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Review of Medication Use in the Prevention of Migraines

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ABSTRACT

Migraines are a neurological disorder that negatively affects the lives of many around the world. This review article will focus on the different medications that are currently used to prevent migraines from occurring, focusing on how they work and if they're effective. Currently most of the medications used to prevent migraines are repurposed oral medications. Antidepressants that are tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors are used. The beta-blockers that are used in migraine prevention are propranolol, metoprolol, and timolol. The anti-epileptics that are used are topiramate and divalproex. Another form of medication that is used is a series of onabotulinumtoxinA injections using the PREEMPT paradigm injection mode. The newest development in migraine preventatives is the CGRP targeting drugs. There are the drugs Galcanezumab, eptinezumab, fremanezumab and erenumab, which use monoclonal antibodies. The second type of CGRP targeting medication uses small molecules and are CGRP receptor antagonists, the only preventive in this category is atogepant. All these medications have evidence that show that they are effective at preventing migraines, but they also all have side effects. When considering which medications are the best option the side effects and a patients other conditions have to take into consideration. Looking at what is currently not understood about migraine pathophysiology and the current direction preventative medication for this condition is headed helps to determine what future trends for this field will be.

Keywords

Migraines, Prevention of Migraines, Medication used for Prevention of Migraines, Antidepressants, Beta blockers, Antiepileptic drugs, OnabotulinumtoxinA (Botox), CGRP Targeting Drugs and future trends.

Introduction

A neurological disorder that affects around 1-3 % of the worlds general population is chronic migraines [1,2]. Those with chronic migraines are defined as having a headache 15 or more days a month and 8 of those days the headaches are accompanied by migraine symptoms for at least 3 months [2,3]. They affect women more often than men and occur most often during the middle years of a person's life [4]. Those suffering from chronic migraines are at the end of the migraine spectrum, having them the most often with severe symptoms. One step lower on the migraine spectrum and much more common is episodic migraines. Those who have episodic migraines have a headache with migraine symptoms less than 15 days a month and they may not have a migraine every month, though chronic migraines do often develop from episodic migraines [4].

Migraines are denoted by moderate to severe pulsing head pain on one side that is usually accompanied by a sensitivity to sound, light and nausea or vomiting [5]. These attacks can last anywhere from 4 hour to 3 days and are made up of three phases: the premonitory phase, the migraine headache, and the postdrome phase [4]. The premonitory phase happens a day or two before the migraine occurs and includes discomfort in the neck, tiredness, and changes in one's mood [4]. Then there is the migraine itself, which is followed by the postdrome phase. This third and final phase of the migraine attack lasts for around 3 days and consists of tiredness, a

stiff neck and trouble concentrating [4]. Time between the ending of the postdrome phase of one attack and of the premonitory phase on the next attack varies in length, but due to how often someone with chronic migraines has an attack many are constantly in one of the 3 phases.

An evolving area of research is in the pathophysiology of migraines. The cause as to why migraines occur is not one well understood by the medical community [4]. Currently it is believed that headaches are a result of the trigeminovascular pathway, which consists of perivascular nerves that innervate major vessels in the brain [4,6]. The stimulation of these neurons releases neuropeptides, like calcitonin gene-related peptide (CGRP) [6]. During migraine attacks there is an increase in CGRP that decreases with treatment and when in between attacks [6]. CGRP has also been seen to trigger migraine attacks [6]. These more recent discoveries into the pathophysiological side of migraines have led to the development of new preventatives for migraines.

When preventing a migraine there are several goals kept in mind when determining whether the method of prevention is working. The goals are to reduce the duration, severity, frequency and disability of the attacks, there is also an aim in reducing the number of times an acute medication needs to be taken [7]. Medication is often used as a method of migraine prevention but changes in one's lifestyle and non-pharmacological methods have also been shown to work at preventing migraines. But when medication is used there are many factors considered when picking the right one. The first one considered is usually the most efficient one but if they have other diseases, the side effects of the medication and the patient's preferences, are also taken into consideration [7]. The medication is then prescribed at a low dose that slowly builds up to a higher effective dose, the patient is kept at this dosage for 8 to 12 weeks to determine if the drug is effective [7]. Then if the drug is ineffective the patient is usually changed to one of a different drug class [7]. Migraine preventive drugs aren't taken with the purpose to eventually cure someone of their migraines but to simply reduce the frequency and severity of them.

As a whole, migraines are the most common debilitating brain disorder, chronic and more frequent episodic ones can negatively affect many aspects of a person's life including their job, social life, and physical health [2]. There are many ways to treat migraines while they are occurring, but there still aren't many effective treatments in preventing them [2]. Also, despite chronic migraines typically evolving from episodic ones the current treatments used for episodic migraines do not always work for chronic ones [4]. Currently to prevent migraines in patients there is a use of repurposed oral medications, onabotulinumtoxinA (Botox) injections or medications that target CGRP. The focus of this review is to describe the medications that are being used frequently to prevent chronic migraines.

Oral Medications

Oral medications are by far the most common type of migraine preventive prescribed. Oral medications include a wide variety of drug classes including antidepressant, beta-blockers, and anti-epileptic [7]. Most oral medications options that are used to prevent migraines are repurposed from other medicines. These drugs originally had a different purpose and were used for their intended purpose but later were found effective at preventing migraines [8].

Oral medications are the most common option due to them usually being the first medication type prescribed as they are low in price, and most are covered by insurance [7]. Despite their popularity the oral medications used for migraine prevention have a large potential to interact with other medications a patient is taking, many also have unfavorable side effects, and these medications often have a low long term adherence rate [7].

Antidepressants

One of the drug types that was repurposed after being found to help with the prevention of migraines are antidepressants. One of the first drugs to be discovered in helping to prevent migraines were tricyclic antidepressants and some studies even show that this type of antidepressant is the second most prescribed medication used for migraine prevention [8]. There are several other types of antidepressant medications that are prescribed and used off labeled for migraines, with amitriptyline and venlafaxine being the antidepressants with the most evidence towards showing that they can prevent migraines [8,9]. It is thought that the antidepressants that work in preventing migraines do so through their targeting of the serotonergic and noradrenergic systems, which are involved with neuropathic pain and likely also involved in migraine pain [8].

A type of antidepressant developed in the 1950s was the tricyclic antidepressants (TCAs). TCAs inhibit reuptake of norepinephrine and serotonin and have a half-life of 24 hours; this long duration of activeness helps with its preventive properties [10]. It is suggested that its pain relieving properties occur through complex anti-neuroimmune actions and through blocking the transmission of pain signals in the spinal cord [11]. The TCA class of antidepressants were the first medication shown to have some level of effectiveness in preventing migraines, which is why it is one of the most popular options [11]. The TCA antidepressant with the most evidence in preventing migraines is Amitriptyline, which received a level B of probably effective by the American Academy of Neurology for preventing migraines [8]. The reason it was kept from an A rating is due to an over 20% drop out rate in the clinical trials, likely due to the side effects of the drug [8]. Though TCAs are useful in preventing migraines, they also come with several adverse effects from their anticholinergic and antihistaminergic activity and interactions with many other drugs due to their extensive binding with proteins [8,10]. The most common side effects being dry mouth, drowsiness, dizziness, weight gain, and constipation [8,11]. These adverse effects and extensive drug interactions are why many now suggest that TCAs be used for patients who suffer with depression and migraines [10].

Another class of antidepressant medication that has proven useful in migraine prevention is selective serotonin reuptake inhibitors

(SSRIs). SSRIs work by selectively blocking the serotonin transporter, which causes serotonin to increase at the synaptic cleft [8,12]. The altered function of serotonin is important for migraines, it has been shown that a decrease in its levels in those who have migraines make it easier for external and internal stimulus to trigger a migraine attack [8]. The most popular SSRI medication used to prevent migraines is Fluoxetine, this is because it is a 5-HT2C antagonist, and it is believed that the 5-HT2C receptor is important to migraines [8]. A study done testing Fluoxetine in patients who had chronic migraines showed that it did decrease the number of headache days they had and improved their mood, but it did nothing to decrease the severity of the migraines they did have [8]. Though these studies done with Fluoxetine showed positive findings most of these studies were small or had major errors in how they were carried out, which led to it's U rating by the American Academy of Neurology for its "inadequate or conflicting data to support or refute medication use" [8,12]. Other SSRIs didn't receive any rating due to lack of evidence [8]. Most SSRIs have adverse side effects similar to those in TCAs and when abruptly quitting the medicine withdrawal like symptoms have the possibility of occurring. When prescribing these medications, a lot of consideration must be taken, as though they can prevent migraines there have also been a consistent number of cases showing that they can also induce or worsen migraines [8,12].

A third class of antidepressant that has been studied for their effectiveness in migraine prevention is serotonin-norepinephrine reuptake inhibitors (SNRIs). There are not very many studies done on these types of antidepressants used in preventing migraines but the ones that have been conducted showed that SNRIs can have a positive effect on chronic migraines [8,13]. One study found that SNRIs are safe for clinical use of preventing migraines, that they were better than the placebo and were good an option for those with migraines and psychiatric disorders [13]. Another study found that SNRIs were successful in preventing migraines but that the level of evidence to support this conclusion wasn't very high due to small sample sizes and underpowered trials [14]. The SNRI Venlafaxine has an evidence rating level by the American Academy of Neurology of a B [9]. Venlafaxine was found in a study to be safe and tolerated in the treatment of migraine prevention and was more effective than the placebo it was tested against [15]. But these medication also have similar side effects to the previous antidepressants discussed, but can also cause anorexia, excessive sweating, and heat intolerance [8]. Along with that, when going off these medications there can be a significant withdrawal syndrome that can become prolonged [8]. Despite several studies coming to the conclusion that SNRIs can prevent migraines, in practice there are many reports that SNRIs actually can cause migraines to worsen [8].

Beta-Blockers

B-adrenergic receptor antagonists (beta-blockers) have long been used and still are extensively used as a treatment for migraine prevention [16]. Beta-blockers are currently the most used drug type in preventive treatment of migraines and studies have shown that they are about effective 50% of the time in cutting down migraine attack by more than 50% [17]. While how beta-blockers work to prevent migraines is not completely understood it is believed to be due to their ability to pass the brain blood barrier, where the lipid solubility is exploited and neuron excitability is modified [17,18]. Evidence also points towards cortical excitability and abnormal cortical information processing that occurs as part of a migraine being regulated by beta-blockers [17].

The most common beta-blockers used for this purpose is propranolol and metoprolol, which are both recommended as the first line treatment for migraine prevention by American Academy of Neurology [19]. Both of these drugs have also been given the highest rating by the American Academy of Neurology, the Canadian Headache Society, and the European Federation of the Neurological Societies guidelines [16]. The highest rating level, A, is achieved by establishing the drugs efficiency with more than 2 class I trials [17]. Besides propranolol and metoprolol, timolol is also considered an A level drug [17]. There is one class B beta-blocker, Nadolol, which means it showed its efficiency in one class I trial or two class II trials [17].

Propranolol has been used in migraine prevention for over 5 decades and is commonly used as the first line medication in the prevention of migraines [20]. This drug is a non-selective beta blocker whose lipid solubility is high, which allows it to eventually reach the central nervous system [16]. It is believed that this medication works through its properties that stabilize membranes and neuron activity [20]. Propranolol also has high affinity with 5-HT receptors, which are serotonin receptors [16]. The synthesis of 5-HT plays a crucial role in the pathophysiology of migraines [17]. The effects of propranolol are seemingly dose dependent, with the higher the dose the better it is at preventing migraines [17]. When compared to topiramate, topiramate was more effective at low doses but when the dose was increased it performed about the same as topiramate [16,17]. The drugs half life is short, only 4-5 hours but there are forms that are available that are long acting, which helps to increase adherence [16]. Though propranolol is protein bonding, meaning it can have drug interaction with other protein bonding medications [16]. When compared to other beta-blockers propranolol and metoprolol performed about the same, but metoprolol's side effect profile was preferable [17]. Compared to timolol they're effectiveness was about the same and their side effects on the central nervous system were similar.

Metoprolol, like propranolol, has the highest rating across the major guidelines but unlike propranolol and timolol it is not approved by the Food and Drug Administration (FDA) for the purpose of migraine prevention [16]. Metoprolol also has a high lipid solubility level, meaning it can also reach the central nervous system easily. Unlike propranolol, this beta-blocker is selective, blocking only beta-1 receptors instead of both beta-1 and beta-2, and also doesn't have any affinity with 5-HT receptors [16,17]. Metoprolol, like propranolol, is dose dependent. It has been shown in studies that metoprolol is more effective than placebos and when compared to propranolol has a similar effect but with preferable side effects [17,21,22]. While it is seen that metoprolol

and propranolol are similar there are no other studies that compare metoprolol with any other drugs that are also designated level A by the American Academy of Neurology.

Timolol is the third beta-blocker that is considered level A by the American Academy of Neurology in the guidelines set for drugs showing evidence in preventing migraines but isn't recommended by the other two guidelines. In 1990 timolol was approved by the FDA for use in migraine prevention [23]. This drug has a good affinity with some of the 5-HT receptors, and while this can help with migraine prevention it also can cause it to interact with other medicines, primarily serotonergic medications. A study with timolol showed when taken twice a day it is more effective than a placebo but that its effectiveness and side effects were similar to propranolol [24].

The beta-blocker nadolol still is highly ranked by the American Academy of Neurology and the Canadian Headache society but does not have as much evidence supporting that it is effective at preventing migraines as the previous three beta-blockers discussed. Nadolol is hydrophilic, meaning it can't pass through the blood brain barrier as easily as the previous drugs that were all lipophilic [17]. This may mean that nadolol doesn't have the side effects on the central nervous system that the other beta-blockers do. The half life of this medication is longer, which can lead to a better adherence rate as it only needs to be taken once a day. The only study done comparing nadolol to other migraine preventives was in comparison to propranolol. It found that at low doses the medication had about the same effectiveness but was more effective when the dose of nadolol was about double propranolol's and with preferable side effects [25].

Anti-Epileptics

Medications originally used for anti-epileptic purposes have also been found useful in the prevention of migraines. One critical part of the physiology of a migraine is thought to be cortical spreading depression, which is the brief excitement of neurons followed by their inhibition which spreads across the brain cortex [26]. Anti-epileptic medications can block cortical spreading depression and prevent the central sensitizations that they cause [27]. Cortical spreading depression can also cause the release of ions and induces a reflex that causes axons that are part of the meninges to release calcitonin gene-related peptide and vasoactive neuropeptides [27]. Anti-epileptic drugs can affect ion channels and reduce the release of vasoactive neuropeptides, which can help stabilize neuronal membranes [28].

There are two anti-epileptic medications that are currently approved by the FDA for use as migraine preventives, topiramate and divalproex. Both of these medications are considered level A by the American Academy of Neurology [9].

Topiramate, better known by its brand name Topamax®, was first made in 1979. It has a structure similar to that found in carbonic anhydrase inhibitors, which contributes to it's properties as an anticonvulsant and migraine preventative [29]. Topiramate is a sulfamate-substituted monosaccharide that can easily enter the central nervous system, which also contributes to the drugs ability to prevent migraines [27,30]. Topiramate modulates the AMPA receptors negatively which leads to the inhibition of NMDA receptors, which are receptors for glutamate found on nerve cells [27]. Glutamate is heavily involved in cortical spreading depression as a major neurotransmitter due to its properties that excite neurons [31]. Through topiramate's unique property of negatively inhibiting AMPA receptors it is also able to inhibit glutamate, which is significant for it ability to prevent migraines.

Topiramate's ability to prevent chronic and episodic migraines is something that has been heavily studied and it is one of the most prescribed medications for migraine prevention. This medication is taken orally and is broken down by liver and has a half-life in plasma of 21 hours [30]. The longer half-life means that it only has to be taken once a day, which can increase the drug adherence. The studies have found that the ideal daily dose is 100-200 mg, but some studies have suggested that 100 mg and 200 mg provide the same benefits but that 200 mg does so with worse side effects for patients who do not have migraines that last for more than 72 hours [27]. Studies have shown that topiramate is more effective than placebos and several other migraine prevention medications like propranolol, and sodium valproate [27,32-34]. Like the other types of oral medications topiramate also has several side effects. The most common side effects seen when taking this medication are fatigue, drowsiness, dizziness, and mood changes that can lead to suicidal thoughts [27]. Some people taking the drug may also develop a pins and needles or tingling sensation due to the drugs inhibition of carbonic anhydrase, though taking potassium supplements can ease this [27]. This medication can cause an increase in birth defects so pregnant individuals should avoid taking topiramate and those with the chance of becoming pregnant should be cautious [27].

The second anti-epileptic that is used as a migraine preventative is divalproex sodium/sodium valproate. The basis of these medications is valproic acid, which was discovered to have anticonvulsant properties in the early 60s. The most common forms of valproic acid taken are sodium valproate, usually a syrup, and divalproex sodium, a tablet with an equal amount of moles of sodium valproate and valproic acid. Valproic acid is able to enter the central nervous system very easily, with the sodium valporate form being able to reach it within minutes of it entering the body [35]. Not much is understood about how this medication is able to prevent migraines. What is known is that valproic acid inhibits GABA-degrading enzymes, causing an increase in GABA, which has neuron inhibitory properties [35]. The increase in the GABA activity contributes to the benefits that valproic acids can provide. The effect it has on GABA along with its ability to inhibit neural excitatory signals that are induced by NMDA likely play a role in blocking cortical spreading depression [27,36]. Not only does valproic acid likely block cortical spreading depression it also can cause a decrease in neurogenic inflammation, and it has been found that at higher dose it can increase serotonin, dopamine, and their related active metabolites [36].

There have been numerous studies on valproic acid medications and their effectiveness at preventing migraines. At doses of 500mg to 1000 mg a day they have been shown to be effective. The studies have found that divalproex sodium is twice as likely to reduce headaches by more than 50% than the placebo and that for those taking sodium valproate it is three times more likely [37]. Studies have also been performed testing these medication against other commonly used preventatives. These studies have shown that they are just as effective as propranolol and are around the same effectiveness to slightly less effective as topiramate [27,34,38,39]. These medications see more side effects than commonly seen in other preventatives. The most common side effects are hair loss and weight gain, though other side effects like fatigue, tremors, nausea, and dizziness can also occur [9,27]. Like topiramate these medications can cause an increase in birth defects so pregnant individuals should avoid taking it, along with those who have the chance of becoming pregnant should be cautious when taking these medications.

Both these medications have a lot of evidence showing that they are able to prevent migraines and have studies showing that they even work better than other commonly used preventatives. Studies have also shown that both these medications are also effective and okay for long term use [40-42]. But, despite these medications being effective they often cause unwanted side effects more often than other preventatives. Along with that, these medications can't be taken by those who are pregnant and those who could become pregnant have to be cautious when taking them due to topiramate and divalproex being teratogenic.

OnabotulinumtoxinA (Botox)

OnabotulinumtoxinA, more commonly known as Botox, is the injectable form of Botulinum neurotoxin type A (BoNTA) [43]. Botulinum toxin is produced by *Clostridium botulinum,* an anaerobic bacteria, and is used for conditions that are involved in muscles contracting in excess because of the toxin's ability to inhibit muscle contractions [43,44]. BoNTA, a preparation of botulinum toxin, is able to inhibit muscle contractions by preventing acetylcholine from being released at neuromuscular junctions [43]. Though the injectable formulation of BoNTA was being used for several conditions it was in the early 1990s when patients started to describe how they found an improvement in their migraines after treatment [43].

It is believed that one of the ways onabotulinumtoxinA is able to prevent migraines is due to its ability to modulate sensory neurons. OnabotulinumtoxinA can affect neuropeptides by inhibiting their release from primary neurons, which is important for migraine prevention because CGRP and substance P are both neuropeptides and are important to migraine pathophysiology [43]. It is likely that onabotulinumtoxinA involvement in migraine prevention is due to this ability to inhibit the release of CGRP. More recent studies have found that drugs that reduce CGRP in the periphery are able to prevent migraines [43]. OnabotulinumtoxinA ability to reduce CGRP has been found in multiple experiments and studies. Some studies that were done as *in vitro* animal experiments were able to show that CGRP release from sensory neurons was inhibited by onabotulinumtoxinA [43,45,46]. Another study that was done on those with chronic migraines found that interictal CGRP plasma levels were reduced in patients who were considered treatment responders to onabotulinumtoxinA [43,47].

Another component as to why onabotulinumtoxinA is able to prevent migraines is its inhibition of SNARE-mediated processes. Migraines are a sensory neurological disease and SNARE-mediated vesicle trafficking which occurs in sensory nerves is inhibited by onabotulinumtoxinA [43]. Specifically, onabotulinumtoxinA inhibits the exocytosis of the sensory neurochemicals and proteins, along with inhibiting membrane insertion receptors that can convey pain from the periphery to the brain in those who have chronic migraines, due to these processes being dependent on SNARE [43]. The neurons that are affected by the injections of onabotulinumtoxinA go through many SNARE-mediated processes, which are inhibited by the injections. These processes are related to migraines as they include the release of neurotransmitters, inflammatory and nociceptive neuropeptides and these processes play a role in inserting receptors that encode for pain into c-fibers [43].

The use of onabotulinumtoxinA injections was approved for use in migraine prevention in 2010. It was approved after a study was done that same year that showed that when it was injected in migraine-specific paradigm that patients migraine days were significantly reduced [48]. The migraine-specific paradigm had 155-195 units of onabotulinumtoxinA injected into 31-39 sites that were located in the head and neck muscles, corresponding to areas of the head and neck that sensory neurons innervate [43]. After these injections are conducted the medication is able to diffuse from the muscles into the surrounding tissue to affect the nerves.

The studies done on the effectiveness of onabotulinumtoxinA in chronic migraine prevention have found that it does reduce the number of headaches days a person has a month significantly in comparison to the placebo [49]. The reduction of migraines was found to start as early as week 4 and they were reduced till as far as week 24 after the injections. Any adverse side effects that occurred due to the injections were mild and the most common ones were neck pain and muscle weakness, with few dropping out of the study due to side effects. Overall studies have found that onabotulinumtoxinA injections are safe, tolerable and effective for use in migraine prevention.

Though onabotulinumtoxinA injections have been proved through multiple studies to be useful in preventing chronic migraines, whether it is effective and safe to use to treat patients with episodic migraines hasn't been fully researched. The studies that have been done on onabotulinumtoxinA use in episodic migraines did not use the same injection model that was proven to be effective in the studies with choric migraines, but clinical benefits when using the same PREEMPT paradigm injection model in real world scenarios have been seen [50].

CGRP Targeting Drugs

The newest medication and the only ones that aren't repurposed medications target calcitonin-gene-related peptides. These CGRP targeting medications that are used for migraine prevention are made of monoclonal antibodies against a CGRP ligand or receptor and a CGRP-receptor antagonists [51]. In the studies of these drugs they have been shown to be effective at preventing migraines and performed far superior to the placebos.

In migraines the trigeminal nerve has been found to be responsible for most of the afferent pain information and these structures that are sensitive to pain are innervated by unmyelinated C fibers [52]. Unmyelinated C fibers store neuropeptides that are known to be important to the pathophysiology of migraines, like CGRP. What mechanism cause the start of a migraine isn't fully understood but what is known is that a release of inflammatory mediators that result in the migraine pain is caused in part by a brain dysfunction that involves the central and peripheral components of the trigeminovascular system. The peripheral component being involved is important, as it means that for a preventative to be effective it doesn't necessarily have to cross in the central nervous system or the blood brain barrier. The neuropeptide that is known to be important to migraines and thus was targeted was CGRP. This is because levels of it, but no other neuropeptides, were found to be elevated in patients experiencing the headache phase of a migraine and that the levels decreased as the headache improved. It was also found that CGRP can trigger a migraine when infused into an individual already susceptible to migraine attacks and that when the migraine was treated the levels returned to normal.

CGRP is a potent vasodilator that was first discovered in 1983 [51,52]. CGRP and all its functions in the body is still not something that is fully understood. What is known is that it plays a role in many cells and systems outside the nervous system, so by targeting CGRP other body systems could be affected as well. In the central nervous system the modulation of pain and sensitization involves CGRP and when it is released in the periphery it causes vasodilation, which results in inflammatory sensitizing in the nociceptors of the trigeminal. CGRP can be found existing in one of two forms in the body, α-CGRP or β-CGRP. The more studied α-CGRP form is the primary form of CGRP, it is found in neurons centrally and peripherally and is much more immunoreactivity [53]. β-CGRP was mainly believed to found in the intestines but more recently has been found in the intrinsic enteric neurons and the pituitary gland [52,53]. Though it is possible that β-CGRP could cause the gastrointestinal that sometime occur with migraines. α-CGRP is the form that is used for the GCRP targeting drugs, this is the form that the antibodies target due to it being the main form found in the central and peripheral nervous systems [44].

There are currently two types of CGRP targeting drugs, monoclonal antibodies and CGRP receptor antagonists, gepants. The way that these CGRP targeting drugs are believed to be able to prevent migraines is through the blocking of CGRP and its transmission [44]. The monoclonal antibodies that inhibit CGRP are believed to be able to bind to CGRP that has been released by the sensory nerve fibers of the trigeminal nerve, which deactivates the CGRP. The other type of CGRP inhibitor medication used in migraine prevention is the CGRP receptor antagonists. These are believed to work by preventing CGRP from being able to access its receptor by targeting the receptor. As CGRP has been found to trigger migraines and during migraines the level of this neuropeptide in the body is found to be elevated, then by reducing the amount of it in the nervous system migraines can be prevented from occurring as often.

Monoclonal antibodies aren't just being used for migraine prevention but are used to treat many other neurological disorders. Monoclonal antibodies are suited for chronic conditions and allow for fewer doses, which helps to increase adherence, due to its long half-life [54]. Along with that, these antibodies are highly specific, which is useful for the prevention of migraines as it allows it to specifically target CGRP. There are currently four monoclonal antibodies that have been approved for use in migraine prevention. Galcanezumab, eptinezumab and fremanezumab target CGRP, while erenumab targets the CGRP receptor. Galcanezumab was approved by the United Stated Food and Drug Administration (FDA) in September of 2018 to be used as once a month subcutaneous injection and at the same time the European Medicines agency issued a positive opinion about it. Eptinezumab was approved in February of 2020 by the US to be delivered intravenously for migraine prevention in adults [56]. Fremanezumab was approved in September of 2018 by the FDA for preventative migraine treatment in adults as a subcutaneous injection [57]. Erenumab was the first one of the monoclonal antibodies medications for migraine prevention approved by the FDA. It was approved in May of 2018 for preventative treatments of migraines in adults and in the EU it received a positive opinion for prevention of migraines for people who have at least 4 a month [58]. Overall all these monoclonal antibodies medications that target the CGRP pathway have been found in their trials to be safe, where the rate of drop out by participants was low and those who switched to the active form of the medication after receiving the placebo reported to have experienced benefits [51].

CGRP receptor antagonists, also known as gepants, are small molecules that compete with CGRP at specific receptors [59]. Seven gepants have been developed but currently only 4 have been approved for use in migraine treatment. Gepants are generally prescribed to patients with cardiac or cerebrovascular risk factors or to those who have tried several other preventative treatments but found them ineffective. The four gepants currently approved for acute or preventive treatments for migraines are: ubrogepant, rimegepant sulfate, atogepant, and zavegepant. Ubrogepant, rimegepant sulfate and zavegepant are only approved for acute treatment of migraines without auras in the US [60-62]. Though rimegepant sulfate in the form of a tablet is being investigated for use as a migraine preventative [61]. Atogepant is the only CGRP receptor antagonists that have been approved in the US for the preventative treatments of migraines [63]. It was approved in September of 2021 and is in clinical development in other countries. Atogepant is the first oral CGRP antagonist that was

developed for the prevention of migraines [44]. The phase 2/3 clinical trial done with the medication found that in comparison to the placebo it significantly decreased migraine days. The most common side effects found during the trial were constipation, nausea, nasopharyngitis and urinary tract infections, though these were all fairly rare with less than 5% of participants experiencing them [59]. It was found that this drug is able to be tolerated, is safe and effective in preventing migraines [44,59].

Despite the results from the monoclonal antibodies and CGRP receptor antagonists medication being promising, the long term affects of these drugs are still unknown. These medication were only approved of in the last few years, so the long-term effects of blocking CGRP and its signaling are yet to be seen and much is still to be learned about the roles CGRP plays in the body [44].

Conclusion

Migraines, both chronic and episodic, can negatively impact a person's life, affecting both their daily life and keeping people from living to their fullest. It is believed with the current research that has been done on migraines that the cause of them is related to the trigeminovascular pathway. Neurons in this pathway are stimulated and release neuropeptides, specifically CGRP, which is believed to be involved with migraines and the triggering of one due to the levels of CGRP being high during attacks. Preventative medications can keep these attacks from ever happening.

The most common preventatives are oral medications that have been repurposed. Preventative medications in this category are most commonly antidepressants, beta-blockers or anti-epileptic medications. Antidepressants that have been proven with some level of evidence to prevent migraines are the tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. The beta-blockers that are used in migraine prevention are propranolol, metoprolol, and timolol. The two anti-epileptics that are approved by the FDA for use as a migraine preventative are topiramate and divalproex. All these oral medications have shown that they have some level of effectiveness at preventing migraines, but they all also have their side effects that must be taken into account before they're prescribed.

Another form of migraine preventive is the drug onabotulinumtoxinA, or more commonly known as Botox. This medication is also one that has been repurposed but is in the form of a series of injections that are delivered into the head and neck muscles. In numerous studies that used the PREEMPT paradigm injection model it has been proven that the drug is effective at preventing migraines in those who have chronic migraines. The newest form of preventive and the only non-repurposed drug reviewed are the CGRP targeting drugs. The most common formulation used to create these migraine preventives includes monoclonal antibodies. There are four different injectable preventives that are approved by the FDA that fall into this category. galcanezumab, eptinezumab and fremanezumab which all target CGRP, and erenumab which targets the CGRP receptor. The second form of CGRP targeting drug is CGRP receptor antagonists, which include small molecules that compete with CGRP. Though there have been several CGRP receptors antagonists that have been developed only atogepant has been approved for the preventative treatments of migraines, the rest have only been approved for acute treatment.

Future Trends

Much about migraines and the way they work is still unknown and will continue to be researched in the future. Not much about the pathophysiology and the mechanism that leads to migraines is known, making it an area that will likely be studied more in the future. Along with that, the pathophysiology of chronic migraines and how it could differ from episodic migraines is another area of research that is being explored [64]. More studies done on CGRP inhibitors effectiveness on the frequency of migraine and the brain function could help with learning more about the differences in central and peripheral mechanisms involved in chronic migraines. Research involving MRI technology is also being conducted in relation of migraines due to the belief that the altered function of the brain stem hypothalamic nuclei are involved with chronic migraines.

Not only will future trends show more research being done on the pathophysiology of migraines but there will likely be a focus on the CGRP targeting medications as well. The medication that targets the neuropeptide CGRP is fairly new, with the first one only being approved for us by the FDA in 2018. These medications and research into creating medications that can prevent migraines in an emerging field. These CGRP targeting drugs are one of the first medications to be created for the purpose of migraine prevention, unlike previous preventatives which were repurposed drugs. So far these medications have seemed effective in preventing migraines, so more research into these drugs and the creation of more in this category is likely a trend that will be seen. Along with that, due to these medications being newer the long-term side effects are not known yet. So future years will likely seem more research regarding looking into what long term side effects might be caused by these medications and the long-term blocking of CGRP.

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