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Exploring the Use of Vagal Nerve Stimulation as an Alternative to Commonly Prescribed Migraine Medicine

Dhruv Veda

Centennial High School

ABSTRACT

Scholars often define migraine as a headache of varying intensity, often accompanied by nausea, sensitivity to light, and sound (Pescador et al., 2022; Yeh et al., 2018; Weatherall et al., 2015). Migraine is a debilitating disease that affects a sizable portion of humans. Currently, the most common method of treatment for migraines is mediation from drugs such as Ergotamines and Triptans. Although medication is a very common treatment, many alternative treatments exist. Although such medications have varying degrees of effectiveness, they are becoming increasingly common, in part, due to their cost effectiveness and simplicity of use. The purpose of the current work is to summarize the research done on one particularly promising alternative method, namely vagal nerve stimulation (VNS) and propose avenues for further research. VNS comes in multiple forms (auricular, cervical, inserted), each of which are associated with differential levels of effectiveness in reducing migraine symptomatology. Importantly, each form of VNS is also associated with distinct drawbacks as well. The current work suggests that more research is still needed to robustly understand the optimal method of VNS for migraine treatment and how VNS interacts with other treatments (e.g., medication). In addressing these topics, the current work seeks to construct a more robust understanding of the promise and future applications of VNS.

Introduction

Migraine is a disorder present in approximately 12% of all people (Yeh et al., 2018). Migraine also appears more commonly in women than men: approximately 18% of women experience migraines, whereas only 6% of men experience this condition (Peterlin et al., 2014). Of those who experience migraines, 57% experience aura, a sensation which can cause dots or zigzag lines to appear in a patient's field of view. Others face more debilitating symptoms such as pain, sensitivity to light and sound, nausea, vomiting, tiredness, etc. (Pescador et al., 2022; Yeh et al., 2018; Weatherall et al., 2015). Migraines originate from the trigeminal nerve in the face. The main cause of migraine has been traced to a neurotransmitter released by the trigeminal nerve called calcitonin gene related peptide (CGRP). CGRP has specific receptor sites on mast cells (immune cells in the tissue whose build responsible for the inflammation response), neurons, and on the external surface of the blood vessels (Russell et al., 2014). CGRP binding to receptors on mast cells causes the three main symptoms of migraine.

The first major symptom associated with CGRP is inflammation of the meninges throughout the brain caused by CGRP binding to mast cells. Some scholars argue that this reaction gives rise to certain migraine symptoms, such as aura or in some cases the other more specific symptoms such as the vertigo of vestibular migraine (Goadsby, 2017). The second symptom, caused by CGRP binding to neurons, is the pain sensation felt throughout the cranial region which is the main sensation associated with migraine (Pescador et al., 2022; Yeh et al., 2018; Weatherall et al., 2015). Its severity varies on a case-by-case basis. Some individuals with relatively less severe migraine symptoms are able to carry out everyday tasks while experiencing migraine; however, others who experience more severe migraine symptoms are incapacitated even hours after the onset of migraine symptoms ((Pescador et al., 2022; Yeh et al., 2018).The

final symptom is vasodilation caused by CGRP binding to blood vessel walls. It occurs throughout the major intracranial arteries–specifically, in the meningeal and the middle cerebral arteries. There are also reports of superficial temporal arteries dilating as well (Mason &Russo, 2018).

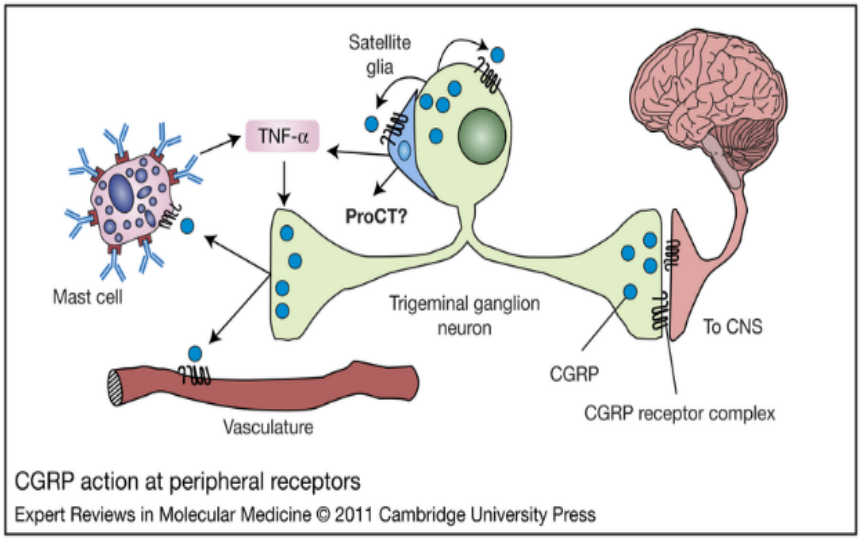

Figure 1 Pathway of CGRP and its receptor sites (Adapted from Russo, 2010, p. 1167)

Migraines are difficult to treat, in part, due to the heterogeneity of severity and type of migraine symptoms experienced across individuals. Migraines can be caused by a variety of different triggers ranging from stress to a change in the weather (Hoffmann & Recober, 2013). This can make it incredibly hard to predict when a migraine attack is going to occur. Importantly, this lack of predictability has shaped how migraine medications work. Many medical treatments must either block the onset of migraine symptoms over long periods of time (increasing the probability that migraine onset will occur within a given window) or acutely treat migraine symptoms when they occur (Booth, 2022). As previously mentioned, migraine symptoms can also vary. Whereas some migraines (i.e., vestibular migraines) are often associated with vertigo (Dieterich, 2016), other migraines (i.e., ocular migraines) are typically associated with pain sensation around the eyes (Metcalf, 2022). Such variation can cause a serious challenge with regards to treatment (Hoffmann & Recober, 2013) as these individual symptoms sometimes require separate treatment from specialized medication (Metcalf, 2022).

Acute migraine treatment (medicine taken after symptoms begin to occur) works by reversing the physiological symptoms in your brain such as cranial vasodilation and inflammation of the meninges tissue within the brain (“Treatment Migraine”, 2019). Acute drugs work in one of three ways. Drugs are classified based on these ways into classes known as CGRP blockers, Receptor Blockers, and tricyclic antidepressants. The first two classes of medication either bind to CGRP (the neurotransmitter that induces migraine) itself or they bind to the receptors that CGRP binds (Booth, 2022). This binding stops CGRP from binding to its receptors either by blocking the open receptors or changing the shape of CGRP and making it unable to fit onto the receptors. Researchers identified the binding portion of CGRP as a(R)-Tyr-(S)-Lys dipeptide chain (Rudolf, 2005). Both forms of medication attempt to either cover the point that this chain attaches to on the receptor itself or cover the dipeptide chain on the molecule itself by binding to it. Such binding facilitates stopping symptom onset due to the blockage of the signal transduction pathway (the pathway by which chemical signals travel into the cell). For instance, Triptans work by blocking the brain pathways that cause the vasodilation in the brain by binding to the CGRP receptors found on the walls of blood vessels. The third class of medication often given to patients are called tricyclic antidepressants. The purpose of these drugs is to allow for more serotonin release in the brain which causes vasoconstriction. However, they have a lower efficacy than most other medications as these drugs treat the symptoms and not the source (Booth, 2022).

Although the use of many medications in the treatment of migraine is popular, the most prescribed are Ergotamines and Triptans (Kamin, 2019). Ostensibly, this trend stems from the fact that Ergotamines and Triptans are relatively more effective in relieving migraine-related symptoms than other medication types (Chun-Pai et al., 2021). Of the two aforementioned medication types, Triptans are by far the most commonly used due to their superior ability to reduce migraine symptoms. Recent work (Chun-Pai et al., 2021) supporting this claim examined the efficacy(reductions of migraine per month) of different medications. More specifically, they compared Triptans, Ditans, and Gepants. The main difference between these drugs is that, although they are all CGRP blockers, Triptans block vasoconstriction in the brain while ditans and gepants do not. Relife (a patient reporting lack of symptoms) was used as a measure of effectiveness after 30 minutes. Triptans had the highest efficacy (up to 10% more than other drugs, mainly CGRP blockers) out of these drugs (Yeh et al., 2018). Another group (Cameron et al., 2015) conducted a review about the effectiveness of Triptans and Ergotamines versus other CGRP blockers such as NSAIDAs, ASA, and acetaminophen. Rates of efficacy marginally differed across groups of medications. Specifically, Ergotamines were 38% effective at relieving headaches for at least two hours at relieving the symptoms of a migraine within two hours, while Triptans were anywhere from 4% to 38% more effective than the CGRP blockers. Both Triptans and Ergotamines achieved better outcomes than other individual drugs or combination therapy which uses multiple drugs in order to treat symptoms more quickly (often consisting of a CGRP blocker and a pain reliever with extra determination on a case-by-case basis). Multiple other studies have also reached similar conclusions. For example, a study concluded that the highest efficacy forms of migraine medication were seven specific Triptan types and discovered the fastest acting was sumatriptan (Hou et al., 2019). A separate study also found that sumatriptan and rizatriptan were among the only medications providing more than 24-hour relief (Thorlund et al., 2013).

Although Ergotamines and Triptans are effective solutions, they have some drawbacks. For instance, some past work has demonstrated a link between taking Triptans and Ergotamines (individually) and adverse cardiovascular events as well as other serious ischemic events, such as heart failure and stroke. One study in support of this idea (Roberto et al., 2014) suggests that patients who had intensive Ergotamine consumption (using more than the prescribed dosage on more than half of the days in a week) were approximately two times more likely to experience ischemic events compared to patients who did not take Ergotamines. Another idea explored was the correlation between the consumption of Triptans and Medication Overuse Headaches (MOHs). Researchers define MOH as a secondary headache that develops from the use of Triptans, Ergotamines, or opioids that occur 10 days a month for more than three months (Takahashi et al., 2021). Researchers have identified the main cause of secondary headaches as damage to the prefrontal cortex of the brain. Beccerea and colleagues (2015) explored this topic by administering sumatriptan (a variety of triptan) to rats through osmotic minipumps; a control group received saline infusions. The rats had magnetic resonance imaging (MRIs) recorded to assess the damage to the prefrontal cortex. After prolonged Triptan use, rats experienced migraine symptoms such as sensitivity to light and repeated activation of the cortical and subcortical networks by the drug which seemed to be the cause of more MOHs. Relatedly, in a different line of work (Takahashi et al., 2021) researchers detailed the current understanding of MOHs as the human body develops a resistance to Triptans and Ergotamines. The most common treatment is to take more medication which becomes untenable due to both health concerns of addiction and the cost of medication. Another line of work provides a general outline of the debates in the medical community surrounding MOHs. Although researchers understand that they can be developed from medication used to treat either migraine or cluster headaches. The exact reasoning for why the occurrence is not fully understood but the basic premise of the brain developing a resistance is widely accepted (Takahashi et al., 2021).

Vagal Nerve Stimulation as an Alternative to Acute Medication

As mentioned in the aforementioned section, acute medication is moderately effective at reducing the negative side effects associated with migraines (Takahashi et al., 2021; Roberto et al., 2014). Despite the efficacy of these medications, some drawbacks exist as well. Perhaps due to these drawbacks, practitioners and researchers alike have begun to turn their attention to understanding the viability of alternative methods to treat migraines. While multiple alternative methods exist, research suggests that one such alternative method–namely, Vagal Nerve Stimulation (VNS)–may be especially promising. VNS involves stimulating the Vagus nerve to induce a response in the brain (Krahl & Clark, 2012).

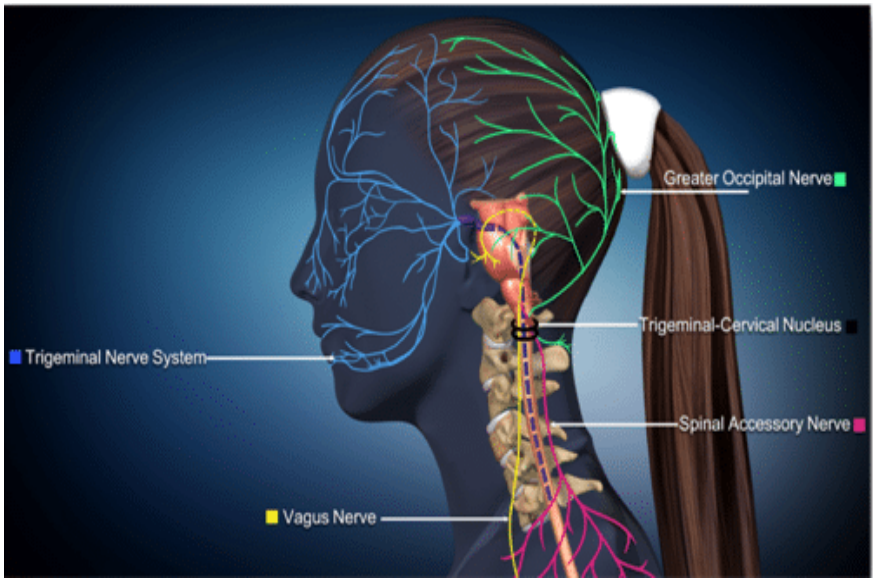

Figure 2 Interface between Trigeminal and Vagus nerves (Trigeminal nerve distribution, n.d.)

One of the most important parasympathetic nerves in the body is the Vagus nerve. The electrode placed around it stimulates the opening of voltage gated ion channels which stimulates an action potential in the Vagal nerve. This destimulates the areas responsible for depression or seizure (i.e., the brain biogenic amine pathways). Due to this, it is often used in the treatment of seizures, and it can also be used to treat depression. Since antidepressants were used as a treatment for migraine due to their ability to cause cranial vasoconstriction, many researchers have hypothesized VNS could also be used the same way. Several lines of research provide support for this possibility.

Although there are multiple types of VNS, few studies have addressed how the efficacy of various NVS methods compare to one another . One line of work examined the efficacy of non-invasive VNSs in migraine treatment (Najib et al., 2022). Here, patients filled out a four-week journal of their migraines in which they were expected to log any migraines they experienced, and what possible triggers occurred. During this period, the experimental group received non-invasive VNS and the control group received a form of stimulation with little physiological impact. Participants who received VNS reported significantly fewer migraines than those in the control group. On average, those who had received VNS treatment indicated approximately three fewer migraines than those in the control group. Another paper also investigated the efficacy of VNS as a migraine treatment option. The researchers gathered patients with varying levels of migraine intensity and frequency and gave some VNS treatment while the control group received nothing. The average reduction for the group that received VNS was 1.4 days of migraine reduction which further supports the use of VNS as a treatment of migraine (Silberstine et al., 2016).

There are multiple variations of VNS, more specific than what was mentioned above, used for migraine treatment each with its own varying benefits and drawbacks. Of the multiple types of VNS, three have been used for migraine with varying degrees of success. The first of these three is inserted VNS. Inserted VNS uses a pre-existing treatment in which an electrode is inserted into the neck and coiled around the Vagus nerve (Krahl &Clark, 2012). The electrodes are coiled around the Vagus nerve and they open the voltage gated channel by direct contact with the nerve itself. A study exists (Mosqueria et al., 2013) looking into the concept of using inserted VNS as a treatment for migraine. Many patients that already had implants for their seizures as well as having been diagnosed with migraine were chosen for the study. The study was done using retrospective data collected over many years. The study found that patients with inserted VNS had up to a 50% reduction in migraine days .

Another VNS method is transcutaneous VNS (tVNS) which involves placing an electrode on the skin rather than using an implant (“About gammaCore”, 2010). tVNS can be further subdivided into multiple other types based on the location that the electrode is placed at. One of the most viable for migraine treatment is cervical tVNS(ctVNS) which positions the electrode on the neck overtop the location of the Vagus nerve. The main difference is that the electrode sits on the surface of the skin, in order to activate the voltage gated channels, it uses a gel to reduce the space between the electrode and the skin which conducts into the nerve. One line of work used the gamma core ctVNS product in order to check the effectiveness of it as a migraine treatment. Some patients were given the ctVNS treatment while the control group was given nothing. The study found that the treatment only worked on around half of the patients while others felt no change. Those that did experience a change had up to seven migraines less per week–a statistically significant decrease from those in the control group (Magis et al., 2012). This shows a high effectiveness of this form of treatment.

Another form of tVNS is auricular tVNS or atVNS which involves placing the electrode on the ear. The optimal position is believed by researchers to be just above the ear canal, and it is well known to stimulate the Vagus nerve (“About gammaCore”, 2010). There are multiple studies concerning its viability as an acute migraine treatment. Researchers conducted a clinical trial on patients that had been previously diagnosed with migraines. Patients who received atVNS treatment had, on average, 3.3 headaches less than the control group over the 28 day period (Straube et al., 2022). Another study (Zhang et al., 2019) also demonstrated the efficacy of the atVNS approach. Here, patients were given MRI scans every week and viewed the effect on the brain associated with migraine. Their study concluded that atVNS deactivates the necessary neurological pathways (the Default Modal Network which contains locus coeruleus, raphe nuclei, parabrachial nucleus, and solitary nucleus) to treat migraine while the control group had activity in those parts of the brain.

In addition to thinking about efficacy, there are other considerations that would factor into a migraine treatment plan involving VNS. ctVNS and atVNS are noninvasive and can cause a minimal amount of discomfort to the patient for an effective cure. Inserted VNS also has a very high efficacy as shown in the earlier section which compensates for the slight discomfort. Another key variable to consider is cost effectiveness. Inserted VNS has a high cost due to the surgery required to place the electrode around the Vagus nerve (“Vagus Nerve Stimulation (VNS) Implantation for Children”, 2009). However, there was a study conducted (Morris et al., 2016) to show the cost effectiveness of noninvasive VNS (nVNS). A one-year estimate was conducted on the cost of nVNS versus the control of zero treatment. They analyzed multiple types of nVNS and compared the costs. Researchers found it can cost around seven thousand euros a year which is much less than most other treatment methods.

To recap all that has been said about VNS, Inserted VNS has the highest efficacy (as studied independently of one another) but also the highest cost which may discount its viability. Although, both forms of nVNS seem viable with low costs and high efficacies.

General Discussion & Future Directions

There has been groundbreaking work in this area; however, the current information that we have on VNS and migraine is extremely limited and the research that has been conducted has an extremely limited sample size. The smallest study cited has a sample size of only 13 patients while the largest has around 113. This is due to the high efficacy of current medication. Before any implementation of VNS or other alternate treatments, further research must be done to fill in our large information gap. There are a few avenues for this research to explore.

One of the key research avenues that has yet to be explored is testing the different types of VNS against one another in the same experimental paradigm. Currently, studies proving effectiveness have focused on a single type of VNS intervention. Therefore, it is hard to understand the relative efficacy of VNS intervention types. Testing in the same paradigm will allow for some measure of relativism. Another gap is the lack of a comparison of VNS and traditional acute migraine medication such as the previously mentioned Triptans and Ergotamines. There was a serious difference in the amount of information we have on traditional medicine with the largest study about acute medication cited(Chun-Pai et al., 2021) having almost 10 times the sample size of the largest VNS study. A potential study to fill this information gap could be a clinical trial in which a large field of volunteering migraine patients were taken as the sample size. The control group (one fifth) of the study would be given no prescription, and the remaining test subjects would be evenly divided, and each group will then be given either inserted VNS, atVNS, ctVNS, or traditional Triptan medication. If this was conducted on a large scale, the expected result would be that Triptans or inserted VNS have the highest efficacy (measured in average reduction of migraines over the given time period) but all four methods(inserted VNS, atVNS, ctVNS, and Triptans) would have very similar efficacies if they performed similarly to how they acted in studies when tested isolation(Cameron et al., 2015)(Thorlund et al., 2013)(Mosqueria et al., 2013)(Magis et al., 2012)(Straube et al., 2022)(Zhang et al., 2019).

Another consideration of this study would be the cost effectiveness of each method could be calculated as some combination of reduction of migraines over the given time period and cost over that time period. This study would need to be conducted for a longitudinal period of time (up to a year) and the expected result would be ctVNS or aVNS having the highest efficacy by a larger margin. The main reasoning for this is due to the high cost of inserted VNS as it requires surgery (Krahl and Clark, 2012) and the study conducted (Morris et al., 2016) showing the high effectiveness.

Another key area of research could be the implementation of VNS not as a separate treatment for migraines but instead used in combination with acute medication such as Triptans for a greater reduction in migraine days. This area of research has not been explored but an experimental set up to test this might look like the following: A sample of volunteer migraine patients would be selected. Similarly to the previous study, the control group would be given no treatment. Of the experimental groups, one would be given only VNS, and one would be given only acute medication. The main experimental group would be given a combination treatment of both VNS and acute medication, the specific types would be determined by studies. The result needed to justify VNS implication would be a significant reduction in headaches for the experimental group.

In addition to more thorough testing to clarify the efficacy of VNS interventions, future work should focus on how VNS interventions may be practically implemented. If we were to reach this point the next logical step would be the optimization of the design for day-to-day use. This would require three main steps: making the VNS treatment cost effective, having lightweight materials, and a more streamlined design for devices. The current most portable and lightweight design is gammacore(O'Connell, 2021). Gammacore takes advantage of ctVNS and is small enough to fit inside of a small personal bag such as a purse. This design fulfills many of the criteria needed for a viable treatment; however, an issue for some may be its relatively high cost of $200 every three months. Gammcore will continue to work on the idea of VNS but as a way to lower its cost and make it more widely usable. Due to the fact that migraine affects 12% of the world population (Yeh et al., 2018) migraine sufferers come from a wide financial background. This leads to the logical conclusion that migraine treatment should be readily available for a wide range of migraine

patients and a focus should be put on trying to find more readily available substitutes for the materials used in the device.

Although the advancements in the field have been rapid and effective, there are serious concerns with how portable a VNS setup can be and how expensive they can be. Outside of the gamma core there could be a device built to take advantage of atVNS in a similar fashion. The idea would depend on a portable setup that could easily be fitted by a patient to their ear at the first sign of symptoms. The feasibility of such an endeavor can be compared to the creation of a hearing aid which uses a similarly complex design and is fit into a small area(Hearing Aids, 2013). The design would require a battery and an electrode which would need to be positioned on the correct point within the ear(as mentioned earlier). These designs would also need to use cost effective materials as mentioned above so readily available metals as well as plastics would be the logical choice.

In sum, future work in this field can center around filling the gaps in our knowledge through experimentation testing all types of VNS in one experimental paradigm and testing VNS in combination with acute medication(triptans). The increase in testing by following these steps would be able to affirm that VNS could be effectively used as a widespread treatment; we would then work on streamlining its design and making it more cost effective.

Data Collection Process

The topic of migraines is a personal area for me as myself and many of my family members suffer from it. My goal with this paper was to create a review of the information that we already had available of VNS and migraine. In order to gather the necessary information, I began by reading all publicly available papers on current migraine treatment as well as the currently available alternate treatments. After realizing the viability and promise of VNS I emailed multiple experts in the field and received responses from Dr. Eric Libeler, an expert with atVNS and migraine, and Professor Andreas Straube, an expert with noninvasive VNS. They were able to point me towards multiple research papers that had been conducted on the subject as well as the product of gamma core which is at the forefront of the field currently. From here I was then able to contact Armin Bolz, the general manager of gammacore who referred me to a large bank of literature that I could use in this study.

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Figure 1. CGRP action at peripheral receptors [Graph illustration]. Adapted from Russo, A. (2010). Journal of Neurochemistry, 112(5), 1165-1179. https://doi.org/10.1111/j.1471-4159.2009.06560.x

Figure 2. Trigeminal nerve distribution with TCN, vagus, and spinal accessory nerves [Illustration]. Retrieved from https://centennialfamilychiro.com/wp-content/uploads/2020/03/Trigeminal-nerve-distribution-with-TCN-vagus-and-spinal-accesary.png

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