

CONCISE REVIEW

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Zolmitriptan and the Triptan Era

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Abstract: Zolmitriptan is one of seven triptans available to treat acute migraine attacks. The introduction of these selective serotonin receptor agonists almost 20 years ago has revolutionized acute migraine treatment. Triptans are now first line migraine drugs, and provide acute treatment that is well-tolerated, safe and effective. This commentary reviews the use of zolmitriptan and other triptans, discusses how to maximize their effect, and examines the controversies surrounding this class of medication such as medication-overuse headache, use in migraine aura or prodrome, pediatric use, and important drug interactions.

Keywords: migraine, zolmitriptan, triptans, migraine pathophysiology, medication-overuse headache, serotonin syndrome

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Triptans are selective serotonin receptor agonists designed to treat acute migraine. The following article by Kalanuria and Peterlin provides an excellent overview of zolmitriptan pharmacology, one of the most popular triptans. Since the introduction of injectable sumatriptan (in Europe in 1991 and the United States in 1992), patients have used zolmitriptan and other triptans to treat millions of acute migraine attacks.¹⁻³ These medications offer acute treatment that is well tolerated and effective, with an excellent safety profile and without the risk of dependence or addiction seen with barbiturate or opioid medications. Triptans alleviate not only the pain of migraine, but the associated symptoms of nausea, photophobia, and phonophobia. Currently there are 7 different triptans available for the treatment of migraine. Each triptan has different pharmacologic properties; some are available in different formulations, such as orally disintegrating tablets, nasal sprays or injection. Given that migraine is often associated with emesis or gastroparesis, non-oral formulations are often needed.

Triptans: An Overview

Zolmitriptan and other triptans are selective serotonin receptor agonists with high affinity for 5-HT_{1B} and 5-HT_{1D} receptors, with variable activity at the 5-HT_{1F} receptor. Serotonin receptors were selected as a target for acute treatment based on their involvement in the pathophysiology of migraine.^{4,5} Migraine can be precipitated by serotonin releasing agents and serotonin and its metabolites are increased in the urine during migraine attacks in some patients.⁶ Serotonin depletion was believed to affect platelet function, resulting in a loss of vascular tone.^{7,8} Serotonin is a vasoconstrictor and experimentally alleviates headache, although in its non-selective form it has numerous undesirable adverse events (AEs), such as bronchoconstriction, gastrointestinal effects, and generalized vasoconstriction.⁹ Triptans cause fewer AEs, since they have a specific receptor affinity.

Agonism of 5HT-1B/D receptors may constrict meningeal arteries which are inflamed and dilated during migraine attacks. Another proposed mechanism is inhibition of neuropeptide and neurotransmitter release including compounds such as calcitonin gene related peptide (CGRP), substance P, and glutamate in the peripheral and central nervous system. 5HT-1D

receptors are also found in the basal ganglia and substantia nigra and may regulate dopamine release. The relative contribution of each specific receptor to pain relief is unknown.¹⁰ Although initial research suggested triptan effectiveness was because of their vasoconstrictive properties, blocking the transmission of pain signals from the trigeminal nerve to the TNC and preventing release of inflammatory neuropeptides may be more important.¹¹ In fact, CGRP antagonism, a potential new migraine-specific treatment, does not cause vasoconstriction,¹² and new research even suggests that vasodilation of meningeal arteries does not occur in migraine.¹³

Although triptans are generally effective, many patients either do not become headache-free or experience recurrence of pain. In clinical practice, migraine patients may elect to treat with more than one medication for severe attacks. Treatment with medications of different classes such as non-steroidal anti-inflammatory drugs (NSAIDs) can produce a synergistic effect. NSAIDs may work by suppressing inflammation and preventing and treating central sensitization by blocking glial production of prostaglandins. They may also treat non-traditional migraine symptoms, such as neck pain, fatigue, or sinus pressure, commonly associated with migraine attacks.¹⁴ Despite the popularity of triptans, some suggest that triptans should be second-line treatment as other combinations such as aspirin and metaclopramide are often effective.¹⁵ There are few head-to-head trials comparing triptans to combination regimens.

Zolmitriptan: When to Use?

Deciding which triptan to utilize is patient-dependant: how they metabolize the medication, their headache patterns, and what AEs they can experience.¹⁶ Injectable sumatriptan is the most effective and fastest-acting triptan, but causes the most AEs.¹⁷ Zolmitriptan 2.5 and 5 mg, has similar effectiveness and AEs compared to sumatriptan 100 mg.¹⁸ One advantage on zolmitriptan is the nasal spray formulation that bypasses the GI tract and works quickly. Zolmitriptan nasal spray is one of the few acute treatments proven effective in cluster headache.¹⁹ Patients vary in their response patterns and trial and error may be necessary to find the best treatment. If another triptan fails, it is worth trying zolmitriptan.



Currently no triptans are indicated for the treatment of migraine in children, but the evidence of their efficacy is mounting, and zolmitriptan nasal spray should be considered. Although most pediatric patients use migraine nonspecific medications, triptans are also effective and well tolerated. Studies of triptans in children show similar efficacy as adult trials, but placebo responses are much higher.²⁰ The zolmitriptan nasal spray 5 mg trial eliminated early placebo responders who responded to treatment within 15 minutes. If they continued to have headache patients were randomized to placebo or medication. The zolmitriptan-treated patients demonstrated significant improvement in pain intensity, pain-free rates, and resolution of migraine-associated symptoms.²¹

Migraneurs that treat with triptans should use zolmitriptan early in the attack. Most of the triptan trials asked patients to treat headaches of moderate to severe intensity. In the initial trials, patients who treated early when pain was mild were considered to have violated protocol, in part because it was unclear that these patients were treating migraine. Yet the protocol violators actually had superior outcomes than the patients who waited.²² Recent studies confirm that using triptans early works better²³ and physicians should instruct patients to take zolmitriptan early for acute headache.

Triptans: Special Clinical Situations

Allodynia is pain in response to a stimulus that is normally non-painful²⁴ and may explain why treating early in migraine is so important. Many patients experience cutaneous allodynia of the face or body with their acute migraine attacks. Central sensitization correlates with allodynia and is an increase in the sensitivity of neurons in the CNS and the likely cause of somatosensory hypersensitivity in migraine.²⁵ During migraine, release of inflammatory compounds such as CGRP, substance P and glutamate promote the development of peripheral sensitization. This leads to central sensitization, manifested clinically by allodynia. Triptans may prevent development of central sensitization at these early stages by blocking neurotransmitter release,²⁶ but cannot reverse the process of central sensitization at later stages. In open-label studies, migraine patients experiencing allodynia respond poorly to triptan therapy.^{27,28}

Although treatment with triptans when pain is mild is often successful, treatment during aura is usually not. Subcutaneous sumatriptan does not prevent headache or change the character of the aura when taken at the onset of aura, before pain begins.²⁹ Triptans are not indicated for the treatment of prolonged, complicated, hemiplegic or basilar auras, since clinical trials excluded these patients. However recent case series report successful treatment of hemiplegic migraine³⁰ or basilar migraine³¹ patients without AEs. In theory, treating complicated aura with triptans should be safe as recent studies suggest cortical spreading depression, not vascular changes, causes migraine aura.

Using triptans for treatment of migraine during the prodrome phase may be helpful.³² One example is menstrual migraine. Triptans can effectively treat menstrual migraine using short-term prophylaxis without risk of dependence or rebound headache.^{33,34}

Triptan Controversies: Medication-overuse, Cardiovascular Effects and Serotonin Syndrome

Although zolmitriptan and other triptans do not cause dependence and addiction, they place patients with frequent migraine at risk for medication-overuse headache (MOH).³⁵ Triptan users may have worsening of their disease or loss of medication effectiveness when using more than 10 days a month. Patients often improve after stopping the overused medication. Compared to barbituates and opioids, patients who overuse triptans have a quicker recovery after withdrawal and are less likely to relapse.³⁶ Patients who use triptans are also less likely to develop chronic migraine than patients who use opioids or barbiturate-containing medications.³⁷ Patients with migraine appear to be at risk for worsening of pain with increasing medication use, even compared with patients with other chronic pain disorders.³⁸

One major limitation of zolmitriptan and other triptans is the potential risk of exacerbating existing cerebrovascular disease. Triptans are contraindicated in patients with ischemic heart disease, vasospasm, uncontrolled hypertension or transient ischemic attacks.³⁹ 5HT_{1B} receptors are present in coronary arteries and the risk of precipitating coronary events was a focus of the initial migraine trials. The rate of serious AEs in these trials was extremely low.



Although triptans do cause vasoconstriction, they do not appear to impair cerebral blood flow.⁴⁰ There have been reports of patients experiencing cerebrovascular events while taking triptans, some resulting in death. In a number of cases, the events were primary and unrelated to migraine: some patients used triptans because they felt their symptoms were due to migraine. The fact that chest pain is common in patients taking triptans is also problematic as most triptan-associated chest pain is generally not serious or related to ischemia.^{41,42}

A final clinical concern is the safety of using triptans in combination with other drugs affecting serotonin metabolism. Monoamine oxidase inhibitors (MAOIs) can affect the metabolism of some triptans, including zolmitriptan and are contraindicated. Triptans, according to the product label, should not be used within 24 hours of ergotamine-containing preparations or ergot-type medications such as dihydroergotamine or methysergide although there is little evidence to support this. There have also been rare reports of possible serotonin syndrome in patients taking both triptans and selective serotonin reuptake inhibitors (SSRIs) or other anti-depressants. Serotonin syndrome is a constellation of symptoms that may include confusion, autonomic nervous system changes, weakness, hypertension, sweating, stiffness, seizures, spasticity, or fever. This has important implications, as migraine and depression are co-morbid conditions. However, the jury is still out on the question of whether or not triptans cause serotonin syndrome. The 5HT-1B/D receptors have not been implicated in the disorder and it would seem that given the popularity of SSRIs and triptans, if triptans truly increased risk this should be a more common problem.⁴³

Disclosure

The author reports no conflicts of interest.

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