

## **Bimodal Neuromodulation of Tinnitus: Finding the Right Wire**

Published May 7th, 2024

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It is always exciting news when a novel treatment for tinnitus makes it to market. Indeed, patients suffering from tinnitus often feel they do not have many options to improve their quality of life. “You have to live with it” is still “advice” given to them when they receive the diagnosis of tinnitus. Therefore, not only do they learn that they have a likely chronic condition for which the evolution is uncertain (will it worsen, will it improve, will it stay the same?), but they also feel abandoned by some professionals who do not seem to know what to do other than give them the advice “to go forward with their life despite their unresolved condition.” When one thinks about it, these are two big pieces of information to integrate at once, and that can be overwhelming: Not only does one have to live daily with an unwanted sound in the ears/head, but that sound may remain forever since there is currently no cure to eliminate it.

Recent basic science and clinical investigations of neuromodulatory approaches for tinnitus management have fostered new hopes among audiologists and their patients but also raise issues regarding their true clinical benefit (beyond a placebo effect), the time course for the occurrence of their beneficial effects, and mechanical differences between the various approaches currently in clinical development.

### **What Have We Learned from the Basic Sciences?**

Susan Shore, a pioneering researcher now Professor Emeritus at the University of Michigan, discovered years ago that the first relay along the auditory pathways, namely the brainstem dorsal cochlear nuclei, receives not only auditory inputs but also somatosensory inputs from the trigeminal nerve (CN V) that mediates sensory innervation of the face, tongue, and neck. She and her team showed that repeatedly presenting sounds of a certain frequency and duration paired with electrical stimulation of the face or neck in a specific timing combination could obtund or enhance firing rates in the dorsal cochlear nuclei output neurons, as a consequence of synaptic (neural) plasticity. As shown in Susan Shore and her colleagues’ studies using animal models of tinnitus, the paired stimulation could either strengthen (e.g., produce long-term potentiation) or weaken (e.g., produce long-term depression) the neural synchrony between neurons in the long term, depending on the bimodal stimulation order and timing. To the extent that increased synchrony between neurons and spontaneous firing in the dorsal cochlear nuclei represent neural correlates of tinnitus, the goal of the neuromodulation would be to regulate/reduce such neural synchrony and spontaneous activity.

The team published a translational study [1] in which human participants with somatic tinnitus received either bimodal neuromodulation or sham (sound only) for 30 minutes daily for four weeks. Somatic tinnitus is a type of tinnitus in which movements such as clenching the jaw or

applying pressure to the forehead change the pitch and loudness of the tinnitus. Depending on their tinnitus spectrum, the auditory stimulus was customized for each participant, and the somatosensory stimuli were given on the cervical spine or cheek. The clinical outcomes were decreased tinnitus loudness (in dB) and scores on the Tinnitus Functional Index (TFI), a validated questionnaire measuring tinnitus severity. Participants reported reduced tinnitus loudness (on average 8 dB) and intrusiveness scores (on average 7 points) over the 4-week treatment, compared with sound-only stimulation that did not yield such improvement. The team is working to obtain Food and Drug Administration (FDA) clearance for treating tinnitus through Auricle Inc., a privately held company.

An alternate bimodal neuromodulatory strategy (applying stimuli to the auditory and somatosensory systems via the ear and tongue, respectively) has been proposed by Neuromod Devices Ltd (Lenire®) under the rationale that such bimodal stimulation increases the brain's sensitivity to sensory inputs other than tinnitus, thereby shifting the brain's attention away from the aberrant brain activity that causes tinnitus. Sound (tones plus noise, or only tones) provided via headphones is presented more or less synchronously with soft electrical impulses delivered on the tip of the tongue (located in the trigeminal nerve sensory territory, as noted above). Both sound and electrical impulses are customized to individual participants. Recommended daily use is about 60 minutes per day for several weeks/months, depending on the recommendation of the prescribing health professional (MD, ENT, or audiologist).

Three studies [2-4] sponsored by Neuromod Devices and a case series from an independent team [5] support a beneficial outcome. After 6 weeks, scores on the Tinnitus Handicap Inventory and Tinnitus Functional Index decreased in most participants among the ~80% who were compliant with the treatment (on average 11 points, with some variations across conditions and studies) and the decrease was maintained for 12 months after treatment ended. On March 7<sup>th</sup> 2023, Lenire® was granted approval from the US Food and Drug Administration for treating tinnitus in patients 18 years and older suffering from at least moderate tinnitus (as defined by the Tinnitus Handicap Inventory). Approval is currently being sought in the European Union and later Canada.

A third bimodal neuromodulation device for tinnitus treatment is the Neosensory Duo™, which combines an auditory application playing tones at various pitches with a vibrating stimulation wristband. One study [6] found that the combined stimulation of sound and wrist improved the TFI after 8 weeks compared to sound stimulation only. Interestingly, the latter also improved significantly from the baseline because sound helps decrease tinnitus severity or by the placebo effect. The science behind the improvements is unclear. It might call on attentional mechanisms whereby the brain learns which sound is real and which is internal because of the pairing between tones and tactile vibrations. In contrast to the Lenire® device available only through health professionals, and with Auricle Inc., which is not commercially available yet, Neosensory Duo™ is available to customers directly on the web. Also, it is noteworthy that the Neosensory Duo™ use modalities not customized per patient.

So, what do we think about bimodal neuromodulation? Well, evidence is building towards positive effects of such novel treatment modalities for the relief of tinnitus, and some aspects are grounded in serious basic and clinical science. However, before recommending them largely to all adults with tinnitus, we must remain careful. There is a known positive bias towards the first clinical studies for new drugs or devices, especially those sponsored by the companies that manufacture them [7]. A variety of publicly funded, independent, well-controlled studies will further our

knowledge by replicating these initial findings over time, providing answers to yet unanswered questions, and allowing greater predictive power regarding which patients will benefit the most from neuromodulation. For instance, neuroplasticity, if such is the mechanism involved, may not be equal across individuals and throughout their lifetime [8]. Factors such as age, sex, psychological traits, health, and brain status, as well as duration, type, and severity of tinnitus, to name but a few, may play pivotal roles in the neuroplasticity process and the potential benefit from neuromodulatory approaches. In parallel, an objective measure of tinnitus and a better understanding of its pathophysiology and subtypes remain important research goals to improve patient care.

Above all, people are not brains, and vice versa [9]. People are not to be reduced to brain circuitry modifiable with devices. Our ordered and disordered states of mind result from complex interactions between our inner self and the social and natural environment – which all come into play together with neurophysiological alterations in tinnitus phenomenology. Therefore, acting on neurons only will – I believe – never cancel the need for a skilled and thoughtful professional caring for their patient with problematic tinnitus. Fortunately, there are several options that audiologists can offer their patients to improve hearing and decrease tinnitus's interference with their daily quality of life. With further studies and expanding clinical experience, bimodal neuromodulation might be useful for managing tinnitus in certain patients with yet-to-be-defined clinical profiles. The technology is also expected to evolve (refining the pulse protocols, miniaturizing, and improving wearability) thereby increasing patients' compliance and treatment efficacy.

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