Neuromodulation for major depressive disorder: innovative measures to capture efficacy and outcomes

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Major depressive disorder is a common and debilitating disorder. Although most patients with this disorder benefit from established treatments, a subset of patients have symptoms that remain treatment resistant. Novel treatment approaches, such as deep brain stimulation, are urgently needed for patients with treatment-resistant major depressive disorder. These novel treatments are currently being tested in clinical trials in which success hinges on how accurately and comprehensively the primary outcome measure captures the treatment effect. In this Personal View, we argue that current measures used to assess outcomes in neurosurgical trials of major depressive disorder might be missing clinically important treatment effects. A crucial problem of continuing to use suboptimal outcome measures is that true signals of efficacy might be missed, thereby disqualifying potentially effective treatments. We argue that a re-evaluation of how outcomes are measured in these trials is much overdue and describe several novel approaches that attempt to better capture meaningful change.

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Introduction

Major depressive disorder is the most common psychiatric disorder and a leading cause of disability worldwide.[1,2] Although many people with this disorder improve with conventional treatment (ie, medication, psychotherapy, or both), up to 30% have treatment-resistant major depressive disorder.[3,4] There is a pressing need to develop novel treatments for these patients.

With compelling evidence that major depressive disorder results from disturbances in corticolimbic circuits regulating affective processing, several strategies, such as deep brain stimulation (DBS), have been developed to directly intervene on these illness-driving circuits.[5–7] Although DBS is approved for the management of movement disorders, it remains under investigation for the treatment of major depressive disorder.

For investigational treatments to gain regulatory approval they must be shown to be safe and effective in late-phase randomised controlled trials (RCTs). Because efficacy is determined by the primary outcome measure, the success of any intervention depends on how accurately and comprehensively the outcome measure captures the treatment effect. A suboptimal outcome measure could result in the loss of important information about the intervention or distort the true results of the study. Measuring treatment outcomes is particularly challenging in psychiatric disorders, such as major depressive disorder, for which there are no reliable biomarkers, and outcomes are based on subjective rating scales assessing various aspects of depression (eg, sadness, guilt, sleep, appetite).

Despite encouraging results from open-label DBS studies for major depressive disorder,[8–12] two large multicentre RCTs did not show a statistically significant improvement in the active stimulation group compared with the sham group.[13,14] Several explanations have been put forth to account for these negative results, including the use of suboptimal outcome measures and poor trial design.[15–18] These possibilities build on previous suggestions that there is a need for improved methods for capturing efficacy in neuromodulation trials for major depressive disorder.[15–17,19,20]

In this Personal View, we argue that the most common measures used to assess depressive symptoms in neurosurgical trials might be missing important treatment effects and that trial-related factors might exacerbate these shortcomings. We advocate that there is a need to re-evaluate how we measure outcomes in neuromodulation trials for major depressive disorder and we describe several novel approaches that attempt to better capture clinically meaningful change.

Fundamental challenges

Commonly used outcome measures

In the absence of objective biomarkers, subjective verbal reports remain the gold standard for assessing treatment efficacy in major depressive disorder. The two most common outcome measures used in neurosurgical trials of major depressive disorder—the Hamilton Depression Rating Scale (HAM-D)[21] and the Montgomery–Åsberg Depression Rating Scale (MADRS)[22]—have limitations and might not be optimal for assessing treatment efficacy in these trials. For one, these clinician-administered scales were not developed or validated for use with patients with treatment-resistant major depressive disorder or for monitoring symptoms over long periods of time, both of which are key features of neurosurgical trials in major depressive disorder. In addition, the MADRS does not capture all of the core criteria of major depressive disorder as defined by DSM-5. For example, it does not include items assessing hypersomnia, weight gain, or appetite increase, even though these symptoms occur in a substantial number of affected patients.[23] By contrast, the HAM-D focuses heavily on physiological symptoms of depression, such as insomnia and somatic symptoms. In addition, neither the MADRS nor the HAM-D captures outcomes that are most important to individuals with major depressive disorder, including reduced negative self-talk, less time spent dwelling on negative experiences, or positive features of mental

health, such as optimism and self-confidence.[24,25] Another limitation of these scales is that they do not dissociate various aspects of depression (eg, anhedonia, melancholic symptoms, emotional dysregulation), which have overlapping but different neurological bases.[9,26–30] The ability to distinguish different aspects of depression might be particularly important for elucidating whether specific depressive symptoms or major depressive disorder phenotypes preferentially respond to neuromodulation of specific brain targets.[27,30,31] A further shortcoming of these rating scales is that they are based on retrospective reports. This limitation is problematic because patients' mood states at study visits might alter their perception of mood symptoms over the previous week or two.[32] Although the MADRS and HAM-D assess some symptoms better than others, failure to capture improvements on missed dimensions might negatively affect the measurement of actual treatment effects and the interpretation of trial results.

Dichotomisation of treatment categories

Most neurosurgical studies in depression, including the two RCTs described above, classify participants as responders or non-responders, with responders typically defined as having a 50% or greater reduction in baseline scores on the HAM-D or MADRS. A small number of studies additionally categorise patients as partial responders (ie, having a >25% but <50% reduction from baseline scores at follow-up). Although classifying patients into discrete categories might be appealing for its simplicity, determining efficacy on the basis of a single cutoff score at a single point in time can have substantial implications for the interpretation of trial results. For instance, reliance on cutoff values negate smaller changes, which might be meaningful to patients.[33] Consider the patient whose score falls just below the 50% threshold yet reports subjective improvements in mood and considers the treatment a success. This patient would be categorised as a non-responder (or a partial responder), and yet might be indistinguishable from a patient whose score falls just above the 50% threshold. Consequently, strict cutoff scores might fail to capture the full spectrum of treatment effects and, by extension, might not be meaningful at the individual level.[34]

Assessing the outcome at a fixed point in time

Most major depressive disorder neuromodulation studies define response as a percentage change on a depression severity measure (typically the HAM-D or MADRS) from baseline to endpoint. One problem with this approach is that it ignores all the datapoints collected between baseline and endpoint, and therefore, might overestimate or underestimate a patient's response to treatment.[20,35] For example, a patient might do well for most of the trial but could have a dramatic increase in symptoms at the endpoint (perhaps due to a life stressor); thus this patient's true response would be underestimated.[35] There have been some attempts to address this problem with statistical approaches that take all datapoints into account (eg, the area under the curve).[20,35] These approaches are simple to implement and could be used to reanalyse previously collected data.[20]

Target symptom reduction thresholds

For patients with chronic, treatment-resistant depression, the question remains whether a 50% reduction in depressive symptoms is necessary to consider the treatment worthwhile. For example, the 90 patients who enrolled in the BROADEN DBS trial,[13] on average, had depressive episodes lasting more than 8 years and tried more than 20 treatments over their lifetime. In this trial, the response was defined as at least a 40% reduction in depression severity on the MADRS; however, this lower threshold might still have been too high given the severity of these patients' symptoms. There are reports that patients with major depressive disorder can perceive clinically relevant changes in symptoms at much lower thresholds.[20,33] A partial response to treatment might be meaningful, particularly if accompanied by improvements in quality of life or daily functioning. In addition, a partial response might be further enhanced by psychotherapy, which patients might not have tolerated before treatment with neuromodulation.[36,37] Moving forward, it must be kept in mind that it is the patient's definition of a successful outcome that matters the most and the sustainability of this effect over time.

Time to follow-up

The time at which the primary outcome is assessed can be as important as the measures selected for a trial. The results from several neuromodulation studies (DBS and vagus nerve stimulation) suggest that improvement in depressive symptoms might occur over many months or even longer.[10,13,17,38] In the BROADEN trial, when patients were tracked for 2 years instead of the 6 months used for futility analysis, the response rate improved from 20% to 50%.[13] In another DBS study, the greatest improvement in depressive symptoms was observed 2 years after treatment (70% reduction on the HAM-D on average) compared with 1 year after treatment (43% reduction on the HAM-D on average) and 24 weeks after treatment (44% reduction).[10] Findings from individuals with obsessive-compulsive disorder also suggest that the benefits from neuromodulation treatments might take more than 2 years to fully emerge.[39,40] Longer study duration might also be necessary to allow patients to benefit from optimal stimulation parameters and for showing the durability of treatment response. Demonstrating the durability of treatment response is particularly important given the invasiveness of neurosurgical treatments and that patients enrolled in these studies have depressive symptoms that are prone to relapse. Extended follow-up times will need to be balanced with financial and logistical considerations

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and the field will need to develop innovative ways of dealing with patient dropout or those lost to follow-up.

Practical solutions

Improved rating scales

Given the subjective nature of depression, rating scales for depressive symptoms will probably remain an important endpoint in neurosurgical trials of major depressive disorder. Because there are limitations associated with current depression scales, there is a need for improved measures that accurately capture patients' symptoms before and after treatment. These scales should be designed with the study population in mind (ie, patients with treatment-resistant major depressive disorder), capture all of the DSM-5 core criteria of major depressive disorder, be sensitive to changes in symptoms, and include items deemed most important to patients seeking surgical interventions. Qualitative methods could be used to develop items that are important to patients and to iteratively refine item phrasing, structuring, and consistency in meaning.[34] In addition, new scales should be developed with modern psychometric models, such as item response theory, to ensure that the resultant measures reliably and accurately measure the dimensions of depressive symptomatology.[34]

In addition to depression severity rating scales that cover a broad range of symptoms, the field might benefit from scales that focus on symptoms and behaviours (ie, clinical phenotypes) that arise from specific malfunctioning neural circuits. Such scales would be crucial for evaluating whether modulating specific circuits is effective at altering the symptoms and behaviours believed to be linked to that circuit.[27,30,31,41] If successful, the efficacy of a particular treatment could then be gauged by its effect on those symptoms and behaviours rather than the entire major depressive disorder syndrome.[27]

Focus on quality of life

Historically, primary outcome measures in treatment studies of major depressive disorder have focused on symptom reduction. However, symptom reduction without substantial improvements in quality of life might be insufficient for continued remission.[25,42,43] Although depressive symptoms correlate with measures of quality of life,[44,45] measures of quality of life capture important information beyond symptom improvement (eg, the ability to carry out activities of daily living, engagement in social and leisure activities, and relationships with others) and should be a key outcome in neurosurgical trials of major depressive disorder. Changes in quality of life could be assessed using existing measures if appropriately validated, or with newly developed measures specific for intervention studies and patients with treatment-resistant major depressive disorder. Additional research is needed to determine the best way to incorporate quality of life measures into neurosurgical trials (ie, as a coprimary endpoint or part of a composite primary endpoint).

Patient engagement

Patients are increasingly invited to play a role in determining what constitutes a clinically important treatment effect.[19,34,46,47] To date, few studies have applied qualitative methods to systematically examine outcomes that are valued by patients,[37,48,49] and to the best of our knowledge, these studies have not been done in patients with treatment-resistant major depressive disorder. Neuromodulation trials for major depressive disorder typically focus on scores on the MADRS or HAM-D; however, it remains unknown whether improvements on these measures translate into meaningful improvements according to patients. Individual interviews could be used to identify content domains that are important to patients with treatment-resistant major depressive disorder seeking surgical interventions, and overlooked in current measures.[47] de Haan and colleagues[37] used an interview approach with patients with obsessive-compulsive disorder to examine changes in patients' lives 9–18 months after DBS. The authors reported that the interviews captured substantial changes in functioning that were not picked up by the primary outcome measure, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Most notably, several of the study participants classified as non-responders by the Y-BOCS did in fact report benefiting from treatment (eg, being more spontaneous and having greater trust, self-reliance, and self-confidence). In fact, one patient classified as a non-responder expressed in the interview that "DBS has saved my life…it made my life bearable."[37] The themes that emerge from patient interviews could ultimately inform the development of clinically meaningful quantitative measures for use in future neuromodulation trials for major depressive disorder.

Goal setting

Achieving specific goals might be an important metric of success to patients with treatment-resistant depression (eg, returning to the workplace or school, increased independence in daily activities, resumption of valued hobbies). With goal setting, patients identify their own goals before treatment, and outcomes are measured on the basis of changes in those prespecified domains.[50,51] Kubu and colleagues[50] applied this approach in patients with Parkinson's disease undergoing DBS for management of motor symptoms. They found that patients' goals for seeking out DBS in terms of their ability to participate in valued activities varied considerably and that the most widely used scales in DBS studies of Parkinson's disease (eg, Parkinson's Disease Questionnaire-39 and the Unified Parkinson's Disease Rating Scale) did not assess the symptoms or behavioural goals that were most important to patients.[50,51] To the best of our knowledge, goal setting has not been applied in neuromodulation studies of major depressive disorder, although this measure would nicely complement other outcomes.

Search strategy and selection criteria

References for this Personal View were identified through searches of PubMed for articles published from Jan 1, 1995, to Jan 1, 2020, by use of the terms "treatment-resistant depression", "major depression", "deep brain stimulation", "DBS", "brain stimulation", "neuromodulation", "neurosurgery", "Hamilton Depression Rating Scale", "Montgomery Asberg Depression Rating Scale", "depression rating scales", and "outcome measures". We limited our results to peer-reviewed articles about studies in humans. References were then selected on the basis of relevance to the content of this Personal View. Only articles published in English were included.

Technological innovation for outcome measures

In neuromodulation studies of major depressive disorder, symptoms are typically assessed on a weekly or monthly basis, requiring patients to retrospectively recollect their symptoms. However, this approach fails to capture the dynamic nature of mood symptoms and is affected by recall bias. Advances in mobile tools now allow for mood symptoms to be monitored in real time,[52–55] enabling a more accurate and comprehensive characterisation of mood symptoms than standard episodic rating measures. Several studies have shown that mobile tools are a valid and feasible approach to assessing mood symptoms,[52,55] including a brain stimulation study in patients with epilepsy.[56] Many mobile phone tools (eg, smartphone applications) also allow for the collection of continuous behavioural data, such as physical activity, sleep patterns, social media usage, typing speed (ie, words per minute), and voice and speech features.[57–59] The collection of these data, termed digital phenotyping, might capture clinically relevant changes[57,58] and prove to be better at predicting clinical outcomes than episodic rating scales. However, these tools have not yet been systematically evaluated in major depressive disorder neuromodulation trials, and, therefore, their clinical utility remains to be shown.

Standard DBS is open loop, in which stimulation parameters are adjusted on the basis of subjective evaluations at clinic visits that occur weeks to months apart. By contrast, a closed-loop system adjusts stimulation parameters on the basis of the direct measurement of abnormal neural activity, thereby providing more precise and patient-specific treatment than the open-loop system.[60,61] Closed-loop approaches have been successfully applied in the management of movement disorders, epilepsy, and pain,[60–63] but have yet to be used in major depressive disorder. The use of such approaches in major depressive disorder has largely been hampered by the inability to identify brain signals that reliably track with mood symptoms, although there has been some initial progress in this area.[64,65] Additional research is needed to make these closed-loop therapies a reality for the treatment of major depressive disorder.

Novel study designs

In addition to outcome measures, trial design plays a relevant role in response rates. When designing double-blind studies, researchers should consider adaptive designs. One possibility is an open-label stimulation phase followed by a blinded crossover phase, in which patients receive active treatment followed by sham or vice versa.[66] An alternative approach is to have open-label stimulation followed by a randomisation phase only for responders, whereby non-responders would continue to undergo open-label stimulation. These study designs could allow patients to benefit from optimal stimulation parameters, thereby providing the highest possible chance of efficacy in the active group. As we have discussed, longer study durations might also be crucial for elucidating true response rates and such studies could benefit from incorporating epidemiological outcomes, such as years of disability, number of hospitalisations, years of work, and suicide attempts. These metrics could be compared against baseline data to gain a broad, holistic perspective of the effect of treatment on patients' lives. Finally, future studies could investigate the combined effect of neuromodulation and psychotherapy given promising results from preliminary studies.[36,37]

Challenges to incorporating novel outcome measures in neurosurgical trials

There are several challenges associated with incorporating additional measures into clinical trials. First, adding scales to trials increases patient burden and, potentially, costs from additional clinic visits. Second, it remains to be determined how quality of life and patient-specific measures should be incorporated into neurosurgical trials. Should trials have coprimary endpoints? Should composites be created from multiple independent scales and if so, should all scales be weighted equally? Further, if patients achieve their pretreatment goals with minimal symptom reduction, should that be considered a successful outcome? Third, there might be challenges convincing regulatory bodies of the importance and validity of non-traditional outcome measures.[67] Finally, there are several ethical challenges that need to be considered when using mobile phone tools to monitor depressive symptoms and behaviours. For instance, will study patients feel comfortable having their day-to-day actions closely monitored? Will these data be shared with patients? Can patients trust that their data will be protected? These questions will need to be addressed before these methods are adopted as clinical standards.

Conclusion

This Personal View highlights the limitations associated with common outcome measures used to assess the efficacy of interventions in neurosurgical trials for major depressive disorder and how trial-related factors might exacerbate these shortcomings. These limitations are particularly acute for innovations in surgical approaches

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for major depressive disorder given that the patients enrolled in these trials have treatment-resistant symptoms and are in urgent need of an effective intervention strategy. The risk of continuing to use suboptimal outcome measures and study designs is that true signals of efficacy might be missed, thereby disqualifying potentially effective treatments for patients who might have exhausted all other treatment options. There is a pressing need for updated assessment approaches that comprehensively capture clinically meaningful change. This need is not only a medical imperative but also a scientific and ethical one.

Contributors

JSR, BD, and NL conceptualised the study, did the literature search, and drafted and revised the manuscript. PG, CH, MC, and JI drafted and revised the manuscript.

Declaration of interests

PG was an unpaid consultant for St Jude Medical and served on an advisory board for Janssen and Bristol-Myers Squibb. CH was part of an unrelated advisory board for Medtronic. JSR, BD, MC, JI, and NL declare no competing interests.

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