Serotonin Receptor Agonists in the Treatment of Migraine: A Meta-Analysis Considering Possible Connection with Paresthesia

Serotonin (5-hydroxytryptamine, 5-HT) receptors are a large family of guanine nucleotide triphosphate-binding protein-coupled receptors and one ligand-gated ion channel that transduce an extracellular signal by the neurotransmitter 5-HT to an intracellular response.[1] They are classified into seven types, 5-HT1 through 5-HT7, and localized in the brain and in peripheral tissues. The majority of 5-HT receptors are postsynaptic, with some exceptions, most notably 5-HT1A and 5-HT1B, which are mainly presynaptic and modulate serotonin release. The signaling pathways to which these receptors are coupled are known; however, it has not been possible to link direct clinical effects systematically to their stimulation.[2] As many neuronal, physiological, and behavioral processes are influenced by 5-HT receptors, it is known that their dysfunction and regulation of 5-HT receptors are implicated in numerous disorders.[1] Serotonin receptors play a central role in the pain mechanism, especially in migraine headaches. At least five different presynaptic and postsynaptic 5-HT receptors are differentiated by dividing them into two groups–$5HT_1$ and $5HT_2$. $5HT_{1B}$ and $5HT_{1D}$ agonists (sumatriptan) have a strong antagonist (pizotifen) that has a preventive effect. α_2, H_3, μ-opioid, and somatostatin were found in the trigeminovascular fibers and may play a role in anti-migraine therapy. Medication that has a direct stabilizing effect are as follows: voltage-gated sodium channel blockers (carbamazepine, phenytoin, and lamotrigine), α_{25} subunits of presynaptic voltage-dependent calcium channel blockers and reducers of presynaptic transmitter release, which was found to be efficient in peripheral pain, and inhibitors of glutamate release and the action of AMPA and kinate receptors, for example, Topiramate, which has been found to be effective, especially in migraine and headache.[3]

Migraine is a primary headache disorder characterized by moderate-to-severe headache attacks lasting 4–72 hours with unilateral location and pulsating quality, aggravated by movement or causing avoidance of routine physical activity and associated with nausea and/or vomiting, photophobia, phonophobia, and paresthesia. Migraine is an important socioeconomic burden and is ranked the sixth cause of years of life lost because of disability in the general population and the third cause of years of life lost in people younger than 50 years.[4] There are three classes of drugs for migraine: over-the-counter Non-steroidal anti-inflammatory drugs for acute mild-to-moderate migraine, specific prescription drugs (triptans and ergot alkaloids) for acute moderate-to-severe migraine, and pharmacological agents for prophylaxis of migraine.

The 5-HT receptor subtype 1B/1D agonists (triptans) are nowadays the mainstay for acute treatment of migraine headaches. Since the introduction of Sumavel DosePro® (sumatriptan) in 1991, other triptan compounds with improved pharmacokinetic properties, efficacy, and safety were developed. Currently, seven triptans are available; in order of release, they are as follows: sumatriptan, zolmitriptan, rizatriptan, naratriptan, eletriptan, almotriptan, and frovatriptan.[4] However, some of the mentioned drugs show considerable incidence of the central nervous system-related adverse events (e.g., chest or neck pain, tightness, limb heaviness, dizziness, limb heaviness, nausea, somnolence, fatigue, and paresthesia). It should also be noted that it is often difficult to determine whether paresthesias occur as part of the clinical picture of migraine or are a side effect of anti-migraine treatment or are even part of the clinical picture of diabetes (around 14% prevalence has been reported for migraine in diabetic patients), various neurological pathologies, or toxic and compressive syndromes with nerve injury.[5]

However, 5-HT agonists are generally contraindicated in specific patients with macrovascular complications (in October 2019, the United States Food and Drug Administration approved Lasmiditan for migraine treatment, which is a 5-HT receptor agonist and produces no vasoconstrictive effect). As per the data of clinical trials, Lasmiditan has positive results for migraine treatment, but paresthesia was significantly reported.[6]

Aliul Hasan Abdi *et al*. in their review article *Serotonin receptor agonist and risk of paresthesia in migraine patients: A Dose-response Model-Based (Network) Meta-Analysis* show results from 30 placebo-controlled clinical trials (29,154 subjects) that evaluated 5-HT serotonin agonist for migraine treatment versus placebo. The main outcomes were to perform dose-response model-based network meta-analysis of different 5-HT serotonin agonists and to compute relative risk for paresthesia so that a precaution may be implicated in the pharmaceutical care plan for migraine treatment. In addition, the probability of paresthesia among various treatments was estimated by the Surface Under the Cumulative Ranking (SUCRA) method. The cumulative SUCRA probabilities indicated that Lasmiditan had the highest probabilities of paresthesia among other 5-HT receptor agonists. However, dose-response model-based network meta-analysis of different 5-HT receptor agonists revealed that Topiramate 200 mg, Lasmiditan 400 mg, and Zolmitriptan 10 mg have a high risk for paresthesia among different categories of 5-HT receptor agonists in this sample size. The authors concluded the

study with recommendations that clinicians should judge each individual case critically because migraine itself is a trigging factor for paresthesia. In addition, special attention has been postulated for migraineur diagnosed with diabetes.

In our opinion, the profusion of new migraine drugs in the past several decades has expanded the therapeutic arsenal and improved pharmacological treatment of migraine. Nevertheless, the field of migraine therapeutics is still in its continuous development. Clinicians faced with daily therapeutic decisions with regard to 5-HT receptor agonist selection still have little comparative data that needs to guide precise prescribing decisions.[7,8]

Darko Katalinic, Aleksandar Vcev, Martina Smolic, Ivan Aleric

Faculty of Dental Medicine and Health and Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

Address for correspondence: Prof. Darko Katalinic, Faculty of Dental Medicine and Health and Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia.
E-mail: darkodominik@gmail.com

References

1. Gresch PJ. Serotonin receptor signaling. In: Lennarz WJ, Lane MD, editors. Encyclopedia of Biological Chemistry. 2nd ed. Elsevier; 2013. p. 224-8.
2. Athar S. Serotonin and tryptophan. In: Komopoliti K, Verhagen Metman L, editors. Encyclopedia of Movement Disorders. Elsevier; 2010. p. 104-8.
3. Lampl Y. Pain. In: Spinath N, editor. Encyclopedia of Human Behavior. 2nd ed. Elsevier; 2012. p. 1-13.
4. Negro A, Koverech A, Martelletti P. Serotonin receptor agonists in the acute treatment of migraine: A review on their therapeutic potential. J Pain Res 2018;11:515-26.
5. López-de-Andrés A, del Barrio JL, Hernández-Barrera V, de Miguel-Díez J, Jimenez-Trujillo I, Martinez-Huedo MA, *et al*. Migraine in adults with diabetes; is there an 283 association? Results of a population-based study. Diabetes Metab Syndr Obes 2018;11:367-70.
6. Tepper D. Lasmiditan for the acute treatment of migraine. Headache 2020;60:1225-6.
7. Bigal ME, Ferrari M, Silberstein SD, Lipton RB, Goadsby PJ. Migraine in the triptan era: Lessons from epidemiology, pathophysiology, and clinical science. Headache 2009;49:S21-33.
8. Goadsby PJ. Can we develop neurally acting drugs for the treatment of migraine? Nat Rev Drug Discov 2009;4:741-50.

Submitted: 20-Mar-2022 **Accepted:** 20-Mar-2022 **Published:** 09-Jun-2022

DOI: 10.4103/aian.aian_266_22