Review Article

Lasmiditan, A Novel Abortive Agent for Migraine Therapy – From Triptans to Ditans

Rishika Addla# PharmD Intern, Soni Gaddam# PharmD Intern, Satyanarayana SV Padi* PhD
Department of Pharmacy Practice, Care College of Pharmacy, Hanamkonda, Telangana, 506006, India.
#Authors contributed equally; ***Corresponding author's E-mail:** ssvpadi@gmail.com

Received: 21-03-2023; **Revised:** 25-05-2023; **Accepted:** 02-06-2023; **Published on:** 15-06-2023.

ABSTRACT

Migraine is a neurological disorder and a common chronic primary headache disorder characterized by acute episodes of recurrent, unilateral, pulsating, throbbing headache. The migraine attack lasts for 4-72 hours associated with or without aura symptoms. According to global burden of diseases, migraine is the second leading cause of disability. Moreover, migraine is poorly managed by the currently available drugs implying that there is an unmet need for effective pharmacotherapeutics for this complex neurological disorder. Triptans are the gold standard drugs; however there are reports of migrainers who are not fully benefited. Moreover, triptans are not recommended in patients with cardiovascular risk factors due to peripheral vasoconstriction. Recently, lasmiditan, a highly selective 5-HT1F agonist, has been approved for the acute treatment of migraine with or without aura. Lasmiditan is the first in the new class of drugs 'ditans' which differ from the triptans in that these do not show vasoconstriction effect. Lasmiditan act on 5-HT1F receptors present on sensory neurons of trigeminal system without causing unwanted vasoconstriction due to its low affinity for 5-HT1B and 1D receptors. Lasmiditan is highly lipophilic and readily cross blood-brain-barrier, showed rapid absorption, and quick onset of action. In clinical trials, it had shown therapeutic effects and met the primary endpoints of headache pain freedom and most bothersome symptom freedom at 2 hours. Importantly, the efficacy of lasmiditan was not affected by the presence of cardiovascular risk factors in these clinical trials. Most frequently reported adverse drug reactions of lasmiditan are dizziness, sedation, somnolence, and paresthesia. Systematic reviews and meta-analysis data reported lasmiditan as safe and effective option for acute migraine treatment. However, long-term data on its use are required to establish safety and tolerability, effectiveness, and potential risk and drug-drug interactions between existing and novel antimigraine drugs in real world situation.

Keywords: 5-HT1F agonist, CGRP receptor antagonists, Ditans, Gepants, Lasmiditan, Migraine, Triptans.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2023.v80i02.021

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v80i02.021

INTRODUCTION

Headaches are one of the most common symptoms and a neurological disorder that general physicians and neurologists evaluate. Globally headache disorders are under-recognized, under-diagnosed, under-estimated, and under-treated and only a minority of those are appropriately diagnosed by a health care provider. Mostly, headache is caused by primary headache disorders and the differential diagnosis is one of the longest in medicine.[1,2] Migraine is a common primary headache disorder characterized by recurrent, chronic, pulsating, unilateral, and throbbing headache. It has been reported that headaches are the second most prevalent disorders in both the genders and about one billion individuals were estimated to have a migraine in 2016.[1,2] Globally about 10% of school aged children suffer from migraine attack. Indeed, women are more prone to migraine than men and the episodes of migraine are predominant during pregnancy and after menopause.[3] Moreover, migraine had a much higher disability weight in terms of years lost to disability as a result of headache globally in 2016.[1] It is not generally considered as a symptom, but a complex neurological disorder occurs in various phases, namely (1) prodrome phase, (2) aura phase, (3) pain phase or silent phase, and (4) postdrome phase. Migraine headache is accompanied by few more symptoms, such as nausea, vomiting, sensitivity to light (photophobia) and sound (phonophobia) considered as 'without aura' and sensory and visual disturbances considered as 'with aura'. The main causes of migraine are genetic, physiological aspects, such as hormonal changes in women, psychological stress, dietary factors, such as excess caffeine and dark chocolates, social habits, such as excess alcohol, sleep-wake cycle disturbances, such as lack of sleep and irregular sleep patterns, and environment factors, such as cold and sudden changes in weather (Figure 1).[3,4] Apart from changes in life style and avoiding triggers that evoke migraine, pharmacological approaches that modulate changes in blood flow (vasoconstriction and vasodilation) due to calcitonin gene-related peptide (CGRP) and serotonin (5-hydroxytryptamine, 5-HT) release remains the best way to manage migraine (Figure 1). Recent advances in understanding of the pathophysiological and neurochemical changes in migraine lead to the discovery and development of target based therapeutic modulators. Owing to successful therapeutic approaches in clinical trials, there has been surge in anti-migraine drug approvals

that has brought tremendous paradigm shift in prescription practice as well as therapeutic choices available for migraine management.[5] Currently available prophylactic (preventive) options include antiepileptics, beta-blockers, antidepressants, anticonvulsants, botulinum toxins, and newly approved CGRP inhibitors (anti-CGRP antibodies) whereas the therapeutic treatment employs abortive agents, such as ergot alkaloids, analgesics, antiemetics, triptans, and newly approved CGRP receptor antagonists (gepants) and (5-HT1F receptor agonists) ditans.[6-9]

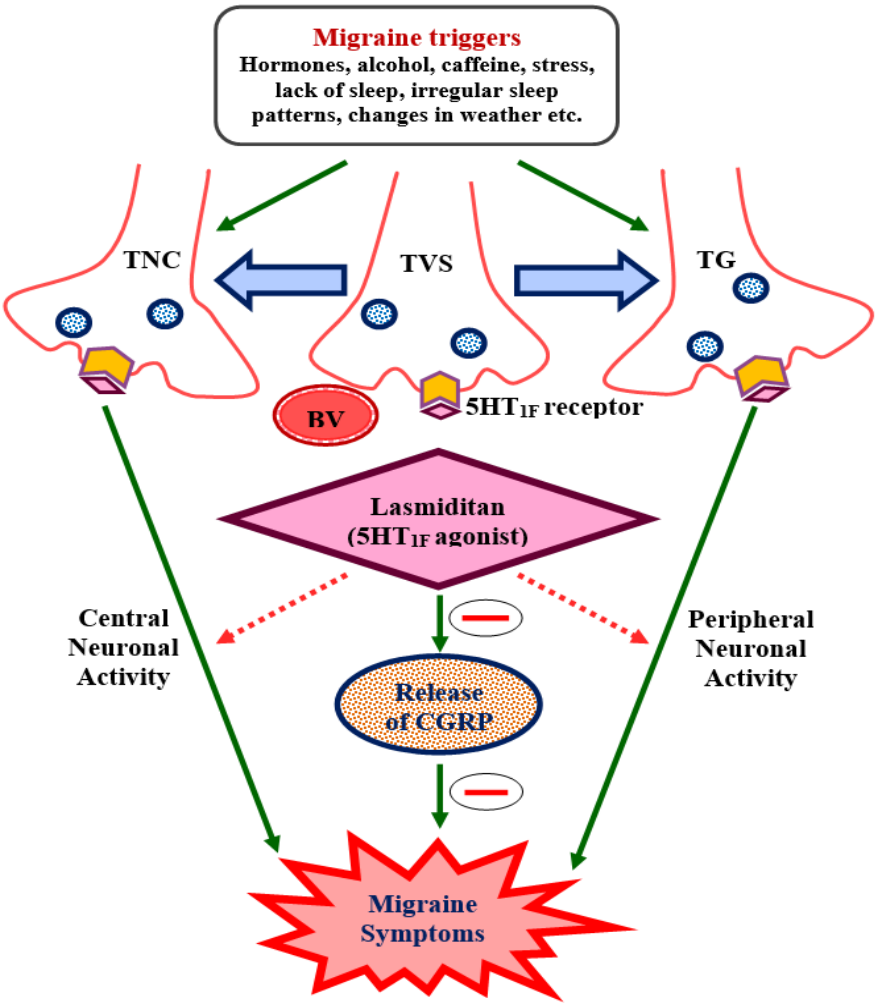

Figure 1: Mechanism of action of Lasmiditan, a 5HT1F agonist

Solid line arrow indicates activation. Dotted line arrow or dash symbol in an oval indicate inhibition. TNC: Trigeminal nucleus caudalis; TVS: Trigeminal vascular system; TG: Trigeminal ganglion; 5HT: Serotonin; BV: Blood vessel; CGRP: Calcitonin gene related peptide

1. ROLE OF SEROTONIN IN MIGRAINE

Many theories are involved in pathophysiology of migraine that includes cortical spreading depression, depolarization theory, vascular theory, among others in which the critical roles of 5-HT and CGRP have been well documented.[5] CGRP is a neuropeptide autacoid and nociceptive mediator that releases from sensory neurons, particularly from trigeminal ganglion, the area involved in the development of migraine.[9,10] It is also a potent vasodilator that causes pooling of blood parallel to decreased levels of 5-HT at the same time.[11,12] Serotonin, a vasoactive substance and a mediator in the endogenous antinociceptive system plays an important role in the pathogenesis of migraine headache. Serotonin causes vasoconstriction at nerve endings and blood vessels consequently affects nociceptive pain.[12,13] It is reported that the level of serotonin metabolite 5-hydroxyindole acetic acid increases significantly in urine suggestive of increased metabolism and depletion of endogenous 5-HT during migraine attack. Moreover, 5-HT releases from platelets at the beginning and after onset of migraine headache, intraplatelet 5-HT level decreases, 5-HT turnover also decreases during an attack.[12,13] This progresses to decreased vasoconstriction which in turn increases level of CGRP and subsequent vasodilation leading to migraine headache.[11,12]

a) Role of serotonergic receptors in migraine

There are at least 15 subtypes of 5-HT receptors divided into 7 families of G protein-coupled receptors except for the 5-HT3 receptor. All 5-HT receptors are found in the central and peripheral nervous systems. Of particular interest, 5-HT1B, 5-HT1D, and 5-HT1F play important role in migraine.

(1) **5-HT1B:** The activation of 5-HT1B receptor on vascular epithelium leads to direct and indirect vasoconstriction of smooth muscle and inhibition of endothelial nitric oxide synthase.[14,15] (2) **5-HT1D:** The activation of 5 HT1D receptor leads to inhibition of CGRP release and to lesser extent substance P, neurokinin A and thereby reduces neurogenic inflammation of duramater blood vessels caused by activation.[15,16] (3) **5-HT1F:** Serotonin 1F (5-HT1F) receptors are expressed in the human trigeminal ganglion, subthalamic nuclei, and walls of meningeal blood vessels. Specifically, these receptors are expressed in the CNS cortex, spinal cord, hippocampus, locus coeruleus, hypothalamus, amygdala, cerebellum, and dorsal raphe nucleus, which have a regulatory role in nociceptive processing.[17-19] Their activation leads to decreases in aseptic neurogenic inflammation in duramater and reduces the release of CGRP from these nerves leading to reduced nociceptive processing in trigeminal ganglion (Figure 1).[15,18] Further, activation of 5-HT1F receptors does not cause vasoconstriction.[7,20,21]

2. ABORTIVE MIGRAINE THERAPY

Abortive migraine therapy should be used as early as possible and should relieve attacks (abort) after onset of symptoms. The first antimigraine drugs that are developed are ergot alkaloids. These are non-specific 5-HT1B and 1D receptor and alpha adrenoceptors agonists causing vasoconstriction and decreases headache pain.[14,15] Owing to their adverse effects, such as vasoconstriction in periphery, ischemia, ergotism (intense chest pain), numbness, and cold extremities their use is limited. Moreover, these agents causes uterine smooth muscle contractions and facilitate abortion hence contraindicated in pregnancy which otherwise may kill both foetus and mother. Currently, it is a reserve drug due to its unfavourable safety profile.[7,22]

a) Triptans, 5-HT1B/1D agonists – Gold standard anti-migraine drugs

The last 30 years, specifically the last decade, have witnessed remarkable discoveries in migraine research ever since sumatriptan is approved. Triptans are the unique class of antimigraine drugs that are usually preferred over ergot alkaloids owing to their wider availability of pharmaceutical dosage forms (oral tablet, oral disintegrating tablet, nasal, intravenous), tolerance, lesser adverse effects, and better efficacy.[23,24] Several triptans namely, sumatriptan, rizatriptan, naratriptan, eletriptan, donitriptan, almotriptan, frovatriptan, and zolmitriptan are the 5-HT1B and 1D receptor agonists that act at blood vessels and nerve endings in brain, and inhibit pro-inflammatory neuropeptides (CGRP and substance P) release.[11,18] Currently, these are extremely successful, highly prescribed, widely consumed prophylactically and therapeutically, available without prescription, have well established safety and tolerability, and remain the 'Gold standard' abortive agents in acute and chronic treatment of migraine globally.

b) Need for novel abortive agents in migraine treatment

Although triptans are widely used and preferred abortive agents in the acute treatment of migraine, however, these agents cause peripheral vasoconstriction due to their high affinity for 5- HT1B/1D receptors. Essentially, these drugs are not preferred in patients with cardiovascular disorders and in those who are at risk of developing such disorders (coronary spasm, peripheral vascular disease, uncontrolled hypertension, coronary artery disease, stroke).[7,8,25] It has been reported that triptans decrease the number of episodes and severity of pain, but aura is not well controlled.[24,26] Adding to this, there are reports of triptan efficacy failure, recurrence of migraine, tolerability issues, and poor responders wherein such patients are not relieved from migraine symptoms leading to poor medication adherence, switching to over the counter medicines including those containing controlled substances like opioids or butalbital, and frequent visits to emergency departments.[7,27,28] Moreover, triptans are contraindicated in pregnancy and breastfeeding and serotonin syndrome is also seen when a triptan is co-administered with other serotonergic modulators and antidepressants, such as monoamine oxidase inhibitors and selective serotonin reuptake inhibitors.[27]

c) Emergence of 'Ditans' - Alternative to Triptans

Continuous efforts in understanding pathophysiology of migraine accompanied by renewed interest in elucidating the mechanisms action of triptans lead to better understanding on the important effects mediated through 5-HT1F receptors. Numerous selective agonists for 5-HT1F receptors with low affinity for 5-HT1B/1D receptors subtypes have been developed and evaluated for a better tolerability profile compared to triptans. It is speculated that such agents with no affinity for 5-HT1B/1D would have reduced or negligible vasoconstriction and offer better safety profile compared to triptans.[15,18,20] Evidence exists that the activation of the 5-HT1F receptor inhibits trigeminovascular neuronal impulses and hyperpolarizes nerve terminals.[19] However, there is a paucity of information on the cell signalling via 5-HT1F downstream pathways. Many 5-HT1F receptor agonists have been developed with a 100-fold higher selectivity for the 5-HT1F receptor than the 5-HT1B and 5-HT1D had shown promising results.[12,20] Originally developed under the pharmacological class as 5-HT1F receptor agonists; now widely popularised as novel antimigraine agents 'DITANS' after the approval of lasmiditan, a highly selective 5HT1F receptor agonist. More importantly, new chemical entities, drug candidates, and lasmiditan belong to this class are initially proposed and developed as an alternative to triptans to exert antinociceptive effect leading to therapeutic antimigraine effect without causing vasoconstriction because of their low affinity for 5-HT1B and 1D receptors.[8,15,29,30]

3. LASMIDITAN – THE FIRST IN THE 'DITANS' CLASS

During the past decade, three compounds have been tested in humans; of which lasmiditan has passed clinical testing due to its favourable safety and tolerability whereas LY344864 and LY334370 are not successful owing to off-target hepatotoxic effects.[15,29] Chemically, lasmiditan is 2,4,6 trifluoro-N-[6-(1-methyl)piperidine-4-carbonyl) pyridine-2yl] benzamide and also known as COL-144 and LY573144. The drug was designed based on selectivity and specificity to 5-HT1F receptors as druggable target and developed to surmount the unmet needs of currently available therapeutic choices to relieve from headache disability, overcome the vascular adverse effects of triptans, and improve patient compliance and adherence as well. It is a highly selective 5-HT1F agonist with an over 440 times more potent binding affinity for 5-HT1F than 5-HT1B/1D.[19,20,31] It is also known as the 'Neurally Active Antimigraine Agent' (NAAMA) due to its selective action on 5-HT1F receptors on sensory neurons of trigeminal ganglion (Figure 1).[31,32] Lamiditan was approved by food and drug administration in October 2019 for acute treatment of migraine with and without aura in adults. It is not indicated for the preventive treatment of migraine.[5,8,17]

a) Safety, tolerability, and efficacy of lasmiditan from clinical trials

The drug approval comes from the result of three successful clinical trials (SAMURAI, SPARTAN, GLADIATOR) under the trade name 'Reyvow' (Eli Lilly, USA). All the three clinical studies included patients with cardiovascular risk factors, and SPARTAN and GLADIATOR allowed patients of known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension. In both SAMURAI and SPARTAN trials, lasmiditan had shown therapeutic effects and met the primary endpoints of headache pain freedom and most bothersome symptom freedom at 2 hours. Importantly, the efficacy of lasmiditan was not affected by the presence of cardiovascular risk factors in these clinical trials. Moreover, it is not associated with significant and potential treatment related emergent adverse events due to vasoconstriction that necessitate cardiovascular treatment.[33-35] In GLADIATOR trial, the safety and efficacy on long-term use of lasmiditan were generally consistent over time for up to one year with those observed in the single-attack studies. In addition, long-term treatment with lasmiditan was associated with marked reductions in migraine-related disability, including both work or school absenteeism and presenteeism.[34,36] It has also been reported that the beneficial effects (headache pain freedom and most bothersome symptom freedom at 2 hours post-treatment) of lasmiditan were not affected by individual patient characteristics, migraine disease history or migraine attack characteristics, such as difficult-to-treat migraine attack, severe headache, co-existent nausea at the time of treatment, or delayed treatment for more than 2 hours from the time of headache onset.[37] Moreover, treatment-by-subgroup analyses showed that efficacy of lasmiditan did not vary significantly between patients with a good or insufficient response to triptans. In addition, lasmiditan also showed higher efficacy than placebo in patients who had not received triptan before at any time (triptan-naïve).[38]

In CENTURION (Phase 3 migraine consistency study) trial, efficacy of lasmiditan was studied in various subgroups of patients who exhibited an insufficient response or tolerability, or who developed a contraindication to triptans, including a subgroup with triptan-naïve. This study reported that lasmiditan was superior to placebo in triptan insufficient responders. Lasmiditan showed pain relief beginning at 0.5 hour (200 mg) or 1 hour (100 mg), pain freedom beginning at 1 hour for both the doses. Besides, lasmiditan markedly improved migraine-related disability freedom and most bothersome symptom freedom at 2 hour, sustained pain freedom, and significantly reduced need for rescue medication. Moreover, lasmiditan showed benefit for consistency of effect across attacks for 2 hours pain freedom and pain relief. Intriguingly, the beneficial effects of lasmiditan were similar in all the subgroups, including triptan responders, triptan poor responders, and triptan naïve.[39,40]

In phase 2, multicenter, randomized, double-blind, placebo-controlled study (MONONOFU) in Japanese patients with migraine, lasmiditan showed relatively more treatment-emergent adverse events (TEAEs) compared to placebo, however, such effects were mild. It is reported that dizziness followed by somnolence were the most frequent TEAEs with lasmiditan, started less than 1 hour after dosing. In most cases, lasmiditan did not show any adverse consequences of neurological effects, particularly, treatment-emergent adverse events, which adversely affect lasmiditan efficacy indicating that TEAEs appeared typically mild, transient, and self-limiting.[41] In this study, lasmiditan (100 or 200 mg) showed headache pain-free, pain relief, free from most bothersome symptom, or total migraine freedom (no headache or migraine-associated symptoms) within 0.5 – 1 hour after treatment. In comparison with placebo, lasmiditan showed rapid onset of action and sustained pain freedom at 24 or 48 h in Japanese patients with moderate to severe migraine.[42,43] In depth analysis of subgroup data indicated that pain freedom at 2 hour after lasmiditan dose (50 mg, 100 mg, and 200 mg) was similar across all patient subgroups irrespective of most patient characteristics, such as age, sex, body weight except in patient subgroup with cardiovascular risk factors. Consistent to this effect, lasmiditan also showed pain freedom at 2 hour similarly in the remaining subgroups with migraine disease characteristics (history of migraine with aura, migraine prevention therapy, triptan response, and triptan use or non-use) and migraine attack characteristics (headache severity, aggressive headache, attack during perimenstrual period, time to dosing, time of dosing, experienced TEAE of dizziness, and experienced TEAE of somnolence). This study results revealed that efficacy of lasmiditan is not affected by patient and migraine characteristics and strongly suggest lasmiditan as a promising therapeutic choice for acute management in Japanese patients with migraine.[41,43]

Recently, a post-hoc analysis evaluated the efficacy and safety of lasmiditan based on pooled patient data of patient subgroups, with and without at least one triptan contraindication, from four randomized, double-blind, placebo-controlled clinical trials (SAMURAI, SPARTAN, CENTURION, and MONONOFU). The study results revealed that the safety and tolerability profiles of patients with or without triptan contraindications were similar. Adding to this, all the subgroups of patients, with and without at least one triptan contraindication, who received lasmiditan showed similar pain freedom, had pain relief, freedom from most bothersome symptom as well as disability freedom. Interestingly, the beneficial effects of lasmiditan in both subgroups were similar and more significant pain relief was seen in patients with contraindications. These results strongly suggest that lasmiditan may be a promising therapeutic choice in migraine patients with contraindication to any triptan.[8,44,45]

b) Mechanism of action of lasmiditan:

CGRP, an autacoid neuropeptide, release increases from activated trigeminal sensory nerves, dilates intracranial and extracranial blood vessels, centrally modulates vascular nociception, and play an important role in the pathophysiology of migraine.[45,46] Indeed, CGRP take part in neurogenic inflammation (plasma protein extravasation and vasodilatation) of the intracranial vasculature and peripheral and central sensitization of the trigeminal system.[47] Indeed, modulation of CGRP and its receptors leads to reduction in migraine headache.[48] Importantly, afferent activation of the trigemino-thalamic pathway and sensory cortex leads to progressive changes in nociceptive thresholds and subsequent central sensitization due to frequent migraine attacks contribute to chronic migraine state.[49] It is proposed that inhibitory serotonergic and non-serotonergic pain projections of descending pathways can attenuate pain signaling plausibly in part by activating 5-HT1F receptors on glutamate-containing neurons.[50,51] These anatomic and neuronal signaling pathways could be potential neurological sites for mechanisms of action of lasmiditan. Precisely, lasmiditan selectively binds to 5-HT1F receptors located in trigeminal ganglion, trigeminal nucleus caudalis, and cephalic blood vessels and inhibits release of CGRP and glutamate at both the PNS and CNS terminals of the trigeminal nerve there by inhibiting migraine attack (Figure 1).[31,51,52] It has shown efficacy in cardiovascular disease patients without any serious events due to vasoconstriction since 5-HT1F receptors are located in trigeminal nerve, but not in vascular smooth muscle (5-HT1B/1D).[17,20,31]

c) Dose: Lasmiditan comes in 2 sizes (50 mg, 100 mg), approved in 3 doses (50 mg, 100 mg, 200 mg). The usual recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. The tablet should be administered as whole and should not be taken more than one dose in 24 hours.[8,20,53] Patient has to take two of 100 mg units and commercially available as tablet and oral dispersible tablet.[8,20,54]

d) Absorption: Rapidly absorbed and reaches peak plasma concentration in 1.8 hours (T_{max}) after oral administration. If taken with high fat meal may delay by 1 hour to reach plasma peak concentration. In patients with migraine, the absorption lasmiditan was not different during a migraine attack and during the interictal period.[8,55]

e) Distribution: It binds to blood proteins (55-60%) and has a biological half life of 5.7 hours ($t_{1/2}$). Further, it is highly lipophilic and penetrates blood-brain-barrier readily. Additionally, there is no accumulation observed with daily administration.[8,56,57]

f) Metabolism: It occurs by non-CYP 450 enzymes hepatically and extrahepatically and the major metabolites (M3, M7) are pharmacologically inactive.[8,55]

g) Excretion: Only 3% of parent drug excreted in urine and mostly excreted as metabolite S-M8 (66% of dose in urine). Renal excretion plays a minor role in drug clearance.[8,55]

h) Dose adjustment: There is no adjustment of lasmiditan dose is required for renal and hepatic impaired patients.[8,20,58]

i) Adverse effects: CNS depression, drowsiness, dizziness, sedation, somnolence, paresthesia, nausea, fatigue.[20,33,34,37] It had no effect on prolonging QTc interval to any clinically relevant extent.[53]

j) Less common adverse events: vertigo, incoordination, lethargy, visual impairment, confusion, euphoric mood, chest discomfort, speech abnormalities, dyspnoea, palpitations, anxiety, tremors, restlessness, sleep disturbances, abnormal dreams, muscle spasm, limb discomfort, cognitive changes, hallucination.[20,33,34]

k) Hypersensitivity: Lasmiditan had shown low incidence of angioedema, rash, and photosensitivity reactions in clinical trials.[8,53]

l) Warnings and precautions: Owing to drowsiness, dizziness, and sedation, activities that require complete mental alertness should be avoided for at least 8 hours after taking lasmiditan. It should not be taken with alcohol. Lasmiditan had shown reactions similar to serotonin syndrome in patients who were not taking any drugs associated with serotonin syndrome during clinical trial period. It should be used cautiously in migraine patients who need selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors.[8,20,53] Lasmiditan inhibits p-gp and BCRP, and also inhibits OCT1 *in vitro*; however, pharmacokinetics of sumatriptan were not affected. Conversely, co-administration of lasmiditan and sumatriptan did not cause serotonin syndrome.[8,55] It is not clear whether lasmiditan cause medication overuse headache; however, excessive use of lasmiditan should be avoided as overuse of acute antimigraine drugs may lead to exacerbation of headache. According to the prescribing information of lasmiditan, detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms

(which often includes a transient worsening of headache) may be necessary.[20,53]

4. GEPANTS vs DITANS

Accumulating data from preclinical and clinical studies cautiously indicate that these new drugs are safe for patients with cardiovascular risk factors.[8,20,30] Recent network meta-analyses revealed that all three novel antimigraine drugs, lasmiditan and two CGRP antagonists (rimegepant and ubrogepant), performed significantly better than placebo with respect to sustained pain freedom at 2 hour and pain relief 2 - 48 hours post-dose. It is also revealed that indicators of therapeutic efficacy outcome (pain freedom and pain relief at 2, 24, 48 hours) observed to be the highest for lasmiditan 200 mg and rimegepant followed lower doses of lasmiditan (50 mg, 100 mg) and all doses of ubrogepant. Adding to this, a systematic review and network meta-analyses data revealed that two-hour freedom from most bothersome symptom of migraine was equally achieved by the higher doses of lasmiditan (100 and 200 mg), rimegepant and the higher doses of ubrogepant (50 and 100 mg).[8,20,59,60] Most commonly reported adverse dug effects (incidence ≥2%) were dizziness, fatigue, paresthesia, sedation, nausea/vomiting and muscle weakness with lasmiditan; nausea with rimegepant; and nausea, somnolence and dry mouth with ubrogepant.[20,59,60] Besides, somnolence and dizziness outcomes were lower for rimegepant than higher doses of lasmiditan. It is reported that the use of lasmiditan is associated with self-limiting neurological events that are mostly mild or moderately severe. [59,61,62] The odds of treatment-emergent adverse events were greatest with all doses of lasmiditan. Of particular note, the use of any of these medications was not associated with cardiovascular adverse events. It is reported that lasmiditan 100 mg or 200 mg might be an appropriate acute treatment option for patients with migraine seeking a fast onset of action.[59] A recent report reviewed several long-term open-label and real-world studies of three drugs, namely lasmiditan, ubrogepant, and rimegepant for the acute treatment of migraine attacks which revealed that the use of lasmiditan resulted in rare instances of palpitations and/or tachycardia within 48 hours. It was reported that alanine transaminase and aspartate aminotransferase levels increased, but the normalized even after continued use of ubrogepant in two cases. A case of first-degree atrioventricular block thought to be related to rimegepant was noticed. On the other hand, sinus tachycardia possibly related to ubrogepant was seen in one participant with a history of supraventricular tachycardia, however, it did not recur despite continued use.[63] Importantly, acute use of rimegepant was associated with a decrease in monthly migraine days over time. Adding to this, there is no data on the risk of developing medication overuse headache that may differ between newer anti-migraine agents, such as triptans, gepants, antiCGRP antibodies, and ditans. However, extensive clinical research and surveillance safety data on long-term use of ditans are highly essential to establish safety and efficacy, including any effect on cardiovascular system and level of therapeutic choice among available therapies as well.

SUMMARY

In all the trials, lasmiditan showed beneficial therapeutic effects by exerting headache pain freedom and most bothersome symptom freedom at 2 hours. The efficacy of lasmiditan was not affected in patients with cardiovascular risk factors. Of particular note, most of the lasmiditan clinical trials used placebo-controlled, single episode of migraine attack design for short-term. Therefore, a long-term data on lasmiditan use are required to establish safety and tolerability, effectiveness, percent of full responders, incidence of medication over use headache, medication switch, medication adherence, and cost-benefit analysis over standard care or existing therapies, particularly in comparison with triptans in real world situation. Moreover, there is paucity in information on potential risk and drug-drug interactions between antimigraine drugs, such as concomitant use of triptans, gepants, ditans, and anti-CGRP monoclonal antibodies (mAbs) in migraine patients. Multicenter and multinational pragmatic as well as randomized controlled trials of acute treatment and combinations of therapies are required to analyse and establish their role and level of therapeutic choice among established therapies in migraine management. In addition, the data on experiences or exposure in special population, such as pregnant and lactating mothers, menstrually related migrainers, pediatric migrainers, and the elderly are also needed to extend its potential therapeutic benefit to wide range of patients.

REFERENCES

1. GBD 2016 Headache Collaborators. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018; 17(11):954-976.
2. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392(10159):1789-1858.
3. MacGregor EA. Migraine, menopause and hormone replacement therapy. Post Reprod Health. 2018; 24(1):11-18.
4. Dodick DW. A Phase-by-phase review of migraine pathophysiology. Headache. 2018; 58 Suppl 1:4-16.
5. Haanes KA, Edvinsson L. Pathophysiological mechanisms in migraine and the identification of new therapeutic targets. CNS Drugs. 2019; 33(6):525-537.
6. Eigenbrodt AK, Ashina H, Khan S, Diener HC, Mitsikostas DD, Sinclair AJ, et al. Diagnosis and management of migraine in ten steps. Nat Rev Neurol. 2021; 17(8):501-514.
7. Ferrari MD, Goadsby PJ, Burstein R, Kurth T, Ayata C, Charles A, et al. Migraine. Nat Rev Dis Primers. 2022; 8(1):2.
8. Karsan N, Goadsby PJ. New oral drugs for migraine. CNS Drugs. 2022; 36(9):933-949.
9. Gaddam S, Padi SSV. Gepants, calcitonin gene-related peptide antagonists, for abortive treatment of migraine: Current status. Int J Basic Clin Pharmacol. 2021; 10(9), 1156–1162.

10. Aggarwal M, Puri V, Puri S. Serotonin and CGRP in migraine. Ann Neurosci. 2012; 19(2): 88–94.
11. Frederiksen SD, Haanes KA, Warfvinge K, Edvinsson L. Perivascular neurotransmitters: Regulation of cerebral blood flow and role in primary headaches. J Cereb Blood Flow Metab. 2019; 39(4):610-632.
12. Deen M, Christensen CE, Hougaard A, Hansen HD, Knudsen GM, Ashina M. Serotonergic mechanisms in the migraine brain - a systematic review. Cephalalgia. 2017; 37(3):251-264.
13. Sokolov AY, Lyubashina OA, Panteleev SS. The role of serotonin receptors in migraine headaches. Neurochem J. 2011; 5, 92-99.
14. Villalón CM, VanDenBrink AM. The Role of 5-Hydroxytryptamine in the pathophysiology of migraine and its relevance to the design of novel treatments. Mini Rev Med Chem. 2017; 17(11):928-938.
15. Rubio-Beltrán E, Labastida-Ramírez A, Haanes KA, van den Bogaerdt A, Bogers AJJC, Zanelli E, et al. Characterization of binding, functional activity, and contractile responses of the selective 5-HT1F receptor agonist lasmiditan. Br J Pharmacol. 2019; 176(24):4681-4695.
16. Deen M, Hougaard A, Hansen HD, Schain M, Dyssegaard A, Knudsen GM, et al. Association between sumatriptan treatment during a migraine attack and central 5-HT1B receptor binding. JAMA Neurol. 2019; 76(7):834-840.
17. Vila-Pueyo M. Targeted 5-HT1F therapies for migraine. Neurotherapeutics. 2018; 15(2):291-303.
18. Razzaque Z, Heald MA, Pickard JD, Maskell L, Beer MS, Hill RG, et al. Vasoconstriction in human isolated middle meningeal arteries: determining the contribution of 5-HT1B- and 5-HT1F-receptor activation. Br J Clin Pharmacol. 1999; 47(1):75-82.
19. Edvinsson JCA, Maddahi A, Christiansen IM, Reducha PV, Warfvinge K, Sheykhzade M, et al. Lasmiditan and 5-Hydroxytryptamine in the rat trigeminal system; expression, release and interactions with 5-HT1 receptors. J Headache Pain. 2022; 23(1):26.
20. Beauchene JK, Levien TL. Lasmiditan: Acute migraine treatment without vasoconstriction. A Review. J Pharm Technol. 2021; 37(5):244-253.
21. Cohen ML, Schenck K. 5-Hydroxytryptamine(1F) receptors do not participate in vasoconstriction: lack of vasoconstriction to LY344864, a selective serotonin(1F) receptor agonist in rabbit saphenous vein. J Pharmacol Exp Ther. 1999; 290(3):935-939.
22. Schardl CL, Panaccione DG, Tudzynski P. Ergot alkaloids--biology and molecular biology. Alkaloids Chem Biol. 2006; 63:45-86.
23. Dodick DW, Martin V. Triptans and CNS side-effects: pharmacokinetic and metabolic mechanisms. Cephalalgia. 2004; 24(6):417-424.
24. Macone AE, Perloff MD. Triptans and migraine: advances in use, administration, formulation, and development. Expert Opin Pharmacother. 2017; 18(4):387-397.
25. Dodick DW, Shewale AS, Lipton RB, Baum SJ, Marcus SC, Silberstein SD, et al. Migraine patients with cardiovascular disease and contraindications: An analysis of real-world claims data. J Prim Care Community Health. 2020; 11:2150132720963680.
26. Thorlund K, Toor K, Wu P, Chan K, Druyts E, Ramos E, et al. Comparative tolerability of treatments for acute migraine: A network meta-analysis. Cephalalgia. 2017; 37(10):965-978.
27. Cameron C, Kelly S, Hsieh SC, Murphy M, Chen L, Kotb A, et al. Triptans in the acute treatment of migraine: A systematic review and network meta-analysis. Headache. 2015; 55 Suppl 4:221-235.
28. Leroux E, Buchanan A, Lombard L, Loo LS, Bridge D, Rousseau B, et al. Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: a systematic literature review. Adv Ther. 2020; 37(12):4765-4796.
29. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? J Headache Pain. 2019; 20(1):37.
30. de Boer I, Verhagen IE, Souza MNP, Ashina M. Place of next generation acute migraine specific treatments among triptans, non-responders and contraindications to triptans and possible combination therapies. Cephalalgia. 2023; 43(2):3331024221143773.
31. Clemow DB, Johnson KW, Hochstetler HM, Ossipov MH, Hake AM, Blumenfeld AM. Lasmiditan mechanism of action - review of a selective 5-HT(1F) agonist. J Headache Pain. 2020; 21(1):71.
32. Xavier AS, Lakshmanan M, Gunaseelan V. The Journey of the non-vascular relief for migraine: from 'triptans' to 'Ditans'. Curr Clin Pharmacol. 2017; 12(1):36-40.
33. Shapiro RE, Hochstetler HM, Dennehy EB, Khanna R, Doty EG, Berg PH, et al. Lasmiditan for acute treatment of migraine in patients with cardiovascular risk factors: post-hoc analysis of pooled results from 2 randomized, double-blind, placebo-controlled, phase 3 trials. J Headache Pain. 2019; 20(1):90.
34. Lipton RB, Lombard L, Ruff DD, Krege JH, Loo LS, Buchanan A, et al. Trajectory of migraine-related disability following long-term treatment with lasmiditan: results of the GLADIATOR study. J Headache Pain. 2020; 21(1):20.
35. Capi M, De Angelis V, De Bernardini D, De Luca O, Cipolla F, Lionetto L, et al. CGRP Receptor antagonists and 5-HT1F receptor agonist in the treatment of migraine. J Clin Med. 2021; 10(7):1429.
36. Brandes JL, Klise S, Krege JH, Case M, Khanna R, Vasudeva R, et al. Interim results of a prospective, randomized, open-label, Phase 3 study of the long-term safety and efficacy of lasmiditan for acute treatment of migraine (the GLADIATOR study). Cephalalgia. 2019; 39(11):1343-1357.
37. Tepper SJ, Vasudeva R, Krege JH, Rathmann SS, Doty E, Vargas BB, et al. Evaluation of 2-hour post-dose efficacy of lasmiditan for the acute treatment of difficult-to-treat migraine attacks. Headache. 2020; 60(8):1601-1615.
38. Knievel K, Buchanan AS, Lombard L, Baygani S, Raskin J, Krege JH, et al. Lasmiditan for the acute treatment of migraine: Subgroup analyses by prior response to triptans. Cephalalgia. 2020; 40(1):19-27.
39. Ashina M, Reuter U, Smith T, Krikke-Workel J, Klise SR, Bragg S, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: Findings from the CENTURION study. Cephalalgia. 2021; 41(3):294-304.
40. Reuter U, Krege JH, Lombard L, Gomez Valderas E, Krikke-Workel J, Dell-Agnello G, et al. Lasmiditan efficacy in the acute treatment of migraine was independent of prior response to triptans: Findings from the CENTURION study. Cephalalgia. 2022; 42(1):20-30.
41. Hirata K, Matsumori Y, Tanji Y, Khanna R, Ozeki A, Komori M. Safety profile of lasmiditan in patients with migraine in an Asian population. Expert Opin Drug Saf. 2023; 22(1):91-101.
42. Matsumori Y, Komori M, Tanji Y, Ozeki A, Sakai F. Rapid onset and sustained efficacy of lasmiditan among Japanese patients with migraine: Prespecified analyses of a randomized controlled trial. Neurol Ther. 2022; 11(4):1721-1734.
43. Takeshima T, Komori M, Tanji Y, Ozeki A, Tatsuoka Y. Efficacy of lasmiditan across patient and migraine characteristics in japanese patients with migraine: A secondary analysis of the MONONOFU Trial. Adv Ther. 2022; 39(11):5274-5288.
44. Krege JH, Lipton RB, Baygani SK, Komori M, Ryan SM, Vincent M. Lasmiditan for patients with migraine and contraindications to triptans: A post hoc analysis. Pain Ther. 2022; 11(2):701-712.
45. Ramón C, Cernuda-Morollón E, Pascual J. Calcitonin gene-related peptide in peripheral blood as a biomarker for migraine. Curr Opin Neurol. 2017; 30(3):281-286.
46. Villalón CM, Olesen J. The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute antimigraine drugs. Pharmacol Ther. 2009; 124(3):309-23.

47. Tajti J, Szok D, Majláth Z, Tuka B, Csáti A, Vécsei L. Migraine and neuropeptides. Neuropeptides. 2015; 52:19-30.

48. de Vries T, Villalón CM, MaassenVanDenBrink A. Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther. 2020; 211:107528.

49. Aurora SK, Brin MF. Chronic migraine: an update on physiology, imaging, and the mechanism of action of two available pharmacologic therapies. Headache. 2017; 57(1):109-125.

50. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev. 2017; 97(2):553-622.

51. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care. 2014; 8(2):143-151.

52. Labastida-Ramírez A, Rubio-Beltrán E, Haanes KA, Chan KY, Garrelds IM, Johnson KW, et al. Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. Pain. 2020; 161(5):1092-1099.

53. Highlights of prescribing information of REYVOW® (Lasmiditan). Available at: https://pi.lilly.com/us/reyvow-uspi.pdf

54. Tepper D. Lasmiditan for the acute treatment of migraine. Headache. 2020; 60(6):1225-1226.

55. Szkutnik-Fiedler D. Pharmacokinetics, pharmacodynamics and drug-drug interactions of new anti-migraine drugs-lasmiditan, gepants, and calcitonin-gene-related peptide (CGRP) receptor monoclonal antibodies. Pharmaceutics. 2020; 12(12):1180.

56. Kovalchin J, Ghiglieri A, Zanelli E, Ings R, Mathers T. Lasmiditan acts specifically on the 5-HT1F receptor in the central nervous system. Cephalalgia 2016; 36(Supplement 1):103.

57. Raffaelli B, Israel H, Neeb L, Reuter U. The safety and efficacy of the 5-HT1F receptor agonist lasmiditan in the acute treatment of migraine. Expert Opin Pharmacother. 2017; 18(13):1409-1415.

58. Sancar M, Altiparmak O, Altan A, Demirtunc R, Izzettin FV, Okuyan B. Evaluation of medication dose adjustments in patients with impaired renal function using different online drug information databases. Eur J Hosp Pharm. 2022; 29(5):255-258.

59. Polavieja P, Belger M, Venkata SK, Wilhelm S, Johansson E. Relative efficacy of lasmiditan versus rimegepant and ubrogepant as acute treatments for migraine: network meta-analysis findings. J Headache Pain. 2022; 23(1):76.

60. Puledda F, Younis S, Huessler EM, Haghdoost F, Lisicki M, Goadsby PJ, et al. Efficacy, safety and indirect comparisons of lasmiditan, rimegepant, and ubrogepant for the acute treatment of migraine: A systematic review and network meta-analysis of the literature. Cephalalgia. 2023; 43(3):3331024231151419.

61. Johnston K, Popoff E, Deighton A, Dabirvaziri P, Harris L, Thiry A, et al. Comparative efficacy and safety of rimegepant, ubrogepant, and lasmiditan for acute treatment of migraine: a network meta-analysis. Expert Rev Pharmacoecon Outcomes Res. 2022; 22(1):155-166.

62. Singh A, Gupta D, Singh A. Ditans vs Gepants: A systematic review and indirect network meta-analysis for comparative analysis of efficacy and safety. Neurol India. 2021; 69(Supplement):S43-S50.

63. Begasse de Dhaem O, Takizawa T, Dodick DW. Long-term open-label and real-world studies of lasmiditan, ubrogepant, and rimegepant for the acute treatment of migraine attacks. Cephalalgia. 2023; 43(2):3331024221137092.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions: All authors contributed to the review design and plan. RA and SG contributed to the data search, collection, extraction, and quality assessment for this review. SP created the figure for the manuscript. All authors wrote the text, reviewed and edited the manuscript, and made substantial contributions to discussions of the content.