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Therapeutic Delivery

The potential use of trigeminal nerve stimulation in the treatment of epilepsy

"...after billions of R&D dollars to develop new drugs, this needle has not budged. A new approach is needed."

Keywords: adjunctive treatment • anti-convulsant • bilateral stimulation • brain stimulation • cranial nerve stimulation • drug resistance • epilepsy • neuromodulation • non-invasive • trigeminal nerve stimulation

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Among neurological disorders, epilepsy poses an enormous clinical and societal problem, affecting approximately 50,000,000 people worldwide [1]. For individual patients, the presence of a chronic brain disorder marked by episodic convulsions and loss of control of mental and physical actions can limit occupational and social achievement. From a macro perspective, epilepsy is associated with considerable societal economic burden, accounting for a substantial proportion of the 'disability adjusted life years' ascribed to neurological illnesses [2]. Critically, approximately a third of patients with epilepsy have 'drug resistant epilepsy (DRE),' characterized as having persistent seizures despite having tried at least two different antiepileptic drugs (AEDs) [3]. Of the roughly three dozen AEDs used in the USA, approximately half have been introduced over the past four decades, and while strides have been made in improving efficacy and tolerability, the clinical challenge of DRE persists at roughly a third of all patients with epilepsy: stated differently, after billions of R&D dollars to develop new drugs, this needle has not budged. A new approach is needed.

Neuromodulation interventions offer an alternative to the administration of pharmaceutical products. These therapies are intended to alter brain function by applying electric or magnetic fields to the CNS, either directly to the CNS as in deep brain stimulation, or via peripheral or cranial nerves, as in vagus nerve stimulation. Some key theoretical advantages of neuromodulation over drug therapy are the lack of systemic exposure to key organ systems, the absence of drug–drug interactions and a reduced risk of teratogenicity. In epilepsy, these approaches have offered new hope because they utilize very different mechanisms of action than the medications, by directly changing regional brain activity, and commercially successful neuromodulation products, such as deep brain stimulation for Parkinson's Disease, have been implanted in approximately 8000 to 10,000 new patients per year worldwide [4]. Although many of these patients have benefited from their implants, the absolute numbers stand in stark contrast to the tens of millions of patients who are inadequately treated with medications and clearly need new therapeutic options. Therapeutic delivery for the surgically implantable devices has been limited, with issues around risks and costs of implantation and explantation, the limited availability of requisite surgical expertise, an inability to screen preoperatively for who will benefit and patient acceptability of an implanted system.

Noninvasive and minimally invasive neurmodulation approaches might offer the advantages of neuromodulation without the challenges of surgical implantation. Trigeminal nerve stimulation (TNS) is a new therapy for epilepsy that can offer 'neuromodulation without implantation.' Noninvasive external TNS (eTNS) offers the therapeutic benefits of neuromodulation with the convenience of a prescribed pharmaceutical and yet without the side effects of a typical AED. In studies to date, subjects have applied an 'electric patch'

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electrode to the forehead for bilateral stimulation of the V1 branch of the trigeminal nerve, for times between 8 and 12 h, predominantly at night while asleep, much as one would use a transdermal patch. Similar to most AEDs, the antiepileptic mechanism of action of eTNS appears to be related to reductions in cortical excitability [5–8], but critically, with physiologic effects focused only on targeted regions of the brain. The efficacy of adjunctive eTNS in reducing seizure frequency has been studied in open-label [9] and double-blind controlled studies [10] and outcomes are in line with other successful adjunctive treatments, albeit with smaller trials to date. As with other neuromodulation treatments, the reduction in seizures grew over time: in a recent Phase II double-blind trial at USC and UCLA, 17.8% of subjects met response criteria at 6 weeks (with response denoting ≥50% reduction in seizure frequency), while the responder rate more than doubled to 40.5% by week 18 [10], a significant within-group improvement ($p < 0.01$). While that study did not have the statistical power to detect a between-group difference, long-term data confirm that the responder rate remains high for 3–12 months after conclusion of the double-blind study [11].

A distinguishing feature of eTNS is its rapid benefit on depressed mood, which addresses a significant co-morbidity in epilepsy. As a class, antiepileptic drugs are reported to worsen mood and are associated with elevating suicidal ideation, as disclosed in their prescribing information inserts. In contrast, eTNS has been shown significantly to improve depressive symptoms under double-blind conditions in adults with DRE ($p < 0.02$) [10], and this effect was detectable at the first followup visit (week six in that study). An open proof-of-concept trial of adults with treatment-resistant major depressive disorder (and who did not have epilepsy) found significant reduction in symptom severity as early as the followup visit at week two ($p < 0.05$), with additional improvement accruing over the remainder of the 8-week trial ($p < 0.001$ across all four symptom change measures) [12]. Because this robust mood improvement occurs rapidly, subjects in research trials and patients using the system overseas have remarked that this promotes adherence to nightly self-administered stimulation: they are already feeling somewhat better early on, and so they continue to use the system while awaiting the full antiepileptic benefit.

Another differentiating feature is the radically different side-effect profile of eTNS compared with other adjunctive treatments for DRE. Many AEDs are commercially successful yet are associated with side effects including increasing suicidal and homicidal ideation, dizziness and ataxia, vision loss, cognitive impairment, aplastic anemia and hepatic failure, among others; the US FDA mandates that several of these drugs carry 'black box warnings.' In contrast, the most common side effects observed with an early prototype eTNS system were skin irritation, headache and anxiety [13].

Any new therapy requires replication of findings with carefully designed and adequately powered clinical studies before it can enter the realm of an evidence-based medical practice. Even then, questions may remain about diurnal dosing strategies, about whether adjunctive eTNS is more effective when added to some drug regimens than to others, and about whether there are subsets of patients who will enjoy greater benefits than others. Those questions can be well addressed in postapproval studies.

As a next step in development, NeuroSigma has received an investigational device exemption to proceed with a Phase III double-blind pivotal trial in DRE to evaluate adjunctive eTNS against a sham control. Positive findings from that trial could facilitate regulatory approval in the USA and support health insurance coverage so that patients could have access to the therapy. In the meantime, other studies may shed more light on mechanism(s) of action of eTNS, and on its potential use in other CNS disorders, such as Lennox–Gastaut syndrome, post-traumatic stress disorder, attention-deficit hyperactivity disorder and traumatic brain injury.

Interest in neuromodulation is growing, with both small and large companies developing new treatment approaches. Academic researchers and medical device companies are developing transcutaneous direct current or alternating current therapies along with transcranial magnetic stimulation approaches, but major pharmaceutical companies are also working to enlarge the scope of therapeutic approaches to include signals as well as molecules: the large multinational company, GSK plc, has announced its growing interest and investment in developing 'electroceuticals' and 'bioelectronic' therapies, which include neuromodulatory approaches [14]. A new era in noninvasive neuromodulation therapeutics promises to bring improved outcomes with well-tolerated and low-risk treatments to many patients, positively impacting them, their families and the physicians who care for them.

Financial & competing interests disclosure

IA Cook, CP Kealey and CM DeGiorgio are named as inventors on patents and/or patent applications concerning trigeminal nerve stimulation that they assigned to the Regents of the University of California (UC) and/or NeuroSigma, Inc. All three physicians also have leadership roles at NeuroSigma, Inc,. the exclusive worldwide licensee of UC's intellectual property on TNS, including employment and stock options. CM DeGiorgio is Vice President, Neurology; CP Kealey is Director of Global Medical

Affairs & Corporate Projects; IA Cook is Senior Vice President and Chief Medical Officer. Additionally, CM DeGiorgio and IA Cook are Professors in Residence at UCLA in Neurology (CMD) and in Psychiatry and Bioengineering (IAC). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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