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RESEARCH ARTICLE

ALSUntangled #75: Portable neuromodulation stimulator therapy

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Abstract

Spurred by patient interest, ALSUntangled herein examines the potential of the Portable Neuromodulation Stimulator (PoNSTM) in treating amyotrophic lateral sclerosis (ALS). The PoNSTM device, FDA-approved for the treatment of gait deficits in adult patients with multiple sclerosis, utilizes translingual neurostimulation to stimulate trigeminal and facial nerves via the tongue, aiming to induce neuroplastic changes. While there are early, promising data for PoNS treatment to improve gait and balance in multiple sclerosis, stroke, and traumatic brain injury, no pre-clinical or clinical studies have been performed in ALS. Although reasonably safe, high costs and prescription requirements will limit PoNS accessibility. At this time, due to the lack of ALS-relevant data, we cannot endorse the use of PoNS as an ALS treatment.

Keywords: Electrical stimulation, PoNSTM Device, neuromodulation

Overview

ALSUntangled reviews alternative and off-label treatments for people living with amyotrophic lateral sclerosis (PALS). Here we review a noninvasive electrical stimulation device called portable neuromodulation stimulator (PoNSTM), a topic for which we have received over 400 requests (1).

PoNSTM is a noninvasive device that delivers electrical pulses to the surface of the tongue to stimulate the lingual nerve (trigeminal nerve branch) and chorda tympani (facial nerve branch) (2–4). It consists of a mouthpiece and a control unit worn around the neck (2–4). The mouthpiece with its electrode array is applied to the tongue and held in place by the lips and teeth. The mouthpiece delivers biphasic electrical pulses to the anterior tongue (2–4). When activated, the device is perceived as a moderate tingling sensation similar to a carbonated beverage (2–4). The control unit has five buttons to allow the user to activate the device and adjust the intensity. The treating therapist may also connect the control device to a computer to review usage data (2–4).

The device is currently FDA-approved as a short-term treatment for gait deficits in patients with multiple sclerosis who are over 22 years old, when used in conjunction with a supervised therapeutic exercise program (3,5). The decision for FDA approval was based on an acceptable safety profile and very small clinical studies, including one randomized controlled trial in 20 adults with multiple sclerosis demonstrating benefits on standardized measures of gait and vestibular function (Dynamic Gait Index and Sensory Organization Test) (3,5,6). Health Canada has also approved PoNSTM for treatment of gait deficits in multiple sclerosis, as well as stroke and traumatic brain injury (7), based on an acceptable safety profile and data from very small trials (8–10).

Given the reported clinical response in multiple sclerosis, stroke and traumatic brain injury, the PoNSTM device has become of interest to people living with ALS and has been discussed in at least one online forum (11). This review will focus on PoNSTM with respect to its possible role in treating ALS.

Mechanisms

The exact mechanism for how the PoNSTM device might work in ALS has not been fully elucidated. Therefore, we assign a Table of Evidence (TOE) “Mechanisms” Grade of U (Table 1).

Theoretically, electrical stimulation of the trigeminal and facial cranial nerves, along with therapeutic exercises, might trigger structural and functional changes in the brainstem and cerebellum via a process called “neuroplasticity” (4). In animal studies, repetitive electrical stimulation can change

Table 1. Table of evidence for PoNSTM.

	Grade	Explanation
Mechanism	U	Unknown
Pre-Clinical	U	No studies in pre-clinical models of ALS.
Cases	U	No cases of device use in PALS
Trials	U	No clinical trials of device in PALS
Risks	C	No exposed patients appear to have experienced serious adverse events related to PoNS therapy, more than 10% with mild or moderate adverse effects

the way brain neurons communicate with each other; these changes are sometimes referred to as “long-term potentiation” or “long-term depression” (reviewed in 12). In case reports and very small human studies, different forms of “cranial-nerve non-invasive neuromodulation” (CN-NINM) including PoNSTM reportedly induced functional MRI and electrophysiological changes in the brainstem and cortex (4,13–16). With specific regard to PoNSTM, the fact that the lingual and chorda tympani branches of the trigeminal (V) and facial (VII) nerves project to the trigeminal and solitary nuclei may allow modulating effects on the vestibular nuclear complex, which in turn may explain the beneficial effects on balance processing (4).

While cranial-nerve noninvasive neuromodulation itself has not been examined in PALS, other noninvasive neuromodulation therapies, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are being tested as non-pharmacologic approaches for ALS treatment (17,18). These non-invasive neuromodulation therapies are proposed to work (17,18) by improving some of the synaptic dysfunction and aberrant plasticity that are occurring in PALS (19). A more detailed understanding of the cortical and synaptic mechanisms will be essential to determine appropriate neuromodulation protocols and treatment.

Pre-clinical models

We found no studies of PoNSTM therapy in recognized ALS pre-clinical models. Based on this, ALSUntangled assigns a TOE “Pre-Clinical” Grade of U (Table 1).

Of possible interest, neither high nor low frequency rTMS demonstrated benefits on disease progression in the G93A mutant SOD1 rat model of ALS (20).

Data in PALS

Cases

In the online community, ALSForums, there is discussion about the device but no reports of

experience using it (11). There are no reported cases on the website “PatientsLikeMe.” As such, ALSUntangled assigns a TOE “Cases” grade of U (Table 1).

Trials

As there are no clinical trials published on the use of PoNSTM Therapy specifically for ALS, ALSUntangled assigns a TOE “Trials” grade of U (Table 1).

Of interest, one randomized double-blinded controlled pilot clinical trial reported safety and efficacy in treatment of gait deficits in patients with multiple sclerosis (6). While these results primarily drove the device’s FDA-approval, the trial had flaws. The study had a small sample size (10 participants in each arm) without extended follow-up to determine if benefits were sustained. Disease characteristics differed between the active group and control groups; for example, 50% of participants in the active arm had secondarily progressive disease compared with only 10% in the control arm. Blinding may have been compromised since patients in the active group could perceive electric stimulation on their tongue, but the control group could not. A second small trial in 14 patients with multiple sclerosis was unable to show statistically significant benefits on gait (13). A new larger clinical trial, NeuroMSTraLS, is underway to try and address these concerns and inconsistencies (21).

Clinical trials of other forms of neuromodulation, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have occurred in PALS with mixed results (reviewed in 17). One randomized trial using rTMS to inhibit motor cortical hyperexcitability in 20 PALS reported slowing in ALSFRS-R progression (22), but these findings could not be replicated in a follow-up trial by the same group (23). A small study employing high frequency rTMS to excite the motor cortex showed acceleration of disease (20). Noninvasive electrical stimulation with tDCS and transcutaneous spinal stimulation have also been tested to modifying disease progression in ALS. Like rTMS, few studies have been performed with inconclusive results (reviewed in 17). An invasive method for applying electrical stimulation to the diaphragm in PALS appeared to shorten survival (24).

Dosing, risks, costs

PoNSTM dosing for ALS has not been determined. The phenotypic heterogeneity of ALS, with some patients having primarily bulbar and others primarily limb weakness, will be a challenge when trying to create a dosing protocol.

The PoNSTM device was considered to have an acceptable safety profile per the FDA, which

granted its approval in multiple sclerosis (3). As an electrical device, potential risks included thermal or electrical injury, muscular injury, and irritation to tongue/mouth (3). No deaths or serious adverse events were attributed to the device in the clinical trials we reviewed (3,4,6,8–10). Mild-moderate adverse events related to treatment included increased salivation, pain, and headache (3,4,6,8–10). Increased salivation is particularly concerning for PALS who may already have this symptom and are at higher risk for aspiration from it due to bulbar dysfunction. As an electrical device, contraindications, precautions, and warnings are similar to those of transcutaneous electrical nerve stimulation (3), including active malignancy, recent mouth wounds and nickel/gold/copper sensitivity. While no serious adverse effects were noted in the above clinical trials, more than 10% of participants did experience at least one mild to moderate adverse event, therefore, ALSUntangled assigns a TOE “Risks” Grade of C (Table 1).

Of note, while it is an alternative form of neuromodulation, high-frequency 20-Hz rTMS was shown to accelerate disease progression in small trial of 2 patients with ALS, leading to discontinuation of therapy within 3 months (20). Electrical stimulation of the diaphragm also appeared to shorten survival in PALS (24). These findings underscore the importance of further study of the device in PALS prior to widespread adoption.

In the United States, the PoNSTM device is only available to adults with multiple sclerosis, only by prescription, and only along with a supervised therapeutic exercise program which can occur in clinics or at home (3,5,25). The device alone reportedly costs \$14,500 US dollars (26) and is not covered by insurance (25). In Canada, the cost of a 14-week in-clinic therapy with the PoNSTM device ranges from between \$10,000–15000 Canadian dollars (27). As of June, 2023, the device is not covered by Canadian government insurance (28). The device’s parent company, Helius Medical Technologies, offers a Patient Therapy Access Program to “partially subsidize the cost” for patients with multiple sclerosis (29); however, it is not clear how much this reduces the out-of-pocket cost.

Conclusion

Considering the fact that electrical stimulation was first used as a medical treatment more than 100 years ago (30), and first used as an ALS treatment 30 years ago (31), it is disappointing that we have yet to find a clear way to use this to help PALS. PoNSTM is a newer version of this. There is a vague theoretical mechanism (neuromodulation) by which PoNSTM could potentially modulate

neuroplasticity in the brainstem and cortex, but whether it provides any beneficial or deleterious effects on ALS progression is currently unknown. While there are early, promising data showing that the PoNSTM device improving gait in patients with multiple sclerosis, this may not translate to PALS. There are no pre-clinical data or clinical trials of PoNSTM therapy in PALS to determine efficacy. The PoNSTM device appears to be relatively safe but its substantial cost and prescription-only status will limit accessibility for PALS. Given the current lack of ALS-relevant data, we cannot currently support the use of PoNSTM therapy to slow, stop, or reverse ALS progression. We hope that this review of PoNSTM and the broader topic of neurostimulation spurs future research toward helping PALS.

Declaration of interest

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