Transcranial magnetic stimulation for major depressive disorder: What a pharmacist should know

Ericka L. Breden Crouse, PharmD, BCPP, CGP, FASCP[1]

[1]Clinical Pharmacy Specialist, Psychiatry
Virginia Commonwealth University Health System
Richmond, VA

ABSTRACT

Transcranial magnetic stimulation utilizes strong pulsed magnetic fields from an insulated coil which generate electrical currents resulting in neuronal depolarization in the cortex. Currently, the user manual only cautions against the use of tricyclic antidepressants, antipsychotics, and other medications that lower the seizure threshold during TMS therapy. However, post-marketing reports suggest caution should also be utilized when combining TMS with other antidepressants (e.g. bupropion, serotonin reuptake inhibitors) and stimulants. Data show efficacy of approximately 30%. Adverse effects more commonly reported include application site pain (35.8%), muscle twitching (20.6%), application site discomfort (10.9%), skin pain (8.5%), toothache (7.3%), facial pain (6.7%), and eye pain (6.1%).

KEYWORDS

transcranial magnetic stimulation, depression

INTRODUCTION

Repetitive transcranial magnetic stimulation (TMS) was first developed in 1985 and received FDA approval (clearance) in October 2008 as a Class II medical device (NeuroStar®, Figure 1 and 2) indicated for the treatment of Major Depressive Disorder in adult patients who failed to respond to a single adequate antidepressant trial.[1,2] Transcranial magnetic stimulation has not been studied in patients who have never been treated with an antidepressant, and approval has not been established in patients who have failed multiple adequate antidepressant trials.[1]

MECHANISM OF ACTION

Transcranial magnetic stimulation utilizes strong pulsed magnetic fields from an insulated coil which generate electrical currents resulting in neuronal depolarization in the cortex.[3-8] The stimulation is localized by applying the magnet to the left dorsolateral prefrontal cortex.[4] Coil placement requires determination of the motor threshold (MT).[7]

MEDICATIONS UTILIZED IN STUDIES

As a pharmacist, it is important to note that patients, in the primary clinical trial utilized in obtaining FDA approval for TMS, were not treated with any antidepressants or other psychotropics that can be used to treat depression. The lack of concurrent medications was to determine the efficacy of the device and ensure that improvement was not related to medications. Treatment with benzodiazepines, up to 14 daily doses of lorazepam 2 mg/day equivalents, was permitted in the randomized-sham controlled trial.[5]

Clinically, however, some psychiatrists have continued antidepressant treatment throughout the TMS treatment course. Initiating TMS with antidepressants concurrently, or adding TMS to existing antidepressant therapy has been studied.[9,10] A recent published observational, naturalistic study of 307 patients allowed for continuation of antidepressants during treatment with TMS, which occurred in the majority of patients.[4,11]

If you are discussing TMS as a potential therapy, it is important to educate patients that they may be discontinued off of their current antidepressant(s). After TMS therapy completion, antidepressant therapy may be resumed.[5]

EVIDENCE FOR TMS

In a double-blind, randomized trial of 301 medication-free patients, the primary outcome was change in clinician-rated Montgomery-Asberg Depression Rating Scale (MADRS) score at week 4. At week 4, change in MADRS scores was not significant versus sham-TMS. However at week 6, response, defined as a 50% reduction in MADRS, was achieved in 23.9% of TMS-treated patients versus 12.3% of sham-TMS patients ($p<0.01$). Remission, defined as a MADRS score < 10, was achieved in 14.2% of TMS versus 5.5% of sham-TMS patients ($p<0.05$) at week 6.[3,5]

A more recent naturalistic study of 307 patients, who had an average failure of 2.5 adequate medication trials, received an average of 28.3 TMS therapy sessions over an average of 42 days. Based on the primary outcome measure, Clinical Global Impressions-Severity of Illness scale (CGI-S) score, at the end of the acute phase, 58% of patients met the criteria for response (score ≤ 3) and 37.1% met the criteria for remission (score of 1 or 2) ($p<0.0001$). The authors compared response and remission rates between patients with low treatment resistance versus high treatment resistance to antidepressants and did not find a difference (response 59.4% vs. 56.8% and remission 39.9% vs. 34.9%, respectively).[4]

Rumi et al.[10] conducted a double-blind, randomized sham-TMS controlled study in 46 patients on concurrent amitriptyline (mean dose 100 mg/day). Their findings suggested amitriptyline-treated patients receiving TMS had a higher HAM-D17 response rate (≥ 50% reduction in HAM-D score) (95% TMS versus 46% sham-TMS; $p< 0.001$) and higher remission rates (HAM-D17 score ≤ 7) (54% TMS vs 12% sham-TMS; $p < 0.002$) at 4-weeks, suggesting TMS accelerated time to antidepressant response.[10]

Another double-blind randomized, sham-controlled study showed no difference between TMS and sham-TMS in 127 patients initiated simultaneously on concurrent antidepressant medication (venlafaxine or mirtazapine). In both groups, 31% of patients showed response at 3 weeks ($p=0.962$).[9] The negative findings may be due to the short duration of TMS treatment. Many studies that included endpoints at 2 or 4 weeks did not have the clinical or statistical response that was seen at week 6, which leads to the recommended frequency listed in Table 1.

TMS CONTRAINDICATIONS AND WARNINGS

Transcranial magnetic stimulation has the potential to affect devices or objects implanted in the head or those that cannot be removed to a distance of more than 30 cm of where the treatment coil will be placed. Therefore, TMS is contraindicated in patients who have "conductive, ferromagnetic, or other magnetic-sensitive metals" such as cochlear implants, implanted stimulators, aneurysm clips, metal plates, stents, or bullet fragments in or near their head. Acceptable metal objects not contraindicated include dental fillings, single post dental implants, and dental bridge work. Caution should be used in persons with pacemakers and implantable cardioverter defibrillators.[1] Furthermore, caution should be exercised in patients who have a history of seizures, or conditions associated with altered seizure threshold (e.g., stroke, dementia, head injury).[1]

DRUG INTERACTIONS WITH TMS

Currently, the user manual only cautions against the use of tricyclic antidepressants, antipsychotics, and other medications that lower the seizure threshold during TMS therapy.[1] However, post-marketing reports suggest caution should also be utilized when combining TMS with other antidepressants (e.g. bupropion, serotonin reuptake inhibitors) and stimulants.

Ziemann[12] published a literature review of medications most likely to affect the MT during TMS. The MT is the minimum intensity needed to produce a motor evoked potential in the targeted muscle.[12] In TMS, the MT is determined by moving the coil and adjusting the power level until exactly five thumb twitches during 10 consecutive pulses are produced.[7] The motor threshold in resting muscles (resting motor threshold or RMT) is higher than that in voluntarily contracting muscles (active motor threshold).[12] Evidence suggests medications that block voltage-gated Na+ channels increase the MT. Specifically, lamotrigine, phenytoin, and carbamazepine have been implicated. Conversely, ketamine, an NMDA antagonist, reduces the MT. Medications that work on GABA such as benzodiazepines (e.g., lorazepam, diazepam), and vigabatrin do not appear to have an effect on the MT.[12] Valproic acid, which works on both Na+ channels and GABA, also did not seem to affect the MT.[12,13] Despite this, the user manual suggests re-determining the MT if a medication known to affect the seizure threshold is added to the patient's regimen.[1]

A case report involving a 41 year old female describes a reduction in the resting motor threshold (RMT) after initiation of bupropion SR 150 mg per day prior to visit 8 for TMS. When the dose was increased to 300 mg per day on visits 10 and 11, a statistically significant reduction in the RMT from 70-74% to 64-66% was observed, which later returned to 73% following dose reduction back to 150 mg. She did not experience a seizure.[13]

Although the manufacturer warns against concurrent use of tricyclic antidepressants, Rumi et al.[10] combined TMS and amitriptyline (mean dose 100 mg/day). No seizures were reported with concomitant amitriptyline administration.[10]

TMS ADVERSE EFFECTS

In the double-blind, randomized, sham-TMS controlled study [n = 158] vs. active TMS [n = 165] the adverse effects that were more commonly reported in the active

Table 1. Comparison of devices utilized in the treatment of MDD[2,6,16]

	TMS	ECT	VNS
Date of FDA-Approval	2008	Developed in 1938 "grandfathered" 2009 reviewed by FDA	2005
Device Classification	II	III	II
Indication	Depression unresponsive to one trial of antidepressant medication	Depression (unipolar & bipolar) Schizophrenia Bipolar mania Schizoaffective Schizophreniform Catatonia	MDD if symptoms >2 years; is severe or recurrent, has not responded to 4 or more treatments
Mechanism	Magnetic pulses	Electric current	Electric pulses
Treatment Course	Daily for 4-6 weeks After acute course completion, followed by a 3 week taper: week 1: 3 TMS treatments Week 2: 2 TMS treatments Week 3: 1 TMS treatment	2-3 times per week for 6-12 treatments	N/A
Session duration	30 – 60 minutes	3 – 6 hours*	N/A
Treatments can be done outpatient?	Yes	Yes	N/A
Anesthesia Required	No	Yes	Yes, during surgery to implant device

TMS = repetitive transcranial magnetic stimulation; ECT = electroconvulsive therapy; VNS = vagal nerve stimulation/stimulator; *ECT session duration dependent on number of other cases scheduled, pre-workup, and post-ECT monitoring.

TMS group include application site pain (35.8%), muscle twitching (20.6%), application site discomfort (10.9%), skin pain (8.5%), toothache (7.3%), facial pain (6.7%), and eye pain (6.1%).[6] In open-label trials, additional adverse events considered device-related included a first-degree burn secondary to device malfunction and left-sided facial numbness. A reported case of tinnitus was considered probably not related to TMS therapy. No changes in cognition nor hearing were noted during 4 or 6 weeks of treatment.[1] The most common adverse effect, headache, appears to improve with each treatment with approximately 65% experiencing headache the first week, versus approximately 35% week 4, and less than 10% week 10.[6]

An infrequent reported adverse effect of TMS is seizures. As of 2012, there have been six post-marketing reports of seizures reported to the FDA. The estimated seizure risk is 0.003% of treatments, or 0.1% of patients.[1,4]

Accessible reports of seizures included two reports thought to be device-related that included medications. The first case was potentially precipitated by the patient taking bupropion, sertraline, and mixed amphetamine salts (doses not provided), along with being sleep-deprived.[4,14] A full tonic-seizure occurred within 15 minutes of beginning her 10th TMS session during her 2nd course of TMS therapy. Another adverse report of a seizure thought to be device-related occurred during the 10th TMS session in a patient with a past medical history of depression and bipolar disorder, and family history of seizure disorder, who was currently taking fluoxetine, aripiprazole, and lithium (doses not reported), all of which can lower the seizure threshold.[15]

MANAGEMENT OF ADVERSE EFFECTS

There are no well-published data on the management of TMS adverse effects. Clinically application site pain or scalp pain has been the most frequently reported adverse effect in our TMS practice, and has been noted to be more severe in male patients with extremely short hair. As suggested by Janicak, the pain appears to lessen as treatment duration goes on.[6] During the first week of TMS therapy, our practitioners apply lidocaine topical 2% jelly to the site where the magnet will be applied and have the patients take ibuprofen 600 mg prior to therapy, and reevaluate if it is needed during week 2. Patients must wear earplugs during treatment to minimize auditory adverse effects.[1,7] Clinicians involved in providing or observing TMS therapy should also wear earplugs.[1,7] One of our TMS staff experienced tinnitus lasting over 10 hours when they forgot to wear their earplugs.

DISCUSSION

Transcranial magnetic stimulation adds to the non-pharmacologic treatment approaches for patients who do not respond to adequate trials of antidepressants (Table 1). In studies, to consider TMS, patients could only have failed one antidepressant trial. However, in clinical practice it appears the insurance companies that cover TMS treatments are requiring failure of four adequate trials of antidepressant therapy, from at least two different antidepressant classes.[16] Currently, TMS is used primarily for an acute episode of depression. A time to response of 6 weeks is similar to many antidepressant medications.

Other devices currently being studied for depression include magnetic seizure therapy (MST) and deep brain stimulation (DBS), but neither are currently approved by the FDA for Major Depressive Disorder. Current studies are underway for repetitive TMS in auditory/verbal hallucinations, tinnitus, migraine, ADHD, and anxiety, but are not currently approved for use.[16,17]

As a pharmacist, if you are involved in the decision of implementing TMS, the pharmacist's role can be to minimize the medications (e.g., antidepressants, antiepileptics) that may affect the motor threshold, and help recognize and manage adverse effects associated with TMS.

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