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Neuromodulation for primary headache disorders: Advantages and challenges

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Abbreviations:

FDA – Food and Drug Administration

REN - remote electrical neuromodulation

eTNS - external trigeminal nerve stimulation

nVNS - non-invasive vagal nerve stimulation

sTMS - single pulse transcranial magnetic stimulation

eCOT-NS - external combined occipital and trigeminal neurostimulation

IHS – International Headache Society

VA – Veteran Affairs

Neuromodulation is a relatively new treatment option in headache medicine. There are currently five FDA cleared and commercially available non-invasive neuromodulation devices for acute and/or preventative treatment of migraine and cluster headache. Currently available neuromodulation devices include: remote electrical neuromodulation (REN; Nerivio), external trigeminal nerve stimulation (eTNS; Cefaly), non-invasive vagal nerve stimulation (nVNS; gammaCore), single pulse transcranial magnetic stimulation (sTMS; SaviDual by eneura), and external combined occipital and trigeminal neurostimulation (eCOT-NS; Relivion). However, these devices are still infrequently used, potentially related to factors such as device efficacy, marketing, or cost raising the question if the advantaqes of neuromodulation outweigh its challenges.`

There are many obstacles to successful development of neuromodulation devices. A good understanding of the various modalities (eg. transcranial magnetic stimulation), targets (eg. occipital nerves), and protocols is necessary to construct an effective device. With the multitude of factors involved in creating efficacious neuromodulation devices, it is not surprising that supportive data is often weak or even lacking. Randomized controlled trials are not always feasible as development of an effective sham is challenging, often leading to studies without sham control. Current commercially available neuromodulation products have been granted FDA clearance, a different process than FDA approval. FDA cleared devices must be comparable to preexisting products or raise no concern about safety. Unlike the FDA approval process, animal studies and multiphase trials are not needed for FDA device clearance, all of which translates to less rigor involved in ensuring a medical device is beneficial for the intended condition. This may lead to device safety and technical issues, often not discovered until they are out to market.

Despite differences in the process for FDA clearance and FDA approval, gaps in treatment for primary headache disorders exist. Pharmacologic therapies for preventive treatment of primary

headache disorders provide variable benefit, often have side effects or medical contraindications. Many acute pharmacologic therapies can also increase risk of medication overuse headache. This provides a space for neuromodulation devices to help address treatment gaps/issues and provide nonpharmacologic options for patients.

Studies have not only demonstrated efficacy in acute and preventive treatment of migraine with overall promising results, but also particular subset populations may have greater benefit. For instance, sTMS has demonstrated benefit for acute use in migraine with aura specifically[1]. The data for REN is particularly impressive in adolescents, a population with fewer FDA approved and/or cleared treatments for headache and migraine. In adolescents with migraine using REN compared to medication 37% vs 8% had pain freedom at 2 hours ($p = 0.004$), 40% vs 9% had consistent pain freedom across multiple uses ($p < 0.001$), and 80% vs 57% had consistent pain relief ($p = 0.033$)[2]. Retrospective data has become available supporting REN as safe to use in pregnancy with no statistically significant differences in pregnancy outcomes between patients who had used REN during their pregnancies compared to controls[3].

Improvement in most-bothersome symptom (i.e. nausea, photophobia, phonophobia), an important metric to patients[4], has been demonstrated in those using eCOT-NS in addition to studies showing a significant reduction in number of headache days per month and pain relief at 2 hours. For acute treatment of migraine, 75% had relief from most bothersome symptom at 2 hours with eCOT-NS compared to only 47% with sham ($p = 0.010$)[5].

Expanding beyond its clearance for preventive and acute treatment of migraine, nVNS has also been evaluated as a treatment for episodic and chronic cluster headache, a primary headache disorder with more limited treatment options. The ACT2 study evaluated nVNS for acute treatment of cluster headache and showed a significantly greater proportion of patients with

episodic cluster who were pain free at 15 minutes compared to sham (48% nVNS vs 6% sham; p = <0.01)[1].

Despite reassuring data, the literature supporting the use of neuromodulation devices is heterogeneous. The International Headache Society's (IHS) guidelines on clinical trials for neuromodulation devices are meant to standardize trial protocols and design including primary and secondary outcomes[6]. However few studies adhere to these principles making it difficult to draw adequate conclusions about device efficacy. When trials deviate from these recommendations, they may also be straying from outcomes important to patients. In a survey of patients with migraine, complete pain relief was voted the most important characteristic of acute medications followed by lack of recurrence[4]. With many device trials for acute use evaluating outcomes other than pain relief and lack of recurrence, they may be failing to assess an outcome that has a direct influence on a patient's decision to use the device again. Adherence to the IHS guidelines for the development of neuromodulation devices is important for ensuring clinical trials are monitoring the appropriate outcomes and allow for data pooling and a broader understanding of device applicability.

When considering neuromodulation for headache, cost is a common and legitimate concern. Most commercially available devices have high upfront and even recurring costs which may not be within reach for many with primary headache disorders. Costs can range from around $400 to purchase eTNS up to nearly that same amount monthly to subscribe to sTMS and nVNS with REN and eCOT-NS pricing somewhere in the middle. The MAST study, a population-based survey, showed that around 30% of those with migraine were unemployed and over 50% had household incomes less than $75,000[7]. Many of these patients are already paying large out of pocket costs for prescription medications and experience indirect costs such as missed work and productivity. Financial support for these devices is rare and only available for those with commercial insurance. Medicaid and Medicare insured patients may not be able to afford trialing and maintaining use of these devices, greatly limiting the population that may benefit.

On the converse, there are also patients with migraine without these same financial limitations, where factors such as desire to use non-pharmacologic treatments may be more important. When effective, the cost of neuromodulation may be offset by a reduction in indirect costs of a primary headache disorder, such as lost productive time at work/school, missed social opportunities, emergency department visits, worsened quality of life and disability. Some device companies offer less expensive introductory trials or money back guarantees that can improve the initial cost-accessibility. Many of these devices are available through the VA healthcare system. Over time and with greater advocacy and lobbying efforts, device costs are likely to reduce and become more affordable. Continued effort with improved research standardization may yield more effective devices and provide more robust evidence from which to guide the role of neuromodulation devices and improve insurance coverage and accessibility.

Overall, there are challenges with current pharmacologic therapies and neuromodulation is one avenue to address these gaps in care. While heterogeneous, there is data showing efficacy of neuromodulation devices for acute and preventive treatment of primary headache disorders and remarkable tolerability with minimal adverse events. It is not yet clear if the advantages of neuromodulation globally outweigh their challenges for primary headache disorders. However, there is a definite market for it and may be worth considering neuromodulation devices as options among certain subsets of patients where treatment options are more limited, when cost is not a limiting factor or among those who prefer a nonpharmacologic approach.

References

1. Halker Singh RB, Ailani J, Robbins MS. Neuromodulation for the Acute and Preventive Therapy of Migraine and Cluster Headache. *Headache*. 2019;59 Suppl 2:33-49.

2. Hershey AD, Irwin S, Rabany L, et al. Comparison of Remote Electrical Neuromodulation and Standard-Care Medications for Acute Treatment of Migraine in Adolescents: A Post Hoc Analysis. Pain Med. 2022;23(4):815-820.

3. Peretz A, Stark-Inbar A, Harris D, et al. Safety of remote electrical neuromodulation for acute migraine treatment in pregnant women: A retrospective controlled survey-study. *Headache*. 2023;63(7):968-970.

4. Lipton, R. B., & Stewart, W. F. (1999). Acute migraine therapy: Do doctors understand what patients with migraine want from therapy? Headache, 39(SUPPL. 2), S20-S26.

5. Tepper SJ, Grosberg B, Daniel O, et al. Migraine treatment with external concurrent occipital and trigeminal neurostimulation-A randomized controlled trial. *Headache*. 2022;62(8):989-1001.

6. Tassorelli C, Diener HC, Silberstein SD, et al. Guidelines of the International Headache Society for clinical trials with neuromodulation devices for the treatment of migraine. Cephalalgia. 2021;41(11-12):1135-1151.

7. Lipton RB, Munjal S, Alam A, et al. Migraine in America Symptoms and Treatment (MAST) Study: Baseline Study Methods, Treatment Patterns, and Gender Differences. Headache. 2018; 58(9).