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Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression

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Abstract

Objective—To provide expert recommendations for the safe and effective application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder (MDD).

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Participants—Participants included a group of 17 expert clinicians and researchers with expertise in the clinical application of rTMS, representing both the National Network of Depression Centers (NNDC) rTMS Task Group and the American Psychiatric Association Council on Research (APA CoR) Task Force on Novel Biomarkers and Treatments.

Evidence—The consensus statement is based on a review of extensive literature from 2 databases (OvidSP MEDLINE and PsycINFO) searched from 1990 through 2016. The search terms included variants of *major depressive disorder* and *transcranial magnetic stimulation*. The results were limited to articles written in English that focused on adult populations. Of the approximately 1,500 retrieved studies, a total of 118 publications were included in the consensus statement and were supplemented with expert opinion to achieve consensus recommendations on key issues surrounding the administration of rTMS for MDD in clinical practice settings.

Consensus Process—In cases in which the research evidence was equivocal or unclear, a consensus decision on how rTMS should be administered was reached by the authors of this article and is denoted in the article as “expert opinion.”

Conclusions—Multiple randomized controlled trials and published literature have supported the safety and efficacy of rTMS antidepressant therapy. These consensus recommendations, developed by the NNDC rTMS Task Group and APA CoR Task Force on Novel Biomarkers and Treatments, provide comprehensive information for the safe and effective clinical application of rTMS in the treatment of MDD.

There is a clinical need for additional antidepressant treatments.[1,2] Repetitive transcranial magnetic stimulation (rTMS) is a safe, noninvasive neuromodulation therapy for major depressive disorder (MDD).[3] rTMS is applied over the prefrontal cortex and induces a magnetic field that results in the depolarization of underlying neurons[4] and the modulation of the neural circuitry involved in emotion regulation and depressive symptoms.[5,6,7–9]

The development of rTMS as an antidepressant therapy is supported by extensive clinical research.[10–12] In 2008, the US Food and Drug Administration (FDA) cleared the NeuroStar TMS Therapy System (Neuronetics, Malvern, Pennsylvania; 510k number: K083538) as the first device for rTMS treatment of MDD. Since then, 4 additional TMS devices have been cleared: the Brainsway Deep TMS System (Brainsway, Har Hotzvim, Jerusalem; 510k number: K122288), the Rapid Therapy System (Magstim, Philadelphia, Pennsylvania; 510k number: K143531), the MagVita Therapy System (MagVenture, Atlanta, Georgia; 510k number: K150641), and the NeuroSoft TMS (TeleEMG, LLC, Los Angeles, California; 510k number: K160309).

Since FDA clearance of these devices in the United States, rTMS has been adopted into clinical practice.[13] In a number of US states, federal and commercial health care insurers cover rTMS therapy for patients with MDD.[14] Although it can vary per clinical practice, the cost for an acute rTMS course comprising 20 to 30 rTMS sessions may range between $6,000 and $12,000. This price range appears to be expensive relative to other available antidepressant strategies, but 2 studies[15,16] found rTMS to be cost effective for patients with MDD who found no benefit from antidepressant pharmacotherapy. Transcranial magnetic stimulation is relatively less expensive than a course of electroconvulsive therapy (ECT). For those patients who have tried and failed 2 antidepressant medications, the chances of

achieving remission and then maintaining that remission for 12 months is very low.[17] Thus, when calculating the cost of TMS, one should factor in the cost of remaining ill with nonresponse. Also, the prospective addition of newer rTMS devices with FDA clearance for treatment of depression, and other economic factors related to rTMS delivery in clinical practice, may impact the future net cost of rTMS therapy.

The vast published literature on rTMS, describing it both as a research tool and as a therapeutic intervention, reflects a variety of coil placements, stimulation parameters, and outcome measurements applied in investigations of a broad array of neuropsychiatric disorders.[18] As such, clinicians face seemingly endless options for rTMS protocols and consequently may implement protocols with no established safety or efficacy for MDD. Other recommendations for the provision of rTMS exist[19–21]; however, given the current and growing use of rTMS, it is timely that up-to-date and specific clinical recommendations be developed to inform rTMS use in clinical settings. Indeed, these current consensus recommendations provide additional information and address real-world clinical practice issues by synthesizing a large and emerging literature and providing expert opinion specific to using rTMS to treat MDD. The goal of these recommendations is to promote consistency in the clinical application of rTMS and to provide knowledge to facilitate evidenced-based psychiatric care. Investigational rTMS application methods (eg, brief bursts of γ frequency [50 Hz] theta-burst stimulation)[22,23] fall outside of the scope of this review and are not included.

METHODS

Participants and Process for the Consensus Recommendations

The National Network of Depression Centers (NNDC) convened a Task Group of expert clinicians and researchers on rTMS. The experts met at NNDC annual conferences and via teleconferences and created consensus rTMS clinical application recommendations. In 2014, the NNDC rTMS Task Group collaborated with the American Psychiatric Association Council on Research (APA CoR) Task Force on Novel Biomarkers and Treatments members to revise the consensus recommendations. These recommendations are informed by the available published research that included 3 large randomized controlled trials in MDD, systematic reviews, and meta-analyses of smaller, sham-controlled trials. Because there were only 3 large randomized controlled trials in MDD available and a large number of published meta-analyses already exist in the scientific literature, we did not perform another meta-analysis. In cases in which research evidence was equivocal or unclear, a consensus decision on how rTMS should be administered was reached by the authors of this article and is denoted as “expert opinion.”

Evidence to Support the Consensus Recommendations

The NNDC rTMS Task Group collected evidence via literature reviews and expert opinions. Task Group members conducted the literature review in OvidSP MEDLINE (dates: 1990–2016) and PsycINFO (dates: 1990–2016) using the following terms: *major depressive disorder*, *MDD*, *depression*, *transcranial magnetic stimulation*, *repetitive transcranial magnetic stimulation*, *TMS*, and *rTMS*. The search was limited to articles written in English

that focused on adult populations and generated approximately 1,500 retrieved studies. Members of the NNDC rTMS Task Group and APA CoR Task Force on Novel Biomarkers and Treatments recommended publications and provided expert opinion and comments. A total of 118 publications were included in the consensus statement (see Supplementary eFigure 1 at PSYCHIATRIST.COM).

RESULTS

Efficacy of rTMS in Depression

Evidence basis for antidepressant efficacy—The acute antidepressant properties of rTMS delivered to the dorsolateral prefrontal cortex (DLPFC) have been extensively examined. A systematic review and meta-analysis of 29 randomized, controlled clinical trials (RCTs) of high-frequency rTMS in 1,371 participants found that the statistically and clinically significant pooled odds ratio (OR) for response was 3.3 (95% confidence interval [CI], 2.35–4.64) with a corresponding number needed to treat (NNT) of 6 (95% CI, 4.4–6.8), and the OR for remission was 3.3 (95% CI, 2.04–5.32) with an NNT of 8 (95% CI, 5.8–10.5).[24] Similarly, another systematic review and meta-analysis of 16 double-masked, parallel-design, RCTs of high frequency rTMS relative to inactive sham rTMS found a statistically significant effect size (Cohen *d*) for antidepressant effect of −0.55 (95% CI, −0.75 to −0.35).[25]

To date, there have been 3 multicenter RCTs of rTMS for the treatment of MDD in antidepressant medication–free patients.[10,26,27] The first, an industry-sponsored study,[27] found that rTMS delivered with a figure-of-eight coil was safe and effective, with a response rate of 24% and remission rate of 17% with active rTMS, compared with 15% response and 8% remission with sham rTMS. The second,[10] a National Institute of Mental Health (NIMH)–sponsored study with rTMS delivered with a figure-of-eight coil, found a 15% response rate and 14% remission rate with active rTMS, compared with 5% response and remission rates with sham rTMS. The third,[26] an industry-sponsored study with rTMS delivered with the H1-coil, demonstrated a response rate of 37% and remission rate of 30% with active rTMS compared to a 28% response rate and 16% remission rate with sham rTMS. At present, no randomized trials have compared the antidepressant effects of rTMS delivered by the figure-of-eight coil versus the H1-coil.

Interpretation of the clinical significance of antidepressant outcomes of rTMS trials is aided by comparing them with outcomes from other prospective studies that involved patients with pharmacoresistant depressive illness. For the 2 RCT studies that assessed the antidepressant effects of rTMS using a figure-of-eight coil, the mean number of ineffective or intolerant antidepressant medication trials in the current depressive episode was 1.5 (range, 0–6)[10] and 1.6 (range not provided).[27] For the RCT study[26] that assessed the H1-coil, approximately 71% of the sample found no benefit from 1 or 2 antidepressant medications. With regard to level of antidepressant treatment resistance, these study samples are generally equivalent to the group treated with next-step pharmacotherapy in step/level 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[28] that showed a 28.5% response and 30.6% remission rate. Approximately 21% of subjects found no benefit to 3 or more adequate antidepressant medication trials in the H1-coil study, which permits comparison

with outcomes for subjects in the STAR*D steps/levels 3 and 4. The STAR*D step/level 3 showed a response rate of 16.8% and remission rate of 13.7%, while step/level 4 showed a response rate of 16.3% and remission rate of 13.0%.[28]

The effect size for the FDA-cleared* protocols with rTMS as monotherapy was in the medium range, but there is potential to improve efficacy. Evidence for potential improvements has emerged in studies that optimized rTMS pulse and train parameters,[29] developed new coils,[30] and combined therapy paradigms (eg, coupled rTMS with psychotherapy and/or pharmacotherapy).[31] However, these approaches are investigational at present.

Predictors of antidepressant response—A consistent predictor of antidepressant response across most therapeutic modalities is the degree of treatment resistance.[1,32] Thus, rTMS is like other known antidepressant treatments in this respect, with greater treatment resistance generally predicting poorer response. An analysis of the predictors of response in the first large rTMS RCT found that patients who failed only 1 medication trial were more likely to respond to rTMS.[33] However, there was no relationship between degree of treatment resistance and response to rTMS in a large, multisite, naturalistic study[34] or open case series.[18] Also, a recent meta-analysis[35] of 18 studies that used the figure-of-eight coil found rTMS to be useful for patients with MDD who failed 2 or more antidepressant medications. Similarly, a recent meta-analysis[36] of 10 studies that used the H-coil found rTMS to be useful for patients in which approximately 89% were treatment resistant, having failed or been intolerant to 1 antidepressant medication or more. A recent survey[37] conducted by the American Society of Clinical Psychopharmacology (ASCP) to better understand what treatments clinical practitioners recommend after a patient has an inadequate response to an initial treatment found that of 154 ASCP member respondents, approximately 47% (95% CI, 38%–56%) had referred patients to rTMS, and in 28% (95% CI, 15%–41%) of those cases, the respondents noted that they observed a “marked improvement.” The present FDA guidelines do not restrict the use of rTMS to patients with only 1 medication failure.

Patient clinical factors that have been correlated with decreased response to rTMS include mood disorders with significant anxiety[33] and longer current depressive episode duration[38,39]; however, neither of these has emerged as a consistent predictor of outcome in large-scale rTMS trials.[34] Comorbid psychotic symptoms were also associated with poor response to rTMS in some studies,[40] although depression with psychotic features has not been extensively tested.[41,42]

The expert opinion is that rTMS is appropriate as a treatment in patients with MDD even if the patient is medication resistant or has significant comorbid anxiety. However, patients who have comorbid psychotic symptoms or acute suicidal ideation should be considered for

*The following are definitions of FDA “clearance” and “approval”: A new device is “cleared” for marketing after its sponsor files a premarket notification, otherwise known as a 510(k), and the FDA establishes that it is substantially equivalent to a an already legally marketed predicate device. A new device and its indication for use are “approved” for commercial marketing after a sponsor submits an application for premarket approval (PMA) that is reviewed by the FDA. Source: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194460.htm

other antidepressant treatments with established efficacy such as electroconvulsive therapy.[43] New models of accelerated rTMS delivery suggest that it may have acute antisuicidal effects.[44]

Efficacy and safety in special populations and comorbid psychiatric conditions—FDA approval of rTMS is limited to adults with MDD. However, there is evidence of safe therapeutic use and clinical benefit of rTMS in adolescents with mood disorders,[45,46] women with perinatal depression,[47] and other neuropsychiatric disorders including bipolar disorder,[48] panic disorder,[49] obsessive-compulsive disorder,[50] depersonalization disorder,[51] posttraumatic stress disorder,[52] and schizophrenia,[53] but at present, there is insufficient evidence to support routine clinical rTMS use in these populations. Children, adolescents, and pregnant women represent special populations in need of safe, effective alternative antidepressant treatments, and ongoing rTMS studies will be important contributions to neuropsychiatric practice. Moreover, routine clinical rTMS use in conditions other than primary MDD is not FDA cleared and awaits substantiating safety and efficacy evidence.

Evaluation of Patients for Transcranial Magnetic Stimulation

Pre-rTMS treatment evaluation—A comprehensive review of the patient's health status (including historical and current medical, surgical, neurologic, and psychiatric conditions and medications) and physical examination are evaluation components to determine the medical safety and necessity of rTMS (Table 1).

The pre-rTMS evaluation should identify risk factors associated with seizure induction during high-frequency rTMS[54,55] such as (1) personal/family history of epilepsy/seizure, (2) past stroke or head injury with neurologic sequelae, (3) concurrent use of medications/substances that lower seizure threshold (eg, stimulants) or dose reduction of a medication with anticonvulsant properties (eg, benzodiazepine), and (4) the presence of neurologic disorders or medical conditions that might be associated with lowered seizure threshold (eg, sleep deprivation, increased intracranial pressure, electrolyte imbalance, withdrawal from substances of abuse or recreational use). Safety evaluation to quantify risk factors can be aided with tools such as the TMS Adult Safety Screen (TASS)[56] or other clinic-specific screening tools. The presence of these conditions could change the risk-benefit ratio and should be discussed during the pre-rTMS treatment evaluation to apprise the patient of potentially increased risk for adverse effects that could mitigate the potential benefits.

At the first TMS treatment session, a TMS procedure is conducted to correctly establish the optimal site for motor response and individual motor threshold (MT) to minimize side effects. Failure to identify the optimal site and/or minimal MT pulse intensity can falsely elevate the MT value and lead to rTMS stimulation at levels potentially above safety guidelines.[55] Also, the MT optimal site location is sometimes used as a reference point to identify the prefrontal cortex treatment location. The appearance of twitching or shaking of the contralateral hand associated with any rTMS stimulation trains with the figure-of-eight coils should alert the clinician to the spread of neuronal action potentials to motor cortex and

heightened risk for generalized seizure. In such cases, rTMS treatment should be stopped until the MT is rechecked and safe protocol parameters are re-established.

Contraindications to transcranial magnetic stimulation—rTMS should not be administered to patients who have ferromagnetic or magnetic sensitive metal objects implanted in the head or neck areas in close proximity to the TMS coil magnetic fields. Eddy currents induced in metal objects by the TMS magnetic field cause the objects to heat and generate risk for thermal injury to adjacent tissue.[57] The TMS magnetic field may also induce movement of metal objects. The patient evaluation should include whether there has been the surgical placement of medical devices (eg, metal plates, clips, electrodes, chips, pumps, stimulators, cochlear implants, pacemakers), as well as past exposure to all metal fragments, tattoos rendered with ferromagnetic-containing ink, permanent piercings, and/or other possible metal sources in the head and neck. Precautions similar to those used in magnetic resonance imaging (MRI) scanning procedures can be followed for patients with tattoos on their head in close proximity to the rTMS coil.[58] To assess if a tattoo has ferromagnetic-containing ink, the provider would need to speak to the tattoo artist to inquire about the tattoo ink chemical composition.[59]

rTMS can induce current in subcutaneous leads in the scalp (eg, deep brain stimulators [DBSs]), which can result in unintended currents flowing in DBS electrodes in the brain.[60] Therefore, DBS is a contraindication to TMS until further safety testing is conducted or device modifications are put in place to ensure safety.

Metal implanted below the head and neck (eg, hip prosthesis) is generally considered safe because the magnetic field falls off rapidly with distance from the rTMS coil.[61] Also, non-ferromagnetic orthodontic hardware (eg, braces, implants, fillings) is considered safe with rTMS. Radiograph studies may be warranted when clinical history is unknown and exposure is suspected (eg, occupational risk); however, radiography is unable to determine if the metal objects are ferromagnetic. Limited safety data have been published to address the potential impact of rTMS on implanted vagus nerve stimulation (VNS) and cardiac pacemaker devices, whose components are typically located in the left cervical region and anterior chest wall.[62] Thus, consultation with other specialists may be needed before beginning treatment in patients with many contraindications.

Treatment Parameters of Repetitive Transcranial Magnetic Stimulation

Parameter selection—Repetitive TMS has different brain effects depending on the location of the coil and the treatment parameters including intensity, pulse frequency, train duration, intertrain interval, and the number of pulses per session (Table 2). Treatment intensity of the magnetic field is based on the individual patient's level of cortical excitability or resting MT. The minimum amount of single-pulse energy to the motor cortex required to induce motor neuron firing and muscle contraction of the contralateral thumb represents the MT for a given patient. The location of the optimal MT site is sometimes used as a reference point for identification of the prefrontal cortex treatment location (see the next section on coil location). Therefore, imprecision in finding the optimal MT site location introduces risk of diminished antidepressant efficacy and a higher risk of seizure induction.

The combination of brief periods of rTMS pulses with relatively long intertrain intervals maximizes safety. The FDA-cleared number of pulses per session is 3,000 for the figure-of-eight coil[27] and 1,980 for the H1-coil.[26] Other research found safety with up to 6,800 pulses per session with the figure-of-eight coil[63]; however, that finding requires replication in larger clinical samples before being implemented in routine clinical practice. Moreover, to date, no data have confirmed that more than 3,000 pulses per session are associated with greater efficacy.[24]

Coil selection—The FDA-cleared coils for treating depressed patients with rTMS include a figure-of-eight–shaped coil (with or without an iron core)[64] or an H-shaped coil.[65] Other coil geometries are the focus of research investigations.[61,66] Coils used in many rTMS clinical trials for depression have been figure-of-eight shapes that produce relatively focal stimulation (with a “hot spot” below the intersection of the 2 round “wings”) in the prefrontal cortex at a depth of 1–2 cm.[67] The H1-coil produces bilateral stimulation in broad regions of the frontal cortex (left greater than right) and allows a slower drop-off in magnetic field intensity.[61] At present, no data have directly compared the safety or efficacy of different coils.

Coil placement—In the large-scale clinical trials, figure-of-eight coils and the H1-coil were positioned over the left DLPFC with stimulation provided at high frequency. Also, in the NIMH-sponsored study,[10] some patients were treated in a later open-label phase with the figure-of-eight coil positioned over the right DLPFC, with stimulation provided at low (1 Hz) frequency.[68] Both high-frequency stimulation over the left DLPFC and low-frequency stimulation over the right DLPFC have shown antidepressant effects.[69]

Clinical performance labeling associated with FDA-cleared rTMS devices specifies placement of the coils over the prefrontal cortex and delivery of high-frequency stimulation. Although considered off label, low-frequency stimulation may be advantageous in cases where there is a high risk of seizure, poor tolerability (eg, pain), or inefficacy obtained with standard high-frequency stimulation. Some evidence suggests that certain patients may respond preferentially to either low- or high-frequency stimulation[70–72] and that there may be benefit from magnetic energy delivered at a pulse frequency synchronized to the patient’s individual α frequency.[73,74]

Acute treatment course planning—Treatment sessions using the parameters found in the large-scale clinical trials[10,26,27] typically last approximately 30–40 minutes (Table 3). Patients should be informed that although some studies show that depressive symptoms decrease following daily rTMS treatments (5/wk) as early as 2 or 3 weeks after treatment commencement,[27] a standard acute course of 20 to 30 treatment sessions over 6 weeks will very likely be needed to achieve results consistent with published regulatory trials.[26,27] Accordingly, patients undertaking an rTMS course need to make the time commitment for a 4- to 6-week treatment course. Several prospectively designed extension trials indicate that patients who show no response to a standard acute course of 20–30 treatment sessions may respond if their course is continued with ongoing daily (5/wk) sessions.[68,75]

While standard high-frequency 10 Hz rTMS to the left prefrontal cortex region is currently the most common practice in clinical settings that use the Neuronetics NeuroStar, Magstim Rapid2, or MagVenture MagVita devices with comparable figure-of-eight coils, 18 Hz stimulation over the bilateral prefrontal cortex is standard with the Brainsway Deep TMS H1-coil for depression. Safety and side effect considerations may vary when stimulation is applied with different methods (eg, other frequencies, coil types).

Recommended rTMS Procedure

Key elements of the rTMS procedure include obtaining informed consent, motor threshold determination, coil positioning, monitoring the patient during rTMS administration, and managing side effects (Table 4).

Informed consent—The risks and benefits of rTMS, and alternate treatments (eg, pharmacotherapy, psychotherapy), should be described in the consent form and thoroughly discussed with the patient. It is important to disclose if the rTMS treatment being used is "off-label." Off-label use of a device or treatment of patients may result in risks or outcomes inconsistent with results described in the FDA-cleared marketing materials. The FDA "label" for an rTMS device is outlined in the "User Manual" created by the device manufacturer that describes the intended use and directions for use based on clinical trials conducted with that specific device. Federal regulations require that "Indication for Use" labels contain a description of the clinical trial population that identifies the study population and directions for use consistent with procedures used in the clinical trials[10,26,27] that generated data for FDA application and regulatory approval.

While data from the large sham-controlled rTMS trials[10,26,27] are currently considered the best quality evidence for guiding clinical application of rTMS, the broader "evidence base" includes published findings from other smaller studies that addressed safety and efficacy of rTMS that are absent from the device labels. Examples include (1) treatment of primary psychiatric conditions other than MDD without psychotic features,[76,77] (2) administering more than 3,000 pulses per session,[78] (3) stimulation of the right prefrontal cortex,[10,72] and (4) use of devices with FDA approval for delivering peripheral nerve stimulation (eg, Neotonus, Model 1000 Muscle Stimulator System) or presurgical motor and speech mapping (Nexstim) rather than brain stimulation. A tick box on the consent form could indicate whether the planned rTMS treatment is considered "on-label" or "off-label" and/or whether the relevant scientific evidence has been reviewed with the patient. Also, a separate consent form can be used for on-label and off-label rTMS.

Patients should be reconsented for rTMS when there is a change in risk or benefit. Each service should develop its own policy regarding how many treatments should be agreed to initially; this could be either a set number of treatments or a set time frame after which reconsent is necessary. Additional scenarios that may warrant reconsent include a transition between in- and outpatient treatment settings, transition from acute to maintenance rTMS, or change from on- to off-label treatment. A record of the reconsent process can take the form of a newly signed consent form including a note in the chart indicating that any changes in risks and benefits were discussed.

Motor threshold determination—The motor threshold is defined as the minimum stimulus intensity that elicits a response in either the abductor pollicis brevis (APB) or the first dorsal interosseous (FDI) on the contralateral side for ≥ 50% of applied stimuli (usually defined as ≥ 5 of 10 stimuli administered).[79,80] Visual observation of finger twitching or measurement of muscle activity with electromyography (EMG) is done to determine MT.[81] Research has demonstrated that visual observation of a single muscle yields significantly higher MTs than EMG of that muscle.[80] The safety guidelines[55] are based on EMG-determined MTs and are specific to figure-of-eight type coils. However, a multicenter sham RCT, 3 sites using an EMG-determined MT compared to 1 site using visual observation, showed no significant differences in side effects or clinical outcome.[10] The standard of practice in the United States has been that visual observation is a safe substitute for EMG-determined MT, and the FDA-cleared device systems for depression may or may not include EMG equipment or instructions. Single pulses delivered no more frequently than every 5 seconds should be delivered to map the MT region to minimize the effect of the single pulses on motor cortex excitability.

The standard practice for dosing rTMS with the figure-of-eight or H1-coils is to administer a stimulus at a percentage (eg, 120%) of the MT.[82] As such, MT determination must be carried out before the first rTMS treatment. When daily treatments are administered, the MT should be redetermined prior to treatment whenever there has been a change in medication with potential to impact cortical excitability, in the face of other clinical events that may alter seizure threshold (eg, sleep deprivation, change in substance use pattern),[83] or consideration should be given to weekly MT redetermination as there is a possibility of drift in the MT.[10,84] While data generally suggest that the MT remains relatively stable over time,[85] those data were based on medication-free cohorts.

The expert opinion is to base treatment on either a visually measured or an EMG-detected MT, and to recheck the MT either weekly or at times during the therapeutic course when there have been changes that could affect the MT.

Coil positioning method—A variety of techniques have been employed for positioning the TMS coil including placing the coil 5, 5.5, or 6 cm anterior to the motor cortex (eg, the centimeter rule), the International 10–20 System, stereotactic frames, and neuroimage-guided frameless positioning technologies (Table 5). The “5-centimeter rule” involves measurement to a location 5 cm anterior to the MT location in the anterior-posterior plane, which corresponds to 5.5 cm if measurement is made directly on the scalp due to convexity of the head.[9] One large-scale clinical trial[27] employed the 5-cm rule with the figure-of-eight coil, and another[10] followed the same rule that was modified with placement informed from MRI. The latter resulted in the figure-of-eight coil being moved forward to 6 cm in 33.2% of participants.[86] The 5-cm rule would have placed the TMS coil on the premotor cortex for 9% of the patients, and none of these patients remitted.

For the H1-coil, a large-scale clinical trial employed the 6-cm rule.[26] The centimeter rule must be considered a rough means of estimating DLPFC given the variation among individuals in skull size, motor cortex anatomy, and relationship of DLPFC to the motor

cortex.[87] Although the RCT for the Neuronetics device[27] used the 5-cm rule for coil placement, the company recommends placing the coil 5.5 cm anterior of the motor cortex.

Another approach employed in clinical research[88] is the determination of coil position using individual scalp landmarks such as F3 (scalp location corresponding with left prefrontal cortex) based on the International 10–20 System for placement of EEG recording electrodes.[89] Since individual variation in cranial size and shape are taken into consideration with anatomic measurements for the International 10–20 System, this method may offer better precision,[90] although clinical outcomes were not directly compared using different coil positioning methods.

The stereotactic frame system for coil positioning fixes the patient's head in place with respect to a frame. This system employs a mechanical coil positioning system, which is anchored to the frame via mechanical arms, to allow registration of the coil position spatial coordinates with respect to the frame and patient's head.[91] This approach allows for more precise coil positioning by holding the coil in place.

Neuroimage (eg, MRI)-guided frameless positioning technologies offer the greatest precision,[91] but this method is expensive, requires a brain MRI scan that is different from a standard diagnostic brain MRI, and has only limited evidence suggesting that this approach confers higher efficacy rates.[92] Among all coil positioning methods, based on research[89,91,93] and expert opinion, coil placement on the F3 position of the International 10–20 System is considered the preferred coil positioning method for routine clinical use when frameless stereotaxy is unavailable or impractical.

Monitoring patient safety and efficacy during rTMS delivery—Patients should be monitored during rTMS delivery to assess for adverse effects or any events occurring during treatment that may impact rTMS safety or efficacy (eg, change in mental status, syncope, change in head location relative to coil). Clinicians should use systematic assessment methods (eg, build templates to an electronic medical record) at every rTMS session and document variables (see Table 1) that may affect the treatment as well as treatment-related side effects.

Systematic measurement of symptoms and outcomes should be used to document efficacy. Depression symptom severity instruments, either clinician-rated, patient-rated, or both, should be completed weekly or every 2 weeks during an acute rTMS course to document depressive symptoms and determine when therapeutic response and remission have been achieved.[94] Systematic evaluation of depressive symptoms allows for the correct classification of treatment-emergent and residual depressive symptoms that can be used to inform measurement-based care.[95,96] Multiple factors must be considered when choosing a depression symptom severity instrument including the patient population, administration method (eg, clinician-rated, self-report), depressive symptoms to be documented, and instrument-associated fees. A plethora of depression symptom severity instruments are available for use in clinical practice (see McClintock et al[97] for a comprehensive review). Two instruments for practical use in most clinical settings include the clinician-rated and

selfreport versions of the 16-item Quick Inventory of Depressive Symptomatology (QIDS)[98] and the self-report 9-item Patient Health Questionnaire (PHQ-9).[99]

Common side effects of rTMS—Safety data and procedure standards relevant to rTMS for both research and treatment of psychiatric disorders have been previously summarized.[54,55] Additional safety data are derived from large RCTs of high-frequency rTMS for depression with 2 types of coils (figure-of-eight, H1).[10,26,27,88]

The most common side effects of rTMS during treatment (Table 1) are transient head or scalp discomfort at or around the location where TMS pulses are applied. Discomfort may extend to adjacent areas of the face including locations around the ipsilateral eye, ear, nose, and jaw. The patient may experience twitching or movement of these areas during stimulation trains due to excitation of superficial nerve branches and contraction of superficial muscle groups.

Headache is sometimes reported after rTMS treatment, particularly early in the course when there has been no accommodation to the high-frequency tapping sensation created by the stimulus. This sensation may be particularly uncomfortable for individuals with high MT levels. Procedural pain and headache typically decrease due to habituation, or direct antinociceptive effect of TMS,[100] that occurs independent of patient outcomes.[3,101]

In practice, rTMS does not increase migraine headache risk in healthy participants or those with a history of migraine.[102] In fact, the FDA cleared a single-pulse device (SpringTMS from eNeura) for the treatment of acute migraine headache. Simple strategies to manage pain and headache include use of oral, over-the-counter analgesic medications (eg, acetaminophen, ibuprofen) taken before or after treatment or topical analgesic products (lidocaine/prilocaine cream or lidocaine gel, available by prescription) applied to the scalp at the location of coil placement at least 30 minutes before treatment.[103,104]

Reduction of TMS pulse amplitude is another strategy to enhance tolerability of rTMS, although antidepressant efficacy of rTMS delivered below 110% MT remains questionable due to limited evidence. Comfortable positioning of the patient in the rTMS treatment chair, with sufficient head, neck, and spine support, is a first step to reduce nonspecific discomfort that may contribute to posttreatment headache or other regional myalgias. Small rolls of towels or cushions tucked under body parts (eg, knees, buttocks) can enhance support and facilitate muscle relaxation during rTMS.

There is no evidence of pathological change in brain tissue resulting from rTMS treatment delivered within the safety ranges,[54,55] but theoretical risks remain for protocols utilizing stimulation parameters outside evidence-based data. Investigations into rTMS dosing modifications for optimizing treatment benefits are ongoing; published data show exposure to “accelerated” dosing (an increased number of total daily pulses) generally appears safe in open-label studies.[29,78] For example, in a double-masked sham study, there were no differences in side effects with a total of 57,000 TMS stimuli delivered across 3 days.[44] Long-term and controlled trials are needed to fully elucidate the safety profile of alternate rTMS dosing strategies.

Uncommon side effects—An uncommon side effect of rTMS is induction of mania or hypomania.[105] Daily assessment of treatment-emergent manic/hypomanic symptoms (eg, agitation, irritability) may alert the clinician to early signs of mania and should prompt a reevaluation of primary diagnosis, concurrent use of stimulating medications, or possible need for a mood stabilizer.

Auditory acuity, if ear protection is worn that protects at minimum up to 30 dB, is unaffected by rTMS.[106] Thus, ear protection for the patient, TMS device operator, and others in the treatment room during active stimulation is warranted to minimize possible hearing loss.[54]

Excessive heating of the TMS coil, a rare occurrence that is mostly associated with continuous device use with long trains and high intensity, may create risk for discomfort and, theoretically, scalp burn. FDA-cleared devices have built-in thermal sensors that interrupt stimulation when coil warming is detected beyond a threshold temperature. Application of the TMS coil to wet hair or the scalp moist with products (eg, hair gel) may reduce ventilation around the coil surface and promote unwanted heating at the contact site. Means to cool the TMS coil or reduce ambient room temperature during or between treatments may be useful in busy clinical settings.

Vasovagal response to pain, particularly in the context of heightened anxiety, hypoglycemia, hyperventilation, or dehydration, can result in syncope during or following rTMS.[55] Syncope can mimic a seizure behaviorally and may include stiffening, jerking, vocalizations, oral and motor automatisms, brief head or eye deviation, incontinence, and hallucinations.[54] Syncope is best differentiated from seizure activity by its rapid termination and return of consciousness. Features suggestive of impending syncope include pallor, dizziness, weakness, narrowing of the visual field or blurring, sweating, nausea, bradycardia, or hypotension.[54] While reports of syncope during rTMS are rare,[107] the treatment team should be prepared to document and manage syncope. The Calgary Syncope Symptom Score[108] may be a useful objective measure for assessment of syncopal events.

Risk of inducing seizure—The risk of tonic-clonic seizure, a rare event during rTMS, is related to the direct stimulation of motor cortex or stimulation of adjacent brain areas with spread of neuronal excitation to motor cortex.[54,109] Inspection of the contralateral hand for signs of twitching or movement during stimulation may ensure that stimulation does not spread from prefrontal to primary motor cortex, which can lead to generalized seizure induction with tonic-clonic movement pattern.

The risk of rTMS-induced seizures under ordinary clinical use with the figure-of-eight coil is estimated to be 1 in 30,000 treatments (0.003%).[34] There were no reports of seizure in 2 of the 3 large-scale controlled clinical trials.[10,27] In the study[26] in which 1 seizure was reported, the seizure occurred in a participant who had heavy alcohol use the night before the rTMS treatment. A published summary of reported seizures related to rTMS[54] found that the majority of rTMS-related seizure events occurred in patients with preexisting risk for seizure or when stimulation parameters exceeded recommended safety ranges. Concurrent use of medications that lower the seizure threshold (eg, imipramine, bupropion, clozapine) may increase risk of rTMS-induced seizure during or after treatment.[54,83] It should be noted

that seizures can occur within safety guidelines, even in patients who present with no known risk factors. For example, Harel et al[48] reported 1 patient who had a generalized seizure in a study of 19 patients treated with rTMS with the H1-coil. Although EEG is the most definitive means to detect seizure activity, routine EEG monitoring is not recommended during rTMS therapy, based on the low incidence of epileptiform activity with rTMS.

All programs administering rTMS should have a documented plan for managing seizures. Those who administer rTMS should be trained as “first responders” to render appropriate care in the event of seizure. Most rTMSinduced seizures have been relatively brief (usually less than a minute and no longer than 5 minutes), with no associated long-term medical complications.[107]

The acute management of an rTMS-induced seizure should focus on ensuring safety and preventing complications during the event. Such management includes removing the coil from the patient’s head and placing the patient in a lateral decubitus position where they are unlikely to be harmed during clonic movements and are less likely to aspirate. The management plan should include a plan to call for emergency medical help in the unlikely event that a convulsive state is associated with injury, aspiration, cardiac arrest, or other complications or in the event the seizure does not terminate within a specified period of time (eg, 5 minutes). Thus, the treatment room will need to have available appropriate equipment (eg, telephone to call for emergency) for managing a seizure before the arrival of emergency response teams.

Training and Credentialing the Clinical Team Providing rTMS

The rTMS prescriber should be a clinician with prescriptive privileges who is knowledgeable about, trained, and credentialed in rTMS. Such training should include proficiency in all aspects of the rTMS procedure. Each service should develop its own policy regarding how many times a prescriber must obtain motor threshold or treat a patient before recredentialing of that prescriber.

The TMS device operator should be a clinical professional who independently administers rTMS under the supervision of the rTMS prescriber. The operator should be trained in assessing the MT and administering the treatment. At all times, the TMS device operator monitors the patient during treatment administration, especially for adverse events, and ensures contact between the TMS coil and the patient’s scalp. The operator should be trained to understand evidence of cortical excitation (ie, movements in the hand during the procedure) and be proficient in managing a potential seizure. The operator must also be able to independently make routine adjustments (eg, move the TMS coil) and have specific guidelines as to when to contact the rTMS prescriber. Examples of TMS device operators include certified medical assistants, medical technicians with relevant experience, physician assistants, and nurses. If the TMS clinical practice is governed within a hospital setting, the TMS device operator should be approved by the hospital bylaws.

Documentation

Documentation in preparation for rTMS should include the following basic elements:

1. Comprehensive psychiatric assessment documenting the diagnosis and indication for rTMS, including risks and benefits of treatment alternatives.
2. Medical history, documentation of physical examination, and assessment of risks and benefits of rTMS, including review of rTMS contraindications.
3. Prescription for rTMS, including selection of rTMS parameters and treatment plan.
4. Written informed consent.

The procedure note documenting rTMS delivery at each treatment should include the following basic elements:

a. Time-out procedure, identifying the correct patient, correct stimulation site, and correct dosage as per Joint Commission Guidelines for implementation of the Universal Protocol for the prevention of wrong site, wrong procedure, and wrong person procedures (https://www.jointcommission.org/).
b. Specific rTMS treatment parameters in sufficient detail to allow another clinician to replicate the treatment (intensity, frequency, train duration, coil type, coil placement, scalp location, number of pulses).
c. Concomitant medications.
d. Description of treatment-emergent side effects.
e. Assessment of clinical response and side effects. Using a structured clinical symptom rating scale is highly encouraged and required for reimbursement of rTMS by most federal and commercial insurers.
f. Reasons for any change in treatment plan.
g. For Medicare documentation, the procedure note must contain the diagnosis and additional clinical information as outlined in the applicable Coverage Determination Guideline document (https://www.cms.gov/Medicare/Coverage/DeterminationProcess).

Maintenance Treatment Recommendations

Following clinical response or remission in the acute rTMS antidepressant treatment course, continued antidepressant management during the maintenance phase is needed in order to prolong the improved clinical state.[110] Research has found that the clinical benefits of rTMS during the acute course are durable and can last up to 3[111] and 12 months.[112] Unfortunately, there is limited randomized controlled trial evidence regarding optimal antidepressant maintenance strategies following response or remission with acute rTMS. One RCT maintenance study[113] compared a scheduled (once-monthly) approach with an observational (monitor symptoms over time and re-introduce rTMS as needed based on depressive symptom worsening) approach in patients who showed clinical improvement with patients who received acute rTMS and remained medication free. The study found that both approaches were approximately equivalent with regard to prolonging clinical benefits over a 12-month period. Moreover, the study found that “rescue therapy,” ie, re-introduction of

daily rTMS triggered by symptom relapse, was successful in restoring clinical benefit in 69% of instances when it was used.

At this time, there is no 1 recommended maintenance antidepressant strategy for patients after a beneficial rTMS acute course. Rather, it is recommended that available evidence-based antidepressant strategies be used after successful acute rTMS treatment. Such strategies include repeat rTMS,[111–113] pharmacotherapy,[114] manualized psychotherapy,[115,116] exercise,[117] and combination of those treatments.[114] Further research is needed to systematically develop evidenced-based antidepressant maintenance strategies following acute clinical benefits with rTMS.

CONCLUSION

Since the FDA's initial clearance of the first device in 2008, rTMS is becoming increasingly incorporated into clinical practice. As such, these consensus recommendations (Table 4) highlight topical issues in rTMS clinical practice (eg, coil placement, patient selection, possible adverse effects)[118] and will help inform clinical practitioners about safe and effective application of rTMS in treating MDD. Practitioners are encouraged to implement rTMS based on available evidence-guided recommendations and to employ systematic measurement for documenting safety and efficacy. Additional research is warranted to determine optimal treatment parameters and algorithms for the implementation of rTMS across different phases of antidepressant therapy and relapse prevention.[18,112]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Points

- Given the current and growing use of repetitive transcranial magnetic stimulation (rTMS), clinicians face seemingly endless options for rTMS protocols and consequently may implement protocols with no established safety or efficacy for major depressive disorder (MDD).
- These current consensus recommendations provide information and address real-world clinical practice issues by synthesizing a large and emerging literature and providing expert opinion specific to using rTMS to treat MDD.
- The goal of these recommendations is to promote consistency in the clinical application of rTMS and to provide knowledge to facilitate evidence-based psychiatric care. Practitioners are encouraged to implement rTMS based on available evidence-guided recommendations and to employ systematic measurement for documenting safety and efficacy.

Table 1

Transcranial Magnetic Stimulation Evaluation

Variables to Assess Before Commencing rTMS	
Variable	**What to Do if the Variable Is Endorsed by the Patient**
• History of epilepsy • Family history of epilepsy • History of seizure • History of head trauma • History of loss of consciousness • History of stroke • History of brain tumor • History of traumatic brain injury • Any implanted medical devices • Any metal in the head	• Determine with the patient the risk/benefit ratio of administering rTMS given the presence of risk variables. • Inform the patient that the presence of 1 or more of these variables could increase the risk of rTMS-associated adverse effects including a TMS-associated seizure. • Consider consultation with other health care professionals (eg, neurologist) to assess risks of possible rTMS-associated adverse effects before commencing treatment with rTMS.
• Current use of medication(s) that lower seizure threshold	• Document the medications including drug name and dosage. Use the information to create an individualized medication checklist and update this list at each rTMS session. • Encourage the patient and their psychiatric provider to keep medications stable during the rTMS course and to inform the rTMS clinical staff of any changes in medication use.
• Current alcohol/substance use	• Document the type and amount of alcohol/substance consumed. • Provide education on the effects of alcohol/substance use on rTMS.
Variables to Assess at Each rTMS Session	
Variable	Actions or Considerations
• Sleep the night before treatment	If the patient endorses insomnia, then • Assess the duration and severity of the insomnia. • Provide education on sleep hygiene. • If warranted (new onset or significant change in sleep pattern), consider rechecking motor threshold before commencing with rTMS treatment.
• Any medication changes	• Document any medication changes and reconcile with the medication history before each treatment. • Provide education to the patient that changes in medication could affect the motor threshold. • If warranted (change in medication could alter seizure threshold), consider rechecking motor threshold before commencing with rTMS treatment.
• Side effects including:	
Headache associated with rTMS	• Document the duration and severity of the headache. • Provide reassurance and educate the patient that headaches tend to occur early in treatment and decrease with successive treatments. • If appropriate, recommend over-the-counter analgesic medication. • Instruct the patient to monitor the headache for resolution and report back to rTMS staff.
Neck pain associated with rTMS	• Document the duration and severity of neck pain. • Adjust the patient's seating position and head position to enhance comfort. • Provide neck support as needed (eg, pillow).
Pain/discomfort at stimulation site (scalp)	• Document the quality, duration, and severity of pain. • Provide reassurance and education to the patient that pain at stimulation site tends to be transient. • If appropriate, recommend over-the-counter analgesic medication. • If appropriate, recommend or prescribe topical analgesic for application to scalp (eg, lidocaine gel). • Make subtle adjustment to coil position. • Slightly reduce magnetic field intensity. • Instruct the patient to monitor the pain and report information at the subsequent rTMS session.
Scalp induration/irritation from rTMS coil	• Document the size and appearance of the erythema or edema at stimulation site on scalp. • Provide education to the patient that redness is transient. • Assess the coil temperature. • Assess the coil contact on the scalp; adjust pressure if appropriate.

Variables to Assess Before Commencing rTMS

Variable	What to Do if the Variable Is Endorsed by the Patient
Induction of manic/hypomanic symptoms	• Monitor closely for treatment-emergent insomnia, anxiety, irritability, agitation; use standard mania assessment scales in susceptible individuals. • Evaluate possible role of concurrent medications. • Consider whether treatment with rTMS should be discontinued.
Hearing loss/tinnitus	• Assess for duration and severity of hearing loss/tinnitus in relation to rTMS sessions. • Check that ear plugs are intact. • Instruct the patient to monitor the hearing loss/tinnitus and report information to the rTMS staff. • Refer the patient to an audiologist as needed.
Vasovagal pre-syncope or syncope	• Document the duration and severity of the symptoms. • Reassure the patient that syncope is a possible, but rare side effect. • Instruct the patient on adequate hydration prior to treatment. • Monitor medication use associated with orthostatic hypotension. • If the patient experiences syncope, stop the current rTMS session and adjust the patient's head to a downward position to increase cerebral perfusion. • Check the patient's blood pressure and pulse before and after each treatment. • Refer the patient to a health care provider (eg, primary care physician, cardiologist) as needed.
Seizure	• Stop the stimulation and remove the coil. • Ensure the patient is safe and is breathing. • Do not try to restrain the patient or put anything in the patient's mouth. • When possible and the patient is safe, turn the patient to the side to minimize possible aspiration. • When possible and the patient is safe, call emergency medical services (EMS). • Document the seizure activity (including start and stop time). • Discontinue treatment with rTMS pending medical evaluation.

Abbreviation: rTMS=repetitive transcranial magnetic stimulation.

Table 2

Transcranial Magnetic Stimulation Variables for Dosing in Major Depressive Disorder

Variable	Description
TMS stimulation parameters	• Intensity—related to resting MT, most often 100%–120% MT. • Pulse frequency—1 Hz or less frequency (“low frequency”) leads to reduced cortical excitability while faster frequency (“high frequency,” eg, 5 Hz, 10 Hz) increases cortical excitability. • Train duration and intertrain interval—impact on safety, with shorter trains and longer ITI being less likely to induce a seizure.
Coil placement	• Laterality—high frequency over left DLPFC or low frequency over right DLPFC with the figure-of-eight coil. High frequency over the left-right DLPFCs with the H1-coil. • Positioning—use a positioning system (see Table 5) to place the coil over the intended cortical location.
FDA label for treating major depressive disorder in adults	• Neuronetics NeuroStar, Magstim Rapid2, and MagVenture MagVita TMS Therapy Systems with figure-of-eight coils. • left DLPFC at 120% MT. • 3,000 pulses/session, at 10 Hz, in 4-second pulse trains with 26-second ITI. • Brainsway Deep TMS Therapy System with H1-coil. • left DLPFC at 120% MT. • 1,980 pulses/session, at 18 Hz, in 2-second pulse trains with 20-second ITI.

Abbreviations: DLPFC=dorsolateral prefrontal cortex, FDA=US Food and Drug Administration, ITI=intertrain interval, MT=motor threshold, TMS=transcranial magnetic stimulation.

Table 3

Parameters for the Safe and Effective Administration of Transcranial Magnetic Stimulation in Clinical Practice[a]

Variable	O'Reardon et al 2007[27]	George et al 2010[10]	Levkovitz et al 2015[26]
Coil placement	Left DLPFC	Left DLPFC	PFC
Coil type	Figure-of-eight	Figure-of-eight	H1
Coil positioning method	5-cm rule	5-cm rule[b]	6-cm rule
Magnetic field intensity relative to resting motor threshold	120%	120%	120%
Hertz (Hz)	10 Hz	10 Hz	18 Hz
Stimulus train duration (on time)	4 seconds	4 seconds	2 seconds
Intertrain interval (off time)	26 seconds	26 seconds	20 seconds
Total no. of pulses per rTMS session	3,000	3,000	1,980
Concomitant medications	Hypnotics or anxiolytics (up to 14 daily doses) during acute phase; antidepressant monotherapy initiated during rTMS taper phase and continued when rTMS was reintroduced during 24-week follow-up study	Sedatives, hypnotics, or anxiolytics (up to 14 daily doses)	Sedatives, hypnotics, or anxiolytics

[a]Additional parameter safety information can be found in the respective transcranial magnetic stimulation device package insert as well as in the US Food and Drug Administration (FDA) 510k application material.

[b]In the study by George et al,[10] patients underwent head magnetic resonance imaging with fiducials (vitamin E capsules), which resulted in 33.2% of patients having the stimulating coil moved an additional 1 cm, for a total of 6 cm anterior.

Abbreviations: DLPFC=dorsolateral prefrontal cortex, PFC=prefrontal cortex, rTMS=repetitive transcranial magnetic stimulation.

Table 4

Summary of Consensus Recommendations for Transcranial Magnetic Stimulation

Variable	Recommendation
Clinical environment for providing TMS	The clinical environment should include space for the TMS device, patient, and rTMS operator. The rTMS operator must be able to directly observe the patient. The room should be maintained at an appropriate temperature such that the TMS device does not overheat. All persons in the treatment room should wear ear protection (eg, earplugs) that provide at minimum 30 dB of noise reduction. During treatment, the patient should be encouraged to remain awake, avoid activities that would make the head move (eg, talking on cell phone), and not consume food or beverage.
Qualification of TMS operator	Qualifications for the rTMS operator may vary across TMS practices, and each practice should have an established written policy. At a minimum, the TMS operator should be trained and certified to deliver rTMS including device operation, TMS coil targeting, and recognition and management of side effects. He or she should be trained as a first responder to a seizure and have basic life support training certification.
TMS information to include in medical record	The medical record should include the diagnosis, device and coil types, treatment phase, cortical targeting information and cortical site for stimulation, motor threshold, stimulus intensity, frequency, stimulus duration, intertrain interval, number of stimuli, treatment-related side effects, and medication usage.
Coil to use for TMS treatment	There is strong evidence that supports the use of the figure-of-eight and H1 coils, but not other TMS coils to treat depression at present.
Cortical target for starting TMS treatment	The majority of evidence with the figure-of-eight coil supports starting treatment by targeting the left DLPFC. There is some evidence that supports the figure-of-eight coil targeting the right DLPFC. There is evidence supporting bilateral targeting of the prefrontal cortex with the H1-coil.
TMS coil positioning method	There are multiple methods for positioning the rTMS coil over the targeted cortical location (see Table 5). Each method has its advantages and disadvantages. One method that may be most practical in terms of time and accuracy is head measurements for identification of F3 using 10–20 EEG coordinates.
How often to check the motor threshold	The determination of motor threshold should occur at baseline, before commencing with the first treatment. See Table 1 regarding other considerations on how often to check the motor threshold.
Preferred length for acute TMS treatment, ie, number of treatment sessions	Number of treatment sessions in an acute course should depend on the risk-benefit ratio for clinical response and remission, take side effects into consideration, and reflect measurement-based care.
Allowable psychotropic medications during TMS treatment	The safety guidelines for rTMS were determined in study participants who were largely free of antidepressant medications. While it is possible that psychotropic medication can affect the motor threshold, there are no known absolute contraindications to psychotropic medication usage during rTMS. All medication use and change should to be documented.

Abbreviations: DLPFC=dorsolateral prefrontal cortex, EEG=electroencephalogram, F3=scalp location corresponding with left prefrontal cortex, rTMS=repetitive transcranial magnetic stimulation, TMS=transcranial magnetic stimulation.

Table 5

Advantages and Disadvantages of Common Coil Positioning Techniques

Variable	Advantage	Disadvantage
5-, 5.5-, and 6-Centimeter rules	• Inexpensive • Employed in large-scale clinical trials • Easy to implement	• Imprecise coil position relative to anatomic target • May underestimate or overestimate cortical target location • Is not individualized to the patient's head size
International 10–20 System (F3)	• Inexpensive • Greater precision in locating cortical target • Individualizes to the patient head size/shape	• Requires tape measure and marking pen • May add additional time to rTMS procedure
Stereotactic frame	• Greater precision in locating cortical target • Greater stability in holding coil steady	• Expensive; requires special equipment/software • May add additional time to rTMS procedure
Frameless MRI-guided navigation	• Greater precision in locating cortical target	• Expensive; requires special equipment/software • Patient will need brain MRI • May add additional time to rTMS procedure

Abbreviations: F3=scalp location corresponding with left prefrontal cortex, MRI=magnetic resonance imaging, rTMS=repetitive transcranial magnetic stimulation.