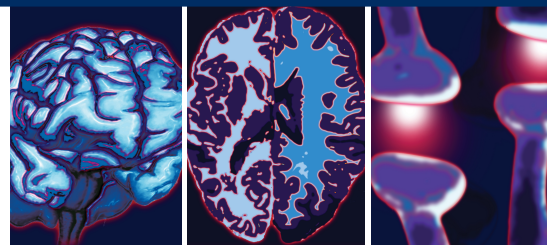


REVIEW



Repetitive transcranial magnetic stimulation for treatment-resistant depression

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Practice points

- Repetitive transcranial magnetic stimulation (rTMS) is an area of clinical research and practice that has increasingly apparent potential for treating mental illness.
- By noninvasively targeting cortical function in certain brain areas and specific functional neural circuits, rTMS treatment represents an increasingly accessible approach toward affecting brain functioning and excitability with limited adverse effects.
- The modulatory effects of rTMS are dependent upon a number of factors including intensity, frequency, train length, intertrain interval, number of pulses, and coil configuration, direction and position. With regard to frequency, high-frequency use (typically greater than 1 Hz and usually between 5 and 20 Hz) generally increases cortical excitability of the targeted tissue, while low-frequency use (less than 1 Hz) is thought to be associated with a reduction in excitability.
- While it has been demonstrated that different frequencies affect both cerebral blood flow and cortical excitability, there is also speculation that transcranial magnetic stimulation engages mechanisms of synaptic plasticity including long-term potentiation and long-term depression of neuronal tissue.
- rTMS is known to affect neuroendocrine functioning, for example, by affecting the dopaminergic system, increasing thyroid-stimulating hormone levels and reversing the results of the dexamethasone suppression test in certain forms of major depressive disorder.
- There is also evidence that transcranial magnetic stimulation can be effective through corrective effects on a hemispheric imbalance in affected patients.
- Antidepressant efficacy from rTMS at the left dorsolateral prefrontal cortex is thought to be related to its anticorrelated downstream effects on the subgenual cingulate and associated connectivity networks.

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Practice points continued

- After examining the data from positive randomized controlled trials, the US FDA approved the use of one specific device for treatment of treatment-resistant depression in 2008, defining it as major depressive disorder that has not resolved to a satisfactory level following the use of one antidepressant medication at or above the minimal effective dose for an appropriate duration. In January 2013, the FDA provided clearance for a second device as a therapeutic intervention for treatment-resistant depression, the Deep TMS H System (Brainsway Ltd, Jerusalem, Israel).
- Cost, access to treatment and ongoing questions about the most efficacious use and ideal patient selection remain issues for consideration.

SUMMARY Repetitive transcranial magnetic stimulation (rTMS) is a treatment option for patients with treatment-resistant depression. By noninvasively targeting excitability in specific functional neuronal circuits, rTMS treatment represents an increasingly accessible approach toward affecting brain functioning with limited adverse effects. By making use of targeted applications of Ampere's and Faraday's laws of physics, rTMS is thought to affect neuronal circuitry in multiple ways, including affecting cerebral blood flow, cortical excitability, neuroendocrine functioning and hemispheric balance. While the noninvasive use of this technology can potentially be applied to any number of brain areas for exploration or modulation, its utility and effectiveness is best demonstrated thus far in the treatment of treatment-resistant depression. The future use of this treatment option will depend upon further technological and logistical advances that can help to clarify effective use, cost-effectiveness, access to treatment and patient selection.

Repetitive transcranial magnetic stimulation (rTMS) represents a growing treatment option for patients with treatment-resistant depression, although it is in its relative infancy when compared with psychopharmacology, psychotherapy and electroconvulsive therapy (ECT). As understanding of the role of complex brain functioning in different kinds of psychopathology increases in the coming decades, it will be imperative for psychiatrists to investigate novel approaches to diagnosis and treatment of mental illness.

Given the tremendous morbidity and economic burden of treatment-resistant major depressive disorder, this review examines rTMS as a treatment option for this disorder through discussion of its origins, proposed mechanisms of function, trials of its clinical effectiveness, cost-effectiveness and safety.

Origins of transcranial magnetic stimulation as a treatment option for major depressive disorder

Although reports of using magnetic stimulation to elicit behavioral changes date back to the late 19th century [1], the first modern attempts to use a noninvasive magnetic device to stimulate focused parts of the brain transcranially occurred in 1985 when Barker *et al.* attempted

to elicit an evoked potential in muscle tissue through neuronal stimulation in the motor cortex; he also described the potential of this method for clinical use of transcranial magnetic stimulation (TMS) in mental illness [2]. With psychiatric applications seemingly beyond feasibility, the decade of research that followed mainly focused on neurologists' use of TMS as a tool for noninvasive mapping of the cerebral cortex [3]. This technology provided clinicians and researchers with a method by which they could localize cortical function using a convergent approach with lesion studies and neuroimaging.

After speculation about mood elevation in neurosurgery patients receiving TMS [4,5], the first known study of rTMS in the psychiatric population occurred in 1993 when Hoflich *et al.* demonstrated significant improvement in one of two patients with psychotic, drug-resistant major depression who received this treatment [6]. TMS is a broad term referring to the process of stimulating the cortex using magnetic coils, while rTMS is the same process narrowed to the specific technique of using frequent, repetitive pulses to affect cortical activity. Since the Hoflich case reports, there have been a number of studies investigating rTMS for the treatment of major depressive disorder.

In 2008, the US FDA approved the use of one specific device (NeuroStar® TMS Therapy System; Neuronetics Inc., PA, USA) for the treatment of treatment-resistant depression in adults greater than 18 years of age, defining it as major depressive disorder that has not resolved to a satisfactory level following the use of one antidepressant medication at or above the minimal effective dose for an appropriate duration [101].

In January of 2013, the FDA provided clearance for a second device as a therapeutic intervention for treatment-resistant depression. Brainsway, Ltd, based in Jerusalem, Israel, has become the second manufacturer to achieve this status with its Deep TMS H System [102].

Mechanism of action of rTMS in major depressive disorder

rTMS relies upon two electromagnetic principles: Ampere's law and Faraday's law. According to Ampere's law, a magnetic field is generated when using an alternating electrical current. Faraday's law specifies that an electrical current is generated when an alternating magnetic field is used. In the case of TMS, an insulated metallic coil is positioned over the scalp, which in turn overlies the targeted brain area. Following Ampere's law, an alternating electric current through the coil generates an alternating magnetic field that is perpendicular to the direction of that current. The induced alternating magnetic field passes through the scalp and skull relatively unimpeded and reaches the level of the CNS where, following Faraday's law, the conductive ability of brain tissue allows for a responsive electrical current localized to the anatomic area of the brain directly under the coil. The direction of that current is in the opposite direction of the current through the coil. This process can be applied through single pulses, paired pulses or more commonly in psychiatric applications, in repetitive trains of varying frequencies for extended periods of time. While high-frequency use (typically greater than 1 Hz and usually between 5 and 20 Hz) generally increases cortical excitability of the targeted tissue, low-frequency use (1 Hz or less) is thought to be associated with a reduction of excitability. The parameters of stimulation include: the number of pulse trains per session, train duration, pulse frequency within a train and inter-train interval, and the stimulator intensity, usually in reference to each patients' motor threshold. The precise site of stimulation

and orientation of the coil also contribute to the quality of stimulation achieved. The motor threshold is defined as the lowest intensity that will cause contraction of a specified muscle in at least 50% of trials when the coil is placed over the motor cortex in five to ten consecutive trials. Using motor threshold as the measure of stimulation, TMS operators can elicit an easily attainable objective assessment of achieved stimulation. While it has been demonstrated that different frequencies affect both cerebral blood flow and cortical excitability, there is also speculation that TMS engages mechanisms of synaptic plasticity including long-term potentiation and long-term depression [3,7,8]. Frequency modulation is thought to be highly dependent upon basal cortical activation states of the stimulated area [9].

The proposed mechanism of rTMS as a treatment for major depressive disorder generally centers around altering the activity level (i.e., excitability) of a localized area of the brain that participates as a critical node in a network that is theorized to be involved in the pathophysiology of depressed mood. Beyond altering excitability, the process is known to affect neuroendocrine functioning such as increasing thyroid-stimulating hormone levels and reversing the results of the dexamethasone suppression test in certain forms of major depressive disorder [10,11]. Monoamines in the brain are also selectively affected by TMS. Ben-Shachar *et al.* examined rats 10 sec after receiving TMS treatment and showed reduced levels of dopamine in the prefrontal cortex and increased levels in the striatum and hippocampus [12]. The dopaminergic systems in the anterior cingulate and orbitofrontal cortex have also been shown to respond to rTMS and are neuroanatomical areas known to be implicated in mood regulation [13,14]. In addition, serotonin levels appeared to be increased by rTMS only in the hippocampus. Norepinephrine was not found to be affected [12]. These changes are consistent with the monoamine hypothesis of major depression.

There is also evidence that TMS can be effective through corrective effects on a hemispheric imbalance in affected patients. While a number of studies have demonstrated the beneficial excitatory effect of high-frequency rTMS on the left side of the prefrontal cortex, in 2006, Fitzgerald *et al.* demonstrated a significant response in patients with treatment-resistant depression

to low-frequency (1 and 2 Hz) rTMS on the right prefrontal cortex (Figure 1) [15]. The findings of that study are consistent with the hypothesis that depressive symptoms are related to a relative hypoactivity of the left prefrontal cortex when compared with the right. The functional imaging study by Grimm *et al.* in 2008 demonstrated that in patients with major depressive disorder, there is a relative hypoactivity of the left dorsolateral prefrontal cortex that is associated with negative emotional judgment whereas hyperactivity of the right dorsolateral prefrontal cortex is linked with attentional modulation [16]. A proposed mechanism is that TMS corrects this imbalance by using either excitatory frequencies on the left side or inhibitory frequencies on the right side. Reported antidepressant efficacy from rTMS at the left dorsolateral prefrontal cortex is also thought to be related to its anticorrelated downstream effects on the subgenual cingulate. When this anticorrelation is powerfully achieved through stimulation of the dorsolateral prefrontal cortex, rTMS has been shown to have greater efficacy [14].

Efficacy of rTMS in the treatment of major depressive disorder

Early studies that evaluated the efficacy of TMS in major depressive disorder were limited by small numbers of subjects and often highly restrictive samples as a result of their particular inclusion and exclusion criteria. Studies in the 1990s at first focused on TMS use over the vertex before exploring shifting emphasis to the left prefrontal area by the latter part of the decade [17]. Meta-analysis data indicate that rTMS over the left prefrontal cortex provides statistically significant improvement as compared with sham treatment in patients with depression [18–21].

The small number of large-scale, multisite trials have come to inconsistent conclusions about the efficacy of treatment. A European trial featuring 127 patients failed to demonstrate that rTMS was any more effective than sham treatment in major depressive disorder [22]. In 2007, however, O'Reardon *et al.* published the results of an industry-sponsored double-blind, multisite randomized controlled trial involving

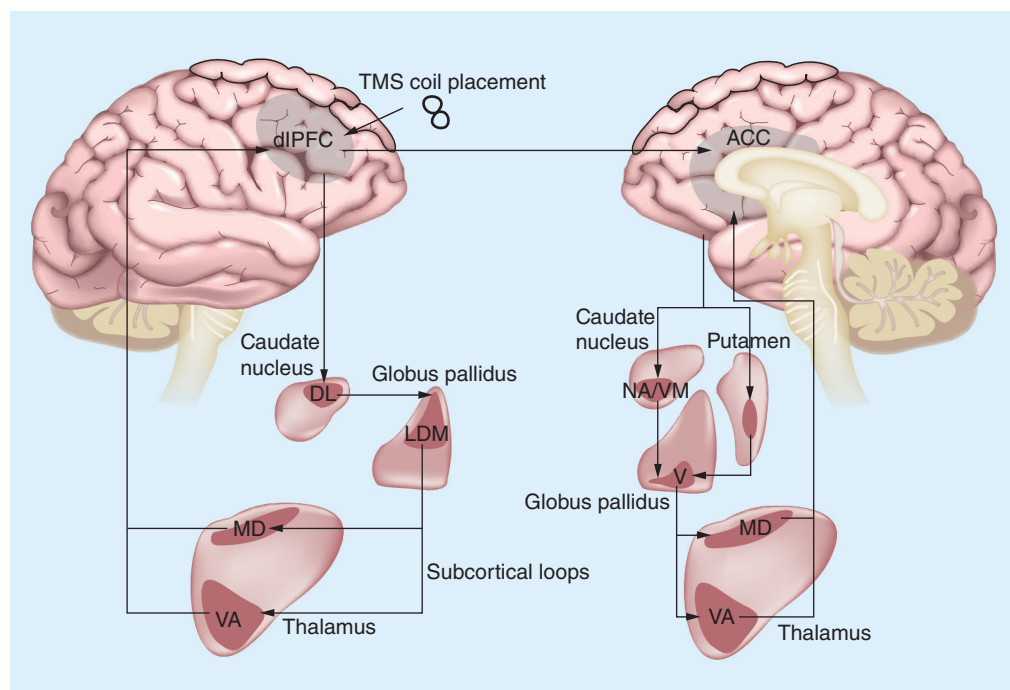


Figure 1. Transcranial magnetic stimulation coil placement over the dorsolateral prefrontal cortex and its connectivity to subcortical loops and associated functional neural networks, including the subgenual cingulate.

ACC: Anterior cingulate cortex; dlPFC: Dorsolateral prefrontal cortex; DL: Dorsolateral; LDM: Lateral dorsomedial; MD: Mediodorsal; NA: Nucleus accumbens; TMS: Transcranial magnetic stimulation; V: Ventral; VA: Ventral anterior; VM: Ventromedial.

Adapted with permission from [35].

301 patients with treatment-resistant depression [23]. The study only enrolled patient subjects between the age of 18 and 70 years suffering from DSM-IV major depressive disorder for less than 3 years who were not currently on any antidepressant medication. The population was defined as having treatment-resistant depression due to either failure of at least one, but no more than four, adequate antidepressant treatments in the current depressive episode or four failed antidepressant medication attempts in their lifetime. Exclusion criteria included any history of psychosis, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, eating disorders, current pregnancy, seizure disorders or other major medical contraindications. Prospective subjects were also excluded if they had previously failed ECT or prior treatments with TMS or a vagus nerve stimulator. The clinical outcomes across different measures consistently showed more improvement in the active treatment group than the sham group, with specific superiority demonstrated in Hamilton Depression Rating Scale on both 17- and 24-item scores at weeks 4 ($p = 0.006$ and 0.012 , respectively) and 6 ($p = 0.005$ and 0.015 , respectively). When correcting for baseline imbalances in the Montgomery-Asberg Depression Rating Scale scores between treatment groups, the Montgomery-Asberg Depression Rating Scale also showed improvement ($p = 0.038$) at 4 weeks. At 6 weeks, the active treatment group was found to be twice as likely to achieve full remission as the sham group across the outcome measurements already mentioned. Closer analysis of the data demonstrates that at least 2 weeks of TMS is necessary before significant effects can be expected [23].

George *et al.* also performed a large, multisite study with NIH support that found significant antidepressant effect of daily prefrontal rTMS on the left prefrontal cortex; remission rates were 4.2-times higher with active versus sham treatment. Almost 30% of subjects went on to remit in the open-label follow-up [24].

An rTMS study featuring 300 depressed veterans sponsored by the Department of Veterans Affairs (DC, USA) is currently underway. The study will distinguish itself from others by allowing patients to remain on stable antidepressant medications and including patients with more diverse comorbid disorders [17].

The durability of rTMS effect over time requires further study. While it is apparent that certain maintenance interventions may be useful

in prolonging the clinical effect of this intervention, the parameters and scope of these treatments are not well defined. One study found that in the 24 weeks following a course of rTMS that resulted in at least a partial remission, 10% of subjects experienced a relapse, while an additional 38.4% reported some level of symptom worsening over the course of the study. These patients had been continued on antidepressant monotherapy and 84.2% re-achieved symptomatic benefit when given adjunctive rTMS. Of the patients who experienced relapse, the mean time of relapse was 164 days into the study [25].

Another study found that the particular form of TMS known as deep TMS was effective as an antidepressant treatment in patients who had relapsed 1 year after initially responding to this treatment. However, the magnitude of this effect was notably smaller than during the first round of treatment [26].

Cost-effectiveness of rTMS treatment in major depressive disorder

Like all relatively new technologies, rTMS faces the obstacles of overcoming relatively high cost of treatment when compared with most other forms of standard of care, such as medications alone. Does rTMS stand as a plausible option for psychiatrists in the face of these costs because of an efficacy in treatment that cannot be obtained elsewhere at equal or lesser cost? In addition, does the upfront cost of rTMS actually represent an investment in patients' mental health that might save significant money and resources in the future, for example, by preventing potential future hospitalizations? These are two of the questions asked by Simpson *et al.* [27].

They applied an incremental cost-effectiveness ratio per quality-adjusted life year (QALY) to three data sets. In these measures of cost utility, incremental cost-effectiveness represents a measure of cost-effectiveness for every unit of benefit estimated by QALY. Estimates of QALY take into account both quality and longevity of the treatment's benefit so that treatments that are both long lasting and effective will reduce the overall number associated with incremental cost-effectiveness/QALY. Lower dollar amounts associated with this ratio correlates with a higher cost-effectiveness and is desirable from a societal perspective with regard to its medical interventions. In this cost-effectiveness study, the authors assumed an average cost per session of US\$300 and assessed this versus symptom

improvements, as seen in three studies. The authors concluded that rTMS is cost effective compared with standard of care in subjects who have failed antidepressant trials and especially so in cases in which they have only failed one antidepressant prior to the start of rTMS treatment. The degree of cost–effectiveness changes with varying estimates of cost and productivity [27].

There are major limitations in attempting to quantify exact costs when using estimates upon estimates. In the case of applying specific costs of treatment and productivity losses to the use of TMS, it is important not to discount the idea that productivity and the costs of treatment vary widely depending upon an individuals' temperament, drive, education, access to care and any number of other factors. Changes in cost per session as well as unclear estimates of productivity losses stemming from major depressive disorder all drastically affect the resulting cost–effectiveness reported. Still, there is value in investigating this issue. While certain antidepressant medications are now relatively inexpensive, clinicians cannot overlook the cost in time, resources and money of frequent follow-up visits for psychopharmacologic management, emergency department psychiatric evaluations and frequent inpatient hospitalizations, all of which have undefined potential to be reduced with rTMS treatment as of yet. The cost of those areas are also extremely varied across the clinical landscape and are difficult to define precisely. However, they are clearly a significant drain on society's collective wealth and warrant the ongoing investigation of novel treatment in cases of treatment-resistant depression.

Prior studies have also attempted to compare cost–effectiveness of TMS and ECT. One 2008 study found that while the cost of a single session of rTMS was lower than that of ECT, there were no treatment cost differences in the following six months and that based on Hamilton Depression Rating Scale scores, rTMS was not as effective as ECT in patients with severe depressive episodes [28]. However, these efficacy results are contradicted by a previous study by Grunhaus *et al.* who sought to directly compare ECT and rTMS in patients who had been referred for ECT with severe depression. They found that in patients with major depressive disorder and psychosis, ECT was more effective but that in patients with major depressive disorder and no psychotic symptoms, there was no statistical difference in efficacy [29]. A cost–effectiveness

study examined the Grunhaus data and determined that TMS alone was significantly more cost effective compared with ECT alone [30]. There is uncertainty in this area and further investigation is warranted.

Adverse effects & contraindications

Extended guidelines for clinicians and researchers using TMS is provided in a 2009 paper by Rossi *et al.* [31]. rTMS is very safe for most patients and generally well tolerated. The Schutter meta-analysis that included 30 studies of rTMS in patients with major depressive disorder described no serious adverse events related to treatment. Specifically, there were no deaths or seizures reported in patients receiving active treatment. The most commonly reported adverse effects were a transient headache, nausea, dizziness and localized scalp discomfort under the area of the coil. Headaches and local pain may be related to intensity of stimulation used, as well as location and position of the coil. Adverse effects were generally reported to be limited in time and severity, and largely responded to supportive and analgesic treatment [18]. There has also been concern that patients may develop hearing loss as a result of noise made by the devices in close proximity to their ears. However, this assertion has been refuted in the literature [32].

While there is no definitive consensus about who should be excluded from treatment with rTMS, the procedure should be used with extreme caution or not at all in certain populations. Absolute contraindications generally include the existence of aneurysm clips, intracranial implants such as brain stimulators, electrodes or any other foreign materials with ferromagnetic properties, as the objects can heat or move. Patients with increased intracranial pressure, seizure disorders or cardiovascular disease are also generally excluded from participating in rTMS treatment given that these conditions increase the risk of harm in the very rare occurrence of seizures seen with this technique. The procedure has also not been shown to be definitively safe in pregnancy as it has not been thoroughly studied, and it is important to be cautious with patients who are on medications that may lower the seizure threshold [23].

The most appropriate patient population for rTMS

There are varying opinions about the most appropriate patient population for rTMS treatment.

While it has been shown in various studies to have significant clinical efficacy in patients with treatment-resistant depression, the borders that define mild-to-severe treatment resistance in this context are not fully known. Patients with very mild depressive symptoms should first be treated with lower cost, less intensive options such as psychotherapy and psychopharmacologic antidepressants. As stated earlier, the FDA has defined the indication for rTMS as a patient who has failed at least one antidepressant after a trial at the appropriate dose for an appropriate length of time, and while there is no consensus as yet about which subgroups of depressed patients are most likely to benefit from rTMS, this population is an appropriate starting point [17,101]. While there is definitely a segment of the antidepressant-resistant major depressive disorder population for whom rTMS represents a safe, reasonable and effective option, there is uncertainty about exactly where on the severity spectrum ECT should be used as the most clinically proven treatment option for severe treatment-resistant depression. Of the population currently relying upon ECT for severe treatment-resistant depression, there is likely a portion who could benefit from rTMS treatment at lower societal and personal cost but still experience similar antidepressant effects. However, there are not many studies that examine this particular possibility and there is no consensus among the ones that do. One study that attempted to examine efficacy differences in rTMS and ECT found that while ECT was the most effective method after 4 weeks of treatment, a specific form of TMS called deep TMS showed better efficacy at 2 weeks when considering both symptom improvement and cognitive performance. However, deep TMS was also noted to exhibit poor tolerability when compared with standard TMS or ECT [33]. The treatment choice between rTMS and ECT is best decided on a case-by-case basis. Practical considerations may prevail in some cases, such as the fact that there is no known adverse cognitive sequelae of rTMS and patients can drive themselves home after each treatment session. Patients and psychiatrists can only make a fully informed decision after having engaged in discussions of efficacy, safety and cost.

Conclusion & future perspective

Through focused stimulation of the cortex, rTMS is a novel treatment option for

treatment-resistant depression. There is sufficient evidence to definitively say that, when applied in certain ways, this technology has clear antidepressant effects that are clinically useful, particularly in cases when first-line antidepressant treatment has failed. TMS is also safe and tolerable for patients and is associated with a much less profound stigma, initial cost and care burden than ECT. While in its current form it does not represent a replacement for antidepressant medications, ECT or psychotherapy, there is a distinct population of patients for whom this treatment acts as an effective and economically feasible therapy that is otherwise unavailable.

The future of this technology depends upon the resolution of several questions. Will rTMS be widely accessible to a broad population given the varying levels of acceptance third-party payers have demonstrated toward its use? A large step towards widespread use occurred recently when the FDA approved two particular devices (NeuroStar TMS Therapy System and Deep TMS H System), but it currently remains a treatment option available only in very distinct pockets of the population for whom it is indicated. Since this approval, mastery of its use has continued to take form, resulting in more consistent usage and demonstrable effects. In a study of 100 consecutive patients at one academic center following this FDA approval, TMS was found to be safe and effective in both acute and maintenance treatments [34]. As more data are accumulated with larger sample sizes, attainable through the increased prevalence of the treatment itself, it is likely that remaining uncertainty about the treatment's role will be clarified, including appropriate indications, contraindications, cost and efficacy. Further study is also needed to improve technical aspects of treatment including experimental investigation of the use of stereotactic guidance and electrophysiologic or functional imaging prior to rTMS therapy, in order to potentially predict efficacy of treatment by more effectively pinpointing targets of stimulation. While these technical approaches remain in an investigational phase, they are potential avenues for further research. Emerging technologies as well as techniques such as deep TMS and use of H-coils, as well as θ -burst stimulation, are also altering the field in ways that are not yet entirely defined.

What steps should be taken, as this technology becomes more prevalent among

psychiatrists to protect the appropriateness of its use? The results of the studies discussed in this paper relied upon careful use of TMS by experts, often pioneers of the field. As the technology becomes more widespread, there is a risk that clinicians without demonstrated expertise or training will utilize it inappropriately, specifically considering that TMS represents a procedure with high income potential in a field with very few procedures. It will therefore be necessary for competency standards to be developed in order for use of this procedure to be reimbursable, a requirement seen in other fields of medicine upon adoption of a new procedural treatment option.

TMS represents an emerging technology with potential to meaningfully contribute toward psychiatric treatment of major depressive disorder. More research will be needed to determine

which clinical avenues will be pursued and what form those contributions will take.

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