatriptan vs. zolmitriptan (abstract) [1]</td>
<td>R, DB, PC</td>
<td>1058 patients S 100 mg N 2.5 mg PL [B:1]</td>
<td>64% [85] 61%</td>
<td>86% 82%</td>
<td>—</td>
<td>Primary outcome: 2-h pain-free rate</td>
<td>S 100 42% Z 41% PL 38%</td>
</tr>
<tr>
<td>Oral sumatriptan vs. naratriptan (abstract) [2]</td>
<td>R, MC, DB, 2-attack, CR</td>
<td>S 100 mg N 2.5 mg [225] Optional 2nd dose for recurrence</td>
<td>—</td>
<td>—</td>
<td>57% 45% (P=0.005)</td>
<td>Primary outcome: 24-h overall efficacy</td>
<td>S 34% vs. N 29%, P&lt;0.05</td>
</tr>
<tr>
<td>Oral sumatriptan vs. rizatriptan [3]</td>
<td>R, MC, DB, PC, PR, single attack</td>
<td>S 100 mg [72] R 10 mg [89] R 20 mg [82] R 40 mg [121] PL [85]</td>
<td>46%&lt;sup&gt;a&lt;/sup&gt; 52%&lt;sup&gt;a&lt;/sup&gt; 56%&lt;sup&gt;a&lt;/sup&gt; 67%&lt;sup&gt;a&lt;/sup&gt; 18%</td>
<td>—</td>
<td>41% (14 h) 41% (14 h) 53% (16 h) 42% (19 h) 36% (5 h)</td>
<td>S, R &gt; PL for % pain-free patients, improved functional disability, associated symptoms and relief</td>
<td>S, R &lt; PL for % patients requiring 2nd dose R40 &gt; S100 for % pain-free patients</td>
</tr>
<tr>
<td>Oral sumatriptan vs. rizatriptan [4]</td>
<td>R, MC, DB, PC, 2-period, S incomplete block CR: PL/PL, R5/S25, S25/R5, R10/S50, S50/R10</td>
<td>R 5 mg [557] R 10 mg [563] R 20 mg [567] R 50 mg [566] PL [141]</td>
<td>68%&lt;sup&gt;b&lt;/sup&gt; 62% 72% 68% 38%</td>
<td>79% 76% 83% 80% —</td>
<td>33% (13 h) 32% (12 h) 35% (13 h) 31% (8 h) 32% (9 h)</td>
<td>S5 &gt; S25 for % pain-free patients, improved functional disability, associated symptoms and relief</td>
<td>R5 &gt; S50 for % pain-free patients, improved functional disability, associated symptoms and relief</td>
</tr>
<tr>
<td>Oral sumatriptan vs. eletriptan [5]</td>
<td>R, MC, DB, PC, PR, single attack</td>
<td>S 100 mg [129] E 20 mg [144] E 40 mg [136] E 80 mg [141] PL [142]</td>
<td>55%&lt;sup&gt;c&lt;/sup&gt; 54%&lt;sup&gt;c&lt;/sup&gt; 65%&lt;sup&gt;c&lt;/sup&gt; 77%&lt;sup&gt;c&lt;/sup&gt; 24%</td>
<td>—</td>
<td>33% 28% 32% 23%</td>
<td>E80 &gt; S100 for % pain-free patients, associated symptoms, and relief</td>
<td>S100 40% E20 34% E40 35% E80 51% PL 17%</td>
</tr>
<tr>
<td>Oral sumatriptan vs. almotriptan [6]</td>
<td>R, MC, DB, AC, PR</td>
<td>S 50 mg [582] A 12.5 mg [591]</td>
<td>57%</td>
<td>58%</td>
<td>—</td>
<td>24% 27%</td>
<td>Pain-free at 2 h S=25%, A=18%</td>
</tr>
<tr>
<td>Oral sumatriptan vs. almotriptan [7]</td>
<td>R, MC, DB, AC, PC, PR</td>
<td>S 100 mg [193] A 12.5 mg [183] A 25 mg [191] PL [99]</td>
<td>64%&lt;sup&gt;d&lt;/sup&gt; 57%&lt;sup&gt;d&lt;/sup&gt; 57%&lt;sup&gt;d&lt;/sup&gt; 42%</td>
<td>—</td>
<td>14% 18% 19%</td>
<td>Pain-free at 2 h S=34%, A 12.5 mg=28%, P=15%</td>
<td>S100 22% A12.5 15% A25 20% PL 12%</td>
</tr>
</tbody>
</table>

ADR = adverse events; R = randomized; MC = multicenter; DB = double-blind; OL = open-label; PC = placebo-controlled; PR = parallel group; CR = crossover; S = sumatriptan; Z = zolmitriptan; N = naratriptan; R = rizatriptan; E = eletriptan; A = almotriptan; PL = placebo.

<sup>a</sup>P<0.05 vs. placebo,  †P<0.001 vs. placebo; ‡nausea, vomiting, photophobia, phonophobia.

<sup>b</sup>P=0.05 vs. placebo,  †P=0.001 vs. placebo; ‡nausea, vomiting, photophobia, phonophobia.

<sup>c</sup>P=0.01 vs. placebo;  †P<0.001 vs. placebo; ‡nausea, vomiting, photophobia, phonophobia.

<sup>d</sup>P=0.005 vs. placebo.
optimal ratio of efficacy to tolerability. Moreover, associated symptoms—
nausea, vomiting, phonophobia, photophobia, and the need for escape med-
ication decreased dose dependently. Single doses of almotriptan 6.25 and
12.5 mg were evaluated in 722 patients who treated three consecutive mod-
erate-to-severe migraine attacks.42 Across all migraine attacks, pain relief
at two hours was 60% with almotriptan 6.25 mg, 70% with almotriptan
12.5 mg, and 38% with placebo (P<0.001), and the proportion pain-free at
two hours was 38.8% with almotriptan 12.5 mg, 29.9% with almotriptan
6.25 mg, and 15.5% with placebo (P<0.001). Recurrence rates were 28.7%
and 30.1% with almotriptan 6.25 and 12.5 mg, respectively, and 23.3%
with placebo. Almotriptan 12.5 mg provided the optimal balance of effi-
cacy and tolerability.

In summary, all triptans are effective agents in the treatment of migraine
attacks and additional comparative efficacy trials are outlined in Table
5.50–55 Nonetheless, variability in patients’ responses to different triptans
attacks and additional comparative efficacy trials are outlined in Table
5.50–55. The most common adverse events reported in less than 3% of patients in

Adverse Events

Because of initial findings of cardiovascular adverse events in the initial
sumatriptan trials and in the postmarketing surveillance studies, all trip-
tans carry a drug-class warning. The use of triptans is contraindicated in
patients with ischemic heart disease, Prinzmetal angina, uncontrolled
high blood pressure, and prior history of cerebrovascular accident. More-
over, the concomitant use of triptans and ergot-containing products with-
in 24 hours is contraindicated because of additive vasoconstrictive effects.

Triptans should also be avoided in patients with risk factors for cardio-
vascular disease, such as postmenopausal females, males older than 40
years, family history of heart disease, cigarette smokers, and those with
hypertension or diabetes mellitus.83

All triptans cause vasoconstriction in the cerebral circulation and might
cause a similar effect on coronary arteries. Numerous electrocardiograms
(ECGs) were completed during reports of chest pain; no study to date
showed abnormalities in ECG pattern. As a drug class, the triptans are ef-
ficacious and well-tolerated. The vasoconstrictive effects of the triptans
are worrisome; however, this action also lends a therapeutic value. The
chest symptoms (pain, pressure) are associated with all the triptans, but
they are more commonly reported with parenteral sumatriptan. This ef-
fact might be caused by higher bioavailability and faster onset of action.
A recent report by Foster et al.84 suggests that chest pain reported with
sumatriptan might be caused by alteration in esophageal motor function.
During this study, no ECG abnormalities were observed. Nonetheless, fur-
ther evaluation is still needed, and the use of triptans in patients with car-
diovascular risk factors or disease is contraindicated.

The safety and tolerability data thus far for almotriptan are favorable.
The most common adverse events reported in less than 3% of patients in
the almotriptan trials included dizziness, nausea, headache, somnolence,
and paresthesia.80 At the recommended therapeutic dose of 12.5 mg, the
incidence of adverse events was not statistically different from placebo.85
The incidence of cardiovascular adverse events, specifically chest symp-
toms, was 0.2% in phase III trials; other symptoms, such as chest pres-
sure, palpitations, and vasodilation, were not reported. The incidence of
adverse events did not change over time with repeated dosing and was
not different from the single-dose studies.

Various cardiovascular events have been reported with sumatriptan,
including coronary spasm with angina, myocardial infarction, and ven-
tricular fibrillation. Thus, a blanket cautionary statement is issued with
all 5-HT1B/1D agonists regarding their use in head-pain patients with car-
diovascular disease, silent ischemic disease, or multiple risk factors. It is
important to note that differences in tolerability might exist among the vari-
ous agents; however, in vitro coronary activity is essentially the same.46,87

CONCLUSION

A multimodal approach to the treatment of the migraine patient is neces-
sary to achieve the most successful outcomes. Our understanding of the
pathophysiology and treatment of migraine headache was revolution-
ized with the availability of sumatriptan and other triptans that followed.
As a consequence, numerous pharmacologic agents are now available for
acute and preventive treatments for these patients. Studies have shown
that successful treatment must include an agent that is fast-acting, pro-
vides them with significant improvement in pain relief or totally abolish-
es their pain, has a low adverse-effect profile, decreases the incidence of
migraine recurrence, and is cost-effective. No agent available has all of the
characteristics of an ideal agent and so the quest is ongoing. The newly
published evidence-based guidelines help guide our treatment strategy
now that the level of efficacy of the various pharmacological agents is bet-
ter defined. Early evidence suggests that treatment should be initiated
early during a migraine attack, with migraine-specific therapies such as
the triptans or ergot derivatives. Treatment strategies might shift in the
coming months, but nonetheless, there are many tools available for use in
various treatment strategies for migraine patients today.

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