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CGRP Inhibitor Use in Migraine Treatments

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ABSTRACT

Several possible remedies for migraines have been discovered to date, the most prominent ones include various antiepileptic drugs such as divalproex sodium and topiramate, as well as beta (Amiri et al., 2021)blockers such as propranolol and timolol. However many of these treatments are not entirely effective treatments for patients who face chronic migraines due to their somewhat prosaic success rates. In 1985, researchers noticed the presence of Calcitonin Gene-Related Peptide (CGRP) in the plasma increased drastically in its levels during the presence of a migraine attack (Deen et al. 2). CGRP is a neuropeptide that is involved in the dilation of both dural and cerebral blood vessels, and this interaction is believed to be the main cause of migraines. Generally, when migraines are treated with triptans (a common symptom relief medication), CGRP levels in the blood generally reduce. It was further found that certain CGRP inhibitors reduced neurogenic inflammation and lead to an increased reduction of pain during the migraine (Deen et al. 4). When faced with a multitude of treatment options for chronic migraines, one must consider inhibitors of the CGRP pathway as a possible alternative. CGRP inhibitors introduce a possible better treatment option than previous medicinal drugs. A few previously used CGRP inhibitors include erenumab, galcanezumab, and fremanezumab, which have recently been used to treat patients of chronic migraines. In this paper we will consider the various CGRP inhibitors and their advantages and disadvantages in the face of conventional chronic migraine treatment options.

Introduction

Migraines are a neurological condition that often result in frequent headaches. These headaches are sometimes associated with nausea, light and sound sensitivity, and visual aura (Shahien and Beiruti 3). The discomfort caused by migraines to millions of people around the world has caused many reputable researchers and doctors to strive to find a cure for this disease, but until then, it is important to take relief medications if suffering from migraines. Migraines have generally been thought of as being around for centuries. The earliest known records of migraines can be traced back to around 1200 BCE, in Ancient Mesopotamia (Migraine and Headache Australia 1). The symptoms inscribed by those in Ancient Mesopotamia include those of throbbing head pain, as well as sensitivity to light and sound. During the Middle Eras in Ancient Greece, the philosopher Hippocrates, also known as the "Father of Medicine," referred to a condition called hemicrania, known as "half skull" in Greek (Migraine and Headache Australia 2). Hippocrates noticed the connection between the throbbing headache, nausea, and light sensitivity. No further advancements in the understanding of migraines came until the 19th century. In 1873, Edward Liveing proposed the name "migraine," and hypothesized that these headaches were caused by abnormalities in brain function (Amiri et al. 7). Further during this time, the aura that often preceded migraines, where flashing lights often appeared in ones vision, were associated with migraines. In the early 20th century, advancements in medicine and technology helped doctors and researchers to better understand the nature of migraines. The first effective medication for migraines was also discovered during this time. In the 1930s, a substance originating from fungi, known as ergotamine, was used as a symptom relief medication for migraines. In the late 1990s, triptans evolved to be the primary form of migraine medicine. Triptans worked by targeting serotonin receptors in the brain to minimize the pain. Greater technology has enabled modern researchers to gain a deeper understanding into migraines and the way they affect the brain. While there is no

cure, there are a multitude of treatment options that one can consider as symptom relief medication if dealing with migraines, and it is extremely important to consider the optimal remedy for oneself, as each one's effectiveness varies depending on the individual.

When dealing with migraines, it is of the utmost importance to consider the various treatment options that are available. The aforementioned remedies include CGRP inhibitors, antiepileptic drugs, and beta blockers. Each of these remedies have both advantages and disadvantages in usage, but because migraines and the way they affect people is specific to the person who is being affected, several factors such as diet, daily routine, physical activity, stress, and many more determine how a migraine might negatively affect someone's quality of life.

The first primary remedy for migraines are antiepileptic drugs. Antiepileptic drugs function by calming excitatory neuron. The abnormal electrical activity in the brain during a migraine is thereby lessened due to this. Several antiepileptic drugs include propranolol and timolol. The antiepileptic drugs further regulate neurotransmitters in the brain, such as gamma-aminobutyric acid and glutamate. These neurotransmitters are mainly involved in the perception of pain and transmission signals during migraines. Thus the antiepileptic drugs are able to lessen the severity of the migraine attack by modulating the pain. Some antiepileptic drugs also have the ability to block calcium channels, which help stop the release of several neurotransmitters during a migraine attack. Several drawbacks of using antiepileptic drugs include red cell aplasia, anemia, and rashes. The figure below illustrates how antiepileptic drugs target the body in order to reduce the intensity of the migraine attack or prevent it altogether. The antiepileptics shown in the figure are topiramate, valproate (divalproex sodium) , and zonisamide. These antiepileptics work by targeting various sites in the brain and altering neurotransmission by affecting ion channels, receptors, and neurotransmitter metabolism. This thereby decreases brain excitability and reduces intensity and frequency of migraines if taken on a schedule.

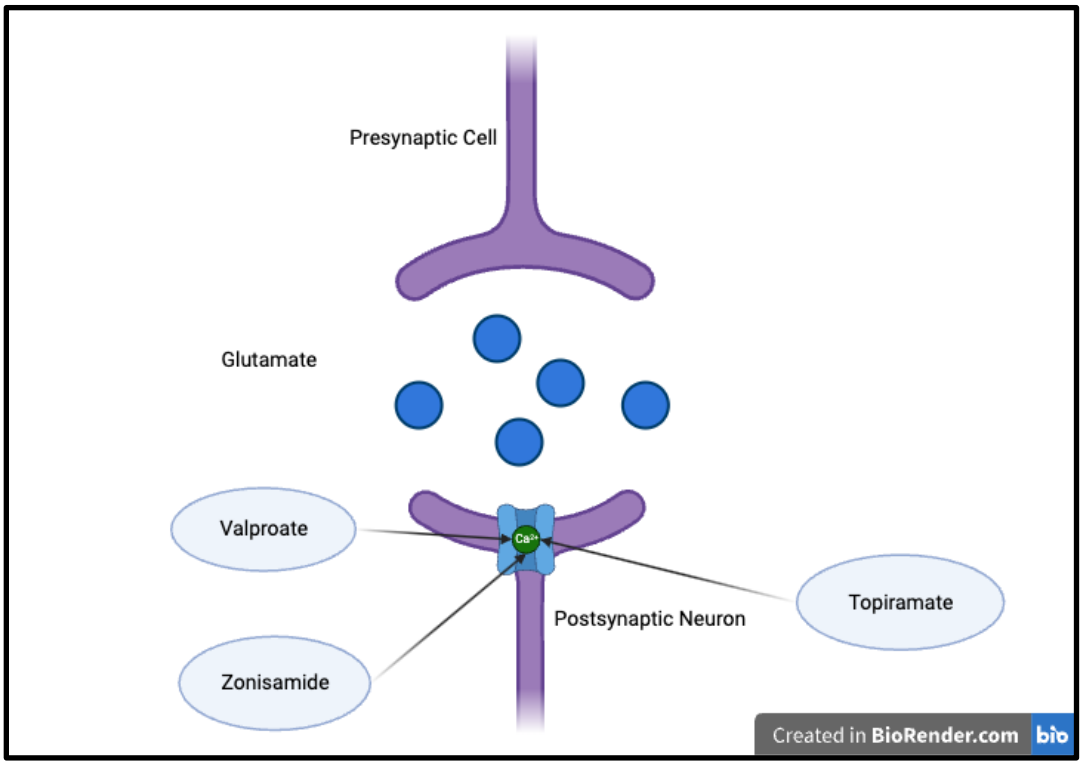

Figure 1. Antiepileptics like Zonisamide, Topiramate, and Valproate all target ion channels, receptors, and neurotransmitter metabolism, thereby lessening brain excitability.

The second migraine treatment that will be considered in this review are beta blockers. Beta blockers primarily function by inhibiting the actions of epinephrine and norepinephrine. During migraine attacks these hormones can cause blood vessels to dilate. Beta blockers further help to reduce imbalance of adrenaline during a migraine attack, as well as reducing the presence of excited neurons during migraines.

The final and relatively novel treatment option for migraines are CGRP inhibitors. CGRP inhibitors act by blocking the CGRP pathway. It is believed that the CGRP pathway has a connection with the presence of a migraine attack. CGRP, also known as Calcitonin Gene-Related Peptide, is a neuropeptide which greatly increases in its levels during a migraine attack, suggesting that CGRP might be a possible cause for migraines. Triptans previously helped to reduce the acute pain caused by migraines, but in 1985, several researchers realized that when triptan was used as medication, CGRP levels reduced in the blood. This therefore lead to further research into CGRP inhibitors as a possible alternative migraine treatment option. CGRP inhibitors are also known as monoclonal antibodies, which work by binding to the receptor (binding site) , and thereby weakening the migraine signaling pathway. The effects that are generally prevented include the intensity of the migraine, reducing inflammation of dural and cerebral blood vessels, and lessening the duration of the attack. Several negative effects of utilizing CGRP inhibitors include fatigue, hair loss, nausea, depression, and anxiety. It is important to keep these effects in mind should one be considering using CGRP inhibitors as treatment. In the CGRP inhibitors shown in the figure, you can see that the second CGRP inhibitor works by vasodilatation, which involves the dilation of blood vessels in order to decrease blood pressure and thereby decrease the intensity of frequency of migraines. CGRP inhibitors generally bind to synapses in the trigeminal nucleus caudalis, which then block signals through the brain stem and the thalamus.

The prediction that I have after reviewing each of the articles and studies is that the use of CGRP inhibitors as a potential migraine treatment will be a better solution to chronic migraines as opposed to antiepileptic drugs and beta blockers due to the reduction in dilation of dural and cerebral blood vessels, thereby decreasing the severity of the migraine. Not only this, CGRP inhibitors generally cause less acute side effects to be experienced by the user, as well as generally less frequency of migraine than when using other forms of treatment.

Method Review

Several experiments were used in this review in order to gain a comprehensive understanding of the advantages and disadvantages of utilizing each treatment method. The first study was *Blocking CGRP in migraine patients - a review of pros and cons,* which conducted several trials using several different CGRP inhibitors (such as fremanezumab) in order to determine its efficacy. The procedure to determine the efficacy of the inhibitors involved injecting the given drug intravenously or subcutaneously. Further, the testing was done on subjects who experienced either episodic or chronic migraines. The testing was conducted over a time period of several months with the results being measured for each subject in migraines per month. The study lasted for a period of 3 months with CGRP inhibitors such as Erenumab, Fremanezumab, Galcanezumab, etc.

The second study I used is *Preventative agents for Migraines: Focus on Antiepileptic drugs.* The clinical studies described in this article revolve around the use of divalproex Sodium, also known as valproate in treating migraines, which is an antiepileptic drug. The first study described in the article was conducted on 107 subjects, some of which were given valproate while some were given placebos. The study was conducted for 3 months, and valproate was given some of the patients at a dosage of 250 mg/day. The second study described in the article involved the similar usage of valproate in comparison to the placebo, but at varied concentrations, still with the same 3 month period at 176 subjects. The third and last study involved the gradual increasing of the valproate dose over a period of 17 weeks on 234 subjects. The dosage started at 500 mg/day for a week, and

was gradually increased to 1000 mg / day. In all three studies the amount of migraines per week was measured, and was later used to determine the efficacy of the drugs.

The third article used is called *Beta-blockers for the prevention of headache in adults, a systematic review and meta-analysis*. This study was primarily chosen in order to develop my understanding of beta blockers in their efficacy in treating migraines. The study in this article consisted of 108 randomized controlled trials, 50 placebo controlled trials, and 58 comparative effectiveness trials. The trials were performed on people who suffered from both episodic migraines and tension headaches, and the results were collected in headache frequency per month. The main beta blocker used was propranolol. The beta blockers were taken with food at meals. The range of study for each of the beta blockers varied from 4 to 64 weeks in length.

The last article used was *CGRP monoclonal antibodies in migraine: an efficacy and tolerability comparison with standard prophylactic drugs*. This article provides research from further experiments into the efficacy of CGRP inhibitors when compared to beta blockers such as propranolol. The CGRP inhibitors used include fremanezumab, eptinezumab, galcanezumab, and erenumab. Three separate trials were conducted for each of the CGRP inhibitors with each trail being conducted over a time period of either 8, 12, or 24 weeks. The monthly migraine days was the dependent variable in this study, also known as MMD, which was used to determine the overall efficacy of each CGRP inhibitor when compared with its fellow inhibitors, placebos, and beta blockers. Dosage was monthly for those using erenumab, galcanezumab, and fremanezumab 225 mg, and every three months for the ones using 675 mg.

Results

The first study, *Blocking CGRP in migraine patients - a review of pros and cons,* saw the use of topiramate as a measure of already existing migraine treatments' general efficacy. The goal of the study was to determine if the use of various CGRP inhibitors, such as erenumab, galcanezumab, fremanezumab, and eptinezumab, were more effective at treating migraines than topiramate, an antiepileptic drug, as well as a placebo. By using data from several previously existing studies, the efficacy of each medication was easily able to be determined. For eptinezumab 1000mg, given through an IV, a 5.75 day reduction was seen in the mean monthly migraine days, as compared to 4.5 with the placebo group. For the substudy involving galcanezumab 150mg, there was about a 4.25 day reduction in mean monthly migraine days, as compared to the 3 day reduction for the placebo. The substudy with fremanezumab 225 mg and fremanezumab 675 mg saw them achieve 6.1 and 6.2 reduction in mean monthly migraine days respectively, compared to the 3.5 with the placebo. For Erenumab, 70 mg, 21 mg, and 7 mg variants were used, with each of them having a reduction in mean monthly migraine days of 3.5, 3.5, and 2.2, compare with the 2.3 of the placebo. Topiramate saw similar results as various CGRP blockers, however much milder adverse effects were reported when dealing with topiramate than the CGRP inhibitors.

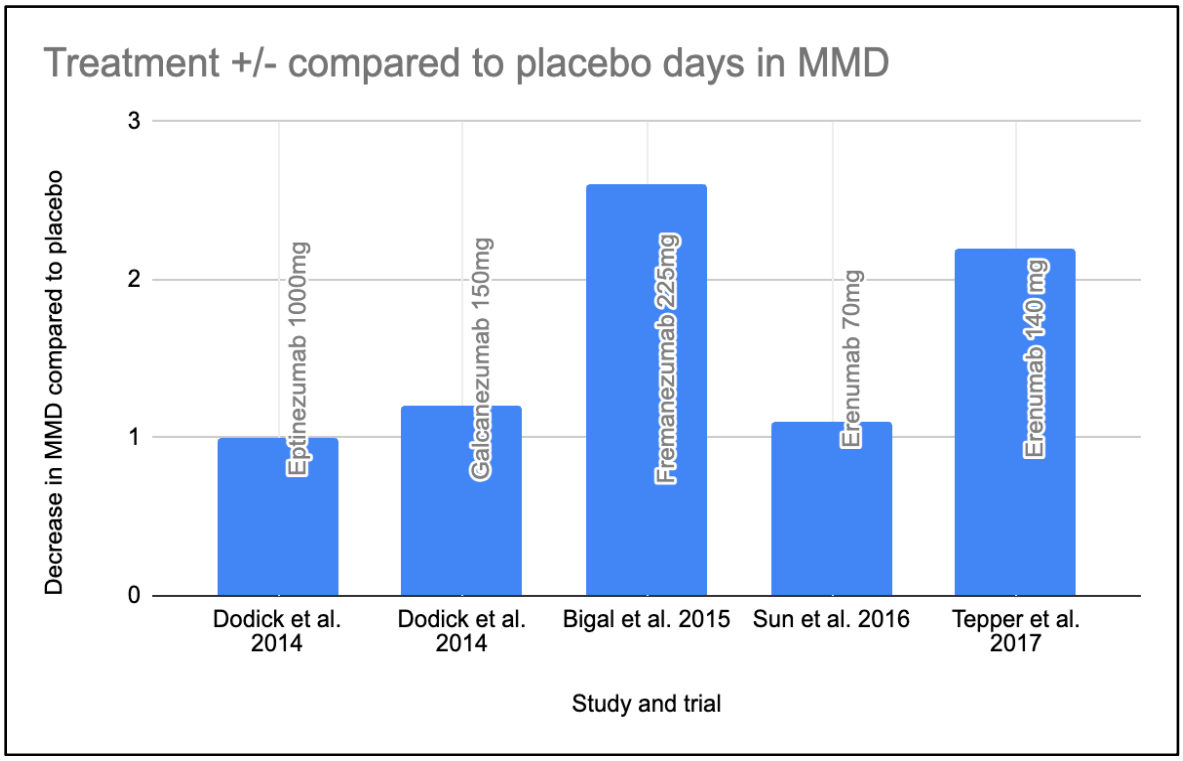

Figure 2. Experiment showcased the reduction in average monthly migraine days over a study period of 12 weeks. Each CGRP inhibitor was paired with a placebo of the same dosage. The studies were carried out in separate labs by separate researchers in different years.

The second study sought to determine the efficacy of utilizing antiepileptic drugs as the main source of treatment for chronic migraines. The trials in this study were separated into three separate trials, The first trial saw 107 subjects be treated with the antiepileptic drug valproate, or divalproex sodium. Out of these 107 subjects, The number of participants who had a 50% reduction in migraines was 48%, as compared to just 14% with the placebo group. The second part of this study saw the valproate being split into various doses, and being compared with various doses of the placebo group, over a three month period. For the 500 mg group, the monthly migraine frequency decreased greatly, from 4.5 to 2.8. For the 1000 mg group, the monthly migraine frequency decreased from 4.7 to 2.7. For the 1500 mg group, the monthly migraine frequency decreased from 4.7 to 3.0. The placebo group saw a decrease from 6.1 to 5.6 in monthly migraine days. In the third part of the study, the subjects were initially treated with a 500 mg concentration of valproate, which was later increased to a concentration of 1000 mg. There was a significant decrease in the monthly migraine frequency for the subjects in this trial, from 5.8 to 3.7, whereas the placebo group decreased from 6.3 to 4.6 in monthly migraine frequency.

The third study saw the use of beta blockers as the main treatment for chronic migraines. The dependent variable in this study was the headaches per month, with the baseline being recorded at 4.9 headaches per month. The 8 week marker in the treatment was the most commonly recorded data point for the various treatments. At the 8 week mark, propranolol, the most effective beta blocker, was reported to have a headache rate per month of 3.4, and at the 12 week mark 3.7. This was significantly more effective than the placebo, which was reported to average out, across the entire treatment period as I mentioned above, at 4.9 headaches per month. The other beta blockers used however, did not yield as impressive results as propranolol. acebutolol, aprenolol, bisoprolol, and metoprolol yielded 0.5, 0.8, 0.6, and 0.9 less headaches per month when compared to the placebo, much less than the efficacy of the propranolol. Several side effects were experienced at a higher

frequency for the beta blockers than for the placebo. These side effects included dizziness, gastrointestinal issues, and depression.

The fourth study was a further study to confirm the efficacy of utilizing CGRP inhibitors as treatment for episodic and chronic migraines. This study mainly focused on the efficacy of utilizing fremanezumab and galcanezumab as the main monoclonal antibodies, also known as CGRP inhibitors. During the 12 week examination of the effects of the inhibitors, fremanezumab had a 3.1 day decrease in monthly migraine days when compared to placebo. Meanwhile, galcanezumab saw a 3.5 day decrease in monthly migraine days. Although other CGRP inhibitors were used, such as erenumab and eptinezumab, they did not see as great of a decrease in the monthly migraine days. Erenumab saw just a 1.6 reduction in monthly migraine days, which was miniscule when compared to the impact that monoclonal antibodies like galcanezumab and fremanezumab had. It is also important to note that the dropout rates of those on the placebo were very high, nearly 52 %, indicating that nearly 150 participants dropped out.

Discussion

When observing the results of the first study, we can see that several CGRP blockers resulted in a greater decrease in monthly migraines days in comparison to use of the placebo. Eptinezumab with the 1000 mg daily does resulted in a 5.75 reduction in monthly migraine days as compared to the 4.5 from the placebo. Meanwhile galzanezumab (150 mg) saw a reduction of 4.25 in the monthly migraine days, however the placebo saw only a 3 day reduction in monthly migraine days. Erenumab (70 mg, 21 mg, and 7 mg) , saw respective decreases in monthly migraine days of 3.5, 3.5, and 2.2 respectively. The placebo in this trial saw a decrease of 2.3 monthly migraine days. Overall when analyzing the results of this study, we can definitively say that both eptinezumab and galcanezumab are good choices for CGRP inhibitors based solely on the effectiveness when compared to the placebo. There was a decrease of 1.25 between the placebo and the trials involving eptinezumab and galcanezumab. However, erenumab's impact was generally much less apparent in comparison to the placebo. There was actually a greater impact done by the placebo than the 7 mg dose of erenumab. This introduces the important question of whether erenumab should be utilized as a CGRP inhibitor. While one make an argument for erenumab being safer and having less adverse side effects, this is generally true for all CGRP inhibitors, as the study states that those who took any one of the CGRP blockers reported similar side effects. These include upper respiratory tract infection, and injection-site pain. These side effects are much milder than those reported by those who were given topiramate as a migraine treatment (an antiepileptic drug). The side effects of those who took topiramate were much more adverse, such as taste disturbance, weight loss, anorexia, fatigue, and memory problems. The range of monthly migraine day decrease was around 1.8 to 2.6 for the topiramate. When considering the side effects of the CGRP inhibitors to be minimal in comparison to topiramate, as well as the blocking of CGRP being more effective at migraine prevention than an antiepileptic like topiramate, CGRP inhibitors present themselves initially as a popular and safe choice for migraine treatment.

Antiepileptic drugs are also a prominent choice for migraine medication. The main antiepileptics focused on in this study were valproate(divalproex sodium) and topiramate. In the first part of the study, 48% of the subjects who were using valproate as their migraine treatment saw a 50% reduction in the monthly migraine days. The second part of the study as mentioned before saw the 500 mg group's monthly migraine frequency decreased greatly, from 4.5 to 2.8. For the 1000 mg group, the monthly migraine frequency decreased from 4.7 to 2.7. For the 1500 mg group, the monthly migraine frequency decreased from 4.7 to 3.0. When comparing these results to the ones found with the first study involving CGRP inhibitors, we can see that the results are quite comparable, both saw a significant decrease in monthly migraine days. CGRP inhibitors clearly have higher efficacy, eptinezumab 1000 mg saw a decrease of 5.75 monthly migraine days. This is much greater than even the 1500 mg group for antiepileptic drugs, which was a 1.7 monthly migraine frequency decrease. Combined with the fact that CGRP inhibitors tend to have much milder side effects than various antiepileptic drugs,

CGRP inhibitors seem to have a better impact while having less acute side effects when treating migraines. While the first study does offer some data as to how effective the antiepileptic might be, no information is given as to how many migraines the subjects had per month prior to the study, thus rendering the results somewhat inconclusive. When examining the results of the third study, the monthly migraine frequency of valproate decreased from 5.8 to 3.7 monthly migraine days. While this does speak more to the effectiveness of valproate, the decrease is simply miniscule when compared to the CGRP inhibitors. Overall, antiepileptics generally have less positive impact on monthly migraine frequency than do CGRP inhibitors, as well as more adverse side effects as mentioned above.

The third study focused on the impact of utilizing beta blockers as the main treatment for migraines. Propranolol was the main beta blocker utilized in this study, but several others, such as acebutolol, aprenolol, bisoprolol, and metoprolol were also used. These beta blockers yielded impressive results, with propranolol having 1.5 less monthly migraine days per month when compared to the placebo. Acebutolol, aprenolol, bisoprolol, and metoprolol all yield less headaches per month than the placebo by no greater than 0.9 headaches per month. While there is still a decrease in the headaches per month, it is imperative to consider that novel technologies in the form of CGRP blockers yield much better results. Overall, there are significantly less headaches per month, and the side effects are still minimal in comparison to the beta blockers. Propranolol saw an average of 3.4 headaches per month, which is hardly better than the standard placebo, especially when CGRP blockers are offering similar if not better results at minimal adverse effects. However, antiepileptic drugs tend to have more adverse side effects than beta blockers. Antiepileptic drugs tend to cause taste disturbance, memory loss, and fatigue at the very least. This is comparatively more acute than beta beta blockers which mainly cause dizziness and fatigue.

The last study involved the use of specifically galcanezumab and fremanezumab as the primary CGRP inhibitors being studied. Both of the inhibitors saw a great decrease in monthly migraine days when compared to those who took the placebo, 3.1 and 3.5 respectively. The great decrease in monthly migraine days observed in the use of intravenous CGRP inhibitors when compared with both beta blockers and antiepileptics is a clear indication of the CGRP's greater efficacy. It can be observed that the miniscule change of 1.5 monthly migraine day from propranolol, the most effective beta blocker, is still insignificant when compared to CGRP inhibitors. Similarly in antiepileptic drugs, the decrease in monthly migraine days of 1.7-2 is simply much less than that of the CGRP inhibitors studied here.

When observing the information, it is clear that there are less adverse effects brought on by utilizing CGRP blockers, these include tract infections and injection site pain, as compared to the multitude of long term health issues that could arise with the others. This combined with the greater efficacy and less monthly migraine days of CGRP blockers confirm the initial hypothesis that CGRP blockers were more effective and safer as of now. Despite these hopeful findings, CGRP blockers are still novel, and just like many other aspects of neurobiology, a lot about them is unknown. These unknowns include not knowing exactly how binding works, or even how directly CGRP is linked to migraines. One thing is clear however, that CGRP inhibitors are a step in the right direction in completely preventing migraines from affecting people around the world.

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