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Migraine Update—The Triptans: A Clinical Primer on Their Use

Author: **Stewart J. Tepper, MD,** Assistant Clinical Professor, University of Washington, Seattle.

Peer Reviewers: **Carmen Montoya, MD,** Medical Director, South Texas Headache and Pain Management Institute, San Antonio, Texas; and **Alan M. Rapoport, MD,** Director and Founder, The New England Center for Headache, Stanford, Conn.

Editor's Note—*The last six years have seen the most profound change in the acute treatment of migraine in the century. As our understanding of the pathophysiology of migraine has expanded and our diagnosis has improved, abortive migraine drugs have become more effective.*

The new medications are the triptans, serotonin agonists that target the specific serotonin receptors that reverse the migrainous process. Sumatriptan, the first triptan, works primarily outside the brain on the peripheral pain mechanisms. The newer triptans, zolmitriptan, naratriptan, and rizatriptan, are all oral tablets, have more lipophilicity, and both peripheral and central activity.

Sumatriptan has flexibility of form, allowing for dosing a patient's migraine according to its clinical characteristics. Zolmitriptan is the only oral triptan shown to be more effective statistically than oral sumatriptan at two hours in the pivotal doses in one study, and it showed greater duration of effect than sumatriptan in that study. Naratriptan is the gentle triptan, with a low side-effect profile and a low headache recurrence rate. Rizatriptan may act sooner than oral sumatriptan, and rizatriptan is available both in a traditional pill and as a dissolvable mint-flavored melt form, a gastrointestinally aborbed oral tablet, which does not require liquid to take by mouth.

Understanding the pathophysiology of migraine helps explain the mechanism of action of the triptans, preparing the clinician for taking aim at a patient's migraine. Learning the various triptans and their pharmacologic characteristics is putting the arrows in the quiver prior to taking out one's bow. Taking a careful history and considering the clinical aspects of a patient's migraine disorder can help in selecting which arrow to use, the correct triptan, and its form for your patient.

Pathophysiology

Anatomy of the system. Migraine headache is probably generated by a nucleus in the brainstem. Patients have a hereditary tendency to neuronal hyperexcitability, and the central generator is episodically active.

In 1995, the putative central generator was demonstrated by PET scanning patients with right-sided migraine without

aura. The contralateral dorsal raphe nucleus of the midbrain turned on at the beginning of the migraine and off at the end of the migraine.[1]

After the dorsal raphe central generator turns on, there is an activation of the trigeminovascular system. This system connects the generator to the nerves and blood vessels of the dura. In response to the central activation, meningeal blood vessels dilate and become inflamed, referred to as neurogenic inflammation.[2]

Once the dural blood vessels have dilated and become inflamed, nociceptive afferents convey the signal back into the brainstem, and the peripheral pain signal is centrally transduced. Activation of the central pathways as a result of the peripheral pain process in turn leads to a turning on of central nausea centers.

Ascending pain pathways then carry the signals to the cortex. Thus, there is a central pain generator, a peripheral pain mechanism, and a subsequent central processing of the migraine.

Serotonin Receptors

Two key serotonin (5-HT) receptors, 5-HT_{1B} and 5-HT_{1D} receptors, reverse some of the migraine processes. The 5-HT_{1B} receptors are vasoconstrictive and are located in the lumen of the meningeal vessels. They are found preferentially, but not exclusively, in the CNS rather than the systemic circulation.

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The 5-HT_{1D} receptors are located both peripherally and centrally in the CNS. Activation of peripheral 5-HT_{1D} receptors turns off neurogenic inflammation presynaptically. Central 5-HT_{1D} receptors, when activated, interfere with the central transduction of the pain signal and nausea.

All of the triptans are 5-$HT_{1B/1D}$ agonists. All of them are agonists at the peripheral 5-HT_1 receptors in the meningeal blood vessel vasoconstriction. And all of the triptans have peripheral 5-HT_{1D} action, inhibiting neurogenic inflammation.

However, Sumatriptan does not appear to cross the intact human blood brain barrier, so its primary action is peripheral. All of the newer triptans are more lipophilic than Sumatriptan, and they all cross the blood brain barrier.

One problem with triptans is that they turn off mechanisms for pain, nausea, and photophonophobia, but they do not turn off the central generator. Because the triptans do not turn off the central switch, a migraine that appears gone after a dose of triptan can recur when the triptan stops working. The switch is still "on."

Clinical Measures to Evaluate Triptans

The International Headache Society (IHS) has published a series of guidelines for clinical headache end points.[3] Several new end points have also been developed.

Headache intensity is measured on a 4-point scale: 0 for no pain, 1 for mild, 2 for moderate, and 3 for severe pain.

Headache response is defined as a change in headache intensity from moderate to severe (2-3) down to no pain or mild pain (0-1) after a treatment. It is optimally measured at two hours. Disability measurements and associated symptoms, such as nausea and photophonophobia, are also measured at the same time end points.

Pain-free is defined as a migraine going from moderate to severe to no pain after treatment with a drug at a particular time.

Both headache response and pain-free numbers are better presented with the placebo rates, since the placebo rates in different studies are variable. The response rate minus the placebo rate is referred to as Therapeutic Gain (TG). Using the absolute headache response without subtracting the placebo is somewhat misleading when comparing drugs.

Time to headache relief measures how long a headache survives after a treatment. The statistical analysis uses headache responses at 30, 60, 90, and 120 minutes, taking into account each response point to calculate how soon the medication works, and allows for comparison between treatments.

Recurrence is optimally defined as occurring when a patient has a headache response at two hours, and then has a return of moderate-to-severe headache within 24 hours of treatment.

Sumatriptan
Efficacy, Dosage, and Forms

Sumatriptan (Imitrex), the first triptan, was synthesized by Dr. Pat Humphrey in the mid-1980s. It is available in the United States in three forms: subcutaneous injection, nasal

spray, and oral tablet.

The half-life of Sumatriptan is about two hours. Sumatriptan metabolism is by monoamine oxidase-A (MAO-A) and use with monoamine oxidase-A inhibitors (MAOIs) is contraindicated.[4]

Sumatriptan is relatively hydrophilic and does not penetrate the intact blood brain barrier well. Its clinical effect is primarily on peripheral 5-$HT_{1B/D}$ receptors in the meninges and neither on the central generator nor on the central 5-HT_{1D} receptors, transducing central pain and connecting to nausea and central pain nuclei.

Injectable sumatriptan comes as a 6 mg dose with options for use with an autoinjector for patients, as prefilled subcutaneous syringes, and in single-dose vials. The autoinjector is well engineered for convenient use by patients at home.[5]

Subcutaneous sumatriptan sets the standard for speed and efficacy with triptans. It works extremely quickly with 50% headache response at 30 minutes, a one-hour headache response of 77% (placebo 26%), and more than 80% at two hours. All three forms of sumatriptan reduce migraine-associated symptoms, such as nausea and photophonophobia, at essentially the same rate as headache pain.

Recurrence of migraine within 24 hours after a headache response with injectable sumatriptan is 34-38%.[6,7] Recurrence with the spray and tablet is generally also in the 35-40% range.

The nasal spray of sumatriptan is available in both 5 mg and 20 mg doses, but 20 mg is clearly the optimal dose, with a two-hour headache response of 64% (placebo 30%).[8] Almost 40% have headache response at 30 minutes, so the spray can be as fast as the injection for some lucky patients.

The spray comes in a single-use device. Unfortunately, when sniffed, it causes a terrible taste in the back of the throat. For this reason, it is now recommended that patients spray it once in one nostril and not sniff in. Then the device is thrown out.[9,10]

The sumatriptan oral tablet has a bioavailability of 14%. The optimal starting dose is 50 mg, with a 61% headache response at two hours (placebo 28%). There is a statistically significant increase in headache response going from 25 mg to 50 mg, but not an increase in significant side effects.[11]

The greatest advantage of sumatriptan is the flexibility that allows patients to switch forms within the same 24 hours, depending on the course of the attack. Maximum dosages are two 6 mg subcutaneous doses, two 20 mg nasal sprays, or four 50 mg tablets per 24 hours. However, if a patient needs to switch, she can use one injection or one spray plus two tablets in the same day, or one injection plus one spray in 24 hours.

Consistency, as measured by the mean percentage of attacks aborted at two hours over a year in an open-label study, was 84% in patients using 100 mg sumatriptan[12] and 77% in patients using the 20 mg nasal spray.[13] Sumatriptan 6 mg shots aborted 70% of attacks at one hour over a year.[14]

Adverse Events

All triptans can cause subjective "triptan sensations," which include heat feelings and flushing, numbness, paresthesias, tiredness and tightening, and heaviness of neck, jaw, and chest. The triptan sensations occur at a higher frequency with the sumatriptan injection than with the tablet or nasal spray.

Triptans can also narrow coronary arteries, but the triptan sensations are not reflective of these generally asymptomatic arterial changes. Recent work by Maassen VanDenBrink and colleagues showed that all triptans at clinical doses administered to explanted human coronary arteries in vitro narrow coronary arteries about 10-20%. Maassen VanDenBrink et al concluded that "these drugs are unlikely to cause myocardial ischemia at therapeutic plasma concentrations in healthy subjects. In patients with coronary artery disease, however, these drugs must remain contraindicated."[15]

The rate of death with sumatriptan in the absence of risk factors for coronary disease is very low and has been estimated to be less than one in 1.5 million.[16]

All triptans are contraindicated in patients with vascular disease, and the FDA has recommended consideration for cardiovascular work-up and administration of first dose in the office in patients with cardiovascular risk factors.

A good primary care rule of thumb for the work-up is to approach the patients as you would a preoperative evaluation. The appropriate preop evaluation would correspond to the pre-triptan evaluation. Obviously, the risks to patients are extremely low as most migraineurs are young, menstruating women.

Other contraindications to the use of triptans are uncontrolled hypertension, basilar or hemiplegic migraine, and, importantly, within 24 hours of another triptan or ergot.

Clinical Use of Sumatriptan

Sumatriptan is the most used and most studied triptan. The injection has the fastest onset for a triptan, and the highest overall efficacy. The nasal spray offers response time close to the speed of the injection for some patients, avoiding the gastrointestinal tract when a patient is vomiting, yet with a side-effect profile more like the tablets.

The great advantage of sumatriptan is flexibility of form. Patients with variable migraine can pick a form of the drug matched to that particular migraine, and switch forms in the same 24 hours.

For example, a patient may begin with a 50 mg tablet, thinking that he has a slow moving, more moderate migraine, and then be surprised by a quick time to vomiting. The patient can then take a 6 mg injection two hours later to achieve results.

A patient who is queasy and, thus, is manifesting the gastric stasis associated with migraine, would do well not to take a pill, but rather nasal spray. And for a patient who wakes up vomiting, the sumatriptan 6 mg autoinjector is the only way to go.

Thus, to summarize, sumatriptan is remarkably effective, flexible, consistent, and safe in the treatment of acute migraine.

Zolmitriptan

Zolmitriptan (Zomig) was the second triptan released in the United States and was the first of the new more lipophilic triptans to become available here. It does penetrate the intact blood brain barrier and may restore the central "noise filter" in patients with phonophobia.[17]

All of the new oral triptans are more bioavailable than

oral sumatriptan, and zolmitriptan has an oral bioavailability of 40%. The half-life is longer than sumatriptan at three hours. Zolmitriptan is also contraindicated with MAO-A inhibitors.[18]

The optimal dose is 2.5 mg. A dose of 5 mg often increases adverse events without improving efficacy. The maximum dose is 10 mg per 24 hours. Two-hour headache response for 2.5 mg is 62-65% (placebo rate 34-36%). Recurrence rate averages about 30%. Adverse events are triptan sensations, similar to sumatriptan tablets.[19,20]

One major comparative study has been presented showing statistical superiority of the optimal dose of zolmitriptan (2.5 mg) compared to the optimal dose of sumatriptan (50 mg) for the best clinical measure, headache response at two hours, 67.1% vs. 63.8%, respectively. Zolmitriptan users were also statistically less likely to require medication for recurrence or persistent headache over the 24 hours following initial dosing than sumatriptan users.[21]

With the 5 mg dose, 81% of attacks were aborted at two hours over a year.[22] If patients were allowed to dose with 2.5-5 mg for the initial dose, and another 2.5-5 mg if the headache persisted at two hours, 95% of attacks could be aborted over a year.[23]

Clinically, then, zolmitriptan is the only tablet to beat sumatriptan tablets for the key clinical parameter of headache response at two hours, and has a longer duration of action, with lower likelihood of use of medication for recurrent or persistent migraine.

Naratriptan

Naratriptan (Amerge) was the third triptan released in the United States. As with all of the newer triptans, it has good oral bioavailability (63-74%), and longer T 1/2 (6 hours). It is the only currently available triptan not precluded from use with MAO-A inhibitors.

It works more slowly, and in a lower percentage of patients, than the other three triptans. Two-hour headache response for the optimal dose of 2.5 mg is 48% (placebo 30%). It takes four hours for the naratriptan headache response to do what the other triptans do at two hours (60-68%, placebo 34%).[24,25] The 1 mg dose is not useful. The maximum dose is 5 mg per 24 hours. Consistency, measured by mean percentage of attacks aborted at four hours over one year, was 70%.[26]

Both side effects and recurrence rate with this drug are low. Side effects are similar to placebo, and recurrence, measured as recurrence within 24 hours after headache response at four hours, ranges from 17-28%.[27] Sheftell and colleagues presented an extremely useful clinical study that showed that patients who did not have recurrence had taken naratriptan in the first 90 minutes of their headache.[28]

So naratriptan is "Imitrex-long, Imitrex-lite." It is Imitrex-long because it takes longer to work than sumatriptan, but has a lower recurrence of the migraine. It is Imitrex-lite because it works in fewer people than sumatriptan, but has fewer side effects.

Naratriptan should be used in patients who have a relatively slow onset to their migraine so that it can be taken in the first 90 minutes of the attack. It should not be used in patients with explosive onset migraine or who wake up with migraine.

Naratriptan should be selected for those patients who are sensitive to side effects. It appears to be a good choice for patients with prolonged menstrual migraines.

Rizatriptan

Rizatriptan (Maxalt) is another high efficacy, quick onset triptan, like sumatriptan and zolmitriptan. It has improved lipophilicity over sumatriptan, oral bioavailability of more than 40%, and a T 1/2 of 2-3 hours. It has a short time to mean peak plasma concentration of 1.3 hours. MAO-A metabolism precludes its use with MAO-A inhibitors.

Rizatriptan has two doses, 5 and 10 mg, and two forms, traditional tablet and mint-flavored, orally dissolvable tablet or melt. Two-hour headache response for the optimal dose (10 mg) ranges from 67% (placebo rate 40%) to 77% (placebo response 37%) with the traditional pill. Recurrence rate ranges from 30-47%.[29-31] Consistency, as measured by mean percentage of attacks aborted at two hours over a year, was 80% for the 10 mg dose.[32]

The melt is not absorbed through the buccal mucosa, but rather dissolves on the tongue, is swallowed, and then is absorbed in the gastrointestinal tract, like any other pill. So, as expected, its efficacy is the same as the traditional tablet, with a two-hour headache response from 66% (placebo response 47%) to 74% (placebo response 28%).[33,34] Adverse events for rizatriptan are similar to those seen with sumatriptan and zolmitriptan tablets.

There is an interaction between propranolol and rizatriptan, with propranolol raising the circulating rizatriptan level, so patients on propranolol should be given the 5 mg rizatriptan dose. Others should take the 10 mg dose. The maximum

Table. The Triptans

Drug	Dose, form	Maximum/ 24 hours	Headache Response, 2 h	Recurrence Rate/24 h
Sumatriptan	6 mg sc injection	2 injections	> 80%	40%
	50 mg tablet	100 mg	61%	35-40%
	5 mg, 20 mg	40 mg	62% for 20 mg	35-40%
	nasal spray	In combination: two injections or sprays; or one of either plus two tablets		
Zolmitriptan	2.5 mg, 5 mg	10 mg	65%	30%
Naratriptan	1 mg, 2.5 mg	5 mg	48% for 2.5 mg	22%
Rizatriptan	5 mg, 10 mg	30 mg, 15 mg in patients on propranolol	71%	40%

rizatriptan dose is 30 mg per 24 hours, but 15 mg per 24 hours for patients on propranolol. The same interaction does not occur between rizatriptan and other beta blockers, or between other triptans at clinical doses and propranolol or other beta blockers.

A comparative study between the optimal dose of rizatriptan (10 mg) and the optimal dose of sumatriptan (50 mg) showed no statistical difference for two-hour headache response (72% vs. 68% [placebo 38%]). Rizatriptan may work sooner than sumatriptan at the pivotal doses, as time to headache relief was statistically shorter for rizatriptan.[35]

Rizatriptan is, thus, the third of the fast onset, high efficacy triptans, and compared to oral sumatriptan, it may act sooner, although the same percentage of patients are helped by two hours.

Selecting the Right Triptan for Your Patient

Given that there are now four and soon will be more triptans, how can a clinician know which drug to pick for a patient and when? Strategies for evaluating a patient for migraine medication include step care and stratified care.

Step care is care by cost. In step care, the clinician selects the cheapest medicine for migraine first, and only steps up to the next level of medication if the cheaper one has failed. This is an algorithm championed by some health maintenance organizations and insurance companies, but not by compassionate caregivers or patients.

What happens with this approach is that a patient is always given an inexpensive oral drug first, even if the patient wakes up vomiting in each attack. When this fails, as it always will since the pill will be vomited, the algorithm allows for the next level up.

This approach makes no sense. Step care, delaying appropriate treatment, results in prolonged work loss and disability, and even worse consequences if a patient lapses from treatment due to frustration.

Stratified care is what clinicians have done for years with all diseases. We individualize our care based on the patient's presentation. There are several easy ways to do this with migraine.

First, the peak intensity, time to peak intensity, associated symptoms, and disability (e.g., nausea, vomiting, photophonophobia, and inability to function) can be assessed. Patients with quick time to peak, and high intensity and disability, stratify to triptan use as the first-line medication for their migraines from the beginning. And if they have significant nausea, suggesting gastric stasis, and the patient has a quick time to nausea with or without vomiting, an oral drug may not be optimal. Rather, a parenteral or nasal spray should be used.

The second way to stratify patients is to ask about work or productivity loss. This can be measured by actual days lost from work or home activities, or as more than 50% loss of effectiveness at work or home. There is a simple disability scale of five questions that can be given to patients to stratify their needs based on these concerns—the Migraine Disability Assessment Scale or MIDAS.[36] A patient with significant work loss merits a triptan as the first acute care agent prescribed.

How would this work in practice? Let's take some clinical cases and apply the stratification and the new information on the triptans:

- A patient wakes up vomiting with a full blown, incapacitating migraine. The patient obviously stratifies to the high treatment-need group by peak intensity, time to peak intensity, functional disability, time to peak functional disability, and the potential for work or productivity loss. A parenteral triptan is most likely going to be needed, although occasionally a patient like this will benefit from a nasal

spray. The only triptan currently with both parenteral and nasal preparations is sumatriptan, and it should be prescribed for this patient. In prescribing the nasal spray, remember to tell the patient not to sniff in!

- A patient is missing multiple days of work each month with stereotypical attacks that are maximal at two hours, with no nausea or vomiting, but with severe photophonophobia. The patient should be given an oral triptan, sumatriptan or zolmitriptan, or rizatriptan with its fast onset of effect.
- The last patient comes back and says that her attacks are no longer stereotypical, and some are coming on more rapidly with vomiting. Also, she is awakening with migraine. The patient with variable migraine should be given sumatriptan, because the FDA forbids switching triptans in the same day, and if the patient starts with a tablet, but mistakes how fast the attack will develop, she cannot switch from zolmitriptan or rizatriptan tablets to sumatriptan injection. She should be given multiple forms of sumatriptan, optimally tablet and injection.
- A patient has slow onset migraine, nonetheless bad enough to reduce her productivity at work. Her worst migraines occur at menses and last at least three days. She had bad throat tightening from sumatriptan. She should receive naratriptan. The slow onset won't matter, the reduced side effects will be welcome, and the low recurrence is useful in long menstrual migraines. Just remember to have her take the naratriptan in the first 90 minutes of the attack!
- A patient is in a corporate board room making a presentation when she feels a migraine coming on rapidly. The rizatriptan melt could be taken discretely without water in this setting. The same patient can use the melt driving, or at a movie, for convenience.

Conclusions

Selection of an abortive agent for a patient's migraine should be based on stratification by intensity, time to peak intensity, functional disability, time to functional disability, and work and productivity loss. Triptans should be used as the first-line abortive agent in patients who stratify to high treatment need.

Sumatriptan provides the greatest versatility and, when in doubt as to the variability of a patient's migraine, should be prescribed in multiple forms to allow a patient various avenues of escape. No two triptans can be used within 24 hours of each other, but patients can switch forms of sumatriptan in the same day. The 6 mg subcutaneous injection offers the greatest speed and the highest efficacy of any triptan.

In one study, zolmitriptan showed superior headache response to oral sumatriptan at two hours, and less chance of recurrence or use of rescue medicine over the next 24 hours.

Rizatriptan may work sooner than oral sumatriptan, and has both a traditional tablet and melt form.

Naratriptan is the different triptan, with fewer side effects, slower onset, and lowest recurrence rate.

Triptans are contraindicated in patients with vascular disease, uncontrolled hypertension, basilar, or hemiplegic migraine.

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Physician CME Questions

55. Activation of 5-HT_{1D} receptors by triptans can do all of the following *except*:
    a. reduce neurogenic inflammation around dural vessels.
    b. abort migraine pain.
    c. vasoconstrict meningeal vessels.
    d. interfere with central transduction of pain.

56. Which triptan does not cross the intact blood brain barrier?
    a. Sumatriptan
    b. Zolmitriptan
    c. Naratriptan
    d. Rizatriptan

57. Which triptan has three forms allowing for switching in the same day depending on variability of the migraine?
    a. Sumatriptan
    b. Zolmitriptan
    c. Naratriptan
    d. Rizatriptan

58. Which triptan has the lowest recurrence rate?
    a. Sumatriptan
    b. Zolmitriptan
    c. Naratriptan
    d. Rizatriptan

59. All of the following triptans are considered fast onset, high efficacy triptans *except*:
    a. sumatriptan.
    b. zolmitriptan.
    c. naratriptan.
    d. rizatriptan.

60. When applying stratified care for a patient with migraines, which of the following must be assessed?
    a. Peak intensity
    b. Time to peak intensity
    c. Associated symptoms
    d. Work or productivity loss
    e. All of the above

61. Which form of triptan would be most convenient for a patient in a corporate board meeting with a migraine rapidly coming on?
    a. Oral
    b. Nasal spray
    c. Oral melt
    d. Subcutaneous injection

Readers are Invited...

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