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Critical Review

Brain Stimulation in the Treatment of Chronic Neuropathic and Non-Cancerous Pain

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Abstract: **Chronic neuropathic pain is one of the most prevalent and debilitating disorders. Conventional medical management, however, remains frustrating for both patients and clinicians owing to poor specificity of pharmacotherapy, delayed onset of analgesia and extensive side effects. Neuromodulation presents as a promising alternative, or at least an adjunct, as it is more specific in inducing analgesia without associated risks of pharmacotherapy. Here, we discuss common clinical and investigational methods of neuromodulation. Compared to clinical spinal cord stimulation (SCS), investigational techniques of cerebral neuromodulation, both invasive (deep brain stimulation [DBS] and motor cortical stimulation [MCS]) and noninvasive (repetitive transcranial magnetic stimulation [rTMS] and transcranial direct current stimulation [tDCS]), may be more advantageous. By adaptively targeting the multidimensional experience of pain, subtended by integrative pain circuitry in the brain, including somatosensory and thalamocortical, limbic and cognitive, cerebral methods may modulate the sensory-discriminative, affective-emotional and evaluative-cognitive spheres of the pain neuromatrix. Despite promise, the current state of results alludes to the possibility that cerebral neuromodulation has thus far not been effective in producing analgesia as intended in patients with chronic pain disorders. These techniques, thus, remain investigational and off-label. We discuss issues implicated in inadequate efficacy, variability of responsiveness, and poor retention of benefit, while recommending design and conceptual refinements for future trials of cerebral neuromodulation in management of chronic neuropathic pain.**

Perspective: ***This critical review focuses on factors contributing to poor therapeutic utility of invasive and noninvasive brain stimulation in the treatment of chronic neuropathic and pain of non-cancerous origin. Through key clinical trial design and conceptual refinements, retention and consistency of response may be improved, potentially facilitating the widespread clinical applicability of such approaches.***

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Chronic neuropathic pain of noncancerous origin is one of the most prevalent disorders, affecting about 8% of the general population.[132] Patients with neuropathic pain report the poorest health and highest disability.[129] The direct medical and societal costs are staggering. Patients not only incur 3 times higher expenditures than those without neuropathic pain[12] but 43% report disruption of employment status, while 80% note reduction in work productivity.[80] The consequent loss in earnings can be significant, ranging between $US45,000 and $US89,000, for certain diagnoses.[100]

Medical treatment of chronic neuropathic pain remains frustrating for both patients as well as clinicians. Response to drugs is unpredictable and varies considerably from one condition to another.[7] Despite advancements, pharmacotherapy demonstrates poor specificity, owing to limited knowledge on pain-syndrome-specific pathophysiology. Further, the high degree of side effects impacts cognition, particularly executive functions, affects the individual's ability to work,[78] and also raises concerns about organ toxicity and addiction potential. In light of evidence that supports only partial, inconsistent efficacy of conventional management in 40 to 60% of patients,[34,123] there is a clear need for therapeutic approaches that provide specific, predictable, effective pain relief while mitigating risks associated with pharmacotherapy.

Neuromodulation: Novel, Specific Therapeutic Technique

Neuromodulation may represent a more specific adjunct or in some cases an alternative to current medical management. As a means of supplanting conventional medical management in chronic pain originating from spinal degenerative and peripheral neuropathy causes, implanted spinal cord stimulation (SCS) has been, traditionally, the most common clinical method of neuromodulation.[56] It is an effective adjunct in failed back surgery syndrome[56] and safe and efficacious in complex regional pain syndrome.[81,126] However, even in failed back surgery syndrome, the most common indication for SCS, 50% of patients fail to respond to SCS and are left with limited therapeutic options.

Poor outcomes of SCS may result from inadequate targeting of the multidimensional experience of pain, patterns of which are ultimately believed to originate from neural networks in the brain.[82] Neuromodulation that adaptively targets brain activity may be a promising, focused method of modifying experience associated with multiple facets of pain. This idea bears origin in Melzack's theory that "brain … (acts) as an active system that filters, selects and modulates inputs," which founded the theoretical framework for pain experience, called the neuromatrix. Envisioned as a matrix of neural circuits with cyclical processing and integrated activity of somatosensory system, limbic, and cognitive pathways as well as thalamocortical interactions,[82] the neuromatrix, correspondingly, processes 3 main spheres of pain experience: sensory-discriminative, affective-motivational, and evaluative-cognitive. Over time, however, repeated central or peripheral sensitization of these components leads to chronification of pain experience,[6,127] further complicating diagnosis and treatment selection.

In the present article, we focus on methods of cerebral neuromodulation, which show promise in addressing limitations of traditional methods in pain management, pharmacotherapy, and SCS. By targeting components subtending different spheres of pain, including suppressing activity of sensitized structures and facilitating adaptive compensatory synergists within the neuromatrix, focused cerebral neuromodulation may produce generalized benefits, interrupting the vicious cycle of sensitization-chronification. We focus on invasive (deep brain stimulation [DBS] and motor cortical stimulation [MCS]) and noninvasive (repetitive transcranial magnetic stimulation [rTMS] and transcranial direct current stimulation [tDCS]) methods and their nodes within pain circuits. Despite promise, cerebral neuromodulation remains investigational and off-label in pain management; the following sections discuss the evidence in support of as well as factors that diminish confidence in the efficacy of these techniques.

Invasive Cerebral Neuromodulation

Deep Brain Stimulation: Thalamic Nuclei, Periventricular Gray (PVG), Periaqueductal Gray (PAG)

In the management of pain, traditionally, the sensory nuclei of the thalamus are targeted for neuropathic, while periventricular gray (PVG) and periaqueductal gray (PAG), both endorphin-releasing regions,[1,115] are stimulated in nociceptive syndromes (such as low back pain). Despite evidence of efficacy,[27,45,75,103] DBS remains off-label for chronic pain management, although it has now become a standard of care for the management of advanced movement disorders.[33,43,58]

Long-term outcome of DBS in chronic pain varies considerably across study designs that affects its therapeutic utility.[24] Preliminary reports support its efficacy and safety in chronic pain,[68,112,115,134] whereas large-scale studies demonstrate mixed results. Levy et al[69] reviewed the long-term outcomes of 141 patients (84 with deafferentation pain mainly treated with sensory thalamic stimulation and 57 with nociceptive pain managed with PAG/PVG stimulation) following implantation of DBS for an externalized trial. Approximately 60% of the total sample responded favorably and subsequently received a fully internalized system. At post-6-year follow-up,

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