Transcranial Magnetic Stimulation: Potential New Treatment for Resistant Depression

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference series "Transcranial Magnetic Stimulation: Potential New Treatment for Resistant Depression," which was held in August and September 2006. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Neuronetics, Inc.*

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Major depression is a common disorder and substantial cause of disease burden worldwide. Nearly 60% of patients with depression may not achieve adequate response following antidepressant treatment.[1] New somatic treatments that are less invasive than electroconvulsive therapy (ECT), such as transcranial magnetic stimulation (TMS), are being added to the repertoire of treatments that have the potential to be effective in depression that is resistant to pharmacologic therapies. In this ACADEMIC HIGHLIGHTS, experts in treatment-resistant depression and the evolution of TMS examine some of the challenges of treating depression as well as the challenges of developing and testing new treatment methods.

Overview

Alan F. Schatzberg, M.D., explained that repetitive TMS (rTMS) is a noninvasive procedure that uses highly focused magnetic pulses to target specific mood circuits in the brain. These magnetic pulses pass through the skull and stimulate the cerebral cortex and deeper neural structures. This stimulation increases blood flow to these areas of the brain and affects specific neurotransmitters. A better understanding of treatment-resistant depression and how rTMS may be of benefit in that patient population is needed in order to meet the needs of patients.

To emphasize the importance of developing effective treatments for resistant depression, Michael E. Thase, M.D., described the process of trial and error that clinicians use for patients who do not respond to standard therapies. Switching medications, psychotherapy, and combination therapy are fairly standard methods that are frequently complicated by patient nonadherence and nonresponse. Dr. Thase reviewed the potential issues surrounding nonresponse and reiterated the importance of working through treatment algorithms in a timely way.

The basic principle of electromagnetism on which TMS is grounded has been around for more than 100 years, but TMS was not introduced as a possible treatment for depression until the 1980s. John P. O'Reardon, M.D., discussed the history and evolution of TMS as a treatment for resistant depression and compared TMS with ECT. He explained that single or paired-pulse TMS typically brings about only transitory changes in the brain, whereas rTMS may provide longer-term changes and be particularly effective in treating resistant depression.

Mark A. Demitrack, M.D., stated that depression is a major clinical target for TMS and that one of the challenges for treating depression is the subjective nature of determining the patient's clinical state. He suggested that new options for treatment-resistant depression may lead researchers to reexamine methods that are not working and explore different types of interventions. Transcranial magnetic stimulation has shown promise within the device-based platform of interventions because it is an effective, noninvasive procedure; however, at the present time, TMS therapy has not yet received U.S. Food and Drug Administration approval.

Finally, the emotional symptoms of major depressive disorder may be linked to abnormal activity in different areas of the brain. Elliott Richelson, M.D., explained that depressed mood, guilt, feelings of worthlessness, suicidality, and anxiety are emotional symptoms associated with the medial prefrontal cortex, anterior cingulate cortex,

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and the orbital prefrontal cortex. Simulation of the prefrontal cortex with TMS affects these critical brain areas thought to be associated with mood. Modulating neurotransmission to specific brain areas through highly focused magnetic pulses (rTMS) may reduce or even eliminate the depressive symptoms associated with specific brain areas.

This ACADEMIC HIGHLIGHTS is rich with current and relevant information regarding the challenges of treating resistant depression, the evolution of using electromagnets to send pulses into the brain to stimulate specific areas associated with mood, and the advantages and issues associated with testing and implementing TMS. Transcranial magnetic stimulation appears to have a favorable risk-benefit profile, is well tolerated, and appears to be equal to or more effective than pharmacologic antidepressants.

Treatment-Resistant Depression

Michael E. Thase, M.D., began by defining *treatment-resistant depression* as a variety of depressive disorders that do not respond to standard treatments. Treatment-resistant depression is not a diagnostic entity per se (it is the treatment that has failed, not the patient), and there are different definitions. According to Dr. Thase, the simplest definition might be that the patient's depression has not responded to an adequate course of one particular treatment. For example, a patient could have sertraline-resistant depression or resistance to several members of a class of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), in which case the patient could be said to have an SSRI-resistant depression. Another way to define treatment-resistant depression is by threshold of response; for example, some clinical trials[2] that have focused on treatment-resistant depression have required that patients lack response to trials of medication.

Classifying Treatment-Resistant Depression

Dr. Thase observed that, in assessing a depressed patient who has not responded to a particular treatment, key considerations include dose, duration, and adherence.[3] Before determining that a patient's depression is treatment-resistant, it is important to ensure that the treatment has been prescribed at adequate doses and taken for an adequate duration of time. Generally, a clinician needs to ensure that the patient took the antidepressant for at least 6 weeks and that the patient was adherent with the medication regimen. The clinician should also grade the patient's response. If a patient showed less than 50% improvement on a particular treatment and still meets the diagnostic criteria for the depressive disorder, then he or she usually would be said to have not responded to that particular medication. Alternatively, if the clinician is using the Clinical Global Impressions-Improvement Scale to grade response, patients who do not score 1 or 2 (much improved or very much improved) after an adequate course of therapy would be considered nonresponders.

Beyond the adequacy of the treatment trial, Dr. Thase also emphasized the importance of ensuring that no diagnostic issues have prevented response to medication. Sometimes, a relevant diagnosis—either a second condition that is masquerading as depression like hypothyroidism or a complicating comorbidity—can be missed. It is possible that, if the overlooked condition or comorbidity were treated, the patient might become more responsive to antidepressant medication. A classic example is an unrecognized substance abuse disorder.

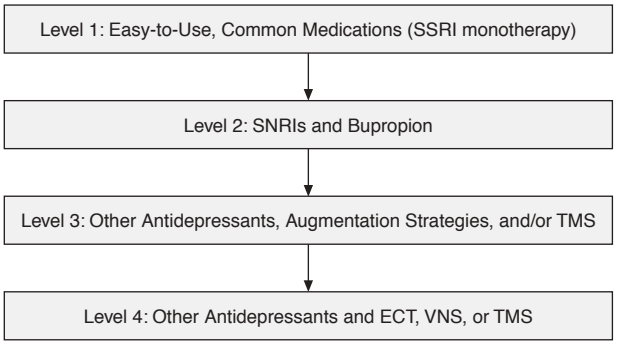
Another example of an overlooked diagnosis is bipolar depression (i.e., a depressed person who has experienced at least 1 prior episode of mania or hypomania), which often does not respond to antidepressant monotherapy in the same way as other forms of depression. Therefore, it is important to consider that a subtle presentation of bipolar disorder has not been missed.[4] Dr. Thase suggested that clinicians might find value in looking for evidence of fluctuations in mood or rapid excursions up or down in mood during treatment, as well as examining family history and past treatment history, looking for more subtle examples of mood swings or different behavioral indicators of bipolarity.

According to Dr. Thase, when proceeding along a treatment hierarchy for resistant depression, clinicians generally start with the easiest and most commonly used medications, and then work their way through more complex treatment strategies (Figure 1). The clinician might construct a treatment plan in which SSRIs are in the first position; serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine, or bupropion, a norepinephrine-dopamine inhibiting antidepressant, is in the second position; augmentation strategies are considered in the third position; and the older antidepressants are in the fourth position along with more invasive treatments, including ECT and the recently approved vagus nerve stimulation strategy. Although rTMS is not yet an approved therapy in the United States, evidence from clinical trials suggests that it might be used in the third or fourth position.

Research Considerations

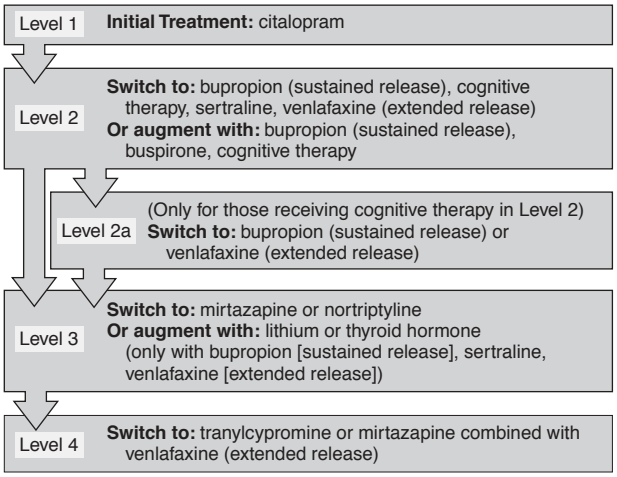
Dr. Thase continued by stating that, from a research standpoint, one challenge is to identify the most useful and ethical comparison group. Studying treatment-resistant depression presents an ethical challenge in that the grounds for exposing the patient to placebo are somewhat controversial. In essence, for a study delimited to patients who have not responded to several antidepressant medications, the justification for including a placebo-controlled group is much less compelling than for a study of more acute, less compli-

Figure 1. Treatment Hierarchy for Treatment-Resistant Depression



Abbreviations: ECT = electroconvulsive therapy, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TMS = transcranial magnetic stimulation, VNS = vagus nerve stimulation.

Figure 2. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Algorithm[a]



[a]Reprinted with permission from Rush et al.[6]

cated depressions. Moreover, if a researcher has prospectively implemented and observed adequate trials of several antidepressants, it is likely that the placebo response would be so low that it may not be necessary to use a placebo. However, the clinical documentation of the history of treatment resistance, particularly at the earlier levels, is often so inconsistent that it is necessary to re-treat patients with one of the standard treatments to ensure that they really are resistant to that type of antidepressant, as opposed to simply assuming resistance by history. According to Dr. Thase, clinical examples exist in which patients who have not responded to a particular medicine the first time they were treated with it have then prospectively responded to that medicine or a related medicine under more controlled circumstances.

The justification for a placebo control group is relatively strong when studying an augmentation or an add-on strategy for patients who have not responded to only a single trial of antidepressant therapy, according to Dr. Thase. When studying an augmentation or add-on strategy, it is easier to continue an ineffective or partially effective medication, adding placebo to it, than it is to withdraw that medication and switch to another treatment option. With respect to the discontinuation of a treatment that had resulted in some symptom reduction, Dr. Thase reiterated ethical concerns that a patient would get worse rather than better if researchers were to discontinue a partially effective antidepressant medication.

Another alternative to a placebo-controlled study is a study of switching to another standard antidepressant medication. For example, if the patient has a history of nonresponse to one SSRI or one SNRI, switching to another member of that class would be a conservative, reasonable, standard benchmark against which a different type of treatment would need to show incremental value. Thus, switching to a second SSRI or SNRI is the most conservative next-step option, and one might expect an alternate treatment to exert an improvement over and above that of the first SSRI or SNRI in order to say that it would be worthwhile to move that treatment up in the hierarchy.

STAR*D as a Research Example

Dr. Thase went on to describe the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[5] study as an example of a large, public health clinical trial that used randomization and independent evaluation of treatments but did not use blinding or placebo control. Led by A. John Rush, M.D., of the University of Texas Southwestern Medical Center in Dallas, STAR*D enrolled nearly 3000 depressed outpatients at more than 40 participating primary care and psychiatric clinics across the country. In the first stage of the STAR*D study, patients were treated with citalopram for up to 12 weeks and up to 60 mg/day to ensure adequate dosing, and those who did not benefit from study therapy were then randomly assigned to 1 of 4 switch strategies or 1 of 3 augmentation strategies (Figure 2).[6,7]

An interesting, novel element of STAR*D was that patients and their doctors could opt out of certain choices, and to the surprise of Dr. Thase and many of his colleagues, the majority of patients chose to opt out of either all of the augmentation strategies or all of the switch strategies. Although the proportion of patients opting out was surprising, the primary reason for making the choice was not. Partially improved patients were more likely to opt out of the switch strategies (in favor of the augmentation strategies), and the citalopram nonresponders and those who had significant side effects were more likely to accept the switch strategies (and opt out of augmentation strategies).

Dr. Thase reported that there were 3 switch medications used in STAR*D: switching from citalopram to a second SSRI (sertraline), an SNRI (venlafaxine), or bupropion (a norepinephrine-dopamine reuptake inhibitor). A fourth option was a switch to cognitive therapy so that researchers could contrast alternate medication strategies with an alternate approach to treatment, namely psychotherapy. The 3 augmentation strategies that were compared were adding bupropion, buspirone, or cognitive therapy to citalopram.

STAR*D demonstrated that under the circumstances of a large, inclusive, public health–relevant design, none of the options in the switch arm or in the augmentation arm were superior to the others. Within the switch arm of the study,[7] there was about a 10% difference in remission rates from the strongest to the weakest strategy; because the study did not have sufficient power to reliably detect 10% between-group differences, none of the primary comparisons were statistically significant. Thus, the results of STAR*D suggested that switching medications within a class was virtually as good as switching classes. Likewise, although there were advantages on some secondary measures favoring bupropion over buspirone, that advantage was not evident in terms of remission rate or other primary outcome measures.

The STAR*D study did suggest that cognitive therapy was a less-desired option than alternate medication strategies for citalopram nonresponders. According to Dr. Thase, this result may represent an unforeseen element in the research design: cost of study treatments. For example, whereas medications were provided at no cost to patients, the investigators were not able to waive the insurance copayments if patients opted for psychotherapy. In future studies, in order to ensure that researchers do not have such biases working against the psychotherapy arm, they should ensure that the cost of the treatment was comparable in both aspects of the study.

Advanced Levels of Treatment Resistance

Dr. Thase reiterated that, when designing a study comparing therapy options for patients with more advanced levels of treatment resistance, it is important to keep in mind that the number of available patients is diminished at each step not only by those who respond, but also by those who, for one reason or another, drop out of treatment. If researchers were to conduct a second-stage study and planned to enroll approximately 200 patients in each arm of the study (in order to have the power to detect about a 15% difference between treatment arms), they would need to take into account not only a 50% response rate of the first stage, but also a 20% attrition rate. Thus, at least 1000 untreated patients would need to be recruited into the first level of treatment in order to conduct a 400-patient study of second-stage interventions. If the calculations were used to plan a similarly sized study of 2 third-stage treatments, then approximately 2000 patients would have to begin the initial stage of the treatment.

A certain level of attention, coordination, and methodological control is required to conduct studies, even relatively simple, large studies like STAR*D, to ensure that the patient flow rate is adequate. Dr. Thase postulated that, because it is unlikely that differences of greater than 10% will exist between different treatment strategies, future studies should be designed to detect small differences. As such, the goal should be to enroll 300 to 400 patients per arm. When effects are relatively small, the need to ensure reliability of assessment is amplified. For every 10% drop in the reliability of a dependent measure, there is a corresponding reduction in statistical power. Reliability of diagnostic and dependent measure assessments becomes paramount in study design.

Dr. Thase concluded that treatment-resistant depression is a large and important public health problem. It is true that many effective treatments for depression are available, but it is also true that these treatments are imperfectly effective and that approximately 50% of depressed patients do not benefit from the first course of antidepressant treatment.[8] In order to facilitate adherence, Dr. Thase recommended that clinicians make sure that their patients know that side effects often precede therapeutic effects and encourage them to persevere. If the first medication is poorly tolerated or ineffective, many alternates are available. In turn, from a clinician-provider standpoint, clinicians should work through available treatment algorithms in a timely way, making certain that the patient maintains a sufficient level of engagement with the treatment strategy and has optimism that the second, third, or, if necessary, fourth option in a treatment hierarchy will be effective.

Evolution of Transcranial Magnetic Stimulation Treatment for Major Depression

John P. O'Reardon, M.D., began his discussion of the evolution of TMS by describing its origins. The scientific foundation underpinning transcranial stimulation dates back to the work of Michael Faraday (1791–1867), who discovered the principle of electromag-

netism, which states that electrical and magnetic fields are interchangeable. In 1959, Kolin and colleagues[9] found that magnetic fields could be used to stimulate frog muscle. In 1985, Barker and Cain[10] developed the first TMS device that was capable of stimulating the human cortex, but their initial goal was not stimulation of the brain, but rather stimulation of spinal roots. TMS was, in fact, first suggested as a possible treatment for depression by Bickford et al.[11] in 1987.

During treatment with TMS, an electromagnet is used to create a pulsed magnetic field of about 1.5 Tesla strength. This pulsed magnetic field passes unimpeded through the scalp and reaches the cortex of the brain, where, according to the counter-current principle, a local electrical current is induced in neural tissue, which results in depolarization of neurons. The magnetic field is about the same strength as a standard magnetic resonance imaging (MRI) one used to capture images of the brain but is a pulsed field rather than a static one. The magnetic field produced by the TMS functions as a transducer that bridges the electrical activity in the electromagnet and the electrical activity in the cortex of the brain. The depth of the magnetic field is such that it reaches to the junction between the gray and white matter.

Transcranial magnetic stimulation is sometimes divided into 2 types: single- and paired-pulse TMS and rTMS. In the former, single or paired pulses are administered to the patient. In the latter, a series or train of pulses is administered to the patient over several seconds. It is rTMS that is believed to have therapeutic potential in the treatment of mood disorders, whereas the former is primarily used for neurologic investigation and as a diagnostic aid.

Dr. O'Reardon went on to say that research shows that TMS has the potential to exert therapeutic effects on mood-regulating systems in the brain. Several animal studies have been published to date on TMS and mood.[12,13] For example, daily TMS has been shown, using the Porsolt forced-swim test, to reduce immobility in rats.[14,15] TMS has also been found to be similar to ECT in its ability to induce neurobiological antidepressant effects in animals. Animal models have shown that TMS can induce serotonergic effects, with enhanced forebrain serotonin output[12] and modulated serotonin receptor function.[13]

In a human study,[16] TMS was found to produce changes in blood flow in both the prefrontal cortex and in the limbic system with left prefrontal cortex stimulation. Szuba et al.[17] found that levels of thyroid-stimulating hormone rose and mood improved in patients with major depression after treatment with rTMS compared with a control group that underwent sham TMS. Pridmore and Belmaker[18] demonstrated normalization of the dexamethasone suppression test in depressed patients after treatment with rTMS. More recently, O'Reardon et al.[19] demonstrated that patients with major depression who had responded to rTMS treatment were resistant to the effects of rapid tryptophan depletion, a probe of the serotonin system. This finding implies that rTMS is not dependent exclusively on serotonin modulation for its antidepressant effects, and in that sense, it can be viewed as having more broadly based effects on neurotransmission in the brain.

Early Studies of Transcranial Magnetic Stimulation for Depression

Dr. O'Reardon stated that although TMS was first suggested as a possible treatment for depression in 1987,[11] initial studies of rTMS in major depression were essentially case reports or case series.[20–22] Not until 1996 was rTMS more systematically examined in the treatment of depression (Table 1).[20–27] On the basis of the hypofrontality or reduced cerebral blood flow that was found in neuroimaging studies of patients with depression, TMS was initially proposed as a noninvasive technique to activate neuronal circuits that were hypoactive in the depressive state.[22]

In one of the first important studies of rTMS, Pascual-Leone et al.[23] enrolled 17 patients who had drug-resistant psychotic depression. These patients received 5 days of stimulation at different sites on the scalp in a double-blind, sequential crossover design. The left dorsolateral prefrontal cortex stimulation site yielded the best therapeutic effects; after 5 days of stimulation at that site, researchers reported a 65% response rate that was maintained for the subsequent 2 weeks. Participants' Hamilton Rating Scale for Depression (HAM-D) scores were reduced from a mean baseline value of 25.2 to an endpoint value of 13.8. This study generated much interest when it was published, but it, unfortunately, has not been replicated. In fact, a subsequent study[28] suggested that rTMS may not be effective in psychotic depression but may be effective in other forms of treatment-resistant depression.

Klein et al.[27] were the first to demonstrate that slow-frequency rTMS at 1 Hz on the right rather than the left prefrontal cortex also had antidepressant properties. This study had a large sample size of 70 inpatients with major depression and used a double-blind design with a sham group. Study participants were not necessarily treatment resistant, as in other trials. Treatment consisted of 2 trains of 60 pulses over the right prefrontal cortex with a 3-minute interval in 10 daily sessions over a 2-week period. Of the participants who were in the active treatment group, 49% responded to rTMS (defined as a reduction of 50% or more on either the HAM-D or Montgomery-Asberg Depression Rating Scale [MADRS]), while 25% of the participants in the sham treatment group responded.

According to Dr. O'Reardon, the early studies were frequently limited by small sample size and short courses of treatment. In addition, despite a subset of robust responders, the overall change in participants' baseline HAM-D scores was modest. This modest outcome led to questions as to whether rTMS produced significant

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Table 1. Initial Transcranial Magnetic Stimulation Antidepressant Studies

Study	N	Frequency (Hz)	Motor Threshold (%)[a]	Pulses Per Session	No. of Sessions	Total Pulses	Reduction in HAM-D Score (%)	Effect Size
Hoflich et al (1993)[20]	2	0.3	105–130	250	10	2500	10.3	0.71
Kolbinger et al (1995)[21]	15	0.25	90	250	5	1250	15	…
George et al (1995)[22]	6	20	80	800	5	4000	26	1.35
Pascual-Leone (1996)[23b]	17	10	90	2000	5	10,000	45	1.76
George et al (1997)[24b]	12	20	80	800	10	8000	17	1.36
Epstein (1998)[25]	32	10	110	250	5	1250	52	1.12
Figiel et al (1998)[26]	56	10	110	500	5	2500	44.4	1.78
Klein et al (1999)[27]	70	1	110	120	140	16,800	…	…

[a]Dose relative to threshold.
[b]Randomized, controlled study; all other studies were open.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression.
Symbol: … = data not available.

antidepressant effects only from a statistical point of view and that, perhaps, these effects were not truly clinically meaningful.

Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy

Seven randomized trials[28–34] have now compared rTMS to ECT in major depression. Overall, the results for rTMS have been encouraging, with 6[28–33] of the 7 studies reporting that TMS produced results equivalent to ECT. One result of the early studies of rTMS was the recognition that the courses of rTMS that were given at the time (1- to 2-week duration, 5 sessions per week) were inadequate to produce robust antidepressant effects, especially in the predominantly drug-resistant patient samples used. Thus, the rTMS courses in the studies that compared rTMS with ECT were of a longer duration, with patients generally receiving up to 20 sessions during 4 weeks of treatment with rTMS.

Dr. O'Reardon continued by describing the first study that compared rTMS with ECT. In this open study by Grunhaus et al.,[28] medication-free, drug-resistant participants (N = 40) were randomly assigned to receive either 20 sessions of rTMS or a course of ECT. ECT was administered with unilateral stimulation with the option to switch to bilateral if clinically indicated. In this study, the response rates with rTMS and ECT were nearly equivalent: 60% response rate with rTMS versus 54% response rate with ECT. However, it was found that in psychotic depression, ECT was superior to rTMS in this study. All 10 of the 10 participants with psychotic depression responded to ECT, compared with 2 of the 10 participants given rTMS.

An important limitation of this first ECT comparison was that although it was randomized, it was open, with unblinded raters. Subsequently, Grunhaus et al. performed a follow-up study[32] that was single-blind; that is, raters were blind to the treatment condition, but patients and ECT administrators were not. As in the first study, this was a treatment-resistant, medication-free population who were willing to be randomly assigned to receive either ECT or rTMS. Response rates were similar for rTMS and ECT: 55% and 60%, respectively. Following this study, patients were maintained on an antidepressant medication regimen. At the end of 6 months,[35] researchers found that relapse rates post-rTMS were no different from those post-ECT treatment. These results are the first important maintenance data to be published with rTMS.

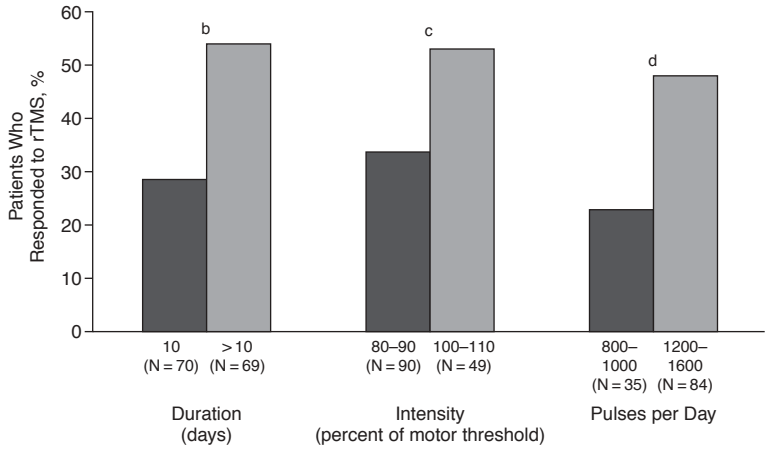
According to Dr. O'Reardon, subsequent studies comparing rTMS and ECT[29,31] have found similar positive results for rTMS. In addition, Schulze-Rauschenbach and colleagues[31] demonstrated that the cognitive profile of adverse effects is more benign with rTMS than with ECT. To date, only 1 study[34] has found rTMS to be inferior to ECT. Of note, though, is that in this study, the course of rTMS was shorter than that in the other studies in which rTMS was compared with ECT; rTMS was given over 15 days. All participants in the ECT group received bilateral stimulation.

Although treatment with rTMS has generally been found to be comparable to ECT, a limitation of the studies that compare rTMS with ECT is the lack of placebo or sham control treatment. In these studies, ECT may not have performed as optimally as expected; thus, the tie-in efficacy with rTMS might represent a false negative considering the relatively small sample sizes. Dr. O'Reardon emphasized that rTMS does not have to be equivalent to ECT to be an effective treatment, clinically. No physician would disregard fluoxetine, for instance, as a valid treatment in major depression on the basis that it failed to show equivalence to ECT efficacy in antidepressant effects after 4 weeks of treatment. Rather, ECT must meet the same standards as other potential treatments for depression, with demonstrated superiority compared with a well-designed control condition.

Meta-Analyses of Transcranial Magnetic Stimulation

Because the TMS literature to date is constrained by small sample sizes, it is difficult to draw definitive conclusions about the true level of efficacy of TMS. One approach to handling this limitation is the technique of meta-analysis, wherein the results of studies using similar methodologies are combined. A total of 6 meta-analytical

Figure 3. Differences in Response Rate Between rTMS Treatment Parameters[a]



[a]Reprinted with permission from Gershon et al.[35] Response was defined as a 50% or more decrease in Hamilton Rating Scale for Depression score.
[b]Significant difference in response rate by duration of treatment ($\chi^2 = 9.0$, df = 1, $p < .01$).
[c]Significant difference in response rate by intensity of stimulation ($\chi^2 = 4.5$, df = 1, $p < .05$).
[d]Significant difference in response rate by number of pulses per day ($\chi^2 = 6.5$, df = 1, $p < .05$).
Abbreviation: rTMS = repetitive transcranial magnetic stimulation.

studies[36–41] have examined the efficacy of TMS in depression.

A meta-analysis by Kozel and George[38] focused on the efficacy of rTMS applied to the left dorsolateral prefrontal cortex. This meta-analysis included 12 sham-controlled trials of rTMS for a total of 230 study participants. Treatment with rTMS was significantly effective compared with the sham condition, with a mean effect size of 0.53 (95% CI = 0.24 to 0.82). This effect size is comparable to that found in controlled studies with antidepressants. In addition, a test for the effect of negative, unpublished rTMS studies showed that, at minimum, 20 negative, unpublished studies would be necessary to nullify the positive result detected for rTMS.[38]

The most conservative meta-analysis[40] to date was performed by Martin et al. using data from the Cochrane database. This meta-analysis included 14 randomized, controlled trials of rTMS, with a median study population of 19. The authors concluded that there was evidence of a benefit in patients with high frequency rTMS with stimulation of the left dorsolateral prefrontal cortex at 2 weeks, although they also found a lack of evidence that this benefit was sustained beyond 2 weeks.

While 4 of the 6 meta-analyses have found positive results for rTMS, 2 have more mixed conclusions.[40,41] According to Dr. O'Reardon, this discrepancy very likely reflects the effect of insufficient sample size and pooling of results from studies in which suboptimal rTMS stimulation parameters resulted in corresponding suboptimal efficacy.

Optimizing Treatment With Transcranial Magnetic Stimulation

The conflicting meta-analytic results suggest that room for further optimization of TMS treatment delivery exists. Dr. O'Reardon pointed to an analysis[35] in which researchers found that longer courses (> 10 days versus 10 days) of higher-intensity motor thresholds (100%–110% versus 80%–90%) and a greater number of pulses per day (1200–1600 versus 800–1000) were more beneficial to patients. Response rates to TMS at more optimized dosing were about 50% in treatment-resistant depressed patients (Figure 3).

A recent controlled clinical trial also supports the view that researchers may have not yet fully optimized TMS. Fitzgerald et al.[42] were the first to use a randomized, controlled trial to compare the application of rTMS to both the right and left prefrontal cortices with a sham control condition. Patients (N = 50) were randomly assigned to receive, for 6 weeks, either slow rTMS on the right followed by fast rTMS on the left (a sequenced combination approach) versus a sham condition with similar duration of stimulation on both the right and left side. On the MADRS, the primary outcome measure of the study, those who received rTMS showed a 44% response rate and a 36% remission rate. On the HAM-D outcome measure, patients receiving rTMS showed a 52% response rate and a 40% remission rate. To put these results in perspective, rTMS produced at least as much improvement in 6 weeks as citalopram did in the STAR*D study[43] at 12–14 weeks. With STAR*D Level 1 treatment, a response rate of 47% and a remission rate of 30% were observed on the MADRS following 12–14 weeks open-label treatment with citalopram.

Advantages and Disadvantages of Transcranial Magnetic Stimulation as a Clinical Treatment

If TMS is approved for use by clinicians in the United States, several unique features could make it an attractive treatment option. It is a noninvasive, office-based procedure; no anesthetic is required, and the patient remains awake and alert throughout. Additionally, there is no postsession recovery period, and the patient is able to resume normal activities immediately. No cognitive side effects have been reported with rTMS, which is a significant advantage compared with ECT. Unlike treatment with antidepressants, rTMS does not cause systemic side effects such as weight gain and sexual dysfunction that can limit patient tolerability.

According to Dr. O'Reardon, rTMS may also have some disadvantages as a clinical treatment. Because rTMS is usually administered 5 days a week and the course of treatment lasts from 10 to 30 sessions, administration of

rTMS is labor-intensive and time consuming for both the patient and the clinician. It is unknown whether less frequent application of rTMS might be equally effective, but less frequent application could improve the efficiency of treatment delivery.

Another challenge with rTMS is that, currently, few data address maintenance of long-term benefit. As discussed earlier, one report[35] found encouraging results for maintenance of benefit over a 6-month period following treatment with rTMS. Additionally, a recent case series[44] of 10 patients with treatment-resistant major depression were given maintenance treatment with rTMS for periods ranging from 6 months to 6 years. Seven of the 10 patients maintained moderate or marked benefits over their maintenance period. Three of the patients were maintained successfully on treatment with TMS alone without adjunctive antidepressant medication. For the majority of patients, 1 or 2 sessions of rTMS per week were successful for maintenance of benefit from rTMS. In this case series, a total 1831 sessions were performed with only minimal adverse effects and with no seizures. Of the 10 subjects, 2 received a total of more than 500 sessions safely, which equates to 1 million electromagnetic pulses over a period of 5 years.

Future of Transcranial Magnetic Stimulation

Dr. O'Reardon noted that, currently, rTMS is available in Canada, Australia, Israel, and several European countries. An application is pending with the U.S. Food and Drug Administration (FDA) for approval of rTMS as a clinical treatment in the United States. Should the FDA grant approval, rTMS will provide a new alternative for clinicians in the treatment of major depression.

In conclusion, a substantial body of evidence appears to support "proof of concept" for the efficacy of TMS for the treatment of major depression. The majority of the studies published show distinct benefit from rTMS either as a monotherapy or as an add-on treatment to medications. However, the published literature is limited by small sample size and variability in both the stimulation parameters and the brain sites targeted with rTMS. Large-scale multicenter trials of rTMS treatment for depression have now either been completed or are nearing completion. The results of these trials, when published, will provide substantial additional information on both the efficacy and optimal use of rTMS in the treatment of major depression. It is likely, though not yet certain, that rTMS will find an important place in the therapeutic armamentarium of the clinician.

Clinical Challenges in the Study of Transcranial Magnetic Stimulation

Mark A. Demitrack, M.D., began by stating that major depression is a main clinical target for the investigational treatment TMS. In depression, one typically assesses outcome not by objective signs but by subjective assessments and reports, the most common method of which involves investigator query of the patient's clinical state.

Dr. Demitrack asserted that the treatment of depression is complicated by its association with a number of varied clinical targets (Figure 4). The main target of interest is obviously depressed mood; of secondary but still large importance is the presence of concurrent anxiety symptoms that are often present in patients with depression. The main goal of the treatment of depression is improvement in those 2 key symptom domains, but the variety of other illness features shown in Figure 4 also deserve attention. These symptoms are thought to be related to the underlying biology of depression and include vegetative symptoms such as sexual dysfunction, sleep disruptions, changes in appetite, and psychomotor changes and systemic manifestations of depression such as muscle or joint pain, fatigue, and gastrointestinal pain. These systemic manifestations of the disorder make depression physically painful to some patients. Dr. Demitrack explained that because so many domains of symptoms exist in depression, measuring outcomes in antidepressant studies can be challenging.

Despite all the interventions available to physicians, depression is still an illness with a substantial unmet need. Dr. Demitrack reported that the recent National Comorbidity Survey Replication[45] found the 12-month prevalence of depression among U.S. adults to be 6.6%, which translates into approximately 14 million adults. Of those, 4 million remain poorly served by existing treatments. The current treatment options for depression clearly are only modestly effective, and nonresponse and inadequate response to medication remain the norm in depression. In addition, adverse events associated with currently available treatments are common, and these adverse events may hinder compliance with long-term treatment.

The Study of Treatment-Resistant Depression

According to Dr. Demitrack, a number of key issues exist in the study of antidepressant treatments, especially in treatment-resistant depression. He noted that medication therapy is a mainstay for treatment, but few proven effective treatments exist for pharmacoresistant patients. Most of the currently available treatments have been studied in patients who were either treatment-naive or relatively early in their illness; there have been few randomized controlled trials in treatment-resistant and chronically ill patients. As researchers plan studies to address the issues of treatment resistance and chronic illness, risk-benefit analysis becomes increasingly important. Treatment regimens for treatment-resistant patients are usually complex combination treatments that may be associated with not only increased effectiveness but also increased problems with tolerability.

Figure 4. Clinical Targets of the Treatment of Depression

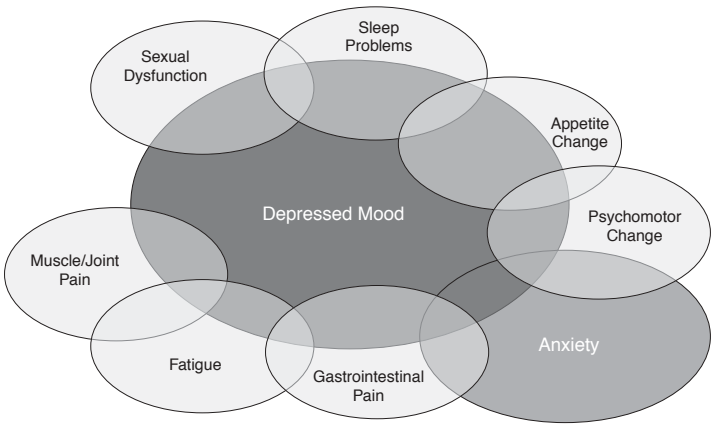


Table 2. Stages of Treatment Resistance[a]

Stage I: Failure of at least one adequate trial of one major class of antidepressant
Stage II: Stage I resistance plus failure of an adequate trial of an antidepressant in a distinctly different class from that used in Stage I
Stage III: Stage II resistance plus failure of an adequate trial of a TCA
Stage IV: Stage III resistance plus failure of MAOI trial
Stage V: Stage IV resistance plus failure of bilateral ECT

[a]Reprinted with permission from Thase and Rush.[46]
Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

Dr. Demitrack then discussed the stages of antidepressant response and resistance proposed by Thase and Rush (Table 2).[46] According to Dr. Demitrack, patients in Stage II through Stage V have the greatest unmet need. Unfortunately, most of what has been learned from current randomized controlled trials has focused largely on patients who are in Stage I or even prior to Stage I.

Dr. Demitrack went on to describe another method of assessing treatment resistance that has been used in clinical trials—the Antidepressant Treatment History Form (ATHF).[47] The ATHF is a semistructured interview that surveys the patient and determines the dose, duration, compliance with treatment, and the outcome of an intervention. The interview establishes an antidepressant resistant rating based on known minimum dose and minimum exposure durations to define adequate treatment. In essence, the ATHF quantifies the number of adequate treatment exposures a patient has experienced, and the measure has been shown to accurately predict future treatment response. The ATHF has practical value because it allows researchers to gauge treatment resistance in a rigorous and reliable way without having to subject the depressed patient to a treatment trial and risk being randomized to placebo treatment. Although randomized controlled trials are the gold standard method of determining response to treatment, they are time consuming, labor intensive, and expensive to implement. An open-label study[48] of vagus nerve stimulation (VNS) in which the ATHF was used to define treatment resistance found that, as the number of failed treatments increased, the proportion of patients responding or achieving remission decreased.

The ATHF can also help clinicians determine whether apparent treatment resistance is due to the inadequacy of past treatment regimens. Dr. Demitrack described a study[49] of ECT in which researchers examined 100 patients who received acute treatment with ECT. Immediately after ECT, these patients had an overall remission rate of 73%. The ATHF was used to determine whose prior treatment had been adequate in dose and duration and what relationship prior treatment had to ECT response. Acute remission with ECT was lowest in those patients who had genuine prior resistance to treatment (63%), in other words, those who had received adequate antidepressant treatment in the past. Patients who had been exposed to inadequate dose or duration of pharmacotherapy in the past had a much higher remission rate to ECT (91%). In this study, prior demonstrated failure of adequate antidepressant treatment predicted a lower response rate to ECT. Dr. Demitrack opined that a diminishing proportion of patients will respond to treatment the further along the treatment-resistance continuum they are.

From a clinical study design perspective, Dr. Demitrack explained that the diminishing proportion of responders has substantial implications for measurement. The further along the target patients lie on the treatment-resistance continuum, the larger the sample size necessary to detect a statistically significant treatment effect among these patients. Study designs that include these truly treatment-resistant patients also have to pay special attention to the tools, rating scales, and methods that should be used to detect the effects of antidepressant treatment.

Dr. Demitrack pointed to the recently reported results of STAR*D as an example of the relationship between previous and current treatment response. The overall architecture of the STAR*D treatment algorithm[5,6] included 4 treatment levels (see Figure 2). Participants in the study had not been exposed to adequate treatment trials of any of the antidepressant options available in Level 1 or 2. Participants were given up to 14 weeks of treatment with the SSRI citalopram in Level 1. From there, participants worked their way through Levels 2 through 4, which included various switching and aug-

Table 3. Remission Rates for Monotherapy Treatment Options at Each Level of Treatment in STAR*D[a]

Study	Level of Treatment	Remission Rate, %
Trivedi et al[43]	1	27.5
Rush et al[50]	2	17.6–24.8
Fava et al[51]	3	12.3–19.8
McGrath et al[2]	4	6.9

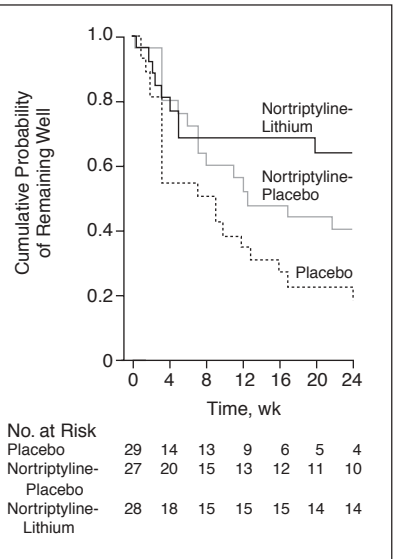
[a]Remission was defined as a score of ≤ 7 at exit on the 17-item Hamilton Rating Scale for Depression.
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

menting strategies, based on whether they had or had not achieved remission at a particular treatment level.

Dr. Demitrack then reported the remission rates associated with each level of treatment. As Table 3 shows,[2,43,50,51] each level was associated with a lower remission rate, from 27.5% in Level 1, in which participants had received no prior treatment of adequate dose and duration, to only 6.9% in Level 4, in which participants had already received at least 3 previous adequate trials of therapy and not responded sufficiently. Dr. Demitrack remarked that pharmacotherapy clearly works, but in a real-world setting such as that in STAR*D, pharmacotherapy does not work as well as one might hope.

Compliance and adverse treatment effects also play a role in treatment response and remission. Dr. Demitrack stated that, overall, compliance can be a problem for some treatment-resistant patients and that patients are unlikely to improve if they do not comply with their medication regimens.[47] In addition, intolerable side effects can lead to discontinuation of treatment, at times without the clinician's knowledge. In STAR*D, 16.3% of participants dropped out of the study at Level 1, 19.5% at Level 2, 25.6% at Level 3, and 30.1% at Level 4 because of intolerable side effects.[52] Dr. Demitrack emphasized that the risk-benefit equation may be more critical than efficacy alone when considering study design and outcomes, especially in studies of

Figure 5. Durability and Persistence of Clinical Effect After Acute Electroconvulsive Therapy[a]



[a]Reprinted with permission from Sackeim et al.[53]

treatment-resistant patients, in which maintaining an adequate sample size is important.

Dr. Demitrack went on to explain that the durability and persistence of the clinical response are also crucial issues in the treatment and study of treatment-resistant depression; treatment effects often subside, leaving the patient with depressive symptoms. The ECT literature contains examples of this phenomenon. In a double-blind, randomized study,[53] after acute ECT response, patients were randomly assigned to treatment with placebo, nortriptyline alone, or nortriptyline plus lithium (Figure 5). Patients in the placebo group were the least likely to remain well, thus highlighting the need for pharmacotherapy after ECT to maintain response. The need for continuation treatment to maintain response in turn raises questions when designing a study of interventions for treatment-resistant depression, such as how long the study should be, how long patients should be followed after the acute treatment period is completed, and what continuation treatment should be used to maintain the acute treatment response.

The Study of Novel Device-Based Interventions in Treatment-Resistant Depression

Dr. Demitrack suggested that researchers might improve the management of treatment-resistant depression by looking for novel interventions that increase the range of available targets, whether genes, proteins or neurotransmitters, cell function, metabolic changes, or neural system effects. For example, TMS is thought, in part, to exert its beneficial effects by alteration of discrete neural systems subserving mood regulation in the brain.

Device-based interventions introduce a new dynamic in the study and treatment of depression in the way therapeutic actions take place. These interventions are typically episodic—a "dose" of TMS, for instance, is applied in a discrete session—and localized anatomically, as opposed to the actions of pharmacotherapy. Dr. Demitrack then posed a question about study design: Will the outcome of a study of a device-based intervention be similar to that of a study of pharmacotherapy? In other words, will the patterns and the timing of the symptom response to treatment look the same?

According to Dr. Demitrack, much of the way that researchers understand how to study antidepressants has been based on experience drawn from drug studies that have shown that antidepressant medications have a sustained, pervasive effect on brain and body function. When researchers study more novel methods of intervention, they have to begin by using the methods and study design used in the investigation of medications. However, in the course of a study, researchers may be able to determine where improvements to methods can be made and whether different patterns of outcomes might be related to the different methods of intervention.

Dr. Demitrack emphasized the importance in clinical research of continually assessing whether the appropriate outcome measures are being used. For example, researchers com-

Table 4. Factors That Affect Clinical Study Design of Novel Interventions[a]

Study population
Demographics
Diagnosis
Comorbidity
Failure of prior treatments
Study design
Duration (acute vs long term)
Visit frequency
Outcome measures
Safety assessment
Rater/treater team organization
Rater performance evaluation
Treatment modality
Medication (single vs combination)
Device
Method of study blinding
Training approach

[a]Based on Demitrack.[54]

monly rely on observer rating scales such as the HAM-D and the MADRS to measure disease state and symptom outcome. He questioned whether these scales would be the best outcome measures when novel interventions that have different types of dynamic effects on brain function are studied. Another question is how well self-rating scales, such as the Inventory for Depressive Symptoms Self-Report and the Beck Depression Inventory, would perform in studies of novel interventions.

Another outcome in clinical research that may be affected by the type of intervention being studied is the time course of response. Studies of antidepressant medications typically look for antidepressant effects over a period of several weeks, but that may be insufficient time to see response to different interventions. In addition, some of the device interventions may have a continuing effect even after the cessation of the acute treatment course. According to Dr. Demitrack, a follow-up period to assess durability of effect is likely to be critically important in the study designs of novel device-based interventions.

As the clinical development of novel interventions progresses, and as the corresponding challenges and innovations arise, 3 broad domains should be addressed when studies are designed: the study population, research design and development, and treatment modality and its effect on outcome measures (Table 4).[54]

Dr. Demitrack then delineated some key factors regarding the design and development of a clinical study for a new intervention such as TMS. First, researchers should determine how the treatment will be used in clinical practice, i.e., as monotherapy, adjunctive therapy, or combination therapy. The study should ultimately reflect the intended clinical use of the device being studied. If it is intended to be used as monotherapy, for example, it should not be studied as an add-on treatment. Another factor to be considered in study design is study population, which has to be clearly defined in terms of diagnosis, symptom burden, and level of treatment resistance. A detailed, rigorous characterization of treatment resistance is essential for interpreting the magnitude of the treatment outcome. In addition, the amount of treatment will differ from the traditional way researchers and clinicians consider dose of a medication, in milligrams per day for a certain time period. A variety of treatment parameters define the "dose" and duration of a device-based intervention.

The blinding of treatments in a controlled study becomes critically important for studies of device-based treatments, which, according to Dr. Demitrack, have the reputation of being very difficult to study in blinded trials. Some methods can improve blinding methodology, particularly in the study of TMS, in which a sham coil has been designed that sounds, weighs, and is administered just like the active treatment coil.

Dr. Demitrack advised that proper training for those who will be rating study outcomes is important for both device trials and all other antidepressant trials. In the context of device trials, researchers also need to determine the knowledge and skills of the person administering the treatment session. Dr. Demitrack speculated that specialized treatment skills might be necessary to correctly apply the technology of device-based interventions. If that is so, it raises the questions of how the clinicians who administer the treatment are trained and how they will be monitored.

The method of outcome assessment is critically important when designing studies of interventions such as TMS. Functional status outcome measures should be included, since the effects of a device-based intervention on functional status may not be adequately characterized by symptom scales. The economic effects, such as the benefits to work productivity and health resource utilization, are also worthy of study with a new intervention, argued Dr. Demitrack. A new intervention may be effective, but if it is neither a practical nor a cost-effective alternative for the patient, then it is not a valid treatment. In addition, as with any study of a new treatment, studies of device-based interventions need to address the safety of the treatment and whether it presents any unique safety risks.

Recently, a clinical trial program of TMS therapy in the treatment of major depressive disorder was completed (J. P. O'Reardon, M.D., et al., submitted), using many of the clinical trial design features mentioned above. This clinical trial program was conducted at 23 centers in the United States, Canada, and Australia. The program consisted of 3 phases. The first phase was a 6-week, randomized, sham (placebo)-controlled, double-blind, monotherapy study. The study population was 325 medication-free outpatients who had been resistant to at least 1, but no more than 4, previous antidepressant medications of an adequate dose and duration during the current episode. In the second phase, 136 patients who responded in the acute study were enrolled in a 6-month extension study. They received single medication treatment and were observed for maintenance of response. In the third phase, 158 patients who did not respond in the acute controlled treatment study entered a 6-week, open-label treatment study. The results of this clinical program have been submitted for publication and are currently under review by

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the FDA as part of an application for clearance of TMS therapy in the treatment of major depressive disorder.

Fitting Novel Device-Based Interventions Into Clinical Practice

Dr. Demitrack then commented on novel treatment technologies and where they might fit into clinical practice. Most antidepressant treatment strategies begin with medication, especially for patients who have not yet entered Stage I of the treatment-resistance criteria described by Thase and Rush.[46] Later stages of intervention become more complicated as treatment resistance increases and more combination therapies are tried. Dr. Demitrack reported that TMS is beginning to show promise within the device-based platform of interventions and that it may be an option in the early stages of treatment resistance, after 1 or 2 medication trials have failed. It will most likely precede some of the more invasive device-based treatment options, such as ECT, VNS, and deep brain stimulation.

One way of determining how device-based interventions fit into clinical practice is to see them along a dual continuum of tolerability and invasiveness. A treatment that is tolerable and noninvasive, such as TMS, would be an option earlier in the course of treatment than one that is invasive, such as VNS, or is poorly tolerated, such as ECT.

As new interventions are developed and approved, clinicians should think about patient selection as a key to how these treatments are applied. Dr. Demitrack stated that, early in treatment, patient preference will play as critical a role as clinician selection in making the decision between continued medication therapy and the introduction of TMS therapy. He speculated that a treatment like TMS would be appropriate after incomplete or no response to prior treatment, when significant disruption has occurred because of adverse events, or if there is evidence of increasing functional impairment as a result of the persistence of the illness. If the patient moves through a number of treatment trials and still has an inadequate response, the clinician may need to take on a more dominant role in choosing a more invasive intervention. More substantial morbidity is likely to be present before these invasive options are considered, and symptoms such as psychosis or acute suicidality might be critical factors in deciding to use interventions like ECT, VNS, or deep brain stimulation. These interventions are appropriate much later in the treatment-resistance continuum, after failure to respond to 4 or more adequate antidepressant treatments.

Conclusion

Dr. Demitrack concluded that clinical urgency clearly remains for depression and that the majority of patients with depression remain poorly served. From a clinical development perspective, these patients reside at an end of the spectrum where the treatment signal diminishes in size, and the risk-benefit ratio plays a more important role in defining useful outcomes from clinical studies. The current research clearly underscores the modest expectations of outcome with existing options for treatment-resistant depression. For the foreseeable future, researchers and clinicians are likely to continue to struggle with the small amount of treatment response at this end of the spectrum. TMS seems to provide the promise of at least equivalent efficacy and, in some instances, perhaps better efficacy and an improved tolerability profile compared with continued, more complex pharmacotherapy.

rTMS Mechanism of Action

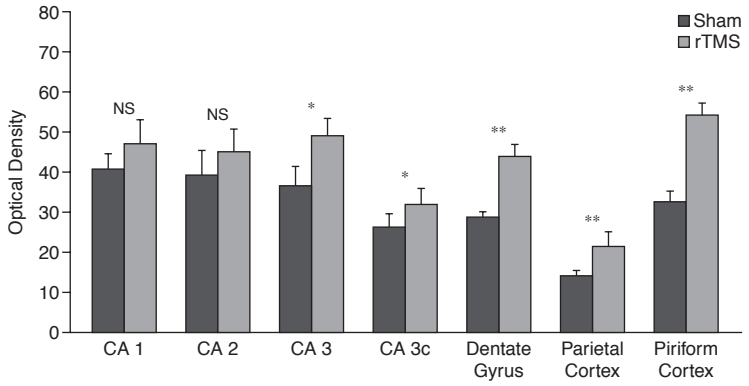
Elliott Richelson, M.D., suggested that the mechanism of action of rTMS is similar to the mechanism of action of antidepressant agents. The experimental conditions under which both rTMS and antidepressant agents have been tested have shown that both were predictive of antidepressant effects in animal behavioral models, such as the Porsolt forced swim test, and in animal and human biological models. Animal biological models indicate increases in brain monoamine turnover, increases in brain-derived neurotrophic factor (BDNF), and normalization of stress in the hypothalamic-pituitary-adrenal (HPA) axis with antidepressant drugs as well as rTMS. In human biological models, antidepressant effects include normalization of stress in the HPA axis; increase in the time to onset of the first episode of rapid eye movement sleep; and increases in regional cerebral blood flow and glucose metabolism in brain mood circuitry.[55–57] Empirically derived and randomized controlled trials have provided compelling evidence for managing treatment-resistant depression with both antidepressant drugs and rTMS.[42,58]

Methodological Issues in rTMS Research

Animal studies[59–64] published over the years have contributed to our understanding of the variables that can be modified or controlled to generate methods or information relevant to treatment in humans. Dr. Richelson stated that one of the methodological challenges of testing rTMS in animal models is the size of the animal's head versus the size of the magnet. Other issues include variances in stimulation conditions and treatment schedules as well as the type of sham testing performed.

Dr. Richelson said that the forced swim test predicts antidepressant effect and has been used for decades for screening antidepressants and predicting efficacy in humans.[62] Rodents used in the forced swim test are placed into a beaker of water where they are forced to swim. After a time, rodents will give up swimming and exhibit helplessness. This test is highly reliable in that antidepressants will prolong the time between the rodents ceasing to swim and behaving in a helpless fashion. Results from another study[63] that included a forced swim test component suggested that rTMS had modest antidepressant properties, but no anxiolytic properties. The swim time was prolonged and

Figure 6. Effects of Long-Term rTMS on the Expression of BDNF in Rat Brains[a]



[a]Reprinted with permission from Müller et al.[60]
*p < .05 (N = 5).
**p < .01 (N = 5).
Abbreviations: BDNF = brain-derived neurotrophic factor, CA = hippocampal area, NS = not significant, rTMS = repetitive transcranial magnetic stimulation.

Table 5. Major Depressive Disorder Symptom Clusters: Emotional Brain Centers[a]

Brain Area	Associated Symptom
Medial prefrontal cortex	Depressed mood, guilt, feeling worthless, suicidality, anxiety
Anterior cingulate cortex	Depressed mood, guilt, feeling worthless, suicidality, anxiety
Orbital prefrontal cortex	Depressed mood, guilt, feeling worthless, suicidality, anxiety
Amygdala	Guilt, feeling worthless, suicidality, anxiety
Nucleus accumbens	Loss of pleasure, feeling worthless, guilt, suicidality
Hypothalamus	Loss of pleasure

[a]Based on Stahl.[67]

time to immobility was decreased with rTMS, both of which are maxims that have been shown in other studies[14,62,64–66] with antidepressant drugs.

Dr. Richelson reviewed a study[64] that compared the effects of rTMS on 2 inbred strains of rats. One group of rats was bred for low anxiety levels and the other group of rats was bred for high anxiety. The rats were subjected to daily rTMS treatment for 8 weeks beginning at 4 weeks of age. By endpoint, rats with high levels of anxiety that had received rTMS showed more active stress coping strategies than the control rats in the forced swim test. Further, chronic rTMS treatment of frontal brain regions in rats also weakened the neuroendocrine response to stress. This response is similar to the effect of antidepressant drug treatment in humans.

Dr. Richelson cited a study by Keck et al.[61] that showed that rTMS increased the release of dopamine. In this study, the acute effects of intrahippocampal, intra-accumbal, and intrastriatal release patterns of dopamine were measured using intracerebral microdialysis probes implanted in rat brains. During stimulation of the frontal brain regions, the probe allowed researchers to remove some of the fluid that surrounds the neurons. Then high-performance liquid chromatography was used to measure the levels of the biogenic amines. The concentration of dopamine in the rat hippocampus was elevated in response to rTMS. Interestingly, only dopamine was increased; none of the other potential neurotransmitters, such as norepinephrine and serotonin, was increased. rTMS has an action in the brain similar to that of antidepressant drugs in that both cause the release of dopamine.

Antidepressant drugs also have been shown to increase BDNF,[60] which is important to maintaining neuronal health. Likewise, long-term rTMS increases the expression of BDNF in specific areas of the rat brain. Compared with sham treatment, rTMS markedly elevates the amount of BDNF in various parts of the brain, particularly in the hippocampus (Figure 6).

Neuroanatomical Mechanism of Action of rTMS

The emotional symptoms of major depressive disorder may be linked to abnormal activity in different areas of the brain. Areas of the brain associated with emotions include the medial prefrontal cortex and orbitofrontal cortex, the anterior cingulate cortex, the amygdala, nucleus accumbens, and hypothalamus. Dr. Richelson stated that signs and symptoms of depression are thought to be mediated by different neuroanatomical areas located in these different areas of the brain and involve the emotional, cognitive, and somatosensory, as well as sleep areas. Since different neuroanatomical areas are associated with different types of functioning, modulating neurotransmission to a specific brain area may reduce or eliminate signs and symptoms associated with those brain areas. Thus, abnormal activity in divergent brain areas may separately modulate symptoms of psychiatric disorders.

In 2003, Stahl[67] pointed out that different malfunctioning neuronal circuits may mediate different symptoms in major depressive disorder, and since all patients with major depressive disorder do not have the same symptoms, the implication is that they do not all have the same malfunctioning circuits. He presented a hypothetical topography of symptoms and symptoms in major depressive disorder that can be matched to malfunctioning circuits in different areas of the brain (Table 5). Not every patient with major depression has the same cluster of symptoms, which implies that different circuits may malfunction in different patients with the same disorder. The "monoamine hypothesis" proposes that depression is related to a deficit of mono-

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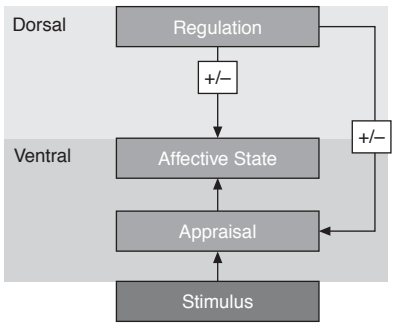
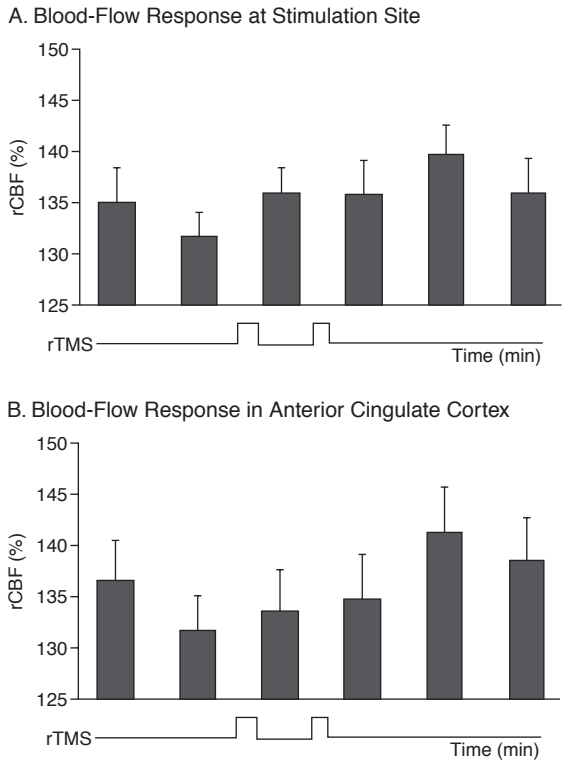
Figure 7. Neurocircuitry Underlying Emotion Perception[a]



[a]Adapted with permission from Phillips et al.[56]

Figure 8. Double-Pulse rTMS of Mid-Dorsolateral Frontal Cortex[a]



[a]Reprinted with permission from Paus et al.[57]
Abbreviations: rCBF = regional cerebral blood flow, rTMS = repetitive transcranial magnetic stimulation.

amines at critical synapses, particularly norepinephrine and serotonin. This hypothesis may better explain the neurobiology of antidepressants than it explains the neurobiology of the symptoms of depression. The fact that rTMS affects these monoamines further supports rTMS as an antidepressant treatment.

Dr. Richelson cited a 2-part article by Phillips et al.[55,56] that attempts to identify potential neural correlates of emotion perception. Using findings from animal, human lesion, and functional neuroimaging studies, Phillips and colleagues hypothesized that the neurobiological underpinnings of emotion processing abnormalities in psychiatric populations are dependent upon the function of 2 major neural systems of the brain: the ventral system and the dorsal region (Figure 7). The ventral region includes the ventral lateral prefrontal cortex, olfactory cortex, amygdala insula, and thalamus. The dorsal region includes such areas as the dorsal lateral prefrontal cortex, the dorsal medial prefrontal cortex, the anterior cingulate gyrus, and the hippocampus. The predominantly ventral region, which also has a medial component, is important for the identification of the emotional significance of a stimulus, resulting in production of an affective state and the autonomic response to regulation. On the other hand, the predominantly dorsal region, which also includes a lateral system, is important for the executive function, selective attention, planning and reasoning, and persistent regulation of the affective state. A reciprocal relationship may exist between these 2 system hierarchies. In healthy individuals, a balance exists between the dorsal and ventral regions. In individuals with depression, a negative bias is suspected with the ventral region predominating and the regulation markedly decreased from the dorsal region. rTMS appears to bring these 2 regions back into balance in patients with depression.

Neurocircuitry Underlying Emotion Perception

Dr. Richelson posed this question: Are the key brain regions involved with depression affected by rTMS? Further, because the rTMS magnet is placed outside the head and near the surface of the brain over the prefrontal cortex, will depression-related structures that are deep in the brain be affected? The data[57] suggest that the answer to both is yes. Stimulation of the relatively superficial area of the prefrontal cortex with the magnet does affect the other parts of the brain, including the critical brain areas that are thought to go awry in depression, such as the prefrontal cortex and the anterior cingulate cortex.

Repetitive transcranial magnetic stimulation has been shown to increase blood flow not only at the magnet site, but also in deeper regions of the brain.[57] Blood flow response was increased in the anterior cingulate cortex, for example, which is far from the site where the magnet was applied and is a key cognitive-affective circuitry area of the brain involved in depression. Researchers applied rTMS to the left mid-dorsolateral prefrontal cortex and administered a probe pulse (a double pulse) to measure the brain's

blood flow response. The rTMS was administered after the first probe pulse and then followed by another probe pulse, followed by another rTMS and then further probe pulses. Blood flow was increased at the site of stimulation after the 2 repetitive pulses (Figure 8).

Summary

Dr. Richelson recounted his main points. Animal and human testing models have shown that antidepressant medications and rTMS are comparable in affecting the mechanisms that regulate mood. Both affect cerebral blood flow, increase BDNF, and normalize stress in the HPA axis. Theoretically, not all parts of the brain mediate all signs and symptoms of depression; however, modulating neurotransmission to specific brain areas through highly focused magnetic pulses that target specific mood circuits may reduce or even eliminate signs and symptoms associated with dysfunction in those brain areas.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, rTMS is not approved by the U.S. Food and Drug Administration for the treatment of major depression.

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