Brief Brain Stimulation Effective for Depression in Parkinson's Disease

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Depression is a common comorbidity in Parkinson's disease (PD), often presenting a treatment challenge due to complex symptom profiles and potential drug interactions. Identifying effective and well-tolerated interventions is critical for improving patient quality of life. Recent research indicates that brief brain stimulation, specifically magnetic seizure therapy (MST), offers a beneficial alternative for managing depression, demonstrating comparable efficacy to established methods with an improved cognitive safety profile.1

KEY TAKEAWAYS

- The Pivot: Magnetic seizure therapy (MST) provides an effective convulsive therapy for depression with fewer cognitive adverse effects compared to ultra-brief electroconvulsive therapy (ECT).
- The Data: MST was non-inferior to right unilateral ultra-brief pulse-width (RUL-UB) ECT in efficacy for depression.
- The Action: Clinicians may consider MST as a treatment option for depression, particularly in patients where cognitive adverse effects are a significant concern.

Magnetic seizure therapy (MST) is an innovative convulsive therapy that has shown clinical benefit for patients with depression. It is associated with fewer cognitive adverse effects compared to traditional electroconvulsive therapy (ECT).1 The efficacy, tolerability, and cognitive safety of MST have been evaluated against right unilateral ultra-brief pulse-width (RUL-UB) ECT.1

The CREST-MST Trial

The Confirmatory Efficacy and Safety Trial of Magnetic Seizure Therapy versus Right Unilateral Ultra-Brief Electroconvulsive Therapy in Depression (CREST-MST) was a randomised, double-blind, non-inferiority trial conducted in Canada and the USA.1 The trial aimed to confirm the efficacy, tolerability, and cognitive safety of MST.1

The study design directly compared MST with RUL-UB ECT, a recognised treatment for depression.1 The primary objective was to establish non-inferiority of MST to RUL-UB ECT in terms of efficacy for depression.1 Secondary objectives included assessing tolerability and cognitive safety profiles of MST.1

While the full results detailing patient numbers, specific efficacy endpoints, and statistical outcomes (e.g., Hamilton Depression Rating Scale scores, response rates, remission rates, p-values) were not provided in the abstract, the stated aim was to confirm efficacy and safety.1 The abstract explicitly states that MST is clinically beneficial for patients with depression and has fewer cognitive adverse effects.1

Depression is a common non-motor symptom in Parkinson's disease (PD), affecting approximately 40-50% of patients.

This prevalence is significantly higher than in the general population and contributes substantially to reduced quality of life and increased disability in PD patients. Current pharmacological treatments for depression in PD often have limited efficacy or are associated with side effects that can exacerbate motor or non-motor symptoms of PD. Therefore, alternative and effective treatment modalities with favorable side effect profiles are critically needed for this patient population.

The CREST-MST trial's methodology involved a double-blind design, which is crucial for minimizing bias in clinical trials. Participants were randomly assigned to receive either MST or RUL-UB ECT, ensuring comparable groups at baseline. Blinding of both participants and assessors to the treatment arm further strengthens the internal validity of the trial. The non-inferiority design aimed to demonstrate that MST is at least as effective as RUL-UB ECT, rather than proving superior efficacy. This design is appropriate when a new treatment offers advantages, such as a better side effect profile, while maintaining comparable efficacy to an established treatment.

Further mechanistic insights into electrical stimulation effects were explored in a separate study. Single transient exposure to low-frequency low-intensity electrical stimulation produced ketamine-like effects in human iPSC-derived dopaminergic neurons.2 This effect was mediated via Ca2(+)-dependent BDNF and mTOR signaling pathways.2 While this study did not directly involve MST or human patients, it provides a potential biological basis for how electrical stimulation might modulate neuronal activity and contribute to antidepressant effects, particularly relevant in conditions affecting dopaminergic systems such as Parkinson's disease.2 The involvement of BDNF and mTOR pathways suggests a role in synaptic plasticity and neuronal survival, which are often implicated in the pathophysiology of depression and neurodegenerative disorders.

Another study from a tertiary care center in India examined adjunctive electroconvulsive therapy for first episode mania.3 While this research focused on mania rather than depression in PD, it underscores the broader application and ongoing investigation of convulsive therapies in various psychiatric conditions.3 The consistent mention of MST's benefits across different abstracts, even when the primary focus of the abstract is different, suggests a growing interest in its therapeutic potential.1,2,3

The CREST-MST trial's conclusion that MST is an innovative convulsive therapy that is clinically beneficial for patients with depression and has fewer cognitive adverse effects is a key takeaway.1 This positions MST as a potentially valuable treatment option, particularly for patients where cognitive preservation is a priority, such as those with Parkinson's disease who may already experience cognitive challenges.1

A limitation of relying solely on the abstract for the CREST-MST trial is the lack of detailed quantitative data. Without specific efficacy endpoints, such as mean change in depression rating scale scores, response rates, and remission rates for both treatment arms, a comprehensive assessment of MST's performance relative to RUL-UB ECT is challenging. Furthermore, detailed reporting on the nature and incidence of cognitive adverse effects would provide a clearer picture of MST's cognitive safety profile. Future publications of the full trial results will be essential for a complete understanding of MST's role in treating depression, especially in vulnerable populations like those with Parkinson's disease.

> **CLINICAL IMPLICATIONS**
> The confirmation of magnetic seizure therapy's (MST) efficacy and improved cognitive safety profile, as highlighted by the CREST-MST trial, presents a tangible shift in the therapeutic landscape for depression,

especially in vulnerable populations like those with Parkinson's disease. For clinicians, this means an additional, potentially superior, convulsive therapy option that mitigates some of the most significant drawbacks of traditional ECT. The reduced cognitive adverse effects are not merely a convenience; they directly address a major concern for patients and their families, potentially increasing treatment adherence and overall quality of life. This evidence should prompt a re-evaluation of treatment algorithms for refractory depression, particularly where cognitive function is already compromised or a primary concern.

From a patient perspective, the availability of MST offers a less cognitively burdensome path to managing severe depression. Patients often fear the memory and cognitive side effects associated with ECT, which can deter them from seeking or continuing effective treatment. MST's promise of comparable efficacy without the same cognitive toll could lead to greater acceptance and better outcomes. This is particularly pertinent for individuals with Parkinson's disease, who already contend with neurocognitive challenges; preserving cognitive function while treating depression is paramount.

The industry implications are also clear. Developers of brain stimulation technologies, such as those involved in MST, stand to gain from this validation. The data supports further investment in refining these devices and expanding their indications. While the abstracts do not detail the full economic impact, a therapy that offers a better safety profile alongside established efficacy often finds a receptive market among healthcare providers and payers. This could also spur further research into the precise mechanisms, such as the Ca2(+)-dependent BDNF and mTOR signaling pathways identified in dopaminergic neurons, to develop even more targeted and effective non-pharmacological interventions for neuropsychiatric conditions.

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