Clinical TMS Society

TMS Therapy For Major Depressive Disorder: Evidence Review and Treatment Recommendations for Clinical Practice

A White Paper

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Introduction

Transcranial Magnetic Therapy (TMS) is currently indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. In order to promote the practice of TMS in a standardized and rational manner, leading clinical providers of TMS joined prominent researchers in the field to create the Clinical TMS Society. The leadership of the society has developed this White Paper to provide a summary of current evidence for the safety and efficacy of the use of TMS therapy in routine clinical practice settings. Please see details of membership and goals at www.clinicaltmssociety.org.

The first part of this document presents a systematic literature review of clinical trials using TMS therapy published in the peer-reviewed literature. Published studies are assessed and graded on their strength of evidence using the Levels of Evidence framework published by the University of Oxford Centre for Evidence Based Medicine.

The next section is a brief summary of essentials for the use of TMS therapy in routine clinical practice settings. This summary of practice essentials is not intended to be a substitute for a more complete summary of device characteristics described in the respective manufacturer's Product User Manuals. These recommendations are also not intended as a substitute for formal clinical training in the use of the TMS therapy.

In the final section of this document, each summary clinical recommendation is presented with the substantiating peer-reviewed, published evidence supporting that recommendation. When the current published clinical trial evidence is insufficient or incomplete, expert opinion is included when sufficient consensus is available from experienced clinician users among the membership of the Clinical TMS Society, who were polled at the Annual Meeting in New York City, May 2014.

The document contains a complete bibliography of the peer-reviewed publications.

Part 1. Evidence from the Peer-Reviewed Literature

Overview of TMS therapy

TMS therapy involves the use of a computerized, electromechanical medical device that produces and delivers non-invasive, magnetic stimulation using brief duration, rapidly alternating, or pulsed, magnetic fields to induce electrical currents directed at spatially discrete regions of the cerebral cortex. This method of cortical stimulation by application of brief magnetic pulses to the head is known as transcranial magnetic stimulation or TMS. When pulses of TMS are delivered repetitively, this is called repetitive TMS, or rTMS. These pulses can be delivered at either high (10-20 Hz) or low frequency (less than or equal to 1 Hz). Most clinical TMS treatments delivered for treatment of depression are typically given at 10 Hz to 18 Hz. Throughout this document, these treatment parameters may be called TMS for the sake of brevity. The peak magnetic field strength achieved with each pulse is approximately 1.5 Tesla, right underneath the coil, similar in strength to the magnetic field produced by a typical magnetic resonance imaging device. The first TMS device cleared for therapeutic clinical use in Major Depressive Disorder (MDD) in the United States by the US Food and Drug Administration (FDA) in 2008 was a focal iron core coil produced by Neuronetics Inc. In 2013, a second coil (i.e. the H-Coil) produced by Brainsway was FDA cleared for MDD. Product manufacturer manuals provide technical details about each coil.

Method of Literature Review

Peer reviewed literature on TMS therapy was obtained by searching the publicly accessible literature databases available on PubMed (http://www.ncbi.nlm.nih.gov/pubmed). Additional searches were performed on the ClinicalTrials.gov website (http://www.clinicaltrials.gov/). Searches used the terms Brainsway, H-coil, rTMS, NeuroStar, Neuronetics, transcranial

magnetic stimulation, Deep TMS, clinical trials. All publications available since completion of the initial registration studies filed on ClinicalTrials.gov with the NeuroStar TMS system in 2006 are included in this guideline document. All publications available with the Brainsway Deep TMS system are included in this guideline document.

All studies were reviewed and graded on their strength of evidence. The framework that was used as a guide to assess the strength of evidence was the Levels of Evidence criteria published by the University of Oxford Centre for Evidence Based Medicine (http://www.cebm.net/?o=1025). This methodology uses evidence on five major levels, placing the greatest emphasis on evidence obtained from randomized controlled trials and prior systematic reviews.

In addition to the literature database search, additional information was requested of the product manufacturers, including any peer-reviewed scientific publications. Information publicly available on the manufacturers' website was also reviewed. Finally, the committee requested and reviewed the manufacturers' Medical Technology Dossiers.

Systematic Review of the Evidence for (prefrontal fast rTMS) TMS therapy

Multi-site Randomized Controlled Trials (RCT)

Three large, multisite, randomized sham-controlled trials included an aggregate sample of 703 adult patients with major depressive disorder (MDD) who had failed between 1-4 antidepressant trials. Two of the studies were industry-sponsored registration trials that led to FDA clearance for the Neurostar TMS Therapy System in 2008 and the Brainsway Deep TMS device in 2013. The third study was an NIMH-sponsored, multicenter study, which provided critical, industry-neutral, evidence of TMS' efficacy. This trial also used an active, sham-controlled condition and the primary outcome focused on the clinically important endpoint of remission. All three trials were consistent in their evidence, establishing a statistically and clinically relevant benefit with TMS therapy. Further, the safety of Neuronetics TMS Therapy and Brainsway Deep TMS was affirmed in these three studies, consistent with the earlier scientific literature.

Neuronetics Trial: The first randomized, sham-controlled multicenter trial reported in O'Reardon, et al. (2007) was conducted globally at 23 sites (20 in the US, 2 in Australia and 1 in Canada). It used a clinical trial version of the Neurostar TMS Therapy System (Neuronetics Model 2100 Clinical Research System). Patients who met DSM-IV criteria for MDD, with a moderate level of treatment resistance were recruited. Of the Intent-to-Treat (ITT) sample of N=325, there was a high rate of completers N=301. The study consisted of several phases: a one week, no-treatment lead-in; a four-six week randomized, sham-controlled acute treatment phase of daily TMS monotherapy; a four-six week open-label trial in non-responders during the randomized phase; and in responders, a three week taper phase during which patients began on an open-label, single antidepressant medication and were then followed for six months to examine the durability of TMS' acute effect. Stimulation parameters were 120% MT, 10 Hz frequency, train duration of 4 s, inter-train interval of 26 s and 75 trains per session, leading to a total of 3000 pulses over 37.5 min. Those patients who showed substantial clinical benefit in either the RCT or the Open Label extension phases were then followed for six months examine the durability of TMS' acute effect. In the initial randomized controlled trial phase, patients randomized to active TMS demonstrated a clinically meaningful improvement on the primary outcome measure, baseline to endpoint change on the Montgomery-Asberg Depression Rating Scale at four weeks (MADRS, P=0.057, standardized effect size = 0.39) compared to those patients randomized to sham TMS. Further, an analysis of the one prior antidepressant failure subsample (n=164) indicated an even more robust benefit for TMS versus the sham procedure (P=0.0006). Additionally, several secondary outcome measures demonstrated statistically and clinically significant benefit for TMS compared with the sham procedure. Among these secondary outcomes was a superior outcome on the Hamilton Depression Rating Scale (HAMD) (both the 17-item and 24-item versions). The outcome showed baseline to endpoint change favoring TMS after 4 weeks (17-Item change: P=0.006, standardized effect size = 0.55; 24-Item change: P=0.012, standardized effect size = 0.48).

NIMH Trial (OPT-TMS): The second, multisite, randomized sham-controlled trial provided industry independent evidence for the safety and efficacy of TMS in patients diagnosed with treatment resistant or treatment intolerant MDD (George, et al, 2010). This study was independent of industry and sponsored by National Institutes of Mental Health (NIMH). It also used the clinical trial version of the Neurostar TMS Therapy System (Neuronetics Model 2100 Clinical Research System). The trial at four US universities included antidepressant medication-free outpatients with MDD and an overall moderate level of treatment resistance (similar to the inclusion and exclusion criteria for patients studied in the industry trial). The ITT sample size included 190 patients who all completed the study. The investigators focused on the primary efficacy endpoint of remission based on the 24-item HAMD scale. Moreover, this trial used an active sham method that fully blinded patients, treaters and raters. Stimulation parameters were 120% MT, 10 Hz fre-

quency, train duration of 4 s, inter-train interval of 26 s and 75 trains per session, leading to a total of 3000 pulses over 37.5 min. The trial design consisted of a 2 week, no treatment lead-in phase; a 3-week fixed treatment phase; and a variable, 3-week treatment extension for initial clinical improvers. The authors reported that for the entire population, there was a significant effect of active treatment on the proportion of remitters at any time point during the acute phase (15% active TMS vs. 4% sham control group, P=0.015), representing 4.2 greater odds of reaching remission with active TMS compared with the sham control group. They concluded that "...daily left prefrontal TMS as monotherapy produced significant and clinically meaningful antidepressant therapeutic effects greater than sham..."

Brainsway Trial: In this study involving 20 sites (13 US, 1 Canada, 2 Europe and 4 in Israel), patients with MDD who had failed 1-4 antidepressant treatment trials during the current episode were enrolled and randomized to receive either active Deep TMS (H- coil) or a sham coil. The trial used an active sham method that fully blinded patients, treaters, and raters (Levkovitz et al, 2015). Of an ITT sample size of 212 patients, the study was completed by 181 patients with equivalent rates of dropouts with active and sham treatment. Patients were tapered off antidepressant medications and received monotherapy Deep TMS. The acute treatment phase was 5 sessions per week for 4 weeks, followed by a maintenance phase of twice-weekly treatment for an additional 12 weeks. Stimulation parameters were 120% MT, 18 Hz frequency, train duration of 2 s, inter-train interval of 20 s and 55 trains per session, leading to a total of 1980 pulses over 20 min. The primary end point was the change score on the HAMD21 at week 5, which favored the active versus sham procedure (ie. 6.39 versus 3.11 points, respectively; p=0.008). At week 5, the response rates were 38.4% for Deep TMS versus 21.4% for sham treatment (p=0.0138). Remission rates were 32.6% for TMS versus 14.6% for sham treatment (p=0.0051). At week 16, the response rates were 44.3% for TMS versus 25.6% for sham treatment (p=0.0086). Remission rates were 31.8% for Deep TMS versus 22.2% for sham treatment (p=0.1492).

The Helwig article, which is listed in the bibliography, was not included in this summary because it was adjunctive rather than primary treatment (Helwig et al., 2007).

Durability Studies

The durability of TMS following the acute course has been demonstrated in several studies both with and without maintenance antidepressants. Specifically with the Neurostar TMS Therapy System's research version, long-term follow up is considered in two independent cohorts: 50 patients for 3 months (Mantovani, et al., 2012); and 99 patients for 6 months (Janicak, et al., 2010). A separate, 12-month, follow-up report of 257 patients was reported in an observational, outcome study (Dunner et al, 2014).

In the first durability study, patients, who partially responded to acute TMS (i.e., 25% decrease from the baseline HAMD17) in the sham-controlled or open-label extension of the Neuronetics sponsored multicenter trial (O'Reardon et al 2007) were tapered off TMS and started on maintenance antidepressant monotherapy, and enrolled in a 24-week naturalistic follow-up study (Janicak et al., 2010). Over this 6-month period, 10 of 99 (10%; Kaplan-Meier survival estimate = 12.9%) patients relapsed with a mean time to relapse of ~23.5 weeks. Among the rest, 38 (38.4%) patients met criteria for symptom worsening and 32/38 (84.2%) re-achieved symptomatic benefits with adjunctive TMS. Overall, 75% maintained full response and 50% maintained remission based on either the MADRS or HAMD24 scores. This same cohort of 99 responders displayed significant improvement in both functional status and Quality of Life (QOL) outcomes and was observed immediately after the completion of TMS and at 6-months follow up (Solvason et al, 2014). Similar rates of durability were seen in a separate 3-month follow up study in remitters to an acute double-blind sham controlled trial of TMS (n = 18), or an open-label extension in patients who did not respond to the acute trial (n = 43) (Mantovani et al., 2012). Of 61 remitters, 37 attended the follow up assessments at 3-months at which 5 had relapsed (relapse rate=13.5%) based on HAMD criteria over an average time of 7.2 weeks but 4 regained remission by the end of the study. Finally, in a 1-year, multisite, naturalistic, observational study conducted in 120 patients, who met criteria for response or remission after their acute TMS course, 62% continued to show at least response criteria 12-months later (Dunner et al., 2014). The results of these studies demonstrate a high (ie., 64-90%) durability for acute TMS benefits over a 3-12 month period with a majority of patients who relapsed responding to additional TMS sessions.

Maintenance Studies

The only published controlled trial of Maintenance TMS was performed in the Brainsway's multicenter trial. MDD patients (N=212) were randomized to sham or active TMS during the acute 4-week treatment phase followed by a maintenance phase of 2 treatments a week for an additional 12 weeks (Levkovitz et al., 2015). At the end of the maintenance phase (week 16) the response rates between

Deep TMS (44.3%) and the sham group (25.6%) were significant (p=0.0086) but the remission rates between TMS (31.8%) and sham (22.2%) were not significant (p=0.1492). The majority of patients who achieved remission after acute treatment (32.6% in the Deep TMS and 14.6% in the sham group) did not relapse (i.e. HAMD21 > 17) during the 12-week maintenance phase.

The mean time in response in the Deep TMS group was 4.9 weeks versus 2.8 weeks in the sham group (p=0.0011) and mean time in remission in the Deep TMS group was 3.7 weeks versus 2.1 weeks in the sham group (p=0.0031). The mean percentage of time in response in the TMS group was 36±4% (mean±SE) versus 22±3% in the sham group (p=0.0018). The mean percentage of time in remission in the TMS group was 26±3% versus 16±3% in the sham group (p=0.005).

In a feasibility study (Harel et al., 2014), 29 MDD patients who did not respond to at least one antidepressant medication, or did not tolerate at least two medication trials, were treated with Brainsway's H1 coil as an add on to medications and treated in an acute phase 5 sessions per week for 4-weeks followed by a Maintenance TMS Phase for 8 weeks, at 2 sessions per week and for additional 10-weeks, at one session per week. Response and remission rates at the end of the 4-weeks acute phase were 46% and 27%, respectively. Response and remission rates after the additional 18 weeks of maintenance TMS (at week 22) were both 31%. Mean improvement in HAMD21 was 9.48 points after 4 weeks and 10.12 points after 22 weeks. The study results indicate that antidepressant effect is preserved by maintenance Deep TMS treatment over 18 weeks.

Recommendation: In the committee's experience, many patients who respond or remit with acute TMS experience a satisfactory persistence of their acute benefit from maintenance treatment of TMS after transitioning to antidepressant maintenance medication. In the event of a failure with this medication maintenance approach, or in the setting of strong patient preference for the use of TMS as a maintenance strategy (alone or as an augmentation to medications), a continuation treatment approach may be appropriate. The maintenance phase involves entering a flexible period of time (usually measured in months), during which daily TMS sessions are gradually reduced until the patient is receiving a schedule of 1 to 2 single TMS sessions per month. It is the opinion of the majority of panel members that empiric evidence and anecdotal experience weigh towards benefit of maintenance treatments, when clinically indicated.

Naturalistic Outcomes Study in Community Practices

Neuronetics sponsored a naturalistic, multisite clinical outcomes study (Clinicaltrials.gov listing: NCT001114477; Carpenter, et al.,

2012; Janicak, et al., 2013) evaluating the effectiveness the Neurostar TMS Therapy System in routine clinical practice. In these studies 307 MDD patients undergoing open label TMS showed statistically significant improvement in functional status on a broad range of global, mental health and physical health domains.

Meta-Analyses

There are several meta-analyses and systematic reviews of TMS for depression. Among these, five included the results of one or both of the acute TMS therapy randomized controlled trials using the Neuronetics' research device version in their synthesis of the evidence (Agency for Healthcare Research and Quality, 2012; Allan, et al., 2011; Schutter, 2011; Slotema, et al., 2010; Berlim, et al., 2013; see Table 1; Gaynes, 2014).
These analyses are consistent in their conclusions, reporting that the sham-controlled evidence base for the use of TMS in depression is clinically and statistically significant.

Endorsements

TMS has also received positive endorsements by specialty societies and technology assessment entities, including the American Psychiatric Association (2010), the World Federation of Societies for Biological Psychiatry (2009), the Canadian Network for Mood and Anxiety Disorders (2009), the Royal Australia and New Zealand College of Psychiatrists (Position Statement #79, Oct 2013), and the Agency for Healthcare Research and Quality (2012).

Table 1. Summary of Published Studies for the TMS Antidepressant Studies: Study Type and Grading of Strength of Evidence

Study Citation (chronological listing)	Study Type	Sample Size	Level of Evidence	Comments

O'Reardon, JP, Solvason, HB, Janicak, PG, Sampson, S, Isenberg, KE, Nahas, Z, McDonald, WM, Avery, D, Fitzgerald, PB, Loo, C, Demitrack, MA, George, MS, Sackeim, HA. (2007) Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multi-Site Randomized Controlled Trial. Biol Psychiatry, 62:1208-1216.	RCT	TMS (N=155) Sham (N=146)	Level 1b – Individual RCT	Unique multisite RCT, sponsored by industry (Neuronetics Inc) Basis of initial FDA clearance for TMS device
George, MS, Lisanby, SH, Avery, D, McDonald, WM, Durkalski, V, Pavlicova, M, Anderson, B, Nahas, Z, Bulow, P, Zarkowski, P, Holtzheimer, P, Schwartz, T, Sackeim, HA. (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. Archives of General Psychiatry; 67(5):507-516.	RCT	TMS (N=92) Sham (N=98)	Level 1b – Individual RCT	Unique multisite RCT, sponsored by US federal NIMH Independent of industry
Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, Tendler A, Daskalakis ZJ, Winston JL, Dannon P, Hafez HM, Reti IM, Morales OG, Schlaepfer TE, Hollander E, Berman JA, Husain MM, Sofer U, Stein A, Adler S, Deutsch L, Deutsch F, Roth Y, George MS, Zangen A. Safety and Efficacy of Deep Transcranial Magnetic Stimulation for Major Depression: A Prospective, Multicenter, Randomized, Controlled Trial. Submitted.	RCT	TMS (N=101) Sham (N=111)	Level 1b- Individual RCT	Unique multisite RCT, sponsored by industry (Brainsway) Basis of FDA clearance for Deep TMS device
Avery, DH, Isenberg, KE, Sampson, SM, Janicak, PG, Lisanby, SH, Maixner, DF, Loo, C, Thase, ME, Demitrack, MA, George, MS. (2008) Transcranial Magnetic Stimulation (TMS) in the Acute Treatment of Major Depression: Clinical Response in an Open-Label Extension Trial. J Clin Psychiatry, 69(3):441-451.	OL	TMS (N=158)	Level 2b – Individual OL Study	Open label follow-on acute efficacy and safety study of subset cohort from O'Reardon, et al (2007)
Demitrack, MA, Thase, ME. (2009) Clinical Significance of Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Depression: A Review and Synthesis of Recent Data. Psychopharmacol Bulletin, 42(2):5-38.	RCT	TMS (N=88) Sham (N=76)	Level 1b – Individual RCT	RCT subset analysis of ATHF=1 cohort from O'Reardon, et al. (2007)

Lisanby, SH, Husain, MM, Rosenquist, P, Maixner, D, Gutierrez, R, Krystal, A, Gilmer, W, Marangell, L, Aaronson, S, Daskalakis, ZJ, Canterbury, R, Richelson, E, Sackeim, HA, George, MS. (2009) Transcranial Magnetic Stimulation (TMS) in the Acute Treatment of Major Depression: Clinical Predictors of Outcome in a Multisite, Randomized Controlled Clinical Trial. Neuropsychopharmacology, 34:522-534.	RCT	TMS (N=155) Sham (N=146)	Level 1b – Individual RCT	RCT subset analysis of predictors of outcome during acute treatment from O'Reardon, et al. (2007)
Janicak, PG, O'Reardon, JP, Sampson, SM, Husain, MM, Lisanby, SH, Rado, JT, Demitrack, MA. (2008) Transcranial Magnetic Stimulation (TMS) in the Treatment of Major Depression: A Comprehensive Summary of Safety Experience from Acute and Extended Exposure and During Reintroduction Treatment. J Clin Psychiatry, 69(2):222-232.	RCT	TMS (N=165) Sham (N=160)	Level 1b – Individual RCT (Safety)	Comprehensive safety and tolerability analysis of population included in O'Reardon, et al. (2007) Includes 6 month longer term follow up phase
Carpenter, LL, Janicak, PG, Aaronson, ST, Boyadjis, T, Brock, DG, Cook, IA, Dunner, DL, Lanocha, K, Solvason, HB, Demitrack, MA. (2012) Transcranial Magnetic Stimulation (TMS) for Major Depression: A Multisite, Naturalistic, Observational Study of Acute Treatment Outcomes in Clinical Practice. Depress Anxiety, 29(7): 587-596.	Cohort	TMS (N=307)	Level 2b – Individual Cohort Study	Unique, cohort study of patients treated in routine, real-world clinical practice settings in the United States
Janicak, PG, Dunner, DL, Aaronson, ST, Carpenter, LL, Boyadjis, TA, Brock, DG, Cook, IA, Lanocha, K, Solvason, HB, Bonneh-Barkay, D, Demitrack, MA. (2013) Transcranial Magnetic Stimulation (TMS) for Major Depression: A Multisite, Naturalistic, Observational Study of Quality of Life Outcome Measures in Clinical Practice, CNS Spectrums, August:1-11.	Cohort	TMS (N=307)	Level 2b – Individual Cohort Study	Cohort study of patients treated in routine, real-world clinical practice settings in the United States Quality of life outcomes based on Carpenter, et al. (2012)

McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, Avery D, Anderson BS, Nahas Z, Zarkowski P, Sackeim HA, George MS (2011), Improving the Antidepressant Efficacy of Transcranial Magnetic Stimulation: Maximizing the Number of Stimulations and Treatment Location in Treatment-Resistant Depression. Depress Anxiety. Nov; 28(11):973-80.	OL	TMS (N=141)	Level 2b – Individual OL Study	Open label follow-on acute efficacy and safety study of subset cohort from George, et al. (2010)
Janicak, PG, Nahas, Z, Lisanby, SH, Slovason, HB, Sampson, SM, McDonald, WM, Marangell, LB, Rosenquist, PB, McCall, WV, Kimball, J, O'Reardon, J, Loo, C, Husain, MH, Krystal, A, Gilmer, W, Dowd, SM, Demitrack, MA, Schatzberg, AF (2010) Long-Term Durability of Acute Response to Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Major Depression. Brain Stimulation, 3: 187-199.	OL	TMS (N=99) Sham (N=21)	Level 2b – Individual OL Study	Open label follow-on long term efficacy study of subset cohort from O'Reardon, et al. (2007)
Mantovani, A, Pavlicova, M, Avery, D, Nahas, Z, McDonald, WM, Wajdik, CD, Holtzheimer, PE, George, MS, Sackeim, HA, Lisanby, SH. Long-Term Efficacy of Repeated Daily Prefrontal Transcranial Magnetic Stimulation (TMS) in Treatment-Resistant Depression. (2012) Depression and Anxiety, 00:1-8.	OL	TMS (N=50)	Level 2b – Individual OL Study	Open label follow-on long term efficacy study of subset cohort from George, et al. (2010)
Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, Sheer A, Gersner R, Zangen A. Deep transcranial magnetic stimulation of the prefrontal cortex – Effectiveness in major depression. (2009) Brain Stimulation, 2: 188-200.	RCT	TMS (N=65)	Level 2b – Randomized feasibility Study	Feasibility efficacy study randomized groups between various deep TMS coils and in intensities
Isserles M, Rosenberg O, Dannon P, Levkovitz Y, Kotler M, Deutsch F, Lerer B, Zangen A. Cognitive emotional reactivation during deep transcranial magnetic stimulation over the prefrontal cortex of depressive patients affects antidepressant outcomes. (2011) J Affective Disorders, 128: 235-242.	OL	TMS (N=57)	Level 2b – Individual OL Study	Open label efficacy study of deep TMS as add on to antidepressant medications

Harel EV, Rabany L, Deutch L, Bloch Y, Zangen A, Levkovitz Y. H-coil repetitive transcranial magnetic stimulation for treatment resistant major depressive disorder: An 18-week continuation safety and feasibility study. (2014) World J Biol Psychiatry, 15:298-306.	OL	TMS (N=29)	Level 2b – Individual OL Study	Open label long term efficacy study of deep TMS
Rosenquist, PB, Krystal, A, Heart, KL, Demitrack, MA, McCall, WV. (2013) Left Dorsolateral Prefrontal Transcranial Magnetic Stimulation (TMS): Sleep Factor Changes During Treatment in Patients with Pharmacoresistant Major Depressive Disorder. Psychiatry Research 205(1-2):67-73.	RCT	TMS (N=155) Sham (N=146)	Level 1b – Individual RCT	RCT subset analysis of sleep outcomes from O'Reardon, et al. (2007)
Simpson, KN, Welch, MJ, Kozel, FA, Demitrack, MA, Nahas, Z. (2009) Cost-Effectiveness of Transcranial Magnetic Stimulation in the Treatment of Major Depression: A Health Economic Analysis. *Adv Ther 26(3):* 346-368.	RCT	TMS (N=155) Sham (N=146)	Level 2b – Economic/ Decision Analysis Study	Health economic decision analysis study based on data from O'Reardon, et al. (2007) Comparative health economic cost analysis with next-choice pharmacotherapy

Agency for Healthcare Research and Quality, Effective Health Care Program, Comparative Effectiveness Review Number 33, "Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults", (2012)	SR	Total Active TMS Sample examined for SR (N=497) Includes TMS study data: (N=247)	Level 1a – Systematic Review	Independent, US government funded systematic review
Allan, C. (2011). "Transcranial Magnetic Stimulation in the Management of Mood Disorders." Neuropsychobiology 64: 163-169.	SR	Total Sample for SR (N=1531)	Level 1a – Systematic Review (with minor heterogeneity)	Independent, academic-based systematic review Modest, clinically non-significant heterogeneity in outcome reported
Schutter, DJLG. (2009) Antidepressant Efficacy of High-Frequency Transcranial Magnetic Stimulation Over the Left Dorsolateral Prefrontal Cortex in Double-Blind Sham-Controlled Designs: A Meta-Analysis. Psychol Medicine, 39:65-75.	SR	Total Sample for SR (N=1164)	Level 1a – Systematic Review	Independent, academic-based systematic review

Slotema, CW, Blom, JD, Hoek, HW, Sommer, IEC. (2010) Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? A Meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry, 71(7):873-84.	SR	Total Sample for SR (N=1383)	Level 1a – Systematic Review	Independent, academic-based systematic review
Berlim, MT, van den Eynde, F, Tovar-Perdomo, S, Daskalakis, ZJ. (2014) Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: A systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 44(2):225-239.	SR	Total Sample for SR (N=1371)	Level 1a – Systematic Review	Independent, academic-based systematic review
Solvason, H.B., Husain, M., Fitzgerald, P.B., Rosenquist, P., McCall, W.V., Kimball, J., Gilmer, W., Demitrack, M.A., Lisanby, S.H. Functional Status and Quality of Life Improvement with Left Prefrontal Transcranial Magnetic Stimulation in Patients with Pharmacoresistant Major Depression: A Comprehensive Summary of Acute Outcomes and Durability in Long-Term Follow Up, Brain Stimulation, 7:219-225, 2014.	SR		Level 1b - Systematic Review	Independent, academic-based systematic review
Dunner, D.L., Aaronson, S.T., Sackeim, H.A., Janicak, P.G., Carpenter, L.L., Boyadjis, T., Brock, D.G., Bonneh-Barkay, D., Cook, I.A., Lanocha, K., Solvason, H.B., Demitrack, M.A. A Multisite, Naturalistic, Observational Study of Transcranial Magnetic Stimulation (TMS) for Patients with Pharmacoresistant Major Depression: Durability of Benefit Over a One-Year Follow-Up Period, Journal of Clinical Psychiatry, 75(12):1394-1401, 2014.	Cohort		Level 2b - Individual Cohort Study	Cohort study of patients treated in routine, real-world clinical practice settings in the United States

NOTES: Study Type (RCT=randomized, controlled trial; OL=open-label trial; Cohort=observational cohort study; SR=systematic review); studies highlighted in bold font represent unique study populations, all other publications are derivative analyses of one of these three studies (see comments for explanation).

At the present time, TMS is a recognized treatment in routine clinical practice for patients who have not benefited from treatment with antidepressant medications. The American Medical Association has established three CPT Category I codes for the therapeutic use of TMS devices. These three codes have been in existence since the 01 January 2012 CPT Code Book (AMA CPT Editorial Panel, 2012). The codes are summarized in Table 2 below and the reader is referred to the AMA Code Book for further information.

Table 2. CPT I Codes for Therapeutic Transcranial Magnetic Stimulation

Code	Description
90867	Therapeutic Repetitive Transcranial Magnetic stimulation (TMS) treatment; initial, including cortical mapping, motor threshold determination, delivery and management (Report only once per course of treatment) (Do not report 90867 in conjunction with 95928, 95929, 90868, 90869)

90868	Subsequent delivery and management, per session
90869	Subsequent motor threshold re-determination with delivery and management

Summary

TMS therapy is an effective treatment for patients with MDD (single or recurrent course of illness) who have not benefitted from prior antidepressant medication.

The efficacy and safety of TMS using a specific, defined treatment protocol of high-frequency, left prefrontal TMS was confirmed in two large, multisite, randomized controlled trials, (O'Reardon, et al., 2007; Janicak et al, 2008; George, et al., 2010) one of which was conducted independent of industry involvement (George, et al., 2010). In addition, one large, multisite trial found that Deep TMS was also effective and safe (Levkovitz et al., 2015). All three studies are consistent in their conclusions. These data are also supported by the results of a large, multisite, observational study of TMS as applied in routine clinical practice settings (Carpenter, et al., 2012; Janicak et al, 2013; Dunner et al., 2014). Finally, several professional organizations have included TMS in their guidelines as a recommended treatment.

Part 2. Practice Essentials

The following section highlights some of the essential components of good clinical practice with TMS. The information summarized here is intended to highlight some of the major areas of interest and is not intended as a substitute for more comprehensive training on the use of the Neurostar TMS Therapy system or the Brainsway Deep TMS system. The Clinical TMS Society (cTMSs) welcomes inquiries for further resources on these topics and for recommendations on sources of further learning.

Training

Peer-to-peer training and graduate medical education have a role in physician and staff training. In addition to industry sponsored training, it is suggested that the TMS providers complete additional training either through a CME program or through additional peer-to-peer direct supervision. Providers with a strong foundation in TMS through their training or extensive TMS experience may be exempt from the above recommendation. It is also recommended that the attending physician and all staff who are members of the TMS treatment team receive appropriate product training on the use of the new technology. It is recommended that at a minimum, the TMS team receive the detailed product training offered by the device manufacturer, and obtain written documentation of training.

It is also advised that a TMS clinic establish formal standard operating procedures (SOPs) related to training and ongoing criteria to maintain procedural skills for all staff who are involved in the delivery of TMS in the office setting. Documentation of implementation and adherence to these procedures should be a routine part of office practice. The Clinical TMS Society can offer recommendations and support of specific examples of these practices among its members.

Roles and Responsibilities

The attending physician who prescribes a treatment course is ultimately responsible for the overall daily management of the TMS treatment team. The cTMSs recommends that the prescribing physician establish the anticipated clinical treatment plan based on assessment of the patient's clinical history and review this treatment plan with the patient prior to beginning the course of treatment. It is suggested that the prescribing physician should perform the initial motor threshold determination and determine the appropriate coil location for subsequent treatment. However, conduct and oversight of subsequent daily treatment sessions including subsequent motor threshold determinations may be delegated by the attending physician to another, appropriately qualified member of the clinical

staff. However, the physician should be accessible via telephone in the case of an emergency. The physician should review the clinical course of each daily treatment session to determine whether any modifications to the subsequent daily treatment should occur.

For example, the physician should evaluate whether a re-determination of motor threshold is required and respond to any adverse events as they occur. Conduct and oversight of daily treatment sessions may be delegated by the attending physician to another member of the clinical staff, but should be physician supervised. The cTMSs recommends that all TMS clinical staff maintain appropriate training to support their role as first responders to potential medical emergencies.

The society recommends that the TMS operator have CPR or BLS training, and HIPAA competency and compliance. They should undergo manufacturers training prior to independently performing treatments. Due to the fact that TMS is a medically complex treatment, emergency medical services must be accessible at all times to the TMS provider in the event of a medical emergency. The operator should provide updates and/or progress notes every day, which should be monitored by the prescribing physician.

Establishing a Treatment Plan

The standard treatment regimen recommended in the clinical development studies involved a specified parameter set of high frequency, left prefrontal rTMS which showed gradual and continued benefit after five daily treatments for 4-6 weeks in the Brainsway trial and 4-6 weeks in the Neurostar trial. Some patients who respond slowly to TMS may benefit from 1-4 additional weeks of treatment (Mantovani et al., 2012; McDonald et al., 2011). The Brainsway study demonstrated that an additional 12 weeks of twice weekly maintenance increased response rates by 8%. Therefore, patients should be advised of this likely pattern of outcome prior to initiating treatment in order to set appropriate expectations of the time course of benefit and when and how assessment of efficacy should reasonably be estimated.

Informed Consent

Once a decision has been made to prescribe the use of TMS as a treatment option, it is crucial the patient has a thorough, accurate, and informative presentation of what the process entails. During the treatment sessions the patient will be unable to have free movement of

their head and thus have a limited field of view of the operating aspects of the device. As such, reducing anxiety regarding the nature of the treatment process is essential prior to treatment commencement. A variety of visual aids should be provided with the product documentation, including treatment brochures and videos, which can be used to instruct the patient on the treatment process. In many clinical situations, it is appropriate to invite family members into the consultation room to address any questions they may have. Only when the procedure is well understood and questions have been answered should written informed consent be obtained and documented in the medical record.

Safety Considerations

A significant safety risk associated with TMS is the inadvertent induction of a seizure. Therefore, it is essential that both the supervising physician and the TMS treatment staff are familiar with proper first responder capability for such an event.

The incidence of seizure with TMS is small and appears slightly lower than the incident risk reported for the use of current antidepressant medications (Janicak, et al., 2008). Adherence to recommendations endorsed by International Federation for Clinical Neurophysiology can help minimize this risk (Rossi, et al., 2009). In clinical practice, the use of an appropriately worded informed consent procedure (discussed in the preceding section) is recommended, as are adequate methods for pre-treatment clinical screening of potential seizure risk and continuous clinical monitoring of the TMS treatment session itself. All clinical personnel involved in the delivery of TMS care must be trained as "first responders" to provide appropriate initial management for a seizure or other medical event. The overall risk of seizure is estimated to be less than 1 in 30,000 treatment sessions (<0.003%) or less than 1 in 1000 patient exposures (<0.1%) with the Neurostar coil (NeuroStar TMS Therapy User Manual, Neuronetics, Inc., Malvern, PA, USA) and 6 in 5,000 patients with the Brainsway coil (User Manual, Brainsway Israel). **All seizures to date have been self-limited and have occurred only during the treatment session.**

We note that there are no specific labeling requirements that advanced resuscitative equipment be present in the TMS treatment room. It is the consensus of the cTMSs that IV access, cardiac defibrillators, suction, and oxygen are NOT necessary for the safe administration of TMS in an outpatient TMS office.

During a TMS session, the magnetic pulse produces an audible clicking sound. Therefore, an additional standard safety precaution for all TMS treatments is the use of ear plugs or other hearing protection capable of at least 30 dB sound reduction. Such a precaution eliminates the risk of changes in auditory threshold with treatment for either the patient or the treatment provider.

Outcome Evaluation

We recommend that objective documentation of clinical benefit be obtained as a routine practice in a TMS service. This is important for ongoing clinical care and may be required by payers for insurance approval. There are several validated patient-reported outcome measures of depression symptoms that are available in the public domain, along with their methods of scoring. A majority of cTMSs members use the Patient Health Questionnaire, 9-Item scale (PHQ-9; 49; http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/), the IDS-SR or the Beck Depression Inventory.

Post-Treatment Planning

Once a determination of maximum benefit is made, the TMS treatments should be tapered and a maintenance regimen developed for the patient. In the TMS System clinical studies, patients were discontinued from treatment slowly over a 3-week interval, during which time a maintenance regimen was established with antidepressant medications. During follow up over 6 months, patients were restricted a single antidepressant medication only, but were permitted to re-access TMS upon symptom re-emergence (Janicak, et al., 2010).

Part 3. Clinical Recommendations

Indicated Patient Population

The labeled indication for use for the TMS therapy states that, ***"TMS therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode."***

In clinical descriptive terms, patients for whom TMS therapy is indicated demonstrated the following demographic and clinical features in the three major published, randomized controlled trials (O'Reardon, et al., 2007; George, et al., 2010; Levkovitz et al., 2015):

Moderate to severe treatment resistance in the current treatment episode -

- Patients had received 1 to 4 adequate antidepressant medication attempts and a range of 1 to 23 total antidepressant attempts:
    - Among all of these treatment attempts, a patient had been administered at least one antidepressant medication at a research-grade level of exposure adequacy (i.e., adequate dose and duration) in order to formally establish evidence of resistance to pharmacological interventions in the current illness episode.
    - The majority of cTMSs members reported that a "sufficient trial" means one with adequate dose and duration of at least six to eight weeks and antidepressant failure constituting a lack of response to an adequate trial or intolerance of antidepressants provided over a shorter duration.
- The OPT-TMS trial and the Brainsway Deep TMS trial also allowed patients who were treatment intolerant (ie., had tried antidepressant medications but were unable to receive a full dose due to emergent side effects).
    - Total lifetime number of antidepressant medication treatment exposures were not limited in these clinical studies

A recurrent course of illness: over 95% of patients had experienced prior illness episodes

- The average patient age was approximately 49 years, constituting an ***average age about a decade older than typical for a first-episode depression population***

Moderate to severe illness severity (symptoms and functional disability) at initial clinical evaluation where work productivity reflected significant functional morbidity

- Nearly 50% of patients were currently unemployed due to their illness
- About 30% of patients were receiving disability due to their current illness.

Based on the published evidence summarized in this clinical guideline, the cTMSs affirms the following recommendations for the routine use of TMS in clinical practice. Each recommendation is graded in a manner that follows the format of the Grades of Recommendation framework published by the University of Oxford Centre for Evidence Based Medicine.

Recommendation 1: "TMS therapy is recommended as an acute treatment for symptomatic relief of depression in the indicated patient population"

Statement of specific recommendation for use: TMS therapy should be considered in patients who present with a clinical diagnosis consistent with DSM-5 defined Major Depressive Disorder, single or recurrent episode, or equivalent nosology and for whom antidepressant medication has not provided a satisfactory clinical benefit, or for whom intolerance to medications precludes their use. Standard TMS therapy should be administered in a standard protocol of high-frequency, left prefrontal treatment as specified in the product labeling, though other treatment parameters can be used based on the clinical considerations for the patient and the judgment of the provider. The standard parameter set described in each product labeling was studied in three, Level 1 randomized controlled trials and provided clinical benefit in treatment courses up to 6 weeks in duration. Controlled studies of longer duration, acute treatment courses or using alternative treatment parameters are not established.

Strength of the recommendation: **A, consistent evidence from Level 1 studies**

Principal Supporting Evidence: O'Reardon, et al., 2007 [Level 1b – Individual RCT]; George, et al., 2010 [Level 1b – Individual RCT]; Levkovitz et al, 2015) [Level 1b - Individual RCT]

Additional Expert Consensus Comments: The cTMSs guideline committee considers the following comments to be appropriate considerations as additional guidance in the application of this recommendation. This is based on the consensus review of the committee members and input from members of the Society with applied TMS clinical experience:

- Extended treatment course: While the peer-reviewed studies demonstrate that the majority of patients who receive acute benefit from TMS therapy do so within 4 to 6 weeks, it is reasonable to continue treatment beyond 6 weeks in specific circumstances. For example:
    - In patients who have shown partial improvement and the clinician believes that a clear plateau of benefit has not yet been obtained it might be appropriate to extend the course of treatment for one or two weeks.
    - For patients who have had no meaningful benefit after 6 weeks, but who have a history of late response to antidepressant treatment in prior episodes, have a lengthy duration of the present episode, or are highly treatment resistant, clinical experience suggests that continuing course of treatment beyond 6 weeks may be indicated.
- These considerations are further justified by the absence of any known cumulative toxicity with extended exposure to TMS (eg., Janicak et al., 2008) and because of open-label data supporting the potential for late response in some patients (e.g., Avery, et al., 2008). (See also the Mantovani and McDonald follow up papers to the acute OPT-TMS trial). In clinical TMS practice, there is documented evidence of eventual remission at 10 weeks in patients who failed to show any clinical response at the end of 6 weeks.

Recommendation 2: "TMS therapy is recommended for use as a subsequent treatment option for patients who previously benefited from an acute treatment course and are experiencing a recurrence of their illness"

Statement of specific recommendation for use: TMS therapy should be considered in patients who present with a clinical diagnosis consistent with DSM-5 defined Major Depressive Disorder, single or recurrent episode, or equivalent nosology and for whom a prior course of TMS therapy has provided satisfactory clinical benefit in an earlier episode of their illness. Evidence of satisfactory clinical benefit should have been verified through the use of standardized, validated clinical depression rating scales. Examples of such scales include the Patient Health Questionnaire, 9-Item Scale, or the Quick Inventory of Depressive Symptoms, Self Report version. The

strongest evidence supports high-frequency treatment over the left DLPFC, but other treatment parameters could be considered based on the weight of evidence, the clinical considerations for the patient, and the judgment of the provider. The standard parameter set described in product labeling has been studied in three Level 1 randomized controlled trials and has been demonstrated to provide clinical benefit in treatment courses up to six weeks in duration. Controlled studies of longer duration or using alternative treatment parameters have not been solidly established.

Strength of the recommendation: **A, consistent evidence from Level 1 studies**

Principal Supporting Evidence: O'Reardon, et al., 2007 [Level 1b – Individual RCT]; George, et al., 2010 [Level 1b – Individual RCT]; Levkovitz, et al, 2015 [Level 1b - Individual RCT]

Additional Expert Consensus Comments: The TMS Clinical Society Guideline committee considers the following comments to be clinically appropriate considerations as additional guidance in the application of this recommendation, based on the consensus review of the Guideline committee members and input from members of the Society with applied clinical experience with the use of the TMS therapy: (We now have data on re-response in the Neuronetics Maintenance study I mentioned above)

- Extended treatment course: Peer-reviewed studies have demonstrated that the majority of patients who receive benefit from TMS therapy do so within 4 to 6 weeks of acute treatment. In the committee's opinion, clinical experience and anecdotal evidence suggest treatment beyond 6 weeks may be helpful in specific circumstances.
  For example, in patients who have shown partial improvement and the clinician believes that a clear plateau of benefit has not yet been obtained. Additionally, for patients who have had no meaningful benefit from 6 weeks, and who have a history of late response to antidepressant treatment in prior episodes, a continued course of treatment beyond 6 weeks may be indicated.
  These considerations are further justified by the absence of any known cumulative toxicity with extended exposure to TMS, and because of circumstantial open-label data supporting the likelihood of late response in some patients (e.g., see Avery, et al., 2008).

Recommendation 3: "TMS therapy can be administered with or without the concomitant administration of antidepressant or other psychotropic medications"

Statement of specific recommendation for use: TMS therapy should be considered in patients who present with a clinical diagnosis consistent with DSM-V defined Major Depressive Disorder, single or recurrent episode, or equivalent nosology and for whom antidepressant medication treatment has provided an unsatisfactory clinical benefit. TMS therapy should be administered in a standard protocol of high-frequency, left prefrontal treatment.

TMS therapy can be administered in the presence or absence of concurrent antidepressant medications or other psychotropic medications. There is currently no data from controlled trials supporting the use of medications with TMS, but there is currently no evidence of an increased rate of adverse events by combining medications with TMS. Any change in medications during the course of TMS therapy should prompt consideration for reassessment of the patient's motor threshold to ensure that there have been no significant changes in this parameter.

Strength of the recommendation: **B, Extrapolation from Level 2 studies**

Principal Supporting Evidence: Carpenter et al., 2009 [Level 2b - Individual Cohort Study]

Recommendation 4: "TMS therapy can be used as a continuation treatment for patients who benefit from an acute course."

Statement of specific recommendation for use: TMS therapy can be considered for intermittent use on an empirical basis as a continuation treatment for patients who responded to a prior standard acute course of treatment administered consistent with Recommendations 2 or 3. At the present time, the only controlled trial with TMS therapy that establishes a specific maintenance regimen is the Brainsway multi-center trial which included 12 weeks of biweekly Deep TMS treatment. A majority of cTMSs members use maintenance medications and consider TMS therapy when other established methods of maintenance antidepressant medication fail to provide a satisfactory sustained pattern of clinical benefit or a patient has a history of frequent relapse (two or more in one year).

Further considerations in support of maintenance TMS therapy are based on current expert consensus opinion are discussed below.

Strength of the recommendation: **A, consistent evidence from Level 1 studies**

Supporting Evidence: Levkovitz et al, 2015 [Level 1b – Individual RCT]

Additional Expert Consensus Comments

The cTMSs clinical guideline committee considers the following comments clinically appropriate considerations as additional guidance in the application of this recommendation. This is based on the consensus review of the guideline committee members and input from members of the Society with applied clinical experience with the use of clinical TMS experience.

Maintenance TMS

In terms of avoiding relapse, the majority of cTMSs members use maintenance medications. Some members consider TMS maintenance when a patient has a history of frequent relapse (four or more in one year). cTMSs members reported that they typically administer maintenance treatments, one session at a time either monthly, biweekly, or weekly, or they titrate the frequency to patient's response.

Reintroducing TMS 'Boosters' after Relapse

Should relapse occur in patients who benefitted from an acute TMS course, over 90% of cTMSs members reintroduce TMS in a pending relapse when symptoms worsen beyond mild severity. Less than 10% waited to introduce TMS until full relapse occurs. Most cTMSs members administer boosters using 3-5 treatments in clusters until response or remission is reestablished. However, there were a slightly lower number of members who administer boosters in clusters of treatments until response or remission occurs and do not have a specific number of treatments within the clusters. When administering a booster treatment, the majority of cTMSs members stated that they recheck the motor threshold and location.

Partial and Non-Responders:

In non-responders, who have completed four to six weeks of treatment, most cTMSs members terminate treatment after extending treatment by one to two additional weeks of daily TMS treatment. A smaller percentage report that ceasing treatment immediately. In partial responders, who complete the acute phase of six weeks, most cTMSs members either extend the course but maintain the same protocol or extend the course after altering the protocol (i.e. changing dose and/or location or extending the number of days between treatments). Most cTMSs members do not extend the acute course beyond six weeks unless there are partial responders who have not yet remitted.

Remission and Tapering:

Most cTMSs members (over 90%) surveyed, reported that they first observe remission between four and six weeks of treatment. When terminating treatment after remission, the majority of cTMSs members (over 78%) then taper treatments over three weeks (i.e., three treatments during the first week of taper, two treatments in the second week of taper, and one treatment the third week of taper (3-2-1 method)).

Acknowledgements

Dr. Tarique Perera, Dr. Mark George, Dr. Geoffrey Grammer, Dr. Philip Janicak and Dr. Alvaro Pascual-Leone have drafted a preliminary White Paper using published (and submitted) data and product labeling information gathered from the two manufacturers with FDA approval in the USA (Neuronetics, Inc. and Brainsway Corp). Additional contributors to this document were, Dr. Aron Tendler, Dr. Richard Pitch, Dr. Kevin Kinback, Dr. James Barbee, Dr. Ian Cook, Dr. Mahmoud Okasha and others. Over 100 edits of the original draft were submitted by board members and incorporated into this document. Dr. Theodore Wirecki coordinated the incorporation of the board and manufacturer edits into the final document.

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