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NEUROMODULATION (A ABD-ELSAYED, SECTION EDITOR)

Advances in Non-Invasive Neuromodulation

Brian Brenner[1] · **Tyler Ericson**[1] · **Lynn Kohan**[1,2]

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Abstract

Purpose of Review Pain medicine is rapidly expanding. The gap in treatment for patients with chronic pain in between traditional conservative therapy and major invasive surgery is closing. Neuromodulation is one therapeutic area that has continued to show promise for treatment of chronic pain. Our aim is to review updates in non-invasive neuromodulation (NIN) techniques as an adjunct for various chronic pain conditions.

Recent Findings Overall, the literature suggests that NIN techniques such as tCDS, TMS, TENS, tVNS, and HIFUS/LIFUS have utility in treating various types of chronic pain and have a promising future.

Summary There is a better understanding of the mechanistic basis for pain relief from NIN, as well as refinement in technology improving NIN therapy success. Future studies will need to focus on continuing to refine protocols for optimal benefit from NIN as well as implementing larger RCTs to improve the quality of data being generated in the field.

Keywords Pain medicine · Non-invasive neuromodulation · Fellowship · Interventional pain · Chronic pain · Headache

Introduction

Neuromodulation is a growing area of pain medicine that involves a variety of different surgical, minimally invasive, and non-invasive techniques that alter nervous system activity at various sites in the body [1]. The International Neuromodulation Society broadly states that "neuromodulation devices stimulate nervous tissue – with pharmaceutical agents, electrical signals, or other forms of energy – by modulating abnormal neural pathway behavior caused by a disease process. Profound effects occur including relief of pain… The reversible therapy delivers stimulation to specific neural circuits in the brain, spine, or peripheral nerves. Depending on the target, the therapy may be non-invasive or minimally invasive… neuromodulation therapies can help reestablish neural balance, similar to the way a cardiac pacemaker or defibrillator corrects heartbeat abnormalities [2]." The field of neuromodulation began in the 1960s formally with the publication of Melzack and Wall's paper on the concept of gate control theory for the control of pain and neural impulses; the idea of electrically stimulating fast myelinated A-beta fibers in the central nervous system (CNS) the slower conducting A-delta and C-fibers that transmit pain perception would be blocked from reaching the brain, thus blocking pain transmission and perception [3]. While not perfect, Melzack and Wall's idea led to the first attempt of intradural electrical stimulation by Shealy which showed promise for the inhibition of pain by generalized dorsal column electrical stimulation [4]. Since then the field of neuromodulation has grown to encompass more refined surgical and non-surgical techniques that have had various levels of success. Alongside the improvements in medical imaging quality, bench research, and medical technology, the field of neuromodulation continues to grow and takes a more sophisticated approach to nervous tissue modulation. This paper aims to cover the recent updates in the literature pertaining to non-invasive neuromodulation techniques. Most frequently described in the literature are

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✉ Lynn Kohan
LRK9G@hscmail.mcc.virginia.edu

Brian Brenner
BRB5EB@hscmail.mcc.virginia.edu

Tyler Ericson
TE4GW@hscmail.mcc.virignia.edu

[1] Department of Anesthesiology, Division of Pain Medicine, University of Virginia, Charlottesville, VA, USA

[2] Pain Management Center, Fontaine Research Park, Third Floor, 545 Ray C Hunt Dr., Charlottesville, VA 22908, USA

transcranial direct current stimulation (tcDCS), transcranial magnetic stimulation (TMS), transcutaneous direct currency stimulation (TENS), high intensity/low intensity focused ultrasound (HIFUS/LIFUS), and transcutaneous vagus nerve stimulation (tVNS). The aim is for the reader to have an overall better understanding of the mechanistic rationale, indications, and success of the aforementioned types of non-invasive neuromodulation for the treatment of chronic pain conditions in 2022 as well as highlight the limitations and areas of promise for further research in the field (Fig. 1).

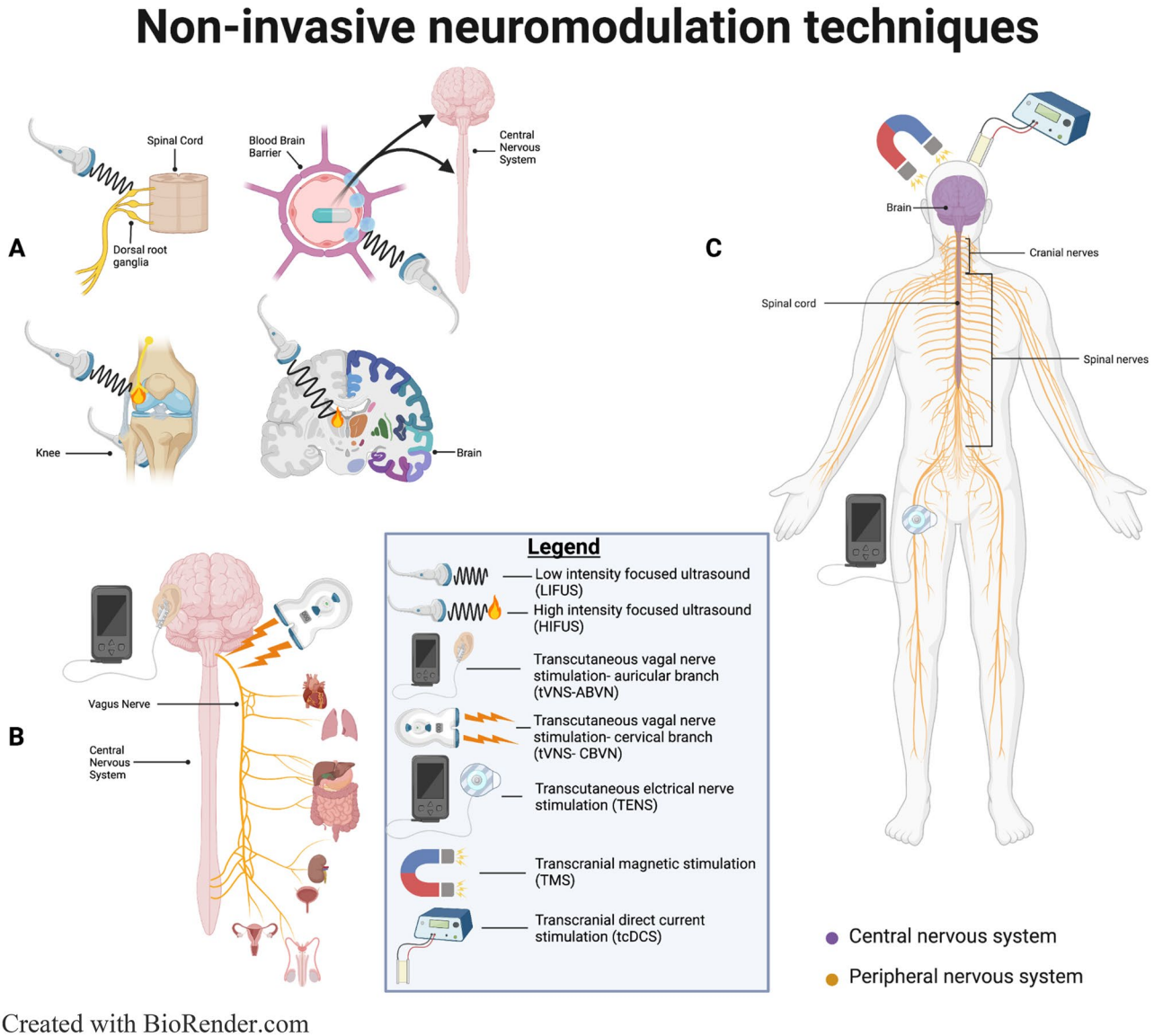

Fig. 1 Non-invasive neuromodulation techniques covered in this review. **A** Low-intensity focused ultrasound (LIFUS) and high-intensity focused ultrasound (HIFUS). This illustrates how LIFUS can be used to modulate nerves (inhibit/excitate) at the level of the spinal nerves, as well as reversibly change the permeability of the blood–brain barrier via oscillating microbubbles causing gap junction stretch and resulting temporary permeability of the blood–brain barrier. Additionally, this image illustrates how HIFUS can be used to selectively ablate nervous tissue at the level of the CNS and PNS for modification of pain perception pathways. **B** Transcutaneous vagal nerve stimulators. This image illustrates the location of action of the transcutaneous vagal nerve stimulators. The tVNS-ABVN shows the placement of the device near the tragus of the ear which stimulates the ABVN that then sends neuromodulatory information down the rest of the vagus nerve illustrated in the image. The tVNS-CBVN is illustrated by the white and blue device that emits electrical signals at the level of the cervical spine to modulate electrical signals of the vagus nerve. **C** Transcranial direct current stimulation, transcutaneous electrical nerve stimulator, and transcranial magnetic stimulation. This image illustrates the anatomic location of action of tcDCS and TMS as well as TENS, signifying the peripheral mechanism of action of TENS vs central modulation of nervous system circuits by tcDCS and TMS. Created with BioRender.com

Transcranial Direct Current Stimulation tcDCS

Transcranial direct current stimulation (tcDCS) is a non-invasive neuromodulation technique that involves the external placement of electrodes in order to generate a constant low-intensity electrical current at a specific area of the brain. The generated currents modulate neuronal tissues by polarizing the resting membrane potential without generating an action potential [5]. This modulation can be used to augment the synaptic plasticity of maladaptive chronic pain pathways. The cathode generally inhibits, while the anode generally promotes excitability in the neurons underneath the electrodes. Findings by Woods et al. found that the efficacy of tcDCS is dependent on electrode placement and recent studies have elaborated on the most effective electrode positioning [6].

tcDCS has been used for a variety of conditions including migraine, low back pain, fibromyalgia, abdominal pain, neuropathic pain secondary to spinal cord injury, pelvic pain, and knee pain after total knee arthroplasty.

Volta et al. utilized thermography in guiding the placement of tDCS cathodes in chronic migraine patients. They found that tDCS is an effective technique in migraine prophylaxis when the cathode is placed ipsilateral to a cold patch determined by thermography [7].

Rahimi et al. further demonstrated in a randomized control trial that application of the tcDCS cathode over the primary motor cortex (M1) or primary somatosensory cortex (S1) can be used for migraine prophylaxis and treatment [8]. De Icco found that anodal tDCS applied to the M1 contralateral to the perceived migraine side resulted in a significant reduction in monthly migraines when compared to sham. Furthermore, they found an increase in alpha rhythms which may represent an underlying change in corticothalamic connections [9].

A double-blinded RCT found that when targeting the left dorsal anterior cingulate cortex directly with tDCS, there was significantly less pain interference, disability, and depressive symptoms in chronic lower back pain patients [10]. A meta-analysis in 2020 regarding the efficacy of tDCS for fibromyalgia pain by Lloyd et al. showed the potential to lower pain intensity but also stated that there is need for more research regarding optimum stimulation parameters [11•]. In a review by Bayer et al. five out of six studies reported significant effects for pain reduction in different types of abdominal pain [12]. An RCT by Young et al. demonstrated that tDCS was effective in reducing Visual Analogue Scale (VAS) scores in multiple sclerosis patients who had chronic neuropathic pain [13]. A double-blinded crossover study by Divandari showed that tDCS was effective in improving quality of life and reducing pain in women with chronic pelvic pain [14]. More recently, post-surgical opioid use was found to be reduced more by dorsolateral prefrontal cortex (DLPFC) than left M1 tDCS when applied at 2 mA in four 20-min sessions after total knee arthroplasty [15].

The European Chapter of the International Federation of Clinical Neurophysiology recently published a new set of guidelines that recommended M1 anodal tDCS for neuropathic pain secondary to spinal cord injury and for fibromyalgia [16].

Other future developments with tDCS involve the use of home systems that allow for real-time feedback regarding ongoing brain activity [17]. Another potential improvement is using an alternating current with transcranial alternating current stimulation (tACS) instead of a direct current used with traditional tDCS. Within the brain, pain has been associated with oscillations at alpha and gamma frequencies. A theoretical advantage of tACS is the ability to generate a sinusoidal current which targets alpha and gamma frequencies [18].

In summary, tDCS has been shown to be effective in the treatment of various different causes of chronic pain. Newer studies are beginning to elaborate on optimal treatment durations, intensity, and electrode placement. These further developments in addition to the increasing convenience of home systems allows for exciting new opportunities for the usage of tDCS.

Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a form of neuromodulation that involves using a coil of wire to rapidly generate a changing magnetic field which, in turn, generates an electrical current that elicits synchronous brain activities. With TMS there is a generation of either activating or inhibiting action potentials on various cortical and subcortical neural networks [19].

TMS has also been reported to show improvement in conditions such as migraine and fibromyalgia as well as chronic neuropathic pain.

A randomized control study by Kumar et al. used fMRI-based neuronavigation to localize the left M1 cortex for TMS application and found that it provides long-term pain relief in chronic migraine patients [20]. Tanwar et al. demonstrated in an RCT that rTMS applied over the right DLPFC significantly reduced pain ratings for up to 6 months in patients with fibromyalgia [21]. Imperatore et al. directly compared the effects of rTMS over the DLPFC versus the motor cortex (MC) to decrease pain in patients using opioids. MC simulations resulted in a significantly greater decrease in pain than DLPFC TMS [22].

A systematic review by Gatzinsky concluded that TMS targeting the M1 resulted in a significant reduction of chronic neuropathic pain and that multiple sessions of rTMS can maintain a more long-standing effect [23].

TMS is a non-invasive form of neuromodulation that has been shown to be effective in the treatment of migraines, fibromyalgia, and chronic neuropathic pain. Newer studies have demonstrated that TMS can be particularly effective if done over the M1 or DLPFC.

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) is a neuromodulatory technique in which electrical currents are delivered transcutaneously via electrodes for localized pain analgesia. There is conventional TENS which uses high-frequency, low-intensity current to inhibit segmental pain pathways. Contrarily, there is acupuncture-like TENS which uses low-frequency, high-intensity electrical current to activate inhibitory extrasegmental pathways [24]. TENS units are usually highly adjustable and user controlled with the ability to adjust pulse width, frequency, and intensity. Conventional TENS activates non-noxious afferent nerve fibers (Aβ fibers) which modulates Aδ and C fiber-mediated nociceptive transmission in the spinal cord. Acupuncture-like TENS primarily stimulates small nociceptive fibers (Aδ and C) and small motor fibers. This mode of TENS is believed to function primarily via the release of endogenous opioids [25].

Similar to other non-invasive modes of neuromodulation, TENS has reported efficacy in headache disorders and knee pain. Chou et al. recently demonstrated in a double-blinded randomized control sham study that TENS targeting the trigeminal nerve can result in significant acute migraine pain relief [26]. A recent systematic review and meta-analysis by Wu found that TENS improved pain scores in patients with knee osteoarthritis [27].

TENS is a minimally invasive method of neuromodulation that has recently been found to be effective in the treatment of migraines and knee osteoarthritis. Future large randomized control trials with more clearly defined treatment protocols are needed before TENS is more generally accepted as an effective treatment for chronic pain.

Focused Ultrasound (FUS)

Focused ultrasound is the utilization of ultrasound waves of various frequencies that converge on a specific location creating a desired effect without affecting the surrounding tissue. A previously theoretical idea that is now possible through the advancement in ultrasound (US) and magnetic resonance imaging technology (MRI). Using high-resolution MRI guidance, it is now possible to target highly specific areas of neural tissue with US beams creating a wide array of clinical effects. The three primary proposed mechanisms of FUS therapy are (1) thermal ablation of tissue, (2) reversible disruption of the blood–brain barrier (BBB) for selective delivery of therapeutic agents, or (3) modulation (excitation/inhibition) of targeted neuronal activity [28••]. This is achieved by creating a device that can emit an array of dispersed ultrasound beams (100 s or 1000 s of beams) that converge on a single point creating a single, small area of varying amounts of energy without disturbing the surrounding tissue. A focal diameter of ~ 2 mm can be created for most transcranial FUS applications with a focal length between 2 and 20 × the focal diameter, potentially providing the ability to modulate tissues at varying depths from the skin's surface (Figs. 2 and 3) [28••].

The various mechanistic hypotheses for how FUS works are complex and beyond the scope of this paper but briefly can be thought of as the following. For thermal ablation, high-energy US waves are emitted with the intent to selectively ablate a small focal area of interest without damaging the surrounding tissue. For disruption of the blood–brain barrier, lower power and shorter bursts of ultrasound waves applied over a longer duration of time are thought to create microbubbles in the area of interest that oscillate rapid enough to cause disruption in the BBB tight junctions. For temporary inhibitory/excitatory neuromodulation, low-intensity focused ultrasound (LIFUS) waves are used to cause oscillations in the neuronal intermembrane space causing potential changes in membrane capacitance or activation of various mechanoreceptors without causing significant heating of the tissue [28••].

FUS has been used for neuroablation in the brain. Elias et al. has been using non-invasive high-intensity focused ultrasound (HIFUS) successfully since 2013 for neurosurgical ablative techniques [29]. Mainprize et al. have begun a clinical trial in 2019 for targeted drug delivery through the disrupted blood–brain barrier [30]. Lee et al. published the first human studies on low-intensity focused ultrasound (LIFUS) neuromodulation of brain activity in 2015 with promising results [31].

However, applications for chronic pain treatment remain largely unexplored. Two studies in 2009 and 2012, respectively, were done looking at ablating the central lateral thalamus with HIFUS for chronic therapy-resistant neuropathic pain, and 9/12 patients had improvement in their pain scores at 1 year [32, 33]. Since then there are 2 active independent trials ongoing at the University of Virginia (Elias) and at the University of Maryland (Gandhi) investigating lesioning the central lateral thalamic nucleus for refractory neuropathic pain at the time of writing [34, 35]. Namba et al.

Fig. 2 Focused ultrasound module (FUSmobile©)-FUS mobile focused ultrasound module used for bedside FUS applications

have recently shown that MRI-guided HIFUS (Mg-HIFUS) is an effective treatment for reduction in knee and facet joint osteoarthritis-related pain as well as bone metastasis-related pain [36]. An investigational device exemption (IDE) has been recently awarded from the FDA for the use of fluoroscopically guided FUS for the treatment of facet joint pain based on results from a promising clinical trial [37]. A multicenter clinical trial is currently recruiting based on the aforementioned IDE that will continue to explore FUS as a viable option for pain medicine physicians treating facet joint pain under fluoroscopic guidance [38]. Additionally, phase I cadaveric studies funded by the focused ultrasound foundation are beginning to examine the efficacy and safety of FUS for the treatment of SI joint pain based on feasibility studies done in a swine model [39, 40].

Overall, FUS seems to be an exciting new treatment option for chronic pain patients. New studies using techniques familiar to the pain medicine physician will enable them to be well positioned to utilize this technology in the treatment pathway for their patients. Given multiple mechanisms of action, the therapeutic potential seems large. Larger randomized control trials are actively being pursued to better

Fig. 3 Focused ultrasound transducer (FUSmobile©)-FUS mobile ultrasound transducer for bedside FUS applications

assess the effects of FUS on chronic pain and will likely lead to widespread use and adoption of the technology in pain medicine (Table 1).

Transcutaneous Vagus Nerve Stimulation (tVNS)

The vagus nerve is the main parasympathetic nerve responsible for bidirectional communication between the brain and viscera and plays an important role in pain modulation, inflammation, and brain excitability. Vagus nerve stimulation (VNS) was initially approved for use in treatment-resistant epilepsy and then major depressive disorder [41, 42]. At first, VNS involved implanted stimulator devices that generated electrical impulses at cervical branches of the vagus nerve [43]. Newer non-invasive methods have been developed which are based on the transcutaneous stimulation of either the cervical or auricular branches of the vagus nerve. Both of these branches terminate in the nucleus tractus solitarii (NTS) where the vagus nerve modulates the activity of various brainstem nuclei and higher brain segments [44]. Literature has demonstrated that tVNS affects the same pathways as invasive VNS without the risk, but the exact mechanism has yet to be completely elucidated [45•].

The cervical branch vagus nerve (CBVN) contains 20% myelinated type A and B and 80% unmyelinated type C fibers [46]. Prior studies have shown that destruction of the C type fibers during VNS did not influence the therapeutic effect of VNS, and thus its effect has been attributed to the recruitment of afferent A and B fibers [47]. Furthermore, tVNS has not been shown to elicit a painful response in individuals suggesting that the afferent C fibers are not activated during stimulation.

The auricular branch vagus nerve (ABVN) seems to have a much less predictable distribution of nerve fiber types compared to the CBVN, which may shed some insight into why stimulation of the ABVN has had more varied results compared to the CBVN. The ABVN is a pure sensory nerve which is an exception for the majority of the branches of the vagus [48]. Thus, it is to be expected that the majority of the myelinated fibers are to be of the A-group rather than the B-group autonomic fibers [45•]. Some studies have shown that ~ 50% of the axons in the ABVN belonged to the A-delta group, while 20% were likely A-beta, nearly 6 × less a-beta fibers than the CBVN [44]. This number also seemed much more widely variable among individuals, making it harder to predict what level of stimulation may be optimal [45•]. Functional and clinical studies are continuing to show the potential therapeutic benefit of tVNS for a multitude of conditions. More recently the implications of tVNS for chronic pain have been explored as a potentially beneficial non-invasive option for challenging conditions, while further work needs to be done to understand the exact mechanism of action of tVNS at the CBVN and the ABVN. The literature is beginning to suggest the success of tVNS in pain medicine. With further refinement of the understanding of ideal stimulation profiles for certain nervous tissue distributions and better tools to map and understand the composition of vagal nerve fibers in an individual patient, the therapeutic potential may continue to rise (Table 2).

Zhang et al. provided recent insights into the proposed neuronal mechanism behind taVNS by using functional MRI in patients receiving trans auricular vagus nerve stimulation (taVNS) [49]. In their study, TaVNS not only resulted in significantly reduced number of migraine days, pain intensity, and migraine attack times after 4 weeks of treatment compared with the sham, but it also resulted in

Table 1 Similarities and differences between LIFUS and HIFUS and potential applications, benefits, and limitations of the technology to date [28••]

	Frequency range	Power density (uW/cm^2)	Indications	Benefits	Limitations
Low-intensity focused ultrasound (LIFUS)	0.2–3 MHz	< 190	- Reversible BBB opening - Inhibition/ excitation of peripheral neural tissue	- Non-invasive - Allows for delivery of therapeutics previously unable to cross BBB - Reversible	- Frequencies at different ranges can have variable effects on neural modulation - Difficult to localize modulation to one neural tissue type in a given area
High-intensity focused ultrasound (HIFUS)	0.2–3 MHz	> 190	-Thermal ablation of CNS or PNS tissue - Mechanical damage of tissue	- Selective ablation of deep small structures - Permanent tissue lesioning - Non-invasive	- Only possible to lesion small area - Limited by surrounding tissue energy absorption

Table 2 Table highlighting the differences between the various types of nervous tissue found in the peripheral nervous system [53]

Class	Type of nerve fiber	Example	Diameter (um)	Conduction velocity (m/s)	Myelination
Sensory and motor	A alpha	Alpha motor neuron	13–20	80–120	Yes
	A beta	Touch and pressure fibers	6–12	35–90	Yes
	A gamma	Muscle spindle motor fibers	1–6	5–40	Yes
	A Delta	Fast pain, touch, pressure, temperature	1–5	5–40	Yes
	B	Autonomic nerves-preganglionic	3	3–15	Yes
	C	Slow pain, post ganglionic autonomic nerves, olfaction	0.2–1.5	0.5–2	No

noticeable changes in brain region connectivity on fMRI scans "between the motor-related thalamus subregion and anterior cingulate cortex/medial prefrontal cortex, and decrease the connectivity between occipital cortex-related thalamus subregion and postcentral gyrus/precuneus."

Aranow et al. recently demonstrated in a randomized, double-blind, sham-controlled pilot trial that transcutaneous auricular vagus nerve stimulation reduced pain and fatigue when compared to sham in patients with systemic lupus erythematosus [50]. Moreover, they found that plasma levels of substance P were significantly reduced from baseline following taVNS.

Muthulingam et al. recently conducted a randomized double-blinded sham controlled, cross over trial in patients with abdominal pain from chronic pancreatitis [51]. Although the study group did not have reduction in mean pain scores compared to control with a 2-week course of tVNS of the CBVN, the patients did have a reduction in their max pain scores compared to sham stimulation. Additionally, they had a reduction in pain score from both the sham and tVNS group compared to pre-study baseline pain scores suggesting a potential placebo effect. The author points out how developing a protocol for tVNS is challenging as the literature suggests a wide variety of intervention periods (2 weeks to 6 months); it has been discussed prior how the CBVN and the ABVN have different nerve fiber composition, thus making it challenging to determine the optimal stimulation intensity, frequency, and duration for maximal effect, as well as sample size ($n = 16$ finished the study) contributing to the potential conclusions. This was the first attempt at using tVNS for control of autonomically mediated chronic abdominal pain and further refinement, patient selection, and therapeutic protocols should be implemented going forward prior to long term conclusions can be made on the efficiency of tVNS for chronic abdominal pain patients.

Natelson et al. implemented a 10-week double-blind, randomized controlled trial of tVNS compared to sham stimulation with the same device followed by a 10-week open-label follow-up with active tVNS to explore the therapeutic potential of tVNS for chronic pain in gulf war veterans with diagnosed gulf war illness [52]. They implemented a CBVN method and similar to Muthulingam found no difference in pain scores between sham stimulation and active stimulation yet, an improvement in pain scores in both groups from pre-trial baseline. Again suggesting a potential placebo effect or need for a better control stimulation group that can eliminate the possibility of sham stimulation inadvertently causing vagal nerve activation. The study had similar limitations of small sample size, uncertainty of optimal protocol for frequency, duration, and intensity of stimulation and anatomic location. They propose a new study using an ABVN approach with an augmented sample size and refined protocol.

While current tVNS studies have conflicting data, overall, the data from prior invasive VNS studies and tVNS studies in select pathologies seem to be optimistic. It seems that much work needs to be done in the anatomy lab and at the bench to better determine optimal stimulation parameters for further studies. It remains feasible that tVNS could be an adjunct for treating chronic painful conditions that involve some component of autonomic transmission, yet at this time would not be a recommended therapy. Given the high potential therapeutic potential to low cost of use, further study into the elucidation of tVNS should be continued to generate more compelling data on the indications and therapeutic potential of the technology.

Conclusions

Through better understanding of the mechanistic effects of non-invasive neuromodulation in pain medicine, we are seeing an increase in the therapeutic potential of these technologies. Studies are starting to be done generating higher quality data looking at the clinical effects of the proposed therapeutic benefits of non-invasive neuromodulation. While conflicting, it appears that for many conditions, non-invasive neuromodulation may be of benefit on the spectrum of therapy for the chronic pain patient. We are years away from strong recommendations and practice

guidelines for the implementation of many types of NIN in pain medicine. With continued research into refinement of the basic science behind NIN as well as improved clinical studies for improvement in protocols and procedural techniques, the literature likely will begin to converge in consensus for the use of NIN for certain conditions in chronic pain. Currently there appears to be reasonable evidence for the use of NIN for various chronic headache conditions, targeted ablation (HIFUS) of painful joint neural tissue, as well as global NIN (tCDS, TMS, tVNS) for syndromes associated with global pain and fatigue (i.e., fibromyalgia, lupus, chronic headache). The evidence for NIN across all subtypes appears to be varied as a result of heterogeneity in the conditions treated, sample sizes, protocols for administration of NIN, as well as overall lack of high quality studies. Going forward it is expected that many of these issues will be addressed in the literature and better consensus on the indications and therapeutic potential of NIN will be elucidated. The arsenal for the pain medicine physician continues to grow closing the gap in treatment disparity for a very challenging cohort of patients; NIN alongside other emerging areas of pain medicine will likely continue to grow and improve treatment options and success for this often marginalized group of patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they do not have any conflicts of interest on the published material.

Human and Animal Rights and Informed Consent The article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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