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Determining the Advantageous Acute Migraine Treatment: Rimegepant and Lasmiditan Review of Literature

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DETERMINING THE ADVANTAGEOUS ACUTE MIGRAINE TREATMENT: RIMEGEPANT AND LASMIDITAN REVIEW OF LITERATURE

by

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Abstract

This research aims to evaluate two new pharmaceuticals on the market. Rimegepant and Lasmiditan target the trigeminovascular system and respectively, are characterized in the gepant and ditan classes of pharmaceuticals. Based on a review of studies, Rimegepant was determined to be the advantageous acute treatment. This is not conclusive due to inequivalent comparison in sample size and amount of research completed. It is encouraged for additional research to be imposed before a conclusive determination of the advantageous acute treatment can be distinguished.

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MIGRAINE PRIMARY HEADACHE OVERVIEW

Introduction to Primary Headaches

The research of primary headache disorders elicits several limitations due to being frequently diagnosed with inadequate pathogenesis comprehension. The primary headaches can be distinguished into four categories including tension type headaches, migraines, trigeminal autonomic cephalalgias, and other primary headache disorders[1 2]. In epidemiological studies, the number of diseased cases within a population is measured by the prevalence. The global prevalence for primary headaches is approximately 50%[3 4], however several regions of the world are not included in this average due to the lack of available data[5]. Reiterating the limitations exhibited in primary headache research, geographical gaps hinder an accurate quantification of individuals afflicted globally[4 6]. Nonetheless, when comparing published reputable studies, tension type headaches and migraines were found to be the most globally recurring. Tension type headache episodes are described to be bilateral obtaining a mild to moderate intensity. They are characterized into chronic and episodic; chronic lasting greater than 15 days and episodic lasting from a few hours up to a few days[7]. Episodic can further be subdivided into infrequent and frequent categories, with the latter requiring 10 episodes minimal between the time-span of 1-14 days/ month[2]. Contrastingly, migraines are distinguished into aura and without aura classifications – both recurrent lasting 4-72 hours. As defined in the International Classification of Headache Disorders (ICHD), migraines without aura are indicative of a unilateral location, pulsating quality, moderate or severe intensity, nausea and/or photophobia and phonophobia[2]. Migraines with aura are similarly unilateral, but obtain visual, sensory, or other central nervous system symptoms that are reversible[2 8]. Discriminating between migraines and tension type headaches is often difficult within a clinical setting due to simultaneous occurrence of attacks in patients who get headaches

frequently. Due to this, a recent development of more specific criteria was established by the ICHD for differentiation of the phenotypic resemblance of migraines and tension type headaches exhibited in some patients[2]. This additional criterion allows for diagnosis precision in the health care setting, thus improving clinical research as well.

A retrospective systemic study was conducted by the Global Burden of Disease in 2016 estimating the prevalence of tension type headaches at 30.8% and migraines at 18.9%[5]. According to this study, although the tension type headaches are more prevalent, migraines have a larger implication of disease burden. A disease burden can be quantified because it is directly proportional to disability weights. Disability weights are defined as the disabling consequence and it is measured by the percentage of health lost during an attack, in comparison to a person with full health. Globally, the disease weight for migraines are significantly greater. They estimate to be around 43.4%, while the disease weight for tension type headaches are around 3.7%[5]. With migraines obtaining such a high degree of burden followed by a high prevalence, there is a significant need in migraine research development for pharmacological advancements. Conflict is induced because migraine primary headaches are independent of underlying medical conditions and lack causative pathology[9]. By determining causative pathology, more drugs can be developed directly targeting the source of affliction, thus resulting in reduced burden amongst populations. Various implications regarding migraine pathology have been the focal point of many studies for this goal, but despite advances in research the genesis remains unknown. There has been lethargic progression of innovative migraine medications to aid in the control of disease burden and temporarily eradicate pain. New medications have emerged targeting the potential inflicted origin of migraines for acute medicinal purposes. The purpose of this research aims to

evaluate two contemporary medications that may be primitive in decreased affliction worldwide. A brief overview of hypotheses that represent the premise of migraine pharmacology will be included in order to better elucidate the mechanistic actions of the new medications. Rimegepant and Lasmiditan target the trigeminovascular system, characterizing within the gepant and ditan classes of pharmaceuticals, respectively. Their mechanisms of attack within the trigeminovascular system will be contrasted. The advantageous acute treatment will be determined based on a review of study evaluations and side effects associated.

AN OVERVIEW OF PROPOSED MIGRAINE HYPOTHESIS

Although pathogenesis of migraines are unknown, neurological changes exhibited during migraine attacks have assisted tremendously in the development of potential drug targets. Historically, a proposed hypothesis by Thomas Willis indicated that migraine etiology solely involved the vasodilation of arterioles, which led to development of the vascular theory[10]. Based on experimentation the vascular theory is credible in some regard, but it can be refuted. Drugs inducing vasoconstriction are quite effective in treatment. Contrastingly, drugs inducing cranial vasodilation, such as nitroglycerine, have been shown to cause hypersensitivity to noxious somatosensory stimulation[11]. Although vasodilation and hypoperfusion of blood flow does occur within migraines, evidence shows this is not the primitive reason for affliction. In fact, vasoactive intestinal peptide (VIP) is a transmitter that imposes cranial vasodilation, but there is evidence of migraines not triggered as a result of intravenous VIP infusion[12 13]. Regardless, it can be stated that vasodilation is a part of a migraine triggering cascade that causes an increase in the release of neuropeptides promoting neurogenic inflammation and noxious stimulation.

Trigeminovascular system in migraines

The neuropeptide release and resulting inflammation that typically appears during a migraine attack is a focal point in generation of drug targets. The mechanistic action leading to the release of neuropeptides remain debatable and unknown. Many hypotheses focus on different mechanistic pathways involved with Dural vasculature and the trigeminovascular system. The discovery by Ray and Wolff in 1940 showed that electrical and mechanical stimulation of the dura mater generated pain[14]. The dura mater of the meninges is where the bulk of meningeal afferents are located, innervated with nociceptors. This coincides with the early work completed by Ray and Wolff, because nociceptors encode for noxious stimuli. It is stated that a triggering event sensitizes and

activates trigeminal nociception, while releasing several neuropeptides that promote neurogenic inflammation and vasodilation. Triggering stimuli such as stress, fatigue, not eating on time, environmental stimuli, and hormonal changes may be indicative of generating this response[15 16 13 17]. The cell bodies of the meningeal afferents are within the trigeminal ganglion. The transmitted information from the meningeal afferent axons are delivered primarily through the ophthalmic branch of the trigeminal nerve, but a small amount of information is transmitted through the mandibular and maxillary branches as well[16]. From here, it is stated that the trigeminal nerve conveys sensory information from intracranial structures, and there is apparent evidence that extracranial structure sensory information is conveyed as well[18]. Using electrophysiological techniques with rats as the model organism, several studies indicated that pericranial tissues are effected in noxious stimulation[19 20]. In continuance with the pathway, information is then delivered into the spinal trigeminal nucleus for relay. The spinal trigeminal nucleus can be subdivided into three distinct parts, with each relaying a different sensory modality. The subnucleus paralis and subnucleus interparalis both relay discriminative tactile information of the trigeminal nerve, while the subnucleus caudalis is responsible for pain and temperature[21]. Figure 1 provides a depiction of this process. This theory is a plausible explanation for migraine occurrence but does not account for additional stimulation that occurs in other neuronal anatomical features. Not only this, but evidence shows various other physiological changes that occur during migraines are pertinent to the type (aura and without aura). This further introduces supplemental proposed hypotheses.

Hypothalamus and Brainstem Activation in Migraine

Hypothalamic and brainstem nuclei activation is a significant physiological occurrence during spontaneous migraine attack. Substantial evidence shows the involvement of persistent activation and increased blood flow to the hypothalamus and brainstem using positron emission tomography[22 23 24].

A study conducted with animal models indicated that there is direct control on spontaneity of the spinal trigeminal nucleus via the paraventricular hypothalamic nucleus[25]. Similarly, brainstem nuclei activation is correlated with migraine because it is proposed to result in either the enhancement or inhibition of neurons facilitating trigeminovascular pain transmission in the spinal and medullary dorsal horn[26 27 28]. The mechanism of action for the modulation of the brainstem to migraines is unspecific, despite occurrence being prevalent during attack. Within Figure 1, the link between hypothalamic and brainstem activation to the trigeminovascular system is evident.

Mast Cell Degranulation in Migraine

A diverged hypothesis from Dural and trigeminovasculature innervation involves the mast cells which are proliferated around the meningeal afferents in the dura mater. A trigger response may degranulate the mast cells to release pro-inflammatory mediators leading to the release of sensory peptides from meningeal nociceptors[13 16]. There are two considerations when discussing mast cell degeneration. Some state that mast cell degeneration results from neuropeptide release from meningeal afferents[13 26]. However, there are implications that mast cells can initiate nociceptor sensitizing neuropeptide release[16]. Migraines can be triggered by hormonal input, and mast cell degranulation occurs in response to the binding these hormonal peptides to the expressed progesterone and estrogen receptors on their surface[16]. Figure 2 provides a depiction of both pathways. This research is not conclusive, but the degranulation of mast cells in migraine allow it to be a potential target in migraine pharmacology.

Aura Physiological Changes in Migraine

As stated earlier, migraine without aura are characterized by photophobia and phonophobia. Evidence has showed a slight increase in blood flow within the brainstem regions and the visual and cingulate auditory cortices[29]. Interestingly, there seems to be an affiliation with the brainstem increased

perfusion of blood in aura migraine attacks as well[30]. A discrepancy that is distinctive to migraine aura attacks is a physiological process entitled cortical spreading depression (CSD). Cortical spreading depression is depicted by a disruption of electrical activity across the cortical grey matter surface of the brain, resulting in suppressed neural activity[29 31]. This disruption is characterized by high extracellular potassium concentration and influx of sodium and chloride. It is linked to migraine with aura because it slowly propagates within the primary visual cortex, generating a retinotopic visual percept[32]. Evidence also shows that CSD can be a triggering factor for activation and sensitization of the trigeminovascular system, thus inducing neurogenic inflammation[13]. Research remains pertinent regarding the mechanism for CSD. It has been implied that sensitization of the blood brain barrier results from CSD[30], and increases the brain's sensitivity to neuropeptides in order to trigger migraines. This has been refuted by experimentation, but the speculation of CSD causing sensitization remains.

Neuropeptide Secretion in Migraine

An association of all the variant proposed migraine triggering cascades is the increased release of vasoactive neuropeptides at nerve endings. The release is dependent on the type of nerve fiber that innervates the dura vasculature. Parasympathetic and sympathetic nerve fibers are innervated throughout the dura resulting in the potential release of various neuropeptides. The parasympathetic fibers typically release vasoactive intestinal peptide, Neuropeptide Y, Acetylcholine, and nitric oxide synthase. The sympathetic fibers of the dura stimulate the release of norepinephrine, neuropeptide Y, as well as ATP[33]. Trigeminal sensory nerves typically release the neuropeptides calcitonin gene-related peptide (CGRP), Neurokinin A, Pituitary adenylate cyclase-activating peptide (PACAP), nitric oxide synthase, and substance P which coexists in the nerve terminal with serotonin (5-HT)[34]. Serotonin is not only located within these nerve terminals, but it is interspersed throughout the

trigeminovascular system[35]. The serotonin neurotransmitter is assumed to play a role in migraine due to an altered concentration during an attack. The mechanism of action and high or low concentration amount remains debatable. Historically, high levels of 5-hydroxyindoleacetic (a serotonin precursor) was found in the urine[36] which was presumed to equate to lower abundance of serotonin in the brain. Low serotonin levels have also been linked to intensifying sensory processing information such as the primary auditory cortex[36]. Contrastingly, other research proves that the plasma levels of the serotonin precursor does not affect the abundance of serotonin in the brain. Recently, a study was published that tracked serotonin levels indirectly using positron emission tomography. A serotonin receptor ($5\text{-}HT_4$) was radiolabeled and could be quantified as inversely proportional to the serotonin levels. The results hypothesized that high levels of serotonin are possibly a result or trait of migraine[37]. The various hypotheses imposed on serotonin levels in migraine elicits the importance of continued migraine research. Serotonergic receptors are successful drug targets for mitigating pain. Stronger targets directly impacting serotonin concentration can be developed when the physiological effects and mechanisms are concluded. See Table 1 for the neurotransmitters released correspondent to the nerve fiber as listed above.

A NEW APPROACH TO ACUTE MIGRAINE PHARMACOLOGY

Impact of Development

Acute migraine treatment is sufficient for short term relief with patients who experience recurrent migraines lasting within the range of 4-72 hours for short term relief. This treatment is typically effective in migraines with aura and without aura. A commonly used over the counter medication are nonsteroidal anti-inflammatory drugs (NSAIDS). As stated earlier, neurogenic inflammation is a characteristic occurrence during a migraine attack. Upon inflammation, prostaglandin secretion is implied to elicit sensitization of nociceptors in the brain[38]. Cyclooxygenase is the enzyme responsible for the conversion of arachidonic acid into prostaglandins, which stimulate pain generation and inflammation. Based on experimentation, both cyclooxygenase 1 and 2 can be found in the dura of the meninges[38]. The inhibition of Cyclooxygenase via NSAIDs can prevent the cascade of nociceptor activation and pain. NSAIDs are only utilized if the patient attains a mild to moderate intensity migraine[39], therefore other acute migraine treatments should be used for those in which NSAIDs are rendered ineffective. Commonly used stronger migraine medications include ergot derivatives and triptans. These are non-specific 5-$HT_{1D/1B}$ agonists obtaining a slight amount of selectivity to the 5-HT_{1F} receptor. These agonists play a role in vasoconstriction of arterioles[35]. Due to this vasoconstriction property of triptans and ergot derivatives, inflicted individuals with cardiovascular problems are eliminated from use. The development of specific drugs would thus make mitigation of migraine accessible to all. Rimegepant and Lasmiditan, were recently developed to manage the degree of affliction worldwide. See Table 2 for a depicted differentiation between the drug classes developed.

Rimegepant

As stated in the preceding sections, neuropeptide release is a key component in migraine occurrence due to promotion of neurogenic inflammation and noxious stimulation. CGRP is a proinflammatory vasodilator that is released from trigeminal nerve fibers to bind to CGRP receptors. There is an additional CGRP binding receptor entitled AMY_1 that is imposed to have an similar binding strength as the CGRP receptor, given they are in the same family[40] [41] [42]. AMY_1 is classified as an adrenomedullary receptor, and all receptors in this class are capable of binding CGRP. The gepant classification of pharmaceuticals is characterized by antagonistic properties towards the CGRP receptor, which should eliminate the activation of the migraine triggering cascade. Gepants are preferable alternatives to acute migraine treatment due to the lack of vasoconstrictive properties that the triptans and ergot derivatives attain. Conflict arose when the clinical development of gepants was temporarily halted due to liver toxicity upon exposure[43]. Evidence coincides with the liver toxicity resulting from development of a potential metabolite byproduct of the drug, so a new drug creation was necessary that rid this property. The ensuing development was Rimegepant – recently approved by the FDA in February 2020[44].

Mechanism of Action

The exact mechanism for Rimegepant binding is unknown, but like other gepants, it is an antagonist to the CGRP receptor (see Figure 3). A recent study was conducted and stated Rimegepant obtained an affinity to the CGRP receptor 65 times higher than the adrenomedullin receptors[40]. They indicated that if AMY_1 and additional adrenomedullin receptors played a role in the CGRP activation cascade with equivalence, Rimegepant would not be effective. However, this can be refuted. A recent in vitro study within Cos7 transfected

cells was conducted, which tested the ability of Rimegepant to antagonize against AMY1 and additional adrenomedullin receptors[45]. This study elucidated that binding occurred to both receptors. Because the study did not take place in human subjects or animal models, a vast amount of limitations is prevalent when analyzing. Additional experimentation should be completed for a better understanding of Rimegepant targeting and mechanism of action.

Evaluation of Studies

Several studies were completed measuring the safety and efficacy of Rimegepant (75 mg oral tablet administered) in migraine treatment by utilizing various methods. One 12-week study estimated the safety of Rimegepant as a preventative treatment by simultaneously administering monoclonal antibodies. There were 16 patients that were screened for the study, but only 13 began treatment, and only a total completion of 10. It was stated that two of the participants who dropped the study gave no indication of why, but the remaining participant elicited lack of efficacy for the drug. Of the 13 individuals that began treatment, the average age of all patients was approximately 49.9 years with 11/13 women participants[46]. The participants had to be afflicted with at least 2-8 migraines per month in order to be involved with the study. Three different types of monoclonal antibodies were used, and the patients were given the medication for approximately 4 weeks. It was concluded that this combination was safe and more effective than singular monoclonal antibody use. One of the major limitations of this study was the small sample size. A small sample size is not generalizable, therefore additional experimentation should be done before normalizing concomitant use of Rimegepant and monoclonal antibodies as a migraine prevention method.

A larger study included 1186 individuals with the intent being to measure the efficacy of Rimegepant solely. The study was not measured overtime, but rather in a single occurrence,

and was also double-blind. This implies that some individuals received the Rimegepant, while others received a placebo. The administers nor participants could distinguish the difference between the two samples. In order to participate in the study, all participants had to have a history of migraine that occurred about 2-8 times per month for at least a year. The number of individuals no longer experiencing pain after oral ingestion of Rimegepant was measured after a time frame of two hours (indicated relief period). The demographics of the participants were predominantly female and an average age of 40.6 years old. Upon attack, patients recorded answers to questions in an electronic diary which pertained to the undergoing symptoms, bothersome features during attack like nausea, phonophobia, and photophobia, as well as ratings pertinent to the intensity of pain[47]. The results indicated that approximately 19.6% of the patients who received the Rimegepant experienced relief of pain and 12.0% that received the placebo experienced relief of pain. Also, results showed that approximately of patients who took Rimegepant had a 37.6% of diminished bothersome symptoms after 2 hours. This was significantly higher than the placebo that was administered which had a 25.2% bothersome symptom relief. There were many limitations within this study, but a major limitation was frequency of recorded data. Earlier, I established how the study was not based overtime, but on one occurrence. There is a lack of credibility because measurement overtime allows for consistency or inconsistency of the results to be determined.

Adverse Effects

The adverse effects caused by Rimegepant use differed for both studies enlisted above. When patients simultaneously used monoclonal antibodies and Rimegepant, 2 out of 13 individuals experienced nasopharyngitis which was rendered a normal adverse effect. Others experienced back pain, dizziness, sinusitis, myalgia, contusion, and a first-degree AV block[46]. These

effects were individualized – only inflicting one patient. The AV block could have possibly been associated with the treatment, which is a plausible downside given that Rimegepant was created to be a more universally used drug in comparison to the triptans. Due to the small sample size, generalized conclusions cannot be made, further advocating for more research. When analyzing the study that screened 1811 participants, cardiovascular adverse effects were not prevalent. However, it is important to note that subjects who obtained cardiovascular disease were eliminated from the study, therefore conclusion upon adverse cardiac effects on inflicted patients cannot be determined. The significant effects with a 1% incidence greater than placebo included nausea and urinary tract infections.

Lasmiditan

Mechanism of Action

Lasmiditan was developed October of 2019[48] in efforts to target migraines more selectively in comparison to triptans and ergot derivatives. Categorized in the ditan class of pharmaceuticals, Lasmiditan aims to act as an agonist towards the 5-HT_{1F} receptor to prevent the occurrence of neurogenic inflammation within the migraine triggering cascade[49] (see Figure 4). Lasmiditan was determined to be a quite effective treatment that could be universally applicable to patients due to the lack of vasoconstriction properties that triptans and ergot derivatives obtain. When discussing the effects of the 5-HT_F receptor within the trigeminovascular system, there is indication that it acts centrally and peripherally[35]. This is primarily due to the location of the receptors being in both the trigeminal ganglion, as well as the nucleus caudalis. Additional details of Lasmiditan discuss its implicated effects throughout the cascade. Due to the agonistic effects of 5-$HT_{F,}$ CGRP release can possibly be inhibited along with other neurotransmitters.

Evaluation of Studies

To determine the efficacy of treatment with and without concomitant prevention methods, a double-blind study was conducted including 3981 participants. Three different doses of Lasmiditan (50 mg, 100 mg, or 200 mg) and a placebo was administered to participants randomly. The criteria applicable was each participant had to be afflicted with 3-8 migraines per month and had to be over the age of 18. The mean age of participants was 45.7 years, and primarily women were involved in the study. In order to analyze efficacy, patients received an electronic journal in which they answered questions pertaining to the pain they experienced throughout attack, burden imposed due to attack, and effectiveness after the medication. The results elicited that patients experienced significant effectiveness when taking Lasmiditan compared to the placebo[51]. 698 of 3981 patients were established to use prevention medications if they were taking beta blockers, epileptic medications, and anti-depressants for a total of three months. The results did not establish a statistical significance between concomitant use and sole use, proving the compound is effective without the addition of a preventative treatment. A major limitation of this study was that although two trials were completed, only one utilized the 50 mg Lasmiditan dosage. This adds a lack of consistency within the study.

Another study completed determined the safety and efficacy of Lasmiditan amongst individuals who obtain cardiovascular risk factors[52]. Approximately 77.9% of the participants had at least one cardiovascular risk. The criteria were similar to the study described above. It consisted of individuals who were afflicted with 3-8 migraines per month and at least 18 years of age. Lasmiditan dosage at 100 mg and 200 mg, along with a placebo was randomly given to 1856 participants and data was analyzed via an electronic diary 2 hours post medication

ingestion. The results indicated that 32.2% of patients were free of migraine pain after Lasmiditan and 15.3% were free after placebo. The most bothersome symptom was also quantified with participants having 40.7% relief after ingesting the Lasmiditan and 29.5% of individuals experiencing relief after ingesting the placebo. A limitation within this study was that there was only a comparison of Lasmiditan with 100 mg and 200 mg in patients with cardiovascular risk. The effect of cardiovascular risk on a 50 mg Lasmiditan tablet was not deduced, which could have further proved effectiveness.

Adverse Effects

The adverse effects included in each Lasmiditan study were not unexpected. The first study had effects of dizziness, paresthesia, somnolence, fatigue, nausea, muscle weakness and hypoesthesia. The rates for individuals taking preventative medications were very similar. The other study had effects of dizziness, paresthesia, somnolence, fatigue, hypoesthesia, nausea, and lethargy. The incidence was higher than 2% in every Lasmiditan group for these effects, and greater than the placebo group[52]. This study also included the incidence of cardiovascular anomalies. These cardiovascular effects were quite low in comparison, comprising of palpitations, sinus bradycardia, tachycardia, and left ventricular hypertrophy.

FIGURES AND TABLES

Figure 1

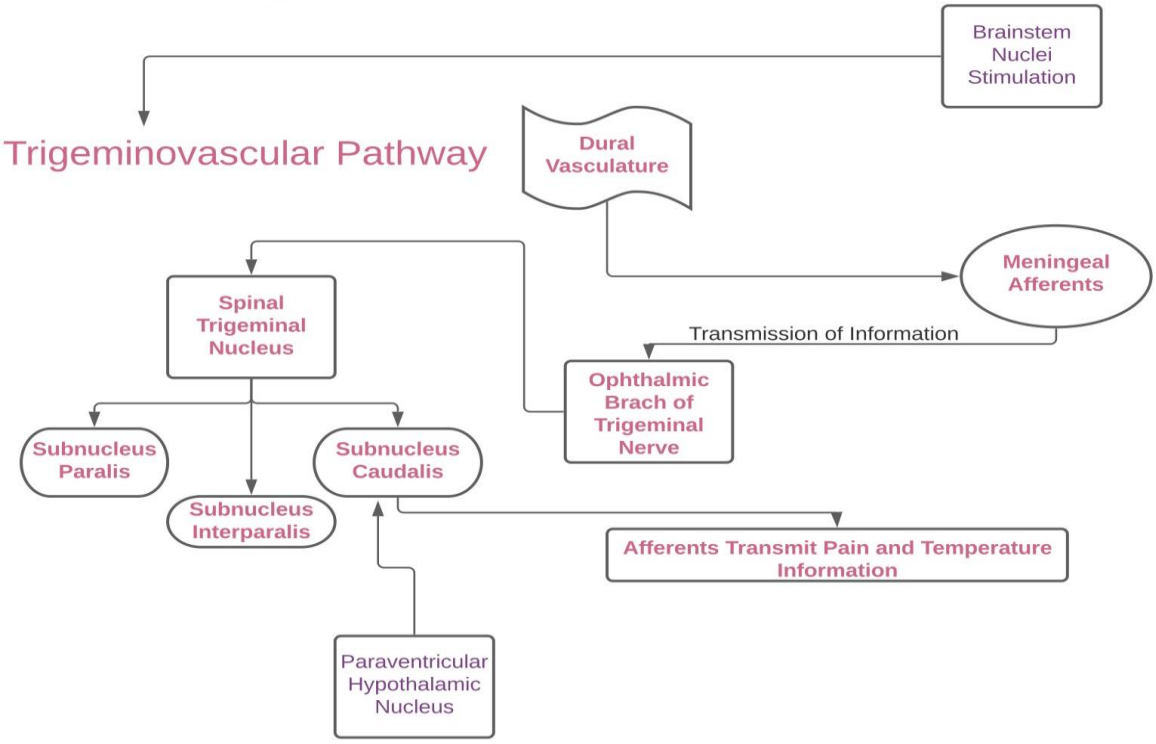


Figure 2

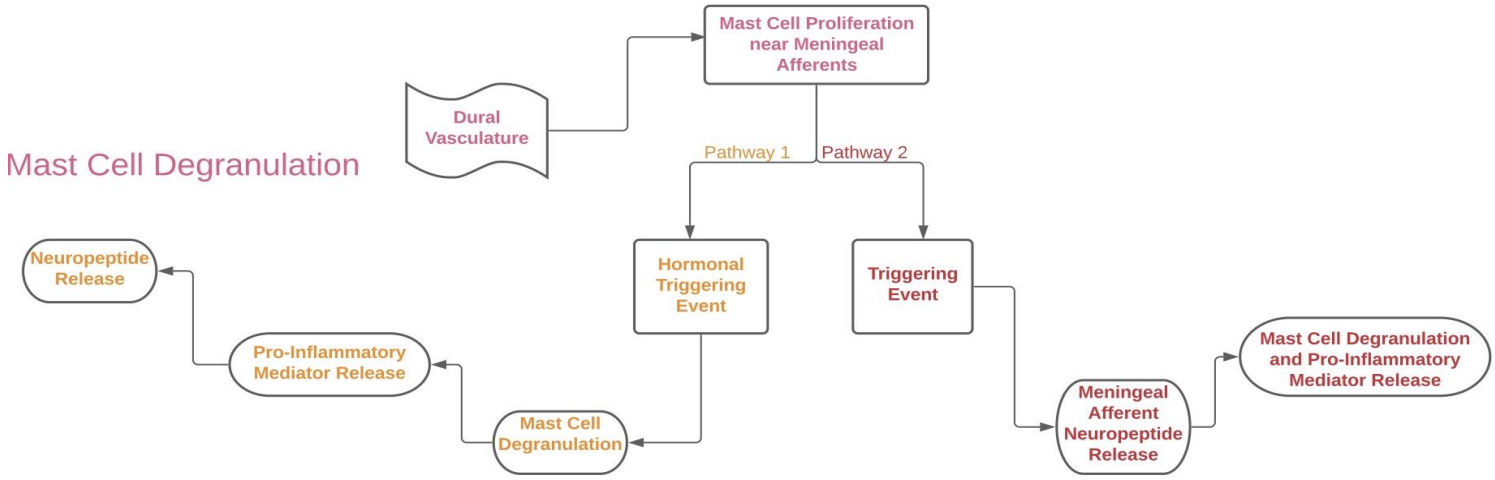


Table 1

Neurotransmitter Release from Nerve Fibers		
Parasympathetic Nerve Fibers	**Sympathetic Nerve Fibers**	**Trigeminal Afferent Fibers**
Vasoactive Intestinal Peptide Nitric Oxide Neuropeptide Y Nitric Oxide Synthase Acetylcholine	Norepinephrine Neuropeptide Y ATP	CGRP Neurokinin A Pituitary Adenylate Cyclase Activation Peptide (PACAP) Serotonin Nitric Oxide Synthase Substance P

Table 2

Differentiation of Migraine Pharmaceutical Classes				
Drug Class	NSAIDS	Triptans and Ergot Derivatives	Gepants	Ditans
Mechanism Of Action	Cyclooxygenase Inhibitor	5-HT1D/1B agonists	CGRP Antagonist	5-HTF Agonist
Effects of Binding	Unspecificity	Vasoconstriction Properties	Liver Toxicity	Various Adverse Effects

FIGURE 3

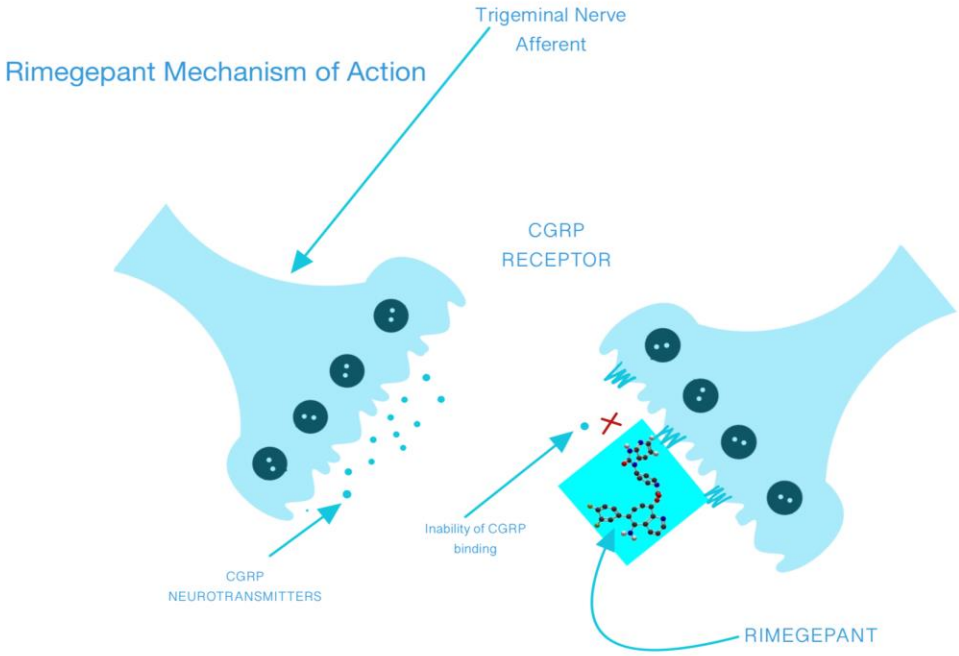
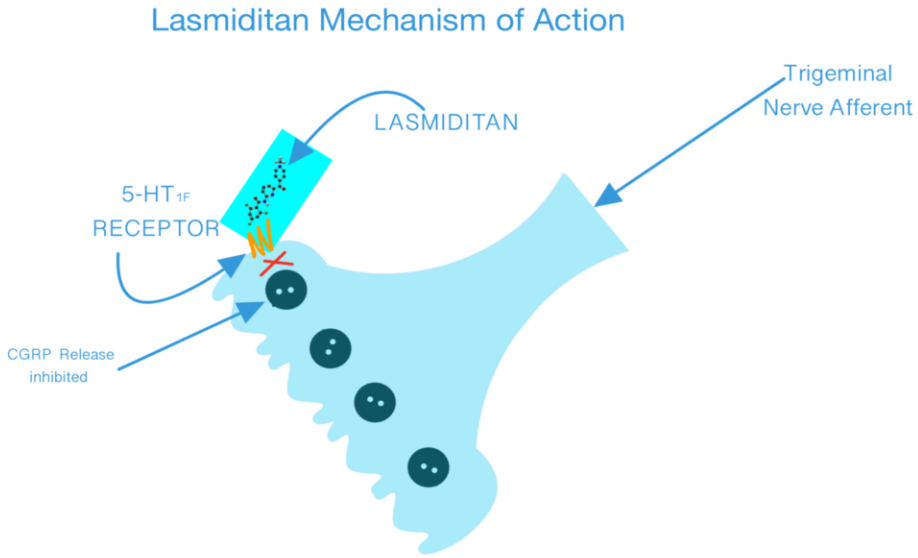


FIGURE 4



DISCUSSION

It is evident that increased research is crucial to determine migraine pathogenesis for production direct targeting medications. However, the acute treatments discussed do not provide pain relief to all patients. As stated earlier, prophylactic treatments include the usage of monoclonal antibodies when discussing CGRP antagonists. Monoclonal antibodies have shown to be effective towards patients with medically intractable migraines[53]. Additionally, a recent advancement has showed that neuromodulation has been very effective towards patients who are resistant to the migraine acute treatments discussed. Neuromodulation is a technique in which there is imposed electrical stimulation on various anatomical structures. The stimulated areas that have proven to be effective for intractable migraines include the occipital nerve, vagus nerve, sphenopalatine ganglion, supraorbital nerve, transcutaneous vagus, and transcranial magnetic stimulation[54]. These techniques provided are conducive to the subset of patients who experience contraindications and resistance to acute treatments.

All the Rimegepant and Lasmiditan studies evaluated in this research were quite similar and were promising in terms of effectiveness and safety. However, a lot of unknowns are prevalent. The full mechanistic action of Rimegepant is unknown, and studies linking effectiveness towards cardiovascular patients have not yet been demonstrated. Similarly, the complete mechanistic action of Lasmiditan is unknown, and various adverse effects are presumable based on the evaluated studies. When reviewing the concomitant use of Rimegepant with preventative treatment (monoclonal antibodies), it was proposed Rimegepant increased efficacy. When reviewing the concomitant use of Lasmiditan with preventative treatments (beta blockers, epileptic medications, and anti-depressants), the efficacy was not increased and remained the same. Additionally, in the second Lasmiditan

study evaluated, the adverse effects included dizziness, paresthesia, somnolence, fatigue, hypoesthesia, nausea, and lethargy. Not only this, but these adverse effects obtained an incidence of greater than 2% when comparing to the placebo. In comparison, the double-blind study of Rimegepant indicated only nausea and urinary tract infections as the adverse effects with an incidence higher than 1% compared to the placebo. Based on these results, it can be stated that Rimegepant is the advantageous acute treatment. This is not conclusive due to several limitations regarding fair comparisons. When comparing drugs, prices can have a huge effect on whether they are deemed more advantageous or not. Comparing two drugs elicits individualized perspectives. The sample sizes are not equivalent, which can account for a misnomer in adverse effects. There has yet to be a study showing the cardiovascular effects of Rimegepant upon at risk participants which can cause additional adverse effects that are not yet established. Also, very little clinical trials on Rimegepant are developed due to its recent approval. Therefore, it is encouraged for additional research to be imposed before a conclusive determination of the advantageous acute treatment can be distinguished.

CONCLUDING REMARKS

Based on the results established in this study, Rimegepant appears to be the advantageous acute treatment. This is not conclusive due to inequivalent comparison in sample size and amount of research completed. It is encouraged for additional research to be imposed before a conclusive determination of the advantageous acute treatment can be distinguished.

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