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Abstract

Worldwide migraines affect millions of people everyday causing significant impact on patient's lives. Oftentimes, these patients have failed several first-line therapies for migraine prophylaxis causing pharmaceutical companies to develop newer therapies. The purpose of this systematic literature review is to evaluate the effectiveness and tolerability of transcutaneous electrical nerve stimulator (TENS) devices versus calcitonin gene related peptide (CGRP) antagonists in the application of migraine prophylaxis. PubMed and ClinicalKey were searched with key terms, 17 sources were selected that were published after 2016. Sources included meta-analysis, literature review, and randomized control trials. The data showed that TENS devices as well as CGRP antagonists were effective and safe therapy options for migraine prophylaxis. TENS devices and CGRP antagonists work on different neural pathways giving them synergistic properties when paired together. More longitudinal research needs to be conducted to further evaluate the efficacy and safety profile of long-term use of these therapy options.

Introduction

Migraine headaches impact millions of people worldwide causing devastating outcomes in overall health and life satisfaction. Current literature reports approximately 16% of the world's population suffers from daily migraines (Stovner et al., 2022). Furthermore, there are numerous theories that explain the pathophysiology of migraines. First, the vascular theory argues that migraines result from variations in cerebral blood flow caused by vasodilation and vasoconstriction (Pescador Ruschel, 2022). More recent theories suggest that neural connections are responsible for migraine symptoms. Specifically, depolarization of trigeminal neurons causes a release of pro-inflammatory cytokines resulting in meningeal irritation and migraine pain (Pescador Ruschel, 2022). Additionally, calcitonin gene related peptide is located in trigeminal neurons and when released produces vasodilation secondary to nitric oxide release, ultimately leading to inflammation within the central nervous system (Pescador Ruschel, 2022). Emerging therapies for migraine headaches have been newly developed in recent years including neuromodulation devices and calcitonin-gene related peptide antagonists. Both treatment options effectively target the underlying physiology of migraine and have been found effective in migraine prevention.

Neuromodulation devices such as the non-invasive vagus nerve stimulators have been found to be effective in episodic and chronic migraine prevention. This type of neuromodulation modality targets the vagus nerve at the neck through transcutaneous electrical impulses. nVNS stimulation leads to slowing of cortical depression by increasing serotonergic and beta-adrenergic activity leading to a reduction in migraine days (Chen et al., 2016). Another common target for neuromodulation devices is the supraorbital nerve branch of the trigeminal nerve. The transcutaneous supraorbital nerve stimulators (tSONS) target the anterior branch of the trigeminal nerve over the forehead preventing release of neuroinflammatory peptides

ultimately reducing migraine days (Chen et al., 2016). A second group of emerging therapies for migraine are the CGRP antagonists. Administered in monthly injections, these medications prevent the release of calcitonin gene related peptides and prevent subsequent vasodilation and release of inflammatory cytokines (Chen et al., 2016). Overall, neuromodulatory devices and CGRP antagonists are effective in reducing monthly migraine days and were well tolerated in the studied populations. Current clinical knowledge lacks standardized guidelines on when to employ these therapies. VNS, tSONS, and CGRP antagonists are clinically effective and safe treatments for the prevention of episodic and chronic migraine.

Statement of the Problem

Migraines impact millions of people worldwide and have become more common over recent decades. Individuals aged 20-64 years of age are most likely to suffer from this potentially debilitating condition. Current treatment options do not serve as a cure, leaving many individuals suffering from this chronic condition. Newer treatment options such as TENS device therapy have recently been developed targeting neural pathways and pain processing centers within the brain to reduce migraine frequency. CGRP antagonist medications have also emerged, targeting a neuroinflammatory peptide to reduce inflammation and frequency of migraines. Both therapies are relatively new leaving healthcare providers questioning the efficacy and side effects of these treatment options.

Research Question

In adult patients with migraine headaches, what is the effect of transcutaneous electrical nerve stimulation (TENS) as treatment for migraine prevention compared to calcitonin gene related peptide (CGRP) antagonists?

Methodology

A literature review was performed using the electronic search database, PubMed. Keywords and mesh terms were used to define literature evaluating the effectiveness of transcutaneous electrical nerve stimulation (TENS) devices as treatment for migraine prevention compared to CGRP antagonists. Studies included were meta-analyses, literature reviews, randomized clinical trials, and clinical observational studies. Literature was systematically searched for migraine prevalence, vagus nerve stimulation, trigeminal nerve stimulation, supraorbital nerve stimulation, and CGRP antagonists all in individual searches. The resulting articles were thoroughly analyzed and were chosen based on applicability. All the articles were published within the last 10 years, with the majority of the articles being published since 2016. Search totals resulted in 388 studies for “migraine prevalence”, 1,679 studies for “neuromodulation migraine”, 38 studies for “TENS migraine”, 391 studies for “vagus nerve stimulation”, 201 studies for “trigeminal nerve stimulation”, 89 studies for “CGRP antagonist”, and 48 studies for “supraorbital nerve stimulation.” Numerous studies were excluded due to focusing on *invasive* electrical nerve stimulation, *magnetic* nerve stimulation, acute migraine treatment relief, and cluster headaches. Additional studies were excluded due to evaluating combination therapies including oral CGRP antagonists and intramuscular CGRP antagonists, as well as combination neuromodulation therapy with occipital and trigeminal applications. All studies not in English were excluded. Thirteen studies met criteria for non-invasive vagus nerve stimulation for migraine prevention, eight studies met criteria for supraorbital nerve stimulation for migraine prevention, and 31 studies met criteria for CGRP antagonist for migraine prevention. Zero studies met criteria for neuromodulation comparative studies with CGRP antagonists.

Literature Review

Prevalence of Migraine

Stovner et al. (2022) conducted a narrative review involving 357 publications to summarize the international presence of all headache, migraine, tension headache, and headache > 15 days per month. Inclusion criteria included PubMed studies focusing on non-clinical samples and population based studies. The goal of the narrative was to evaluate data from these specific sources to broadly capture headache prevalence internationally. As a result, inclusion criteria was broad and included population based studies originating from epidemiological studies, health registers, and hospital data. Exclusion criteria filtered out studies with conflict of interest, bias, and clinical studies. Patient demographics were variable due to broad inclusion criteria. The mean adult age from the reviewed studies was calculated to be 20-85 years of age. The narrative focused on reporting the prevalence for all headaches, migraines, tension headaches, and chronic headaches lasting > 15 days. Headache timelines included one year, six month, three month, and current headache ranges. Additional time frames included headaches now and headaches yesterday.

The primary outcome of the narrative was to determine global prevalence of headache, revealing 15.8% of the world's population suffers from daily headaches. Populations studied from the 357 identified articles found headache to be prevalent in 52% of participants, consisting of 44% males and 57.8% females. Tension type headaches accounted for 26% of headaches (males 23.4%, females 6%) and were most prevalent in age groups 20-64 years of age in both genders. Migraine headaches accounted for 14% (females 17%, males 8.6%) and were most prevalent in age groups 20-64 years in females, with males aged 10-19 years with highest migraine prevalence. Chronic headaches lasting > 15 days included 4.6% of headaches (females

6%, males 2.9%). Overall, headaches were more common in females specific to migraine (females 17.0%, males 8.6%) and chronic headache > 15 days (women 6.0%, males 2.9%). The least amount of observed gender differences were in the age group 0-9 years. Secondary outcomes noted an increase in prevalence of headache from 46% to 52% based on data from 2007 summaries. Additionally, migraine and chronic migraine > 15 days also increased in prevalence (migraine 11% to 14%, H15+ 3% to 4.6%). Tension type headaches actually decreased based on these comparisons from 42% to 26%.

Shortcomings of the narrative were noted throughout studies including lack of adequate population demographics. Numerous studies failed to identify median ages of participants, with studies having unequal representation of male and female. The screening questions to obtain data were not standardized across studies. Some studies used 1-year prevalence timelines, while others used 3-6 months, suffering from headache currently, and lifetime headaches with no time specification. Additionally, researchers identified an association with smaller studies and increase in chronic migraine prevalence. This was to be believed that the lower number of participants allowed for more sensitive data acquisition. Lastly, less than 30% of variability could be attributed to variables in the studies suggesting influence that is not recognized or measured (Stovner et al., 2022).

Katsarava et. al (2012) reviewed population based studies to evaluate the burden of chronic migraine versus episodic migraine. The researchers acknowledge that chronic and episodic migraines are on the same migraine spectrum, but define distinct characteristics between the two conditions. Since episodic and chronic migraines are differentiated by clinical data, the international classification of headache disorders criteria was used defining migraine without aura to consist of recurrent headaches, unsuccessfully treated headaches lasting 4-72

hours, and unilateral, pulsating headaches with moderate to severe intensity, and aggravated by daily physical activity. Episodic migraine was defined as having 0-14 headaches per month, whereas chronic migraine was defined as 15 or more headache days per month for more than three months. Episodic migraine progresses to chronic migraine at a rate of 2.5% per year, while 26% of chronic migraine will revert to episodic migraine after two years.

The primary outcome of the review found that in the United States and Europe, 6-8% of men and 15-18% of women suffer from migraines annually. Episodic migraines were more common in women at 17.1% compared to 5.6% for men. The average age of onset for episodic migraine was 46.0 years consisting of 80% women and 87.3% consisting of Caucasians. Severe episodic migraines were reported as 78.1% of total migraines, with the mean duration of headache lasting a total of 38.8 hours. The duration of episodic migraines with use of medication dropped to 12.8 hours in duration. Comorbidities impacting episodic migraine consisted of depression (17.2%), anxiety (18.8%) and obesity (21.0%). Chronic migraines were also more common in women at 1.3% compared to 0.5% for men. The average age of onset for chronic migraine was 47.7 years consisting of 78.6% of women and 90.7% of Caucasians. Chronic migraine was most prevalent in women aged 40-49 consisting of 1.9%. Severe chronic migraines were reported 92.4% of the time, with mean chronic migraine duration without medication lasting 65.1 hours. Mean chronic migraine duration with medication lasting 24.1 hours. Overall, chronic migraine makes up 7.7% of the total migraine population.

Secondary outcomes measured sociodemographics, individual burden, and economic burden between episodic and chronic migraines. Chronic migraines were more prevalent in lower household income levels, these subjects had lower prevalence of full time employment and higher rates of being occupationally disabled. Individuals suffering from chronic migraines were

also significantly more likely to have a range of comorbidities. Chronic migraine sufferers were found to have a higher mean body mass index (BMI) of 25.9 for versus mean BMI of 24.1 for episodic migraine sufferers. Depression was also linked to chronic migraine in 30.2% of cases versus 17.2% of episodic migraine cases. Additionally, anxiety was found in 30.2% of chronic migraines, whereas anxiety was only found in 18.8% of episodic migraines. Individual burden for chronic migraine was evaluated through observational studies. The Headache Impact Test-6 (HIT-6) was used to assess individual burden between chronic and episodic migraines. 72.9% of individuals suffering from chronic migraine were classified as having a severe impact on their daily lives, whereas 42.3% of individuals suffering from episodic migraines were classified as severe impact on daily life.

Shortcomings and biases were not mentioned in the study. Lead investigator Katsarava currently serves as a consultant to Allergen, a pharmaceutical company, that provided funding to publish the review causing a conflict of interest. To conclude, both chronic migraines and episodic migraines have a substantial impact on life. Chronic migraine has been shown to have a greater negative effect on individuals' burden, socioeconomic burden, and overall health profile of individuals (Katsarava et al., 2012).

Application of TENS Therapy in Migraine Prevention

Cheng et al. (2022) conducted a meta-analysis of randomized controlled trials (RCTs) involving 19 articles and 1493 participants evaluating the effectiveness of noninvasive nerve stimulation for migraine prophylaxis. Inclusion criteria consisted of only RCTs involving human subjects with episodic and chronic migraines. Interventions included non-invasive brain/nerve stimulation with sham control comparisons. Studies were excluded if they were not specific to migraine, were not randomized clinical trials, and lacked outcomes supporting interest.

Publication bias was reported, finding that 82% of studies had low bias whereas 9% of studies had high risk of bias. The average age of the patient was 38.2 years with 82% of participants being female. Recruited participants within selected studies had at least two migraines per month or chronic migraines. The number of average migraines per month in experimental groups ranged from 7.6 ± 3.7 to 20.8 ± 5.0.

The primary outcome of the study was to compare noninvasive brain and nerve stimulation therapy efficacy in migraine prophylaxis measured by reduction of monthly migraine days in patients. Transcranial direct current stimulation (tDCS) over the right parietal region anode had the greatest reduced monthly migraine days by 8.73 days at 95% CI. Specifically, transcutaneous auricular vagus nerve stimulation (taVNS) reduced monthly migraine days by 1.90 days with 95% CI. Percutaneous electrical nerve stimulation (PENS) reduced migraine days by 1.5 days, 95% CI. Response rates were also studied showing high frequency transcutaneous occipital nerve stimulation (hf-tONS-Oz) yielding the highest response rate when compared to all other neuromodulating interventions. hf-tONS-Oz displayed response rate; (RR = 9.00, 95%CIs: 1.24 to 65.16), compared to percutaneous electrical nerve stimulation over left frontoparietal (FP1) and right frontoparietal (FP2) locations (PENS-Fp1Fp2); (RR = 3.00, 95%CIs: 1.09 to 8.29), high frequency rTMS over left frontal lobe (F3) location (hf-TMS-F3; RR = 2.41, 95%CIs: 1.58 to 3.68). Subpopulations between chronic migraines (migraine days >15 days/month) and episodic migraine (migraine days < 15 days/month) were further evaluated. Patients experiencing episodic migraine had the greatest response rate to taVNS reducing migraine days by 1.80 days per month 95% CI when compared to control/sham groups. None of the non-invasive brain stimulation therapies were associated with significant response rate

findings in chronic migraine. In the episodic migraine subgroup there were significantly more positive response rates when compared to placebo groups.

Secondary outcomes were measured in studies noting reduction in migraine pain severity and reduction in use of rescue medication for migraine. Results showed the greatest standardized mean difference (SMD) in migraine severity reduction with transcutaneous direct current stimulation followed by transcutaneous occipital nerve stimulation and vagus nerve stimulation

Groups between the RCTs had limitations due to study design differences including patient characteristics, medical history, concurrent medications, and trial duration. Some studies had small sample sizes, resulting in less reliable findings. Overall, this study was effective in showing hf-TMS-C3 was associated with the most effective reduction in migraine days, whereas hf-tONS-Oz was associated with the greatest response rate (Cheng et al., 2022).

Patel et. al (2021) conducted a review of randomized controlled trials evaluating the efficacy of electrical nerve stimulation (ENS) including vagus nerve stimulation (VNS) and supraorbital transcutaneous nerve stimulation (SONS). Initially, 232 randomized controlled trials were identified and published between 2015 and 2021, with 18 studies making up the final systemic review. These studies focused on electrical nerve stimulation and migraine headaches. Studies that were excluded lacked relevance or were duplicated results. The primary outcome of the study was to evaluate the efficacy of VNS and TNS modalities for migraine prevention. Review of VNS studies revealed that non-invasive VNS (nVNS) was superior to sham control devices in reducing acute migraine pain at 30 minutes and 60 minutes. nVNS was also found to be effective in reducing monthly headache days by an average of 2.27 days compared to 1.53 days for the sham control group ($p = 0.0043$). Another nVNS study achieved a 7.9 day reduction in monthly migraine days ($p < 0.01$). With regards to tSONS therapy, an average of 1.32 day

reduction in monthly migraine days was achieved. Additionally, SONS therapy reduced the number of acute medication days by 0.92 days. Study outcomes demonstrated a range of ENS device applications ranging from acute migraine therapy, preventative migraine therapy, and reduction of use of acute migraine medication.

After review of the included studies, there was a consensus that ENS was effective as treatment for those with chronic migraine. Therapeutic benefit was seen in acute and chronic applications, both reducing migraine pain and reducing the occurrence of future migraines. In one study, participants suffering from migraine without aura showed greater benefit of ENS. Other studies did not demonstrate a clear trend with migraine subtypes of ENS benefit. Overall the ENS devices were well tolerated and displayed a low side effect profile. Comparative studies showed that ENS devices reduced cost for migraine treatment by $1,577 compared to conventional treatments for migraines. To conclude, previous reviews have shown inconclusive results. ENS device technology improvements have allowed more benefits to be documented and show future promise in treating migraines (Patel et al., 2021).

Efficacy of *Vagus* Nerve Stimulation for Migraine Prevention

Diener et. al (2019) conducted a randomized clinical trial to evaluate the effectiveness of non-invasive vagal nerve stimulation (nVNS) in reducing migraines. The masking of the trial was double-blinded, and included 12 weeks of nVNS treatment compared to sham control. The study involved 477 participants with 332 participants meeting criteria for treatment. Inclusion criteria consisted of migraine onset that was < 50 years of age, with an average of 5-12 migraine days per month in the previous four months. Exclusion criteria consisted of previous diagnosis of chronic migraine, medication overuse headaches that regressed to episodic migraines in the previous six months, and conditions requiring treatment with steroid medications. Patients with a

history of secondary headaches, aneurysms, intracranial hemorrhages, seizures, brain tumors, and cervical spine hardware were excluded from this study.

The patient population ranged in ages from 18 to 75 years of age. The participants were predominantly female, making up 86.1% of the nVNS group and 82.6% of sham control. The average mean age for nVNS therapy was 43.5 years, and the mean age receiving sham control was 41.4 years. The nVNS therapy population consisted of 138 participants with baseline monthly migraine days of 7.9 days. This was compared to the sham control of 140 participants with 8.1 monthly migraine days. Participants received structured therapy consisting of 120 second stimulations to the neck bilaterally three times per day.

The primary outcome of the trial demonstrated a reduction of monthly migraine days in individuals who received nVNS therapy. Migraine days were defined as a migraine occurring within a 24 hour period. Mean reduction of monthly migraine days in nVNS group was 2.26 and 1.80 for sham ($p = 0.15$). Reduction in monthly migraine days >50% was seen in 31.9% for nVNS group and 25% ($p = 0.19$) in the sham group. Response rate > 50% in migraine reduction occurred in 33.6% of nVNS group and 23.4% of sham control group. Greater therapeutic gains were seen in participants who experienced migraine with aura, reducing monthly migraine days by 2.83 compared to reducing migraine without aura days by 2.22 ($p = 0.15$). Researchers believe the mechanism responsible for greater reduction in migraine days with aura is the nVNS effect on cortical spreading depression (CSD), defined as suppressed brain activity following wave depolarization nVNS devices have shown to reduce CSD, improving benefits in participants experiencing migraine with aura.

Secondary outcomes included reduction of headache days and use of acute medication days were evaluated. Headache days were defined as any headache occurring within a calendar

day. Response rate >50% to nVNS therapy for headaches was 28.5% ($p = 0.57$) with a 2.73 day reduction in monthly headache days ($p = 0.10$). Compared to the response rate > 50% to sham control was 28.5% response rate with a reduction of 2.11 days ($p = 0.10$) in monthly headache days. Baseline headache days were reported at 9.1 headaches per month. Acute medication days were reduced in the nVNS group by 1.9 days compared to 1.35 days ($p = 0.14$) in the sham control group. Interestingly, the nVNS group had a higher response rate to migraine relief with acute medication at 30.9% compared to 23.1% of the sham control group. Baseline acute medication days were 6.8 days per month ($p = 0.14$).

Satisfaction between nVNS group and sham control were 77.5% and 73.5% respectively. nVNS therapy was well tolerated with reports of minimal side effects. Usual side effects included application site rash, erythema, and discomfort. No serious adverse events during the trial were reported. Major limitation of the study was the sham device causing vagal activity. The sham device stimulated parasympathetic activity and subsequent vagal nerve stimulation. This was identified as a significant study limitation as the sham device delivered stimulation causing vagal activity, this was likely subtherapeutic and served to provide the patient with physical perception without being therapeutic. Researchers did not investigate the level of sham device excitation further weakening the study. This limitation is consistent with the minimal gain seen in the nVNS group in reduction of monthly migraine days (Diener et al., 2019).

Najib et. al (2022) performed a randomized double blind sham-controlled study consisting of a four week baseline period and 12 week double blind treatment period using non-invasive vagal nerve stimulation (nVNS). Participants recorded headaches in their headache diaries during the four week baseline period. During the 12 week treatment period, 336 participants were initially enrolled and 231 participants were randomly assigned to undergo

nVNS therapy or sham control groups. A total of 113 participants completed the double-blind treatment period. Participants underwent nVNS therapy three times daily in the morning, afternoon, and before bedtime. Treatment sessions consisted of two 120 second stimulations consisting of 5-kHz pulses delivered at a rate of 25 hz, peak voltage consisted of 24V with a maximum output of 60 mA. Overall the treatment period was well tolerated, only one subject withdrew from the nVNS group due to reported adverse effects. Interestingly, four participants withdrew from the sham control group due to adverse effects.

Patient ages range from 18-75 years of age with clinical diagnosis of episodic or chronic migraine, with or without aura using international classification of headache disorders criteria. The vNS group consisted of 56 participants, 23 with chronic migraine and 33 with episodic migraine. The nVNS group mean age was 40.3 years, consisted of 87.55% females, and 71.4% of the group experienced migraines without aura. The sham control group consisted of 57 participants, 23 with chronic migraine and 34 with episodic migraine. The sham control group mean age was 44.6 years, 77.2% females, and 66.7% of the group experienced migraine without aura. Inclusion criteria required subjects to be under the age of 50 when they were diagnosed with migraine and experience 8-20 monthly headache days during the previous three months. Of those monthly headaches, at least five of them must be reported as migraines with headache duration lasting longer than four hours or treated with acute therapy. Subjects using over the counter medications for acute migraine therapy were included in the study. Exclusion criteria included medication overuse headaches that transformed to migraines, suspicion for a secondary migraine disorder, and known or suspected cardiac disease or cerebrovascular disease. Individuals taking more than two abortive therapies in the last six months were also excluded from the study.

The primary outcome of the study measured the mean difference in number of monthly migraine days during weeks 9-12 of the double-blind treatment period. Results showed that participants who underwent nVNS therapy had a baseline 9.2 monthly migraine days and achieved a mean reduction of monthly migraine by 3.12 days ($p = 0.2329$). The treatment population was represented by 23 chronic migraine and 33 episodic migraine participants. Participants experiencing migraine with aura had a more significant response to nVNS therapy with a reduction of 4.04 monthly migraine days ($p = 0.1004$). Oddly, the mean reduction in monthly migraine days without aura was not reported. The sham control group had a baseline of 9.9 monthly migraine days and achieved a mean reduction of monthly migraines by 2.29 days ($p = 0.2329$). The response rate in the nVNS group was significant, 44.87% ($p = 0.0481$) of the nVNS group reached >50% reduction in the number of monthly migraine days, whereas only 26.81% of the sham control group achieved >50% reduction in monthly migraine days . Participants in the nVNS group reduced monthly headache days by a mean of 4.56 days and 3.0 days in the sham control group ($p = 0.0530$).

Secondary outcomes of the study resulted in decreased use of acute medication days, reporting a 2.53 day reduction in the nVNS group and 1.36 day reduction in the sham control group ($p = 0.1132$). Headache burden was measured using the HIT-6 questionnaire, the nVNS group had a significant reduction in headache impact on daily life by a reduction of 4.9 points, whereas the sham control group achieved a reduction of 2.3 points on the HIT-6. Another significant finding was that migraine related disability was also reduced in the nVNS group measured by migraine disability assessment test (MIDAS). Twenty-five percent of the nVNS group achieved a shift from moderate to severe MIDAS classification to mild or none, whereas 9.1% of the sham control group shifted from moderate to severe to mild or none. Lastly, 53.8%

of the nVNS group was satisfied with their treatment, compared to 21.8% of the sham control group ($p = 0.0006$). Ultimately, statistical significance was not achieved in the primary outcome of mean reduction of monthly migraine days, however statistical significance was demonstrated in secondary outcomes such as response rates, HIT-6 scores, and MIDAS classifications.

At the end of the double-blind period, 58% of nVNS participants and 62% of sham control participants guessed their group assignment correctly. Blinding was maintained throughout the study determined by the Bang Blinding Index. Both groups were given devices to suggest they were both receiving treatment. The sham control group was told their devices may produce an audible tone and may experience muscle stimulation when receiving therapy from the sham device. Additionally, the sham device used was completely inactivated and did not produce vagal stimulation, opposite to other vagal nerve stimulation studies. The COVID 19 pandemic did impact the study resulting in early termination of the study. In conclusion, nVNS therapy does have clinical value in prevention of migraines with aura, the study also reinforces safety and tolerability of nVNS devices based on minimal participant attrition secondary to reported adverse effects (Najib et al., 2022).

Silberstein et. al (2016) conducted a multicenter double-blind sham controlled study of the non-invasive vagus nerve stimulation (nVNS) in chronic migraine prevention. The study contained a baseline period of 1 month where participants recorded the quantity and qualities of their headaches. The following treatment phase with nVNS therapy was two months and was compared to the sham control group. nVNS therapy sessions were self-administered in two 2-minute intervals approximately 5-10 minutes apart three times a day, once in the morning, afternoon, and evening. The sham control group was given an identical device that produced zero stimulation and followed the same treatment regimen. Initially 73 participants were enrolled in

the study, 59 participants composed of the intent to treat the population and 27 participants completed the study. The nVNS group consisted of 30 participants, and the sham control group consisted of 29 participants. Inclusion criteria required participants to have a previous diagnosis of chronic migraine before the age of 50 years, and suffered > 15 headache days per month in the previous three months. Use of acute medication for headache was allowed throughout the study. Exclusion criteria disallowed participants with a history of cerebrovascular disease such as aneurysms, tumors, and stroke. Additionally, participants with history of cardiovascular disease, uncontrolled hypertension, and recent myocardial infarction were excluded from the study. Implanted cervical devices or devices near the site of stimulation were also excluded from the study. Participants who changed prophylactic migraine treatment medications in the previous 30 days, and/or who received migraine injection therapy in the last six months were excluded from the study. Patients' ages ranged from 18-65 years of age with a mean age of 39.2 years and mean monthly headache frequency of 21.5 days. The nVNS group consisted of 87% female and averaged 20.8 headache days per month. The sham control group consisted of 93% females and reported 22.3 headache days per month.

The primary outcome measured the mean reduction of monthly headaches days following two months of nVNS therapy. Participants baseline headaches were 20.8 days in the nVNS group and 22.3 days in the sham control group. The nVNS group achieved a 1.4 day reduction in monthly headache days, while the sham control group had a 0.2 day reduction in monthly headaches ($p = 0.56$). The mean reduction in monthly headache days was significant between the two groups. 10% of the nVNS group achieved a response rate > 50%, and 3.3% of the nVNS group achieved a response rate > 75%. Zero participants from the sham control group achieved > 50% response rate. Notably during the open label phase, the nVNS group achieved a 6.2 ($p <$

0.0001) and 7.9 day reduction ($p = 0.0009$) in monthly headache days at 6 and 8 months respectively. A total of 38% of six month nVNS completers achieved a > 50% response rate, and 46.7% of eight month nVNS completers achieved a > 50% response rate. These findings highly suggest the added benefit of nVNS therapy with continued treatment.

Secondary outcomes measured acute medication usage, tolerability, and safety profile of the vagus nerve stimulation device. Rates of baseline acute medication usage consisted of 89.8% of participants, this remained significantly unchanged through the treatment period resulting in 81.5% of participants using acute medication. Overall the nVNS device was well tolerated and participants reported minimal side effects. Six participants from the nVNS group and five participants from the sham control group reported device related adverse effects. The most common device related adverse effects were facial pain/numbness and eye twitching in the nVNS group. Zero participants were removed from the study due to device related adverse effects. At the end of the two month treatment phase, 58.3% of nVNS participants and 41.7% of sham control participants were satisfied with their migraine treatment.

Overall the study produced non-significant results. Blinding was maintained in the nVNS group, however was not maintained in the sham control group based on Bang index values. Limitations of the study included high attrition rate and small sample size. Additionally, since acute medication usage was permitted throughout the study this could have positively impacted study results. Researchers demonstrated that nVNS therapy was not significant compared to the sham control group within the two month treatment period. The open label phase portion of the study demonstrated that continued nVNS therapy was found to significantly reduce monthly headache days. The study was sponsored by electroCore, a migraine device producer (Silberstein et al., 2016).

Efficacy of *Supraorbital* Nerve Stimulation for Migraine Prevention

Vikelis et. al (2017) conducted a multi-center clinical study utilizing supraorbital nerve stimulation in the treatment of episodic and chronic migraine sufferers who have failed topiramate migraine prevention. The study consisted of a one month baseline period followed by a three month treatment period with the transcutaneous supraorbital nerve stimulation (t-SNS) device. Thirty-seven patients were initially enrolled through headache centers and evaluated monthly, 32 patients completed the study with 81.8% device compliance. The t-SNS device was used daily for 20 minutes. Inclusion criteria required that patients have a history of failing topiramate for migraine prevention and must have been off of topiramate for at least three months. Patients had a diagnosis of episodic or chronic migraine based on the international classification of headache disorders. Exclusion criteria was not mentioned. Of the 32 patients, ages ranged from 22-62 years and 31 patients were female. The Baseline monthly headache days was 8.9 and monthly acute medication days was 8.2.

The primary outcome measured reduction of monthly headache days following t-SNS treatment. After three months of treatment with the t-SNS device, headache days were reduced by 2.3 days ($p < 0.001$) demonstrating a 29.2% decrease in monthly headaches. Acute medication days were reduced by 3.8 days ($p < 0.001$), demonstrating a 46.3% reduction in acute medication days. One out of 31 patients achieved 50% or greater reduction in headaches. Secondary outcomes demonstrated that headache severity was reduced with device usage. Monthly migraine days with > 5/10 intensity were 5.3 at baseline, and after three months of t-SNS treatment monthly migraine days with > 5/10 intensity were 4.3 days. Patients with chronic migraine and episodic migraine reported similar levels of satisfaction, 66.7% and 65.5% respectively. 34.3% of patients reported adverse effects, primarily consisting of paresthesias over

stimulation site. Zero patients reported severe adverse events. Limitations of the study include small sample size, lack of control group, and vague study criteria. The study was funded by Cefaly-technology and Brain Therapeutics, covering the processing and publication fee (Vikelis et al., 2017).

Ordas et. al (2020) conducted an open label quasi-experimental design involving 25 chronic migraine patients and the effectiveness of transcutaneous supraorbital stimulation for migraine prophylaxis. A baseline of one month was established, with three months of treatment having patients meet with the researchers monthly to record findings. A headache diary was used during the one month baseline period by each patient to record headache occurrence, intensity, duration, and use of acute medications. Headaches were defined as lasting greater than four hours with moderate to severe intensity and reported at monthly meetings. Treatment settings for migraine prophylaxis consisted of biphasic rectangular impulses of 250 ls pulse width, 60 Hz frequency, and 16 mA current intensity for 20 minutes nightly.

Patients consisted of men and women with ages ranging from 19-66 years of age. Mean age of 41.9 years in the treated group. Participants were at least 18 years of age and struggled with chronic migraine for at least six months. Baseline headache days for the treated group was 22.24 days. Days with moderate to severe headaches consisted of 17.52 days in the treated population. Aura was reported in 38% of patients, bilateral headache reported in 62% of patients. Interestingly 42.9% of headaches were classified as medication overuse headaches in the treated population, with 47.6% of participants experiencing refractory chronic migraine. Prior to treatment, 47.6% of patients reported supraorbital nerve tenderness. 12 patients (57.14%) were taking headache prophylaxis during the study. Mean baseline HIT-6 scores were 67.81 in the treated population. Inclusion criteria included patients on migraine medication that had been

unchanged within the last three months. Medication overuse headaches and additional preventative headache therapies were not excluded as long as they were not modified within the last three months. Exclusion criteria included local headache treatments (ie. pericranial nerve blockades) in the last three months, history of cranial surgery, pregnancy, breastfeeding, and severe physical or psychiatric illnesses.

The primary outcome of the study was to reduce the amount of monthly headache days. A total of 24 patients who completed transcutaneous supraorbital stimulation achieved a 4 day reduction in headaches ($p = 0.0163$) reported at three months. Mean reduction in monthly headaches was 2.43 days ($p = 0.05$) at one month, and 3.33 ($p = 0.022$) days at two months. Secondary outcomes reported reduced number of symptomatic painkillers taken monthly by participants was reduced from 21 painkillers monthly to 16 painkillers monthly. A total of 12 (57.1% of treatment population) patients experienced $> 30\%$ reduction in monthly headache days. Mean baseline HIT-6 scores were 67.81 and decreased to 63.6, 61.1, and 62.1 at one month, two months, and three months respectively. These results indicate a significant decrease in HIT-6 scores, however remained greater than 60 indicating patients headaches continue to have an severe impact on their daily lives.

Three patients dropped out of the study due to lack of therapeutic benefit after one month of treatment. Another patient was removed from the study due to lack of diary documentation, totaling loss of four patients. Six patients reported feeling uncomfortable with the device, with four patients reporting paresthesias and headaches to the forehead region during the first 3-15 days of treatment. Seven patients reported somnolence as a side effect from the device. One patient reported dizziness following use of the stimulation device. Limitations of the study include a small sample size and 50% of the patient population suffering from refractory chronic

migraines negatively impacting results. Future efforts will explain that preventative headache treatments reach therapeutic levels closer to 2-4 weeks of treatment to reduce patient attrition. Overall the device was well tolerated with no serious or life threatening adverse events reported. Researchers found that since the supraorbital device covers a limited area of the trigeminal nerve correlates with a lesser therapeutic outcome, other reported cases have discovered a synergistic effect with combining occipital and supraorbital stimulation areas to strengthen the devices therapeutic effects (Ordas et al., 2020).

Schoenen et. al (2013) conducted a double blind randomized sham-controlled trial evaluating the efficacy of supraorbital neurostimulation for the prevention of migraine. The study involved five headache clinics with patients who experience greater than two migraines per month. The study consisted of a one month baseline period followed by a double blind three month treatment period. Patients were randomly assigned to the treatment and placebo groups. Patients used the supraorbital stimulation device for 20 minutes daily. A total of 67 patients were in the treatment population with a reported baseline of 6.94 monthly migraine days.

The primary outcome of the study was to evaluate the reduction of monthly migraine days after device use for three months as well as 50% responder rate. After three months of device use, patients reported a reduction in monthly migraine days by -2.06 days ($p = 0.023$). The sham control population reported a baseline of 6.54 monthly migraine days, with a reduction of -0.32 monthly migraine days ($p = 0.608$). Additionally, 38.1% ($p = 0.023$) of the treatment population achieved >50% reduction in monthly migraines compared to the placebo control group at 12.1%. Monthly headache days and use of acute migraine medication days was significantly reduced with use of the supraorbital stimulator device, however data was not provided in the study.

Shortcomings of the study included lack of necessary data points. Patient demographics were not identified such as age, gender, weight, and types of migraines being experienced. Additionally, the study did not identify specific inclusion and exclusion criteria, which may have benefitted study results. Details regarding the blinding process were not mentioned, the sham-control device was not described in detail. The device was reported to be well tolerated and safe, although study attrition, side effects, and adverse effects were not mentioned in the study. Overall, the study reports the supraorbital neurostimulation device is effective for migraine prevention, however lacks a significant report of study design and discussion sections (Schoenen et al., 2013).

Danno et al. (2019) conducted an open clinical trial studying 100 patients who suffered from headaches and were treated with Cefaly, a transcutaneous supraorbital nerve stimulator. The patients' ages ranged from 18-75 years of age with 68% of the subjects being female, and mean age of 43.6 years. 23 subjects suffered from migraine, involving six with medication overuse headache. 60 subjects experienced episodic migraine, 55 subjects migraine without aura, four subjects experienced migraine with and without aura, occurring at least two times per month and four total days of migraine per month. Additional inclusion criteria consisted of no medication changes within three months. Exclusion criteria included medication changes within three months, previous botox injections within three months, severe neurological/psychiatric disorders, epilepsy, secondary headache conditions, and patients using opioids. These subjects underwent a 16 week study involving a four week baseline and 12 week treatment period. Four subjects dropped out of the study due to adverse effects, and seven subjects did not meet the migraine inclusion criteria during the baseline period. As a result, 83 subjects were analyzed throughout

the study. Subjects used the Cefaly device for 20 minutes with a pulse width of 300 μsec, frequency of 60 Hz every 24 hours for 12 weeks.

The primary outcome of the study showed that the Cefaly device decreased headaches by an average of 1.32 days ($p = 0.0036$). The number of headache days was reduced from 8.16 days in the baseline period to 6.84 days after the 12 week treatment period. Migraine attacks decreased from 5.33 in the baseline period to 3.94 ($p = 0.0002$) after 12 weeks of treatment. Secondary outcomes found that use of 35.4% of subjects reduced abortive medicine usage from 8.75 days at baseline to 7.83 days ($p = 0.0166$) at 12 weeks of treatment. 19.3% of subjects who were 50% responders had a reduction of migraine days by at least 50%. Patients with chronic migraine slightly benefitted over episodic migraine subjects minimally, this mechanism is unclear. Headache severity was not significantly changed. The study also compared effectiveness of Cefaly treatment between subjects on prophylactic migraine therapy and those without prophylaxis. Of the 53 subjects receiving migraine prophylaxis and 30 subjects not receiving prophylaxis, results did not produce significantly different findings and no trends were observed.

Compliance was 90% at 75.6 days over 12 weeks. Adverse effects were minimal, seven subjects reported adverse effects including sleepiness, headaches, and stimulus site discomfort. Overall, the device was tolerated without severe adverse effects; only 52.4% of subjects satisfied with treatment would purchase the device. 40.4% of subjects reported that Cefaly effectiveness was similar to abortive treatment medications. The device was determined to be an effective adjunct in chronic migraine treatment (Danno et al., 2019).

Efficacy of CGRP Antagonist Therapy for Migraine Prevention

Detke et. al (2018) performed a randomized clinical trial to evaluate the efficacy of galcanezumab in migraine prevention treatment. The study was a phase-3 randomized double

blind placebo controlled study focusing on the efficacy of humanized monoclonal antibodies in the prevention of migraine. The study duration consisted of a three month treatment phase with three populations receiving either Galcanezumab 240 mg monthly injections, Galcanezumab 120 mg monthly injections, and placebo monthly injections. This was followed by a nine month open-label phase to further evaluate continued treatment. Blinding was maintained by requiring all subjects receive 1mL injections at each monthly visit in blinded prefilled syringes. A total number of 1,113 subjects met criteria for intent to treat.

Subject demographics consisted of men and women aged 18-65 years. The placebo group consisted of 87% females with a mean age of 41.6 years. The Galcanezumab 120 mg group consisted of 85% females with a mean age of 39.7 years. Lastly the Galcanezumab 240 mg group consisted of 82% females with a mean age of 41.1 years. These subjects were screened for chronic migraine conditions defined by the international classification of headache disorders, with inclusion criteria consisting of chronic migraine diagnosis before 50 years of age, experiencing 15 headaches per month, with at least 8 headaches containing migraine qualities, occurring for more than three months. Subjects were excluded who did not have one headache free day per month, reported daily headache, and head or neck trauma within the last six months. Additionally, subjects were excluded if they have a history of severe psychiatric disorders, a history of stroke, and received monoclonal antibodies for headache within the past year.

The primary outcome of the study showed that both doses of galcanezumab were more effective in mean reduction of monthly migraines than the placebo. Researchers identified a headache day as a calendar day including migraine, probable migraine, and headaches lasting longer than 30 minutes in duration. The placebo group had a reduction in monthly headache days by -2.7 days with 15.4% of the population obtaining > 50% response rate. The group receiving

120 mg galcanezumab had a reduction in monthly headache days (MHDs) by -4.8 days ($p < 0.001$), with 27.6% of the group obtaining > 50% response rate. The group receiving galcanezumab 240 mg had a reduction in monthly headache days by -4.6 days ($p < 0.001$), with 27.5% of the group obtaining > 50% response rate. Monthly intervals were used to measure the effectiveness of the galcanezumab dosages and found greatest reduction of migraine days at one month occurred for the galcanezumab 240 mg population, and the greatest migraine reduction at two and three months occurred in the galcanezumab 120 mg population. Response rates > 50% occurred in 27.6% and 27.5% for the galcanezumab 120 mg and galcanezumab 240 mg populations respectively. Response rates > 75% occurred in 7.0% and 8.8% for the galcanezumab 120 mg and galcanezumab 240 mg populations respectively. Both doses of galcanezumab were more effective than the placebo in reducing monthly headache days.

Secondary outcomes included reduction of acute medication use for the galcanezumab 120 mg population by -.4.7 days ($p < 0.001$). Reduction in acute medication use for galcanezumab 240 mg was -4.3 days ($p < 0.001$). Monthly migraine headache hours were reduced by -36.2 hours ($p < 0.001$) and -31.5 hours ($p < 0.001$) for the galcanezumab 120 mg and galcanezumab 240 mg populations respectively. The two populations receiving galcanezumab doses did not report significant adverse effects with either dose, galcanezumab 120 mg; three adverse effects compared to galcanezumab 240 mg; two adverse effects. The galcanezumab 240 mg population noted an increase in the number of subject withdrawals of seven participants, compared to the galcanezumab 120 mg population with four subject withdrawals. These subject withdrawals were not due to adverse effects. Interestingly, the placebo group experienced the greatest number of subject withdrawals (19) and greatest amount of adverse effects (6). Lastly, the Migraine Disability Assessment Score (MIDAS) was used to

compare the number of days affected by migraine from the subject's baseline during galcanezumab treatment at three months. Baseline MIDAS score for subjects in this study was 65.8, considering migraine disability to be very severe. A mean reduction of MIDAS score was -11.5, -20.3, and -17.0 for the placebo, galcanezumab 120 mg, and galcanezumab 240 mg populations respectively, classifying migraine involvement to be reduced from very severe to severe.

Overall, monthly headache days were reduced by five days and a mean increase in functioning of 23 points on 100 point Migraine Specific Quality of LIfe Questionnaire (MSQ) Role Function Restricted domain for galcanezumab 240 mg population was observed. The increase in the MSQ displays improved ability to function, most consistent with episodic migraine rather than previously observed chronic migraine functioning. Additionally, the study shows high rates of completion at 95% and low rates of subject withdrawal due to adverse effects at 1% for galcanezumab treatment groups. Between the two doses of galcanezumab there were no significantly different outcomes on efficacy. Injection site reactions were higher in the galcanezumab 240 mg vs. the galcanezumab 120 mg groups. Study limitations included inclusion criteria, restricting patients with complex medical histories and patients with history of treatment resistant migraines. The inclusion criteria benefitted study results and will limit generalizability of the study. The study duration was only three months, further analysis of a nine month open-label study would be beneficial (Detke et al., 2018).

Goadsby et. al (2020) conducted a double blind clinical trial evaluating the efficacy and tolerability of orally administered calcitonin gene-related peptide (CGRP) antagonist in the preventative treatment of migraine. The study involved 78 practices in the US with participants committed to undergo a four week screening baseline period followed by a 12 week double-blind

treatment period. The study did differentiate between migraine and headache episodes. Migraine was defined as a headache lasting greater than two hours with unilateral, pulsating, and moderate-severe pain characteristics. Migraines were worsened by activity, and presented with nausea, vomiting, photophobia/phonophobia, or aura. 834 participants were randomly assigned to placebo and treatment groups. Atogepant treatment groups consisted of 10 mg daily, 30 mg daily, 60 mg daily, 30 mg twice daily, and 60 mg twice daily dosing. The placebo and treatment populations both received identical blister packets of capsules that maintained blinding. The study ended with a four week follow up as a safety check in for patients.

Inclusion criteria required patients to be 18-75 years of age and were diagnosed with migraine with or without aura prior to 50 years of age. The patients must have received this diagnosis at least 12 months prior to the study start time. Participants experienced 4-14 monthly migraines in the last three months prior to the study and 4-14 monthly migraine days during the four week baseline period. Exclusion criteria involved patients experiencing 15 or more migraines per month in the last three months or during the four week baseline period. Additional exclusions include history of failing migraine preventative medications in two different categories, including opiates, triptans, and non-opioid analgesics such as nonsteroidal anti-inflammatory drugs. Initially, 1773 patients were screened for the study and 834 patients were randomly assigned to the atogepant treatment and placebo groups. The mean age of patients was 40.1 years of age and consisted of 87% females. The mean duration of migraine history was 19.4 years. The baseline mean monthly migraines were 6.7 and baseline monthly acute medication days were 6.5 days.

The primary outcome of the study aimed to measure the reduction in mean monthly migraine days over the 12 week treatment period. The mean reduction in monthly migraine days

ranged from 3.9 to 4.3 days in the atogepant treatment groups, compared to the 2.9 day reduction seen in the placebo group. Researchers found that there was no clear trend based on doses from the atogepant treatment groups. The highest monthly migraine reduction was seen in the 30 mg twice daily group with -4.8 day ($p = 0.0034$) migraine reduction, compared to the lowest reduction of monthly migraine days of 3.6 days ($p = 0.039$) in the 60 mg once daily group. Atogepant treatment groups achieved a response rate >50% reduction in monthly migraines ranging from 52-62%. The atogepant group with the highest response rate of > 50% reduction in monthly migraines was the 60 mg twice daily group at 62%. Participants who achieved 75% reduction in monthly migraine days were notably observed 37% in the 60 mg twice daily group. In the 30 mg twice daily group, 11% of patients achieved a 100% reduction in monthly migraine days. Secondary outcomes measures change in monthly days of acute medication. Acute medication days were reduced by 3.5 to 3.9 days based on atogepant dose. The patients receiving 30 mg once daily had the greatest reduction of acute migraine medication use by 3.9 days. Placebo groups achieved a 2.4 reduction in acute medication use.

Adverse effects were greater in the atogepant treatment groups, with 58-66% of patients experiencing adverse effects with the most common being nausea. Interestingly, 49% of the placebo group reported adverse effects. The 10 mg atogepant group reported the highest amount of adverse effects at 66%, while the 60 mg once daily group reported 58% adverse effects. Specifically, treatment related adverse effects were associated with the atogepant dose. 18% of the 10 mg once daily group reported drug specific adverse effects and 26% of patients in the 60 mg twice daily group reported drug specific adverse effects. 16% of the placebo group reported drug specific adverse effects. Adverse effects causing withdrawal from the study were reported in 5% of the treatment group and 3% of the placebo group. All serious reported adverse effects

were not related to treatment. Study limitations include excluding chronic migraine patients likely favoring study results. Researchers will include chronic migraine in future studies. Ongoing evaluation of atogepant safety needs to be addressed in the open-label study and determine hepatic safety of the drug. In conclusion, the study results support the use of atogepant, a CGRP antagonist, in the preventative treatment for episodic migraine (Goadsby et al., 2020).

Reuter et. al (2018) conducted a 12 week double blind placebo controlled study involving 16 countries and 59 sites, studying the efficacy of erenumab in patients with refractory episodic migraine. The study included a zero to two week screening phase and four week baseline period where patients would document daily migraine frequency and characteristics using an Ediary. 80% compliance with self-reporting migraines was required to move forward in the study. This was followed by a 12 week treatment phase involving patients to be randomly assigned to receive erenumab 140 mg. The erenumab therapy was administered every four weeks over the 12 week treatment period. Masking was obtained by having the treatment group and placebo group receive monthly prefilled subcutaneous injections that were identical in appearance. Inclusion criteria required patient age to range from 18-65 years and have a history of diagnosed episodic migraine for at least 12 months. Patients must have experienced an average of monthly migraines ranging from 4-14 days in the last three months prior to trial screening, and failed two to four preventative migraine treatments. Failure of preventative migraine treatments were due to lack of efficacy, lack of tolerability, or both. Preventative treatments included propranolol, topiramate, valproate, and amitriptyline. Exclusion criteria involved patients diagnosed with migraine over 50 years of age, cluster headaches, seizures, psychiatric disorders, MI, stroke, unstable angina, and TIA. Additionally patients with chronic pain syndromes, known malignancy, and use of

preventative medicine within five times a drug's half life within one month prior to enrolling in the study were excluded. Device placement or procedures within one month prior to the study were excluded as well. Patients who received botulinum treatment in the head or neck region within four months prior to the study were excluded.

Patients enrolled in the study ranged in age from 18-65 years and had a previous diagnosis of episodic migraine for at least 12 months. Initially, 333 patients were screened and 246 patients were randomly assigned to the erenumab group (n = 121) and placebo group (n = 125). All patients had previously failed two to four preventative migraine treatments, the most common failed drugs were amitriptyline (46%) and propranolol (45%). The erenumab and placebo populations contained similar baseline characteristics. The erenumab group had a mean age of 44.6 years of age, population was 93% Caucasian, and primarily composed of females at 80%. Monthly migraine days for the erenumab group averaged 9.2 days. The placebo group mean age was 44.2 years, 92% Caucasian, and primarily composed of females at 82%. The placebo group averaged 9.3 monthly migraine days.

The primary outcome of the study was to evaluate the response rate to having greater than 50% reduction in monthly migraine days. At 12 weeks, 30% of the erenumab group achieved a >50% reduction in monthly migraines compared to 14% of the placebo group ($p = 0.002$). Additionally at 12 weeks, 12% of the erenumab group and 4% of the placebo group achieved a >75% reduction in monthly migraine days ($p = 0{\cdot}025$). The effectiveness of erenumab was also noted during weeks 1-4 as well as weeks 5-8, with the erenumab group achieving 23% and 31% reduction >50% in monthly migraines respectively ($p < 0.001$). The early benefits of erenumab were significant when compared to the placebo group during weeks 1-4 and weeks 5-8, with the placebo group achieving 5% and 12% reduction in monthly

migraines by >50%. During weeks 9-12, the 30% of the erenumab group achieved >50% reduction in monthly migraines, compared to the placebo group achieving a 14% response rate to >50% reduction in monthly migraines ($p < 0.001$).

Secondary outcomes evaluated the reduction in monthly migraine days, use of acute medication, and change in baseline scores measuring migraine burden. During weeks 1-4, the erenumab group had a mean reduction of monthly migraines by 1.8 days, compared to the placebo group of 0.1 days ($p < 0.001$). During weeks 5-8 the erenumab group had a 2.4 day reduction ($p < 0.001$) in monthly migraine days, compared to the placebo group with 0.1 day reduction ($p < 0.001$) in migraine days. The greatest difference in monthly migraine reduction was observed during this 5-8 week treatment period. Weeks 9-12 displayed similar data, showing 1.8 day monthly migraine reduction in the erenumab group ($p = 0.004$), with 0.2 day reduction in monthly migraines for the placebo group ($p < 0.001$). Acute medication days were reduced in the erenumab group by 1.8, 2.3, and 2.4 days at weeks four, eight, and 12 respectively. The placebo group did not observe a significant reduction in acute medication days. At eight weeks, the erenumb group experienced 3.3 day reduction in physical impairment secondary to migraine, and 4.4 day reduction in everyday activities according to the Migraine Physical Function Impact Diary (MPFID). At 12 weeks, the erenumab group experienced 1.9 day reduction in physical impairment and 3.4 day reduction in everyday activities.

Interestingly, weeks 5-8 showed the most benefit with >50% migraine reduction, reduction in migraine days, acute medication days, and functional status improvement. Overall erenumab was well tolerated. 55% of the erenumab group reported at least one adverse effect, with zero adverse effects leading to study attrition. Only 2% of the treatment group reported serious adverse effects. Interestingly, 54% of the placebo group reported adverse effects, causing

one patient to withdraw from the study. The most common adverse effects included injection site reactions, nasopharyngitis, and injection site redness. Due to the patient population and failure of two to four migraine treatments, results displayed lower efficacy when compared to similar studies with more treatment naive patients. The limitation of the study was the short 12 week duration, resulting in the inability to evaluate benefits of long-term therapy. Treatment failure was required to be documented lacking further control of variables. Overall, erenumab therapy at 12 weeks did show a significant reduction in monthly migraine days when compared to the placebo group, and was more effective in reducing all secondary outcomes than the placebo. This migraine therapy may be appropriate for patients who have refractive migraine conditions (Reuter et al., 2018).

Discussion

The main finding of the literature review was that vagus nerve stimulators and supraorbital nerve stimulators were effective in the application of migraine prophylaxis, with benefit reported in patients who suffer from episodic and chronic migraine. Secondary findings revealed that prolonged usage of nVNS devices up to six and nine months showed increasing benefits of reducing monthly migraine days. CGRP antagonists were also found to be effective in the application of migraine prophylaxis with therapeutic onset measured at the fourth week of treatment. Meta-analysis studies between the numerous neuromodulation devices have been published exploring the wide range of applications and devices available in the market. However, the specific area of TENS devices and CGRP antagonists, have not been directly compared to one another in the application of migraine prophylaxis. Moreover, vagus nerve and supraorbital nerve stimulators will be compared to CGRP antagonists for application of migraine prophylaxis. The following discussion will compare analyzed studies and their findings.

Literature reviews performed by Stovner (2022) and Katsarava (2012) show a strong prevalence of migraine in Caucasian women aged 20-64 years of age without a clear causation. Altered pain processing pathways and comorbid conditions such as anxiety, depression, and obesity have also been correlated with migraines. From these findings, it is reasonable to conclude there are multiple factors involved in the etiology of migraines. Additionally, low socioeconomic status was also found to have higher rates of chronic migraines, this may be due to poor access to care and unmanaged chronic comorbid conditions. Further studies will be needed to better understand the impact of comorbidities and one's environment on the influence of migraine prevalence in these populations.

Meta-analysis performed by Cheng et al. (2022) compared the application of numerous TENS devices as preventative migraine therapy. The primary focus is comparing the efficacy of vagus nerve stimulators to supraorbital nerve stimulators and the reduction of monthly migraine days. Supraorbital nerve stimulators reduced monthly migraine days by -1.34 days (95% CI) compared to non-invasive vagus nerve stimulators reducing monthly migraine days by -1.34 days (95% CI) as well (Cheng et al., 2022).

In a clinical trial, Diener and colleagues (2019) explored the application of nVNS therapy in migraine prophylaxis and observed a reduction in monthly migraine days by -2.26 days (95% CI). Interestingly, patients suffering from migraine with aura had the greatest reduction of monthly migraine days -2.83 days ($p = 0.15$) (Diener et al., 2019). Another study evaluating nVNS therapy performed by Najib et al. (2022) using nVNS therapy for migraine prophylaxis achieved a -3.12 ($p = 0.2329$) day reduction in monthly migraine days using the same device. Furthermore, device settings between the two studies had the same settings and application. Devices were used three times per day, for 120-second stimulation durations at a time.

Stimulation was delivered at the neck. Both studies consistently showed a more significant response to treatment in patients who suffer from migraine with aura. In both studies, inclusion criteria was similar, however Diener (2019) excluded patients with chronic migraine; whereas, Najib (2022) excluded patients who were using more than two abortive therapies in the last six months, as well as those participants who have used GammaCore which is another nVNS device. Excluding patients who have previously tried nVNS therapy may also have benefitted results. Additionally, the average age between the treatment populations differed which may have been a contributing factor to the differences in monthly migraine reduction. The population group in Najib's study was younger by 3.2 years on average (Najib et al., 2022). This finding could have benefitted the reduction of monthly migraine days. This finding may also support that younger patients with newer diagnosis of migraine may have a higher response rate to nVNS therapy. Secondarily, the younger treatment population in the Najib (2022) study had a greater reduction in monthly acute medication days by 0.63 days, when compared to the older treatment population in the Diener (2019) study. These findings may suggest that migraines in younger patients may be less resistant to treatment and the benefits of nVNS therapy may have longer therapeutic effect in younger populations due to the reduction in acute medication usage. This claim may be further supported since Najib (2022) treatment (nVNS) population also suffered a higher baseline monthly migraines at 9.2 days per month compared to Diener (2019) population of 7.9 monthly migraine days.

Diener nVNS population (PREMIUM I TRIAL)	Najib nVNS population (PREMIUM II TRIAL)
● Device: electroCore, used in two 2-minute intervals, three times daily	● Device: unspecified, used in two 2-minute intervals, three times daily

• Indication: Episodic Migraine • Treatment n (nVNS) = 138 participants • nVNS therapy duration: 12 weeks • nVNS population: 86% female • Average age: 43.5 years • Baseline monthly migraine days: 7.9 days • Monthly migraine reduction: -2.26 days (95% CI; p = 0.15) • Acute medication usage: -1.90 days (95% CI) • >50% monthly migraine reduction: 28.5%	• Indication: Episodic & Chronic Migraine • Treatment n (nVNS) = 113 participants • nVNS therapy duration: 12 weeks • nVNS population: 88% female • Average age: 40.3 years • Baseline monthly migraine days: 9.2 days • Monthly migraine reduction: -3.12 days (p = 0.2329) • Acute medication usage: - 2.53 days (95% CI) • >50% monthly migraine reduction: 44.9%

Silberstein et al. (2016) conducted another nVNS clinical trial including participants who suffer from chronic migraine. This inclusion criteria was defined as having > 15 migraines per month. Due to this inclusion criteria, and shortened treatment phase of eight weeks compared to 12 weeks in other studies, outcomes had less promising results. In this study 30 participants underwent 8 week treatment of nVNS therapy and achieved a -1.4 day monthly migraine reduction with only 10% of the treatment population achieving a >50% reduction in monthly migraines (Silberstein et al., 2016). This supports the claim that nVNS therapy provides greater benefit to those patients suffering from episodic migraine compared to chronic migraine, and additional therapeutic benefits are observed past eight weeks of treatment with nVNS therapy. Additionally, another key finding in this study was during the open-label phase at 6 and 8 months. Chronic migraineurs who continued to use the device achieved -6.7 day and -7.9 days

reduction at six and eight months respectively, with 46.7% of the population achieving > 50% reduction in monthly migraines (Silberstein et al., 2016). Minimal adverse effects were associated with prolonged use. Common complaints were stimulation site redness, facial pain/numbness, and eye twitching. Zero participants left the study due to adverse effects. This open-label phase demonstrated that prolonged nVNS therapy had significant reduction in monthly migraine days and improved response rate amongst participants. More research will be needed to strengthen these findings, however it appears promising that continued nVNS therapy is beneficial. Overall, nVNS devices reviewed in this discussion achieved a mean monthly migraine reduction of -2.26 days between the nVNS studies analyzed in this literature review. We will compare these findings to another TENS device known as supraorbital nerve stimulators.

Silberstein nVNS population
● Device: unspecified, used in two 2-minute intervals, three times daily ● Indication: Chronic Migraine ● Treatment n (nVNs) = 30 participants ● nVNS population: 87% female ● Average age: 39.2 years ● nVNS therapy duration: 8 weeks ● nVNS therapy open-label phase: 6 months, 8 months ● Baseline monthly migraine days: 20.8 days ● Monthly migraine reduction (8 weeks): -1.4 day reduction, (95% CI; p = 0.44) ● > 50% migraine reduction: 10% Open-label phase: 6 months: ● Monthly migraine reduction: -6.7 day reduction ● > 50% monthly migraine reduction: 38%

8 months: ● Monthly migraine reduction: -7.9 day reduction ● > 50% monthly migraine reduction: 46.7%

Vikelis et. al (2017) conducted a trial using t-SNS for a 3 month treatment period used daily for 20 minutes. Participants included in this study experienced episodic migraines and chronic migraines. Interestingly, device satisfaction scores were similar amongst the chronic migraine and episodic migraine subgroups despite lack of benefit observed in nVNS device studies. This may suggest that t-SNS therapy may be more beneficial for chronic migraine sufferers as compared to nVNS therapy. A second t-SNS trial was conducted by Ordas et al. (2020) using t-SNS therapy for 20 minutes for a treatment period of 12 weeks. This study included participants who have suffered from chronic migraine for at least six months, and found t-SNS therapy to be effective in reducing monthly migraine days in chronic migraine. These findings further strengthen the claim that t-SNS therapy may be more beneficial in patients who experience chronic migraine when compared to nVNS therapy. When comparing these two t-SNS studies, the Ordas population had a greater monthly migraine reduction when compared to the Vikelis population. Another correlation is the difference in age of the t-SNS treatment populations, with Ordas t-SNS population having a mean age of 41.9 years, compared to the median age of Vikelias t-SNS population of 45 years. The positive correlation of age and reduction in monthly migraines may allow us to infer that t-SNS therapy is more beneficial in younger patients with a shorter history of migraine duration.

Vikelis t-SNS population	Ordas t-SNS population

• Device: Cefaly, used 20 minutes daily • Indication: Episodic & Chronic Migraine • Treatment n (t-SNS) = 32 participants • t-SNS population: 96.5% female • Age range: 22-62 years • Median age (t-SNS): 45 years • t-SNS therapy duration: 12 weeks • Baseline monthly migraine: 8.9 days • Monthly migraine reduction: -2.6 days ($p < 0.001$) • > 50% migraine reduction: 3.22% ($p < 0.001$) • Acute medication usage: -3.8 days ($p < 0.001$) Device satisfaction: • Episodic migraine: 65.6% • Chronic migraine: 66.7%	• Device: unspecified, used 20 minutes nightly • Indication: Chronic Migraine • Treatment n (t-SNS) = 24 participants • t-SNS population: 96.5% female • Mean age (t-SNS): 41.9 years • t-SNS therapy duration: 12 weeks • Baseline monthly migraine: 22.4 days • Monthly migraine reduction: -4.0 days ($p = 0.0163$) • > 50% migraine reduction: 35% • Acute medication usage: -5.0 days ($p = 0.11$) Open-label phase (40 week extension): • >50% migraine reduction: 47.8%

Schoenen et al. (2013) conducted a clinical trial evaluating t-SNS therapy in the application of episodic migraine prophylaxis. Between the treatment and sham control populations there were some notable differences. The treatment population was 4.47 years younger on average and had a shorter migraine disease duration of 3.46 years benefitting the outcome of monthly migraine reduction. Similar findings were associated with a study conducted by Najib (2022) involving nVNS therapy for migraine prophylaxis. This further supports the claim that younger patients with a shorter disease duration may respond better to TENS device

therapy. A second t-SNS study conducted by Danno (2019) using an open-label study evaluating t-SNS therapy in episodic and chronic migraine. Results indicated that chronic migraine participants benefited from t-SNS therapy over episodic migraine patients, although the mechanism is unclear. In this study, participants who had received additional unspecified migraine prophylaxis had no significant difference in t-SNS response when compared to participants without migraine prophylaxis treatment. This finding may suggest that t-SNS therapy works by reducing migraine days through a different mechanism as compared to medication migraine prophylaxis. This suggests that the t-SNS device is an appropriate adjunctive therapy for those patients already receiving migraine prophylaxis medication.

Schoenen t-SNS population	Danno t-SNS population
● Device: Cefaly, 20 minutes daily ● Indication: Episodic Migraine ● Treatment n (t-SNS) = 67 participants ● t-SNS population: unspecified ● Mean age (t-SNS): unspecified ● t-SNS therapy duration: 12 weeks ● Baseline monthly migraine: 6.94 days ● Monthly migraine reduction: -2.06 days (p = 0.023) ● > 50% migraine reduction: 38.1% (p = 0.023)	● Device: Cefaly, 20 minutes daily ● Indication: Episodic Migraine ● Treatment n (t-SNS) = 100 participants ● t-SNS population: 68% female ● Mean age (t-SNS): 43.6 years ● t-SNS therapy duration: 12 weeks ● Baseline monthly migraine: 5.3 days ● Monthly migraine reduction: -1.39 days (p = 0.0036) ● > 50% migraine reduction: 19.3% ● Acute medication usage: - 0.92 days

Detke et al. (2018) study conducted a double-blind controlled study evaluating the efficacy of CGRP antagonist, galcanezumab in patients who suffer from chronic migraine.

Treatment population consisted of two different galcanezumab doses with similar results. Results suggested that the higher dose of galcanezumab 240 mg showed earlier benefits with a lower migraine reduction at one month, compared to the lower 120 mg dose of Galcanezumab with greater monthly migraine reductions at two and three months (Detke et al., 2018). Common side effects such as injection site reactions were associated with the higher dose of galcanezumab. Adverse effects were not associated with participant withdrawal, while the placebo group reported the greatest number of withdrawals related to adverse effects. Another study investigating the application of CGRP antagonists in episodic migraines was conducted by Goadsby (2020) utilizing atogepant. The study showed greatest migraine reduction in the atogepant 30 mg twice daily group compared to the lowest group of atogepant 60 mg daily. This finding may suggest that the benefits of atogepant are not solely reliant on initial dosing, rather more consistent dosing throughout the day is beneficial for migraine reduction. When comparing galcanezumab in chronic migraine and atogepant in episodic migraine, the reduction in monthly migraine days was similar with both CGRP antagonists reducing monthly migraines by approximately four days.

Detke CGRP Antagonist	Goadsby CGRP Antagonist
● CGRP Antagonist: Galcanezumab ● Indication: Chronic migraine ● Treatment n = 555 participants ● Treatment population: 87% female ● Mean age (treatment): 40.4 years ● Treatment duration: 12 weeks ● Baseline monthly migraine: 19.3 days ● Galcanezumab 120 mg migraine reduction: -4.8 days ($p < 0.001$)	● CGRP Antagonist: Atogepant ● Indication: Episodic migraine ● Treatment n = 647 participants ● Treatment population: 87% female ● Mean age (treatment): 40.1 years ● Treatment duration: 12 weeks ● Baseline monthly migraine: 7.6 days Atogepant Dosages:

○ > 50% migraine reduction: 27.6% ● Galcanezmab 240 mg migraine reduction: -4.6 days ($p < 0.001$) ○ > 50% migraine reduction: 27.5%	● Atogepant 30 mg QD migraine reduction: -3.8 days ($p = 0.039$) ○ > 50% migraine reduction: 53% ($p = 0.11$) ● Atogepant 30 mg BID migraine reduction: -4.8 days ($p = 0.0034$) ○ > 50% migraine reduction: 58% ($p = 0.034$) ● Atogepant 60 mg QD migraine reduction: -3.6 days ($p = 0.039$) ○ > 50% migraine reduction: 52% ($p = 0.15$) ● Atogepant 60 mg BID migraine reduction: -4.1 days ($p = 0.0031$) ○ > 50% migraine reduction: 62% ($p = 0.0097$)

Reuter et. al (2018) study evaluating the effectiveness of erenumab for migraine prevention. The results indicated that continued treatment measured at 4, 8, and 12 weeks showed improved response rates for > 50% migraine reduction, as well as reduction in total monthly migraines. This is clinically relevant, highlighting the importance of educating patients that even with injection medication the therapeutic effects of migraine reduction are not immediate. Additionally, this study required patients to have failed two to four preventative medications. With that, the results of monthly migraine reduction were significant in these refractory episodic migraine patients. This specific finding may suggest that erenumab would be preferred in treating refractory episodic migraine. When comparing erenumab to atogepant and galcanezumab, erenumab is approximately 50% as effective in reducing monthly migraine days.

This may be due to the patient population who was required to have previously failed preventative migraine therapy. Additionally, erenumab was less effective than nVNS therapy in Najib's (2020) study in the setting of episodic migraine therapy, however this may largely be related to differences in the treatment populations between these two studies.

Reuter CGRP Antagonist
● CGRP Antagonist: Erenumab 140 mg IM ● Indication: Refractory Episodic migraine ● Treatment n = 121 participants ● Treatment population: 80% Female ● Mean age (treatment): 44.6 years ● Treatment duration: 12 weeks ● Baseline monthly migraine: 9.2 days ● Monthly migraine reduction: - 2.4 days ($p < 0.001$) ● > 50% migraine reduction: 30% ($p = 0.002$)

Conclusion

Overall, research shows that the use of vagus nerve stimulators, supraorbital nerve stimulators, and CGRP antagonists are generally effective in the application of migraine prevention. Conclusions made regarding TENS device responses have shown effectiveness in both episodic and chronic migraines, as well as reduction in acute medication usage. More specifically, vagus nerve stimulators were shown to be effective in the application of episodic migraine prevention, while supraorbital nerve stimulators displayed more benefit in the setting of chronic migraine when compared to vagus nerve stimulators. Furthermore, CGRP antagonists were studied in the setting of episodic, chronic, and refractory migraine and were found to

reduce monthly migraine days twice as effectively as supraorbital nerve stimulators in the setting of chronic migraine. When comparing TENS devices and CGRP antagonists, researchers found that these therapies targeted different pathways and reduced migraine days independent of one another. Ultimately, CGRP antagonists are more effective in migraine prevention than TENS devices.

Applicability to Clinical Practice

Clinical takeaway from these studies is that prolonged and continued use of vagus nerve stimulators, supraorbital nerve stimulators, and CGRP antagonists all displayed increased benefit and minimal reported side effects. TENS devices are not routinely recommended in clinical settings, however based on this research they are a potentially effective option for many patients given their low side effect profile. Providers should educate patients that the benefits of these therapies may take 8-12 weeks to reach full effect and that discontinuing therapy before therapeutic effects are reached may be a significant factor in poor response rates to these treatment options. Additionally, more research is needed to determine the prolonged effects of using TENS devices as well as CGRP antagonists. Concurrent use of both TENS devices and CGRP antagonists have been shown to work on different pain pathways reducing migraines synergistically without additional side effects. The research conducted shows that TENS devices are safe effective treatments in the setting of migraine prevention.

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