Commonly used outcome measures in neurosurgical trials for major depressive disorder might not capture clinically meaningful treatment effects

There is a pressing need to develop effective treatments for individuals with major depressive disorder (MDD) who have not responded meaningfully to conventional treatments (eg, pharmacotherapy and psychotherapy). For these patients, possible therapeutic alternatives include neurosurgical treatments, such as deep brain stimulation (DBS) or ablative surgery. However, response rates in studies examining the efficacy of these treatments have been mixed. Several explanations have been proposed to account for the mixed findings, including patient selection, trial design, target selection and DBS parameters.[1] One commonly overlooked reason might be that the primary outcome measures used in these trials (eg, measures of depressive symptom burden) do not fully capture improvements in all patients who in fact demonstrate improved quality of life and functioning.[2]

The Hamilton Depression Rating Scale (HAM-D) and the Montgomery–Åsberg Depression Rating Scale (MADRS) are the two most commonly used primary outcome measures in neurosurgical trials for MDD. Patients in these trials are most often classified 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. The HAM-D and MADRS have been criticised for failing to measure functional domains that matter most to patients.[3] Here, we present the case of a 28-year-old woman who underwent MR-guided focused ultrasound (MRgFUS) capsulotomy for treatment of refractory MDD. Despite being classified as a non-responder based on her HAM-D and MADRS change scores, the woman reported significant improvements in her quality of life and functioning, and expressed that in her view, the treatment was successful. The woman's case demonstrates that reliance on the HAM-D or MADRS as the sole criterion for response might miss clinically meaningful treatment effects in patients with refractory MDD.

The 28-year-old woman has a long-standing history of MDD characterised by low mood, anhedonia, poor concentration as well as feelings of worthlessness and hopelessness. She has a history of self-harming behaviour and chronic suicidal ideations with multiple past suicide attempts. Prior to treatment, she was largely homebound and spent most of her days in bed. She had been unable to work for many years and was supported on disability. She has a history of anxiety. She was diagnosed with anorexia nervosa in her teens and benefited from inpatient treatment. Her body mass index at the time of MRgFUS was 17. In terms of treatment for MDD, the woman failed multiple medication trials and derived little benefit from psychotherapy, repetitive transcranial magnetic stimulation and electroconvulsive therapy. Given her degree of treatment resistance, she was referred and ultimately treated as part of a phase I pilot trial of MRgFUS capsulotomy for refractory MDD (NCT03421574).[4] At baseline, the woman's 17-item HAM-D score was 26 and her MADRS score was 40, both of which fall in the severe range.

At 12 months post-treatment, the woman's HAM-D score was 22 (moderate range; 15% reduction from baseline) and her MADRS score was 28 (moderate range; 30% reduction from baseline), classifying her as a non-responder on both outcome measures. At 14 months post-treatment, the woman participated in a semistructured qualitative interview that inquired about changes in symptoms and daily functioning since treatment. At that time, her scores on the HAM-D and MADRS were similar to her 12 month scores. She obtained a score of 19 on the HAM-D (moderate range; 27% reduction from baseline) and a score of 30 on the MADRS (moderate range; 25% reduction from baseline), once again classifying her as a non-responder. At odds with her non-responder status, the woman reported a significant improvement in her mood and described feeling 'brighter' overall. She reported that she no longer experiences

suicidal ideations or urges to self-harm. She resumed some of her hobbies and had taken on a part-time job, which she worked on sporadically throughout the day. She additionally described a significant improvement in her ability to concentrate and focus on tasks. As a direct result of this improvement in functioning, she was able to apply to a PhD programme, fulfilling a longstanding goal. She was accepted into the programme, and she described a newfound hope about the future. These positive changes helped to improve her relationship with her partner, in part because he is no longer in a caregiving role. She has been in more frequent contact with her friends, although due to COVID-19 related restrictions, she has not seen them in person. The woman continues to experience depressive symptoms, including feelings of sadness, worthlessness and hopelessness. Despite these residual symptoms, the woman considers the treatment a success and in hindsight would not hesitate to make the same decision to undergo MRgFUS.

The woman's case illustrates that the most commonly used primary outcome measures in neurosurgical trials for MDD might not capture clinically meaningful treatment changes. Similar cases have been referenced in DBS studies of refractory depression,[2 5 6] suggesting this issue might be widespread. The HAM-D and MADRS have been criticised for measuring domains that do not matter to patients.[3] These scales do not consider functional changes (eg, social, academic, occupational, family functioning and other daily living activities), which are often recognised by patients as more important than symptom relief.[7] Sole reliance on the HAM-D or MADRS to determine response efficacy might dismiss potentially beneficial treatments for patients who have exhausted all other available options. To better capture clinically meaningful treatment changes in neurosurgical trials for refractory MDD, measures of functional capacity and quality of life ought to be included as primary endpoints. While there are existing validated scales that assess these constructs, further research is needed to determine the most appropriate measures for neurosurgical trials and the clinically relevant cut-off values. The issues raised here likely extend to neurosurgical trials for other neuropsychiatric illnesses.

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