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New Drug Approval for Lasmiditan: A New Approach to Migraine Treatment

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Abstract

Millions of people worldwide suffer from migraines, and current treatment may not be suitable for all patients. Patients who have cardiovascular risk factors as well as migraines are not able to take triptans, which are the mainstay of acute migraine treatment, because triptasns can cause an increase in blood pressure and potentially cause an unwanted cardiovascular event. Lasmiditan (Reyvow™) is a newly FDA-approved drug that is indicated for acute treatment of migraine with or without aura in adults that is safe for patients who have cardiovascular risk factors. This new drug gives hope to many patients who have untreated migraine pain and has the potential to greatly change the current treatment guidelines for migraines.

A migraine is a neurological condition characterized as a very severe headache.[1] It can present with a variety of symptoms, but it is most commonly described as an intense head pounding that lasts from hours to days and can worsen upon movement or activity and exposure to bright light or noise.[1] Pain associated with migraines is normally on only one side of the head but is on both sides in about ⅓ of patients.[2] Nausea, vomiting, irritability, extreme sensitivity to light or sound, and tingling/numbness are commonly experienced with a migraine attack.[2] Classical migraines (also referred to as complicated migraines) start with an aura.[1] An aura usually precedes a migraine but can also follow a migraine. Auras can last from 15 to 30 minutes and are typically characterized by vision changes such as flashes of light, color, or patterns.[1] It could also be associated with loss of vision in an area of the field of vision. Common migraines do not have an aura associated with them.[1] Common migraines may last longer, have a slower onset, and interfere more with daily activities than classical migraines.[1] Common migraines are also more prevalent than classical migraines.[1]

Migraines are an increasingly prevalent neurological disease that affects over 1 billion people worldwide.[2] It is now ranked in the top three most prevalent illnesses worldwide and is considered the sixth most disabling illness.[2] About 85% of people who suffer from migraines are women, and 1 in 4 women experience a migraine in their lifetime.[2] Women are more likely than men to experience migraines because fluctuations in estrogen can cause an onset of a migraine.[2] Migraines due to estrogen fluctuations are usually more severe and more frequent.[2] Before puberty, boys are more likely to experience migraines than girls, but after puberty, girls are more likely to experience migraines.[2] Migraines also tend to be more frequent and severe in girls after puberty compared to boys after puberty.[2] While this neurological condition is more common in women, it does not discriminate as it also affects men and children.[2] Migraines alone are responsible for costing the United States over 157 million lost workdays annually and up to $36 billion in healthcare and lost productivity costs.[2]

Medications for migraine treatment belong in the drug classes of triptans, ergot alkaloids, and analgesics. While all of these classes are options, triptans were specifically designed for treating migraines and therefore, are the mainstay of migraine treatment.[3] Analgesics include ibuprofen, acetaminophen, and opioids and are typically only used for very mild migraines.[3] Although not specifically designed for migraine treatment alone, ergot alkaloids, are only successful in treating headache-related pain when used as pain relievers.[4] However, these medications are typically reserved as last-line for those who are unresponsive to analgesics or triptans for migraine relief.[3] Any kind of acute migraine treatment should not be used longer than 10 days per month because medication-overuse headaches can occur.[3]

Triptans are not only the mainstay of migraine treatment in general, but have also shown to be more effective in treating

moderate to severe migraine episodes than other analgesics.[3] There are 7 FDA-approved triptan medications which include sumatriptan, rizatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, and zolmitriptan. As a class, all triptans work as selective agonists for specific serotonin receptors in cranial arteries in an effort to cause vasoconstriction and alleviate inflammation.[5] Each triptan produces the desired effect by selectively activating the 5-HT_{1B} and 5-HT_{1D} receptors, with the exception of eletriptan which selectively activates 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors.[5]

Although triptans are successful in treating moderate to severe migraines with or without aura, they still have their own limitations. Although they are selective for specific serotonin receptor subtypes, they are not specific for the location of those subtypes. Triptans will activate the 5-HT_{1B} and 5-HT_{1D} receptors at any place those receptors may be located throughout the body.[6] The 5-HT_{1B} and 5-HT_{1D} receptors are found throughout the central nervous system as well as the vascular system; hence, activating these receptors can lead to vasoconstriction.[6,7] As a result of this, triptans are contraindicated in those with uncontrolled hypertension, ischemic heart disease, ischemic bowel disease, or a history of cerebrovascular syndromes such as stroke.[5]

Lasmiditan (Reyvow™) is a new oral drug with the indication of acute treatment of migraine with or without aura in adults that was recently approved in October of 2019.[5] Lasmiditan represents the first drug in a new class of medications for acute migraine treatment (5-HT_{1F} receptor agonists). Lasmiditan is unique because it is specific to 5-HT1F receptors, while triptans are not. Triptans cause vasoconstriction in the brain as well as the rest of the body which means that people with existing hypertension or other cardiovascular risk problems cannot take triptans due to the risk of worsening their cardiovascular health.[7] Lasmiditan does not have the same risk as triptans of worsening patients' cardiovascular health because it does not affect some receptors that cause vasoconstriction, unlike triptans.[7] This makes lasmiditan a novel new option for patients with cardiovascular risk factors who have an unmet need for acute migraine treatment.[7,8]

Lasmiditan's effectiveness has been shown in two double-blind, randomized clinical trials.[9] In these phase-3 studies included in the New Drug Application for lasmiditan, over 3,000 adult patients who suffer from migraines with and without aura received either lasmiditan (100 mg or 200 mg) or placebo. Two hours after taking either placebo or drug, the percentages of migraine pain resolution as well as resolution of the patients' most bothersome symptoms (nausea, light or sound sensitivity) was significantly higher with lasmiditan at any dose than with placebo.[10] These studies also showed that lasmiditan is generally well-tolerated. Adverse effects of lasmiditan in the phase-3 studies were mostly mild to moderate in severity and the most common were dizziness, fatigue, paresthesia, sedation, nausea, vomiting, and muscle weakness.[8]

In one phase 3 study, over 75% of patients had at least one cardiovascular risk factor in addition to migraines which is a strength of the study because it shows that patients with cardiovascular risk factors can take lasmiditan with successful results.[10] However, patients with known coronary artery disease, clinically significant arrhythmias, uncontrolled hypertension, and patients with >15 migraine days per month were excluded from the trial, which is a limitation because it is unclear how these patients would respond to the drug.[10] There are currently no contraindications listed in the manufacturer's labeling for lasmiditan.[5]

While lasmiditan shows a lot of promise as a new acute treatment for migraines, it does have limitations and side effects. 9-17% of patients reported experiencing dizziness with lasmiditan.[5] Other less frequent (<10%) side effects include paresthesia, chest discomfort, drowsiness, nausea, and vomiting.[5] Due to the CNS depressant effects, there is a significant risk of impairment while driving while taking lasmiditan.[9] Patients are advised not to drive within eight hours of taking lasmiditan.[9] Patients are also cautioned not to drink alcohol or use other CNS depressants while taking lasmiditan.[9] Furthermore, clinical trials have resulted in patients having symptoms consistent with serotonin syndrome while taking lasmiditan.[8] The risk of serotonin syndrome increases if patients are on other serotonergic drugs. Patients and providers are advised to discontinue lasmiditan immediately if serotonin syndrome is suspected.[8]

A precaution of lasmiditan that differs from the current mainstay of migraine treatment is its abuse potential. A study on human abuse potential compared lasmiditan to alprazolam 2 mg and placebo in recreational multi-drug users.[8] The lasmiditan doses studied were therapeutic doses of 100 mg and 200 mg as well as a supratherapeutic dose of 400 mg.[8] The study found that with all doses of lasmiditan, subjects reported higher "drug liking" than placebo, but lower "drug liking" than alprazolam.[8] The researches deemed these results statistically significant.[8] These results were attributed to the propensity of lasmiditan to cause euphoric mood when taken as 200 mg and 400 mg doses.[8] This adverse event occurred to a similar extent as alprazolam.[8] Conversely, subjects experienced more relaxed feelings with alprazolam than with lasmiditan, regardless of the lasmiditan dose.[8]

While phase 2 and phase 3 studies demonstrated that lasmiditan causes euphoria and hallucinations more than placebo, the incidence of these adverse events was low, occurring in only 1% of patients.[8] However, because lasmiditan does demonstrate significantly higher "drug liking" than placebo, each patient must be evaluated and observed for signs of drug abuse both prior to and during lasmiditan therapy. Lasmiditan is currently under review by the DEA for its controlled substance classification and is expected to be decided within 90 days of the drug's FDA approval date.[8] Once the classification is determined, lasmiditan will be available in community pharmacies.[8]

Moving forward, lasmiditan has great potential and is expected to positively impact the strategies for treating migraines. As migraines continue to incapacitate millions of people, the addition of new and successful therapies is warranted. Patients with a contraindication to triptans may now be able to effectively treat their migraines and increase the time they are pain-free.

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