EXPERT REVIEWS

Transcranial magnetic stimulation for the treatment of depression

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Repeated daily left prefrontal transcranial magnetic stimulation (TMS) was first proposed as a potential treatment for depression in 1993. Multiple studies from researchers around the world since then have repeatedly demonstrated that TMS has antidepressant effects greater than sham treatment, and that these effects are clinically meaningful. A large industry-sponsored trial, published in 2007, resulted in US FDA approval in October 2008. Most recently, a large NIH-sponsored trial, with a more rigorous sham technique, found that a course of treatment (3–5 weeks) was statistically and clinically significant in reducing depression. However, consistently showing statistically and clinically significant antidepressant effects, and gaining regulatory approval, is merely the beginning for this new treatment. As with any new treatment involving a radically different approach, there are many unanswered questions about TMS, and the field is still rapidly evolving. These unanswered questions include the appropriate scalp location, understanding the mechanisms of action, refining the 'dose' (frequency, train, number of stimuli/day and pattern of delivery), understanding whether and how TMS can be combined with medications or talking/exposure therapy, or both, and how to deliver maintenance TMS. This article summarizes the available clinical information, and discusses key areas where more research is needed. TMS reflects a paradigm shift in treating depression. It is a safe, relatively noninvasive, focal brain stimulation treatment that does not involve seizures or implanted wires, and does not have drug–drug interactions or systemic side effects.

Keywords: depression • TMS • transcranial magnetic stimulation • treatment-resistant

Transcranial magnetic stimulation

Description of the method & devices

Transcranial magnetic stimulation (TMS) involves inducing an electrical current within the brain using pulsating magnetic fields, which are generated outside the brain near the scalp. The essential feature is using electricity to generate a rapidly changing electromagnetic field, which in turn produces electrical impulses in the brain. A typical TMS device produces a fairly powerful magnetic field (~1.5–3 Tesla), but only very briefly (a fraction of a millisecond for each pulse). TMS is not simply applying a static or constant magnetic field to the brain, and differs from the other brain stimulation techniques that are either invasive (e.g., deep brain stimulation), or require a seizure for therapeutic effects (electroconvulsive therapy [ECT]). There are now entire journals devoted to the field of brain stimulation [1], and books devoted to each of the individual techniques [2], as well as in-depth overviews [3]. The interested reader is referred to these references for reviews of the other brain stimulation methods or about TMS in other clinical or research applications. This article is limited to covering TMS as a clinical antidepressant.

With respect to TMS, by the year 1820, scientists had discovered that passing an electric current though a wire induces a magnetic field. In 1832, Michael Faraday demonstrated that the inverse was also true – passing a wire through a magnetic field generates an electrical current [4]. Thus, a changing magnetic field can generate electrical current in nearby wires, nerves or muscles. A static magnet will not generate a current. For most TMS applications, it is probably is the electricity induced in the brain from the pulsating magnet, and not the magnetic field itself, that produces neurobiological effects. In fact, most people assume that the neurobiological effects of most TMS applications stem from the actual depolarization of neurons, causing them to fire, and that massively subthreshold TMS, far

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below what it takes to cause neurons to depolarize and produce movement in the thumb, referred to as the motor threshold (MT), would have only minimal biological effects. However, at least one group (Neosync, CA, USA) is pursuing using lower intensity TMS, sometimes coordinated with the patient's EEG, to potentially treat depression, shifting membrane potentials in a coordinated fashion and not actually depolarizing large neurons [5]. Additionally, there is new information regarding the regional brain effects of low-level magnetic fields, including using even standard MRI scanners [6].

In 1959, Kolin and colleagues demonstrated that a fluctuating magnetic field could stimulate a peripheral frog muscle in preparation [7]. However, it was not until 1985 that the modern era of TMS started. That year, Anthony Barker (Sheffield, UK) described the use of a noninvasive magnetic device resembling modern TMS instruments [8]. The device was slow to recharge and quick to overheat, but it was able to stimulate spinal cord roots, and also superficial human cortex.

Transcranial magnetic stimulation requires a unit to store and deliver a charge (called a capacitor), and an electromagnetic coil (typically round in the shape of a doughnut or two round coils side-by-side and connected in a figure of eight). A system can be cumbersome (resembling a small refrigerator), although some have shown that the entire system could be made portable and weigh less than 20 lbs [9,10]. The devices are regulated by the US FDA for general safety, and most machines have FDA approval for sale in the USA. They are also then regulated with respect to the ability to advertise their therapeutic use in a particular disorder. In the USA, a device manufactured by Neuronetics (PA, USA) was approved by the FDA in 2008 for treating depression (**Figure 1**) [11].

Early TMS devices only emitted a single, brief pulse. Modern devices can generate a rapid succession of pulses, called repetitive TMS (rTMS). These devices are used for behavioral research or clinical treatments and can discharge on and off for several minutes. For example, the typical treatment for depression is a 20–40-min session, 5 days a week for 4–6 weeks, with approximately 3000–6000 pulses in each session. In order to keep the patient still and the device correctly placed, the patient reclines in a chair and the device is held securely against their head while they are awake and alert without needing anesthesia.

Conventional TMS coils generate a magnetic field impulse that can only reach the portion of the cerebral cortex that lies on the brain surface [12]. The main effect of the impulse penetrates just 2–3 cm below the device [13,14]. However, a deep TMS device has been invented and is in early clinical trials for depression and several other indications [15–17]. There has been some excitement, but no convincing clinical evidence (yet) about whether one could build complex assemblies of coils that might summate and stimulate deep within the brain, while sparing superficial cortex [18].

When the TMS device produces a pulse over the motor cortex, descending fibers are activated and volleys of electrical impulses descend through connected fibers into the spinal cord and out to the peripheral nerve, where it can ultimately cause a muscle to twitch. The minimum amount of energy needed to produce contraction of the thumb (the abductor pollicis brevis muscle) is called the MT [19–22]. Because this is easy to generate and varies widely across individuals, the MT is used as a measure of general cortical excitability, and most TMS studies (both research and clinical based) report the TMS intensity or dose as a function of individual MT (and not as an absolute physical value) [23]. Although this convention has helped in making TMS safer, it is insufficient, in that it is referenced only to each patient, and thus is not a universal number or actual measurement. Future work is focusing on more universal, constant measures of the magnetic field delivered.

In general, a stronger, more intense TMS pulse results in greater activation of the CNS tissue, and a wider area of activation [24–28]. The situation with frequency is more complex. In general, frequencies of less than 1 per second (<1 Hz) are inhibitory [29]. This may be because low-frequency TMS more selectively stimulates the inhibitory GABA neurons, or this frequency resembles the frequencies used in animal and cell studies that produce long-term depression (LTD). One particular TMS sequence builds directly from the neurobiological studies of long-term potentiation and LTD, and is called 'theta burst', as it has short bursts of TMS at theta frequencies [30,31]. Conversely, higher frequency stimulation is behaviorally excitatory [32]. Interestingly, high-frequency TMS over some brain regions can temporarily block or 'knockout' the function of that part of the brain, while the TMS pulses are being delivered [33,34].

A handheld TMS device is being developed and studied as a treatment to interrupt migraine headaches (Neuralieve, Inc., CA, USA). The device delivers a single large pulse and when the patient experiences the aura phase of an impending headache they hold the device to the back of their head and direct the pulse toward the occipital cortex [35,36].

Putative mechanisms of action

Transcranial magnetic stimulation can produce different brain effects depending on the brain region being stimulated, the use parameters (intensity, frequency and duty train) and whether the brain region is engaged or 'resting'. Thus, it is difficult to review a single 'mechanism of action' for TMS. However, in general and as stated previously, a single pulse of TMS over a cortical region, such as the motor cortex, causes large neurons to depolarize. That is, the powerful transient magnetic field induces current to flow in neurons in superficial cortex (induced current). Both modeling and simple testing have shown that the fibers most likely to depolarize are those that are perpendicular to the coil, and are bending within the gyrus [22,37–40]. Some lower TMS intensities do not cause large neuron depolarization, but can still affect resting membrane potentials, and thus alter brain activity and behavior. The most striking positive phenomena that TMS can produce are motor twitches (thumb, hand, arm or leg movement) when applied over motor cortex, or 'phosphenes' when TMS is placed over the occipital cortex. To date, TMS cannot produce acute memories, thoughts or sensations or percepts, apart from the sensation of the coil on the scalp. rTMS can produce measurable effects lasting for minutes to hours after the train [30,31,41,42].

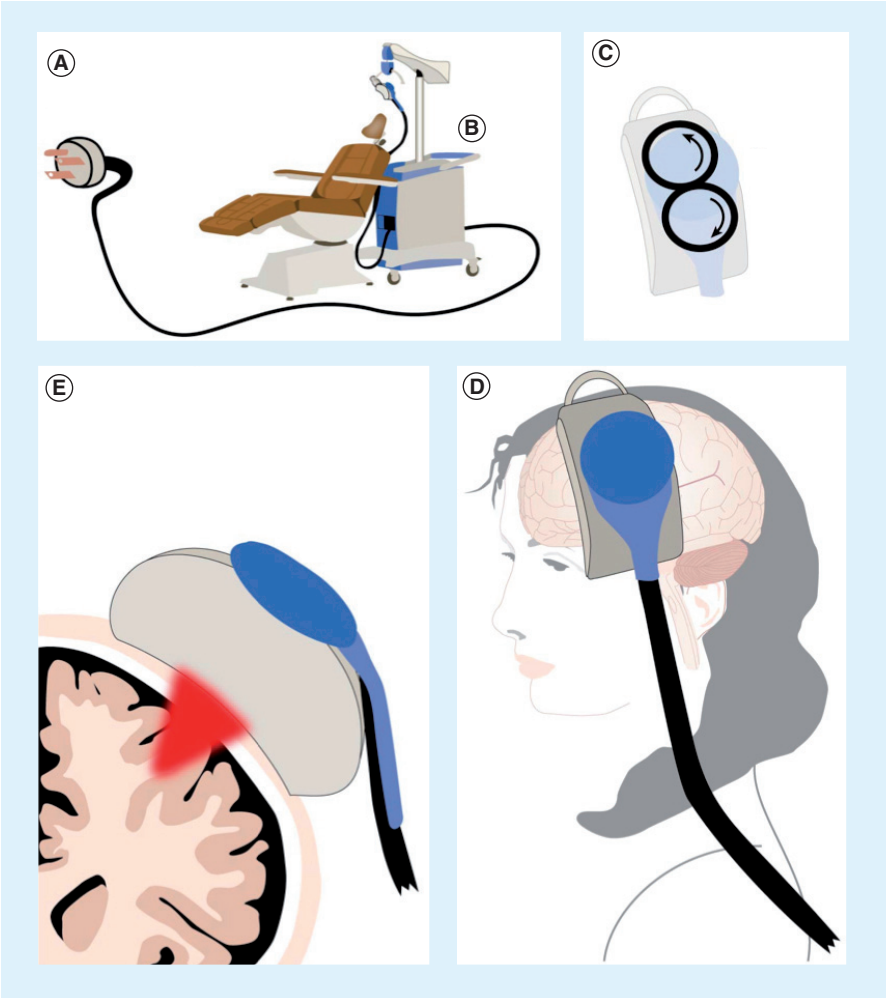

Figure 1. Transcranial magnetic stimulation. Current from the wall **(A)** is used to charge a bank of large capacitors **(B)**. These capacitors send a pulsing electrical current to the coils **(C)** resting on the scalp **(D)**. The powerful but brief electrical current in the coil creates a transient magnetic field that passes unimpeded through the skin and skull, and results in electrical impulses in neurons in superficial cortex under the coil **(E)**. Depending on the type of cell that is engaged, this then results in secondary trans-synaptic effects.
Reprinted with permission from APPI, from [3].

Transcranial magnetic stimulation over some cortical regions can produce a transient disruption of behavior. This is most striking when the coil is placed over Broca's area and one can produce a transient expressive aphasia. Much interest involves whether TMS can produce short-term or even longer-term changes in plasticity [32,43]. Simple studies in motor and visual systems clearly indicate the potential for this approach [44], which is now being applied in studies of post-stroke recovery and other forms of rehabilitation [45,46].

Coupling TMS with electrophysiological measures allows one to use TMS as a measure of motor cortex excitability, and then to measure how behavior, medications or other interventions might change excitability. Several groups are using this TMS excitability measurement technique to investigate new CNS-active compounds [32,41,47,48].

Coupling TMS with imaging (PET, SPECT, functional MRI [fMRI] or blood-oxygen-level dependence fMRI) allows one to directly stimulate circuits and then image the resultant changes (Figure 2) [49,50]. With respect to the neuropsychiatric uses of TMS for depression or pain, at a molecular level TMS is known to have similar effects as those seen with ECT, for example, increased monoamine turnover, increased brain-derived neurotrophic factor (BDNF) and normalization of the hypothalamic–pituitary–adrenal (HPA) axis.

The initial use of daily prefrontal TMS to treat depression was based on the theory that clinical depression involves an imbalanced relationship between prefrontal cortex and limbic regions involved in mood regulation (insula, cingulate gyrus, amygdala and hippocampus), and that, in some patients at least, the prefrontal cortex was hypometabolic [51]. The basic hypothesis back in 1994, was that repeated subconvulsive stimulation of the prefrontal cortex would initiate circuit activity involving regulatory pathways interacting with the limbic system [51,52]. These circuits have recently been described in motor, sensory and prefrontal systems [53]. Before allowing clinical trials, the FDA initially required safety testing in healthy controls, and some evidence of limbic changes with prefrontal TMS. Single sessions of prefrontal rTMS in healthy adults found no side effects, with evidence of HPA interaction (serum thyroid levels) and slight mood changes [54], clearing the way for case series [55], followed by a double-blind trial [56].

There is now increasingly direct support, primarily coming from brain imaging studies [24,48,57], that prefrontal TMS in depressed patients is changing limbic activity and the regulatory circuit. To date, no one has linked these changes directly to the antidepressant effects.

Recently, work in the learned helplessness model of depression also supports the important role of prefrontal regulation, and may explain how TMS works as an antidepressant. In 1975, Miller and Seligman developed the learned helplessness model in rats, which bears resemblance to depression or post-traumatic stress disorder (PTSD), or both [58]. In this paradigm, normal healthy rats are yoked or paired, and subjected to intermittent stressors, typically a tail shock. One animal is provided a lever in its cage that, when pressed, terminates the shock. The other yoked animal has no control lever. Both animals receive the identical amount of shock, but only the yoked animal that does not have a control

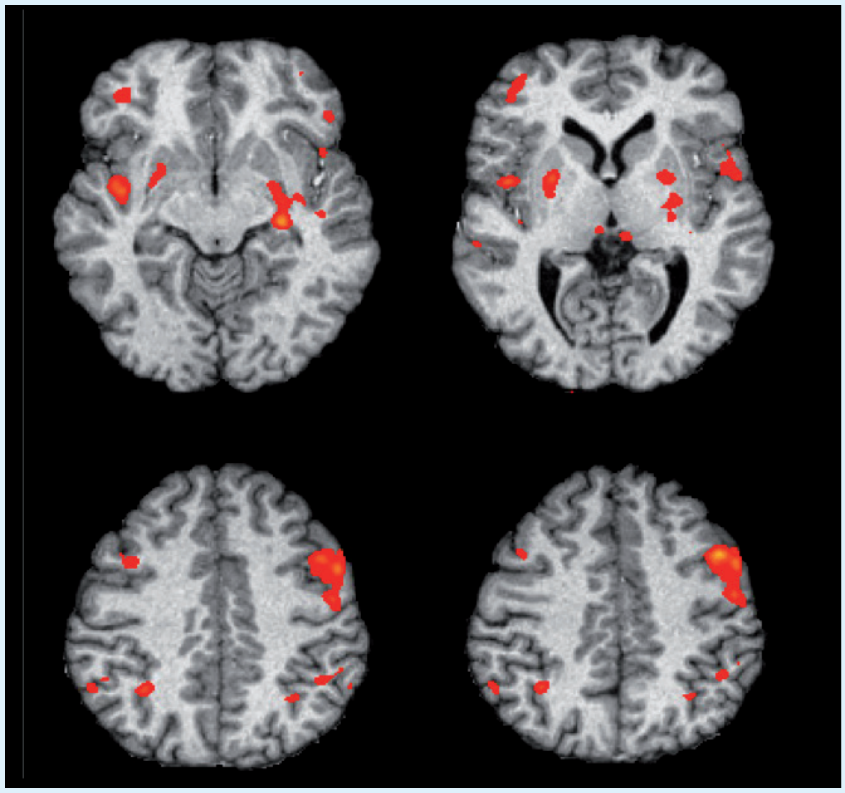

Figure 2. Functional MRI image of local and limbic effects of prefrontal transcranial magnetic stimulation from Li and colleagues [24].

lever develops behaviors that resemble depression (social isolation) or PTSD (hyper-startle) [59]. The animal that has 'the sense of control' does not develop abnormal depression or PTSD-like behavior. Recently, Maier and colleagues have completed a series of studies that fairly convincingly demonstrate that the 'sense of control' is actually a signal from the medial prefrontal cortex (mPFC) to the dorsal raphe nucleus (DRN) [60–63]. That is, one can lesion the prefrontal cortex in the animal that has the control lever, and although they learn to abort the shock, they go on to develop social isolation (helplessness). Disconnecting the prefrontal cortex blocks the therapeutic effects of having control. Interestingly, one can also not actually provide a control lever to the rat, but instead pharmacologically activate the mPFC during shock, and the animal does not develop depression [60]. That is, prefrontal cortical stimuli can substitute for having the control lever that turns off the tail shock. They speculate that "pharmacological activation of the ventromedial prefrontal cortex (vmPFC) appeared to give rats the 'illusion of control'" [60].

One can also take a previously yoked 'depressed' rat in this model, and re-expose the animal to co-occurring tail shocks and a control lever, and the animal becomes 'undepressed' and is actually 'resilient' to later episodes of uncontrollable stress. They refer to this phenomenon as 'behavioral immunization'. This may be partially what is happening with TMS in depressed patients, and would imply that one should perform exposure therapy and cognitive–behavioral therapy (CBT) while patients are receiving TMS. Currently, in most TMS depression studies, patients have been allowed to rest with their eyes closed, but not sleep, and there is no attempt at exposure or cognitive therapy during the actual TMS session.

Safety & side effects

In general, TMS is regarded as safe and without enduring side effects. There have been no reported lasting neurologic, cognitive or cardiovascular sequelae. However, TMS can alter brain function and is a relatively new technology, so vigilance is required. A recent international conference on TMS safety updated the use guidelines [64,65].

Inducing a seizure remains the primary safety concern with TMS, although these are rare. There have been less than 20 reported seizures induced with TMS, with a sample size of several thousand patients or subjects exposed to TMS. The risk is likely to be less than 0.5%. Most of these TMS-induced seizure subjects were healthy volunteers without a history of epilepsy. Fortunately, there are no reports that the individuals affected experienced recurrence. Also, all of the seizures occurred during TMS administration when the patient was sitting down and near an investigator. Also, all of the seizures were self-limited without needing medications or other interventions. Published safety tables concerning the proper intensity, frequency and number of stimuli have helped minimize the numbers of seizures [64]. Of the reported cases the majority were receiving TMS to the motor cortex – the most epileptogenic region of the cortex. Additionally, most (but not all) were receiving trains of stimulation outside of suggested limits. These cases suggest that TMS-induced seizures will remain a small but significant adverse event, even in patients without histories of seizures, and even when TMS is used within suggested guidelines. For these reasons, TMS for most research uses and all clinical purposes needs to be supervised by a medical doctor, in a facility capable of quickly responding to a potential seizure [66,67].

Studies in rabbits, as well as some human studies, suggest that TMS can cause hearing loss, and subjects, patients and operators should wear earplugs [68,69]. One patient reported a temporary hearing loss after TMS. In light of this, an extensive study of auditory threshold was conducted before and after 4 weeks of TMS in over 300 patients in the pivotal TMS depression study [70]. No changes were found. Nevertheless, patients should wear earplugs when receiving TMS.

Headaches are the most common complaint after TMS; however, there was no difference in headache frequency between sham and control in the recent large trials [71]. Repeated analysis of neurocognitive functioning of TMS patients has not found

any enduring negative effects from the procedure [72,73]. After a TMS session, patients or subjects are able to drive home and return to work.

The TMS procedure itself causes some scalp pain, which is almost always worse during the first few sessions, and then largely disappears [74,75].

Research uses

A thorough overview of TMS research uses cannot be included here, but several active areas are highlighted. TMS can be used as a measure of cortical excitability, and has been used to investigate medication effects, emotional states, plasticity in learning and stroke recovery, sleep [76,77] and a host of disease states. TMS can be combined with brain imaging to directly stimulate circuits and image the resultant changes [78]. When precisely applied over critical brain regions, TMS can help causally determine whether a brain region is involved in a behavior, and how information flows through the brain during a task. There is much excitement, but little hard evidence, that TMS might be used to actually augment task performance, memory formation or recovery from injury.

Clinical studies in depression & pain

Largely because of its noninvasiveness, TMS has been investigated in almost all neuropsychiatric conditions. Until only recently, there has not been a TMS industry to promote or perform this work and thus, much of the clinical work has been single site and nonindustry funded, with relatively small sample sizes.

Depression has been the most widely studied condition with TMS. Three initial studies from Europe used TMS over the vertex as a potential antidepressant [79–81]. In the USA, George, Wassermann and Post performed initial safety studies in healthy controls, an open study and then a double-blind controlled trial of TMS for 2 weeks [54–56]. This work has now dramatically grown, but without much change in many of the initial treatment choices (coil location, frequency and dosing). There have now been several meta-analyses of the procedure [82–86]. Several years ago, a meta-analysis of repetitive TMS for depression examined 25 published sham-controlled studies [87]. The authors concluded that left prefrontal TMS provided statistical superiority over sham treatment for patients with depression. However, they concluded that the clinical benefits are marginal in the majority of reports and there is still considerable uncertainty concerning the optimal stimulation parameters. Two, more recent, positive meta-analyses suggest that the overall effect size with TMS in major depression is at least as good as that of standard pharmacotherapy [83,88]. The clinical features that appear to be associated with a greater response include: younger age, lack of refractoriness to antidepressants and no psychotic features [73].

There have now been three large multisite trials of TMS for depression. The first, a European trial, used TMS in 127 patients as an adjunctive treatment to recently started medications and failed to find an augmenting effect of TMS over sham. That is, TMS or sham was added to patients who were also simultaneously starting a new antidepressant medication. Thus, they were investigating whether TMS had an augmenting effect while also starting a new medication, attempting to show an effect on top of a medication effect. They failed to find a TMS effect in this design, and their sham system might have had biological effects [89]. Second, a TMS manufacturer conducted the largest multisite trial to date, which resulted in FDA approval. They randomized 301 medication-free patients with major depression to either active TMS or sham treatment, which they received for 4–6 weeks [11]. There was some controversy about the results of the trial. Before conducting the experiment, the company chose a continuous variable – the change from baseline on the Montgomery–Asberg Depression Rating Scale (MADRS) – as the primary outcome measure (and did not tell investigators in the field), while using the Hamilton Depression Rating Scale as the entry criteria. Unfortunately, after 6 weeks of TMS or sham, the continuously measured MADRS change from baseline for the active treatment group was not quite statistically different from the control group ($p = 0.058$). The Hamilton Depression Rating Scale scores, considered secondary outcome measures, were indeed superior for those in the active treatment group. The company argued, successfully for the publication, that they should be able to exclude six subjects who had entry MADRS scores that were very low and could not reflect clinical improvement. Thus, the manuscript was published as a positive trial, but the FDA initially rejected the application, and only agreed for approval after reviewing response data on subgroups [70,72]. Because there was such a large effect seen in those who were less treatment resistant, the FDA labeling is for the treatment of major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant treatment, at or above the minimal effective dose and duration, in the current episode. Note that in clinical practice, only approximately one in four antidepressant treatment trials meets criteria for minimal dose and duration, so this translates in a clinical practice to patients with a moderate level of treatment resistance [90–92]. Most recently, the NIH has funded a large multisite trial in depression that was recently completed [93]. Using a new sham technique [94,95], these researchers created an effective sham with no differences in side effects, and effective blinding of patients, raters and, to a substantial degree, TMS technicians. There was a statistically significant difference in remission rates between sham and real TMS, with remission rates larger than seen with medications in similar treatment resistant medication trials [96]. In the active arm, 15% of patients remitted with 3–6 weeks of treatment, compared with a 5% remission with sham. In the later, open-label phase, 30% of patients remitted, which is better than seen at a comparable level of treatment resistance in the open-label Sequenced Treatment Alternative to Relieve Depression (STAR*D) trial, where medications were given not as monotherapy, but as augmenting agents [97]. The Veterans Administration (VA) has launched a large cooperative study (#556) of daily left prefrontal TMS in 300 depressed veterans. That trial resembles an effectiveness trial, as patients will be allowed to remain on stable antidepressant medications, and patients can have co-existing medical disorders, PTSD or past substance abuse. Data should emerge in 5 years.

These three completed multisite trials augment the larger database of more than 30 single-site TMS depression trials. The discussion about TMS for depression has appropriately now shifted from asking whether it works, to examining how large of an effect it has, how durable the response is and what methods might be adjusted to increase its effectiveness.

In terms of improving its effectiveness, one recent development in TMS positioning has highlighted that better understanding of the TMS methods used will likely boost clinical antidepressant efficacy. The early National Institute of Mental Health studies used a rough measurement technique known as the 5-cm rule to place the TMS coil roughly over the prefrontal cortex [54–56]. Because the location of the motor strip varies between individuals, and skull size (hat size) also varies, this simple rule results in a large variation of actual location on scalp across different patients. It became obvious that this was an insufficient technique, but was nevertheless used in most trials, including the one for FDA approval. One study suggested that the 5-cm rule resulted in 30% of patients being treated over supplementary motor area (SMA) rather than prefrontal cortex [98]. Two retrospective analyses of clinical trials where brain imaging was performed to document the coil location have independently confirmed that a coil position that is anterior and lateral is associated with a better clinical response to active but not sham TMS [99]. An Australian group has performed a randomized controlled trial examining different prefrontal locations, and a more anterior and lateral location did indeed produce superior antidepressant response [100]. These findings suggest that the TMS effect is sensitive to different positioning algorithms. The location of the coil clearly matters, even within broad boundaries of a specific lobe. It is not clear whether individualized location will be needed or used, or whether general algorithms will suffice for a probabilistic positioning for most patients.

In several of the early TMS depression studies, researchers noted that TMS did not work well for older patients [101]. A study integrating TMS with MRI demonstrated that this was probably a consequence of older patients having more prefrontal atrophy, and thus needing a higher magnetic field in order to overcome the added distance from the coil [25,26]. An open-label study [102] and more recent randomized trial [103] in geriatric depression showed robust responses using doses that are sufficient to overcome the prefrontal atrophy seen in geriatric depression. Because it is focal and nonsystemic, and does not require general anesthesia as ECT does, there is much hope that TMS may be especially helpful and effective in managing geriatric depression.

Another area of rapidly evolving research has to do with the general TMS 'dose' and whether higher doses (number of stimuli per day or in a session) will produce better responses [104]. A meta-analysis [105] and prospective clinical trial [103], suggest that higher doses of TMS are more effective. Largely because of safety concerns, researchers have used relatively low doses, and full safety studies have never been performed in terms of the maximum tolerated daily, weekly or lifetime dose. Figure 3 shows the number of pulses/session, pulses/week and pulses for the full treatment session for selected left prefrontal TMS depression studies over time [56,71,106–108]. Note how periodically, and with continuing safety data and comfort, researchers have delivered in a week of treatment doses, that were previously given in a full course.

To our knowledge, the largest dose of TMS given within a week (38,880 stimuli) was reported by Anderson and colleagues, in healthy adult men participating in a sleep deprivation study [108]. There were no side effects or problems, and cognition was extensively measured with no deleterious outcome. Following this trend in the literature of the safety of higher doses, and the suggestion that higher doses of TMS may have greater efficacy, we recently carried out an effectiveness and safety study in order to determine whether daily high dose left prefrontal rTMS is safe, tolerated and effective in a broad clinical setting in adult depressed patients with concomitant medical problems, and who may also be taking other antidepressant medications. A total of 20 depressed patients on concomitant medications tolerated 6000 stimuli per day and 30,000 per week without side effects or problems [109]. Additionally, recently Epstein and colleagues treated 14 Parkinson's disease patients who also had comorbid treatment-resistant depression in an open, 10-day inpatient study of 10-Hz rTMS, undergoing extensive psychiatric, neuropsychological and motor testing from baseline to 6 weeks after treatment. rTMS was well tolerated in this medically fragile group, even with very high doses of 19,000 TMS pulses in a week. Highly significant improvements in depression scores were seen 3 days, as well as 3–6 weeks, after treatment [107]. Thus, one trend in TMS for depression involves using higher doses, or more compacted and dense treatment regimens than merely on weekdays.

Another area with insufficient information involves what to do after patients have responded to TMS. How durable is the antidepressant response? Do some patients need maintenance TMS and, if so, how should this be delivered? Unfortunately there is insufficient information in this domain, other than to say that the TMS antidepressant response appears to be at least as durable as that following ECT, which is not very good [110,111]. Several groups have performed maintenance TMS, but there have been no controlled clinical trials [112,113].

Although this is a review of TMS and depression, discussing TMS for pain is relevant as depression and chronic pain frequently co-occur and overlap in neuroanatomy, particularly the affective labeling circuits for pain recognition. Moreover, pain thresholds can be quickly measured in healthy volunteers in laboratory-based settings, making it easier to answer several TMS-related questions with pain, rather than in depression. Several small controlled studies have evaluated the utility of TMS in patients with pain. Multiple sites have been tested, including prefrontal cortex, motor cortex and parietal cortex [114–119]. In general, TMS provides effective pain relief in these different locations in diverse pain conditions. Unfortunately, the effect of TMS on pain only lasts for a short duration. Consequently, the utility of TMS as a practical treatment for chronic pain conditions has yet to be established.

Recent studies suggest that TMS may have some utility in managing acute postoperative pain. In two different studies of patients recovering from gastric bypass surgery, 20 min of real or sham TMS was administered to the prefrontal cortex of every

patient. Their use of self-administered morphine was then followed over the next 48 h. Those receiving real TMS used 40% less morphine in the next 24 h, with the majority of the reduction occurring in the first 8 h after TMS [120,121].

Expert commentary

After much controversy over the past 15 years, the data now convincingly demonstrate that daily prefrontal TMS treats acute depression in treatment-resistant unipolar patients, and that the effects are at least as large as current medication options in that group. TMS is an exciting, focal, nonsystemic and relatively side-effect-free option for treating acute depression, and its role will grow in its role in treatment guidelines and managing depression, which is one of the worlds most prevalent and costly diseases.

The debate and research thus shifts now from determining whether it works in the acute setting, to trying to improve the technology and perhaps making it even more effective. Research should also now focus on studying whether TMS can be used as a maintenance treatment or works in depression subgroups (e.g., bipolar depression and adolescents). Additionally, the way TMS is delivered today (location, intensity and delivery schedule) closely resembles studies 15 years ago, with only incremental improvements in positioning, intensity and dosing. Critical studies are needed to more fully explore each of the current choices regarding TMS as an antidepressant (e.g., scalp location, dose and dosing schedule), hopefully discovering ways to improve the method.

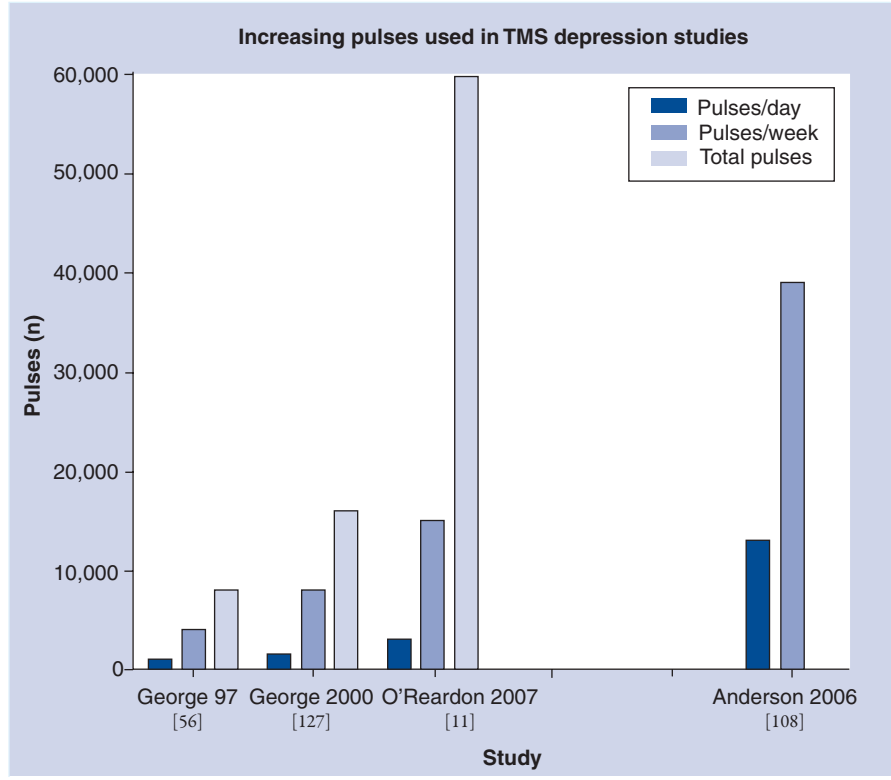

Figure 3. Transcranial magnetic stimulation dose increases over time.

In terms of when to use TMS with a depressed patient, the trials to date have largely been performed in moderately treatment-resistant adult unipolar patients in an acute episode. That is, it is probably much easier and less expensive to prescribe an antidepressant for a new depressed patient than it is to deliver TMS, as it is currently performed [85,122,123]. Thus, one would use TMS to treat depression only in patients who have tried and failed, or could not tolerate, at least one antidepressant medication and some form of talking therapy. In those who respond, one should attempt to maintain the remission with prophylactic oral medications. If the patient relapses or does not tolerate the medication side effects, one can attempt maintenance TMS, although the evidence base for this is meager.

Five-year view

With the recent FDA approval of TMS, and the rapid expansion of the clinical use of the technology, one would hope that there would be more rapid improvement. Radically new treatments like TMS for depression do not come along very frequently in psychiatry. However, the history of ECT shows that mere clinical adoption of a treatment does not necessarily speed better understanding, or advances in how to use the tool. The ongoing VA study should inform whether TMS can be used as an adjunctive treatment in combination with medications. There are also a host of small trials underway examining TMS in special depressed populations (e.g., depression in pregnancy, post-partum and with Parkinson's disease). Thus, in 5 years there will probably be a larger volume of literature on how to use TMS as an antidepressant in these other conditions, and for incremental changes in methods.

However, skeptically, real advances with a treatment come only with large NIH-funded rigorous trials, or focused centers trying to discern how TMS works, as was clearly the case with the recent advances in ECT. That is, ECT practice did not change much from 1960 to 1985, and then there were a series of NIH-funded advances showing that a prefrontal and not parietal cortex seizure is necessary [124], that changing the pulse-width can alter the cognitive sequelae without affecting efficacy [125] and that with even the best follow-up medication therapy, most patients relapse at 6 months [126]. Unfortunately, currently there are no NIH-funded centers focusing on TMS (although there are centers examining other brain stimulation techniques, such as deep brain stimulation), and no large clinical trials addressing the many important questions in the field, such as whether larger effects are seen with adjunctive medications, or how to design more efficient delivery schedules. The TMS manufacturing industry is currently quite small and not capable of funding these types of clinical trials.

Thus, real advances in TMS as an antidepressant over the next 5 years will occur if, and only if, there is better understanding of how TMS is acting in the brain to relieve depression, and if there are federally funded large clinical trials to test the hypotheses about how to improve the technology.

Financial & competing interests disclosure

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Key issues

- Repeated daily left prefrontal transcranial magnetic stimulation (TMS) for 3–6 weeks has been convincingly shown in large-scale clinical trials to have clinically significant acute antidepressant effects in patients who have failed to respond to at least some antidepressant medications.
- TMS is no longer an experimental therapy, is US FDA approved, and represents a paradigm shift in therapy for depression.
- It is a noninvasive, focal treatment, with no drug–drug interactions or major side effects, and appears safe and well tolerated.
- The maximum tolerated or safe daily dose limit has not been found, and higher doses than those used in the recent large trials are probably safe. However, rigorous studies are needed to determine whether higher doses (number of stimuli/day) are safe, more effective or more rapid in onset, as recent small studies suggest.
- Although TMS was approved in patients who were free of any antidepressant medications, clinically it is being used as an adjunctive treatment with stable medications, in the absence of much data [126]. Studies are needed to inform whether TMS works well as an adjunctive treatment, and with which medications.
- To date, most researchers have ignored what patients were doing during the treatment sessions, other than keeping them awake. Exciting new findings from the learned helplessness model in rats suggest that one could effectively couple TMS with exposure therapy or cognitive–behavioral therapy, with improved results. That is, bringing the prefrontal regulatory circuit online and engaging it during treatment may allow for better plasticity and therapeutic change. More research is needed to confirm this.

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