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The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder

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ABSTRACT

Background: Prefrontal Transcranial Magnetic Stimulation (TMS) therapy repeated daily over 4–6 weeks (20–30 sessions) is US Food and Drug Administration (FDA) approved for treating Major Depressive Disorder in adults who have not responded to prior antidepressant medications. In 2011, leading TMS clinical providers and researchers created the Clinical TMS Society (cTMSs) (www.clinicaltmssociety.org, Greenwich, CT, USA), incorporated in 2013.

Methods: This consensus review was written by cTMSs leaders, informed by membership polls, and approved by the governing board. It summarizes current evidence for the safety and efficacy of the use of TMS therapy for treating depression in routine clinical practice. Authors systematically reviewed the published TMS antidepressant therapy clinical trials. Studies were then 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 authors then summarize essentials for using TMS therapy in routine clinical practice settings derived from discussions and polls of cTMSs members. Finally, each summary clinical recommendation is presented with the substantiating peer-reviewed, published evidence supporting that recommendation. When the current published clinical trial evidence was insufficient or incomplete, expert opinion was included when sufficient consensus was available from experienced clinician users among the membership of the cTMSs, who were polled at the Annual Meetings in 2014 and 2015.

Conclusions: Daily left prefrontal TMS has substantial evidence of efficacy and safety for treating the acute phase of depression in patients who are treatment resistant or intolerant. Following the clinical recommendations in this document should result in continued safe and effective use of this exciting new treatment modality.

Introduction

TMS therapy uses a computerized, electromechanical medical device to produce and deliver 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) [1]. Most clinical TMS treatments delivered for treating depression are typically given at 10 Hz to 18 Hz [2,3]. 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 (MRI) device [4,5]. The MRI field is large (filling much of the room) and is constantly on. TMS magnetic fields are focal and brief [5]. In 2008, the United States Food and Drug Administration (FDA) cleared the first TMS device for

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therapeutic clinical use in Major Depressive Disorder (MDD). This device was a focal iron core coil produced by Neuronetics Inc. (Malvern, PA, USA). In 2013, the FDA cleared a second device (i.e. the H-Coil) produced by Brainsway (Jerusalem, Israel). In 2015, two additional devices were FDA cleared, the Magstim Company's (Wales, UK) figure eight coil and Tonica's (Magventure) figure eight coil. Product manufacturer manuals provide technical details about each coil and system, which are beyond the scope of this review.

Methods: 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, Magstim, Magventure transcranial magnetic stimulation, Deep TMS, major depressive disorder, depression, clinical trials. The authors reviewed over 100 peer-reviewed publications dealing with TMS therapy in depression and referenced (see References). Twenty-three key studies were graded on their strength of evidence (see Table 1). The framework used was the Levels of Evidence criteria published by the University of Oxford Centre for Evidence Based Medicine (http://www.cebm.net/idex.aspx?0=5653) [29]. This methodology uses evidence on five major levels, placing the greatest emphasis on evidence obtained from randomized controlled trials and prior systematic reviews [30]. Level 5, the lowest level, includes anecdotal evidence or non-human animal based evidence. Level 4 includes case series. Level 3 includes systematic reviews or controlled individual cases. Level 2 includes systematic reviews of controlled trials. Level 1, the highest level of evidence, includes large, prospective, positive, randomized controlled trials. 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. This approach is similar to a recent overall TMS guidelines paper published by a European group of experts [31]. Unlike this guidelines document, the European review extensively covers many other potential clinical uses of TMS (e.g. pain, movement disorders), and does not present a consensus of practicing clinicians, and is not exclusively focused on using TMS for treating depression.

User survey and consensus: The Clinical TMS Society conducted a survey on typical clinical TMS practices at its Annual Meeting in Toronto, Canada, on May 28th 2015. The Clinical Standards and Insurance committees created the survey with contributions from Drs. Tarique Perera, Max Okasha, Michelle Cochran, and Kevin Kinback. A total of 68 members representing over 75 TMS practices participated in the survey using PollEverywhere software. Only full members who were practicing clinicians owning or operating outpatient TMS clinics were eligible to vote. Although the Clinical TMS society is international in scope, it is based in North America. At the time of this survey, only 9 members were from outside of North America (13% of the total). The US based practitioners are likely heavily influenced by the FDA approval trials. The results were tabulated by the society administrators and are available as supplementary material.

Results: 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 and 4 antidepressant trials. [A European multisite trial was not included in this summary because it involved adjunctive TMS and medications starting simultaneously, rather than TMS as the primary treatment or monotherapy [32].] Two of the studies were industry-sponsored registration trials that led to FDA clearance for the NeuroStar TMS Therapy System in 2008 [6] and the Brainsway Deep TMS device in 2013 [8]. The third study was a National Institute of Mental Health (NIMH)-sponsored, multicenter study, which provided critical, industry-independent evidence of TMS effects on depression [7]. This NIMH trial also used an active, sham-controlled condition [33] and the primary outcome focused on the clinically important endpoint of remission [34]. All three trials were consistent in their evidence, establishing a statistically significant and clinically relevant benefit with TMS therapy compared to the sham condition. Furthermore, 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) [6]. Patients met DSM-IV criteria for MDD, were antidepressant medication free, and presented with a moderate level of treatment resistance. The study consisted of several phases: a one week no-treatment lead-in; a four to six week randomized, sham-controlled acute treatment phase of daily (weekday) TMS monotherapy; a four to six week open-label trial in non-responders during the randomized phase; and in responders, a three week taper phase during which patients began an open-label, single antidepressant medication and were then followed for six months to examine the durability of TMS's acute effect. Stimulation parameters were 120% motor threshold (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. In the initial 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, $p = 0.06$, standardized effect size = 0.39) compared to those patients randomized to sham TMS. Furthermore, an analysis of the one prior antidepressant failure subsample ($n = 164$) indicated an even more robust benefit for TMS versus the sham procedure ($p < 0.001$).

National Institute of Mental Health (NIMH) trial (optimization of TMS, 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 [7]. This study also used the clinical trial version of the NeuroStar TMS Therapy System (Neuronetics Model 2100 Clinical Research System) and a similar location and the same parameters as in the Neuronetics trial (left DLPFC, 10 Hz, 120% MT, 3000 pulses). The trial at four US universities included 190 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 investigators focused on the primary efficacy endpoint of remission based on the 24-item Hamilton Depression Rating Scale (HAMD24). Moreover, this trial used an active sham method that fully blinded patients, treaters and raters [33,35]. 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. For the entire population, there was a significant effect of active treatment on the proportion of remitters at the end of the acute

Table 1
Summary of published studies for the TMS antidepressant studies: study type and grading of strength of evidence.

Study citation (chronological listing within category)	Study type	Sample size	Level of evidence	Comments
O'Reardon J.P., Solvason H.B., Janicak P.G., Sampson S., Isenberg K.E., Nahas Z., McDonald W.M., Avery D., Fitzgerald P.B., Loo C., Demitrack M.A., George M.S., Sackeim H.A. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007;62:1208–16 [6].	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 M.S., Lisanby S.H., Avery D., McDonald W.M., Durkalski V., Pavlicova M., Anderson B., Nahas Z., Bulow P., Zarkowski P., Holtzheimer P., Schwartz T., Sackeim H.A. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010;67(5):507–16 [7].	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 S.H., Bystritsky A., Xia G., Tendler A., Daskalakis Z.J., Winston J.L., Dannon P., Hafez H.M., Reti I.M., Morales O.G., Schlaepfer T.E., Hollander E., Berman J.A., Husain M.M., Sofer U., Stein A., Adler S., Deutsch L., Deutsch F., Roth Y., George M.S., Zangen A. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 2015;14(1):64–73. [8].	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 D.H., Isenberg K.E., Sampson S.M., Janicak P.G., Lisanby S.H., Maixner D.F., Loo C., Thase M.E., Demitrack M.A., George M.S. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. J Clin Psychiatry 2008;69(3):441–51 [9].	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. [6]
Demitrack M.A., Thase M.E. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. Psychopharmacol Bull 2009;42(2):5–38 [10].	RCT	TMS (N = 88) Sham (N = 76)	Level 1b – individual RCT	RCT subset analysis of ATHF = 1 cohort from O'Reardon et al. [6]
Lisanby S.H., Husain M.M., Rosenquist P.B., Maixner D., Gutierrez R., Krystal A., Gilmer W., Marangell L., Aaronson S., Daskalakis Z.J., Canterbury R., Richelson E., Sackeim H.A., George M.S. Transcranial Magnetic Stimulation (TMS) in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology 2009;34:522–34 [11].	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. [6]
Janicak P.G., O'Reardon J.P., Sampson S.M., Husain M.M., Lisanby S.H., Rado J.T., Demitrack M.A. Transcranial Magnetic Stimulation (TMS) in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. J Clin Psychiatry 2008;69(2):222–32 [12].	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. [6] Includes 6 month longer term follow up phase
Carpenter L.L., Janicak P.G., Aaronson S.T., Boyadjis T., Brock D.G., Cook I.A., Dunner D.L., Lanocha K., Solvason H.B., Demitrack M.A. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29(7):587–96 [13].	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 P.G., Dunner D.L., Aaronson S.T., Carpenter L.L., Boyadjis T.A., Brock D.G., Cook I.A., Lanocha K., Solvason H.B., Bonneh-Barkay D., Demitrack M.A. Transcranial Magnetic Stimulation (TMS) for major depression: a multisite, naturalistic, observational study of quality of life outcome measures in clinical practice. CNS Spectr 2013;18:322–32 [14].	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. [13]
McDonald W.M., Durkalski V., Ball E.R., Holtzheimer P.E., Pavlicova M., Lisanby S.H., Avery D., Anderson B.S., Nahas Z., Zarkowski P., Sackeim H.A., George M.S. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the number of stimulations and treatment location in treatment-resistant depression. Depress Anxiety 2011;28(11):973–80 [15].	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. [7]
Janicak P.G., Nahas Z., Lisanby S.H., Solvason H.B., Sampson S.M., McDonald W.M., Marangell L.B., Rosenquist P.B., McCall W.V., Kimball J., O'Reardon J., Loo C., Husain M.H., Krystal A., Gilmer W., Dowd S.M., Demitrack M.A., Schatzberg A.F. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: assessment of relapse during a 6-month, multisite, open-label study. Brain Stimul 2010;3:187–99 [16].	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. [6]
Mantovani A., Pavlicova M., Avery D., Nahas Z., McDonald W.M., Wajdik C.D., Holtzheimer P.E., George M.S., Sackeim H.A., Lisanby S.H. Long-term efficacy of repeated daily prefrontal transcranial magnetic stimulation (TMS) in treatment-resistant depression. Depress Anxiety 2012;29:883–90 [17].	OL	TMS (N = 50)	Level 2b – individual OL study	Open label follow-on long term efficacy study of subset cohort from George et al. [7]

(*continued on next page*)

Table 1 (*continued*)

Study citation (chronological listing within category)	Study type	Sample size	Level of evidence	Comments
Levkovitz Y., Harel E.V., Roth Y., Braw Y., Most D., Katz L.N., Sheer A., Gersner R., Zangen A. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. Brain Stimul 2009;2:188–200 [18].	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 outcome. J Affect Disord 2011;128:235–42 [19].	OL	TMS (N = 57)	Level 2b – individual OL study	Open label efficacy study of deep TMS as add on to antidepressant medications
Harel E.V., Rabany L., Deutsch 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. World J Biol Psychiatry 2014;15:298–306 [20].	OL	TMS (N = 29)	Level 2b – individual OL study	Open label long term efficacy study of deep TMS
Rosenquist P.B., Krystal A., Heart K.L., Demitrack M.A., McCall W.V. Left dorsolateral prefrontal transcranial magnetic stimulation (TMS): sleep factor changes during treatment in patients with pharmacoresistant major depressive disorder. Psychiatry Res 2013;205(1–2):67–73 [21].	RCT	TMS (N = 155) Sham (N = 146)	Level 1b – individual RCT	RCT subset analysis of sleep outcomes from O'Reardon et al. [6]
Simpson K.N., Welch M.J., Kozel F.A., Demitrack M.A., Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv Ther 2009;26(3):346–68 [22].	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. [6] 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.L., Herrmann L.L., Ebmeier K.P. Transcranial magnetic stimulation in the management of mood disorders. Neuropsychobiology 2011;64:163–9 [23].	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 D.J. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009;39:65–75 [24].	SR	Total sample for SR (N = 1164)	Level 1a – systematic review	Independent, academic-based systematic review
Slotema C.W., Blom J.D., Hoek H.W., Sommer I.E. 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 2010;71(7):873–84 [25].	SR	Total sample for SR (N = 1383)	Level 1a – systematic review	Independent, academic-based systematic review
Berlim M.T., van den Eynde F., Tovar-Perdomo S., Daskalakis Z.J. 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 2014;44(2):225–39 [26].	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. Improvement in quality of life with left prefrontal transcranial magnetic stimulation in patients with pharmacoresistant major depression: acute and six month outcomes. Brain Stimul 2014;7:219–25 [27].	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 for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. J Clin Psychiatry 2014;75(12):1394–401 [28].	Cohort		Level 2b – individual cohort study	Cohort study of patients treated in routine, real-world clinical practice settings in the United States

Study type (RCT = randomized, controlled trial; OL = open-label trial; Cohort = observational cohort study; SR = systematic review).

phase (15% active TMS vs. 4% sham control group, $p < 0.01$), representing a 4.2 greater odds of reaching remission with active TMS compared with the sham control group. The authors 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 enrolling sites (13 in US, 1 in Canada, 2 in 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 [8]. The trial used an active sham method that fully blinded patients, treaters and raters. All patients were tapered off antidepressant medications and received monotherapy Deep TMS or sham a coil. Of the ITT sample of 212 patients, 181 patients completed the study, with equivalent rates of dropouts with active and sham treatment. The acute treatment phase was 5 sessions per week for 4 weeks, followed by a continuation phase of twice-weekly treatment for an additional 12 weeks. The stimulation site was the left DLPFC, but the H-coil also likely stimulates more broadly and deeper than the other figure eight coils [5,36]. 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 endpoint was the change score on the HAMD21 at week 5, which favored the active versus sham procedure (i.e. 6.39 point improvement active versus 3.11 points sham, $p < 0.001$). At week 5, the response rates were 38.4% for Deep TMS versus 21.4% for sham treatment ($p = 0.014$). Remission rates were 32.6% for TMS versus 14.6% for sham treatment ($p < 0.01$). At week 16, the response rates were 44.3% for TMS versus 25.6% for sham treatment ($p < 0.01$). Remission rates were 31.8% for Deep TMS versus 22.2% for sham treatment ($p = 0.15$).

Durability studies

The durability of TMS following the acute course has been demonstrated in several studies both with and without maintenance antidepressants. Durability studies struggle with a selection bias since with patients lost to follow up, it is unclear if they are well and no longer need treatment, or if they have worsened and started other treatments. Specifically, the NeuroStar TMS Therapy System's research version was studied in two independent cohorts: 50 patients for 3 months [17] and 99 patients for 6 months [16]. A separate, 12-month, follow-up report of 257 patients was reported in an observational, outcome study [28].

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 [6] were tapered off TMS, started on maintenance antidepressant monotherapy, and enrolled in a 24-week naturalistic follow-up study [16]. Over this 6-month period, 10 of 99 (10%; Kaplan–Meier survival estimate = 12.9%) patients relapsed within a mean time 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, at 6 months, 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 [27]. Similar rates of durability were seen in a separate 3-month follow up to the NIMH OPT-TMS 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 ($n = 43$) [17]. 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. These remitters had been started back on maintenance antidepressant medication. Additionally, 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 meet response criteria 12 months later [28]. The results of these studies in patients placed back on antidepressant medications demonstrate high (i.e. 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.

Continuation/maintenance studies

When TMS is used for the treatment of an acute episode, it is reasonable to consider continuation TMS (C-TMS) or maintenance (M-TMS) to prevent relapse of the current episode or recurrence of a new episode. The term 'continuation TMS' (C-TMS) and 'maintenance TMS' (M-TMS) are frequently used interchangeably and indiscriminately across the mood disorder treatment continuum. For the purpose of this report, we will use the following definitions: an index/acute course is the initial series of treatments given to relieve acute symptoms of the illness. C-TMS is a course that begins after the index course, lasts up to 6 months and is designed to prevent relapse of the episode (return of the symptoms to full syndromal criteria before the end of the natural duration of the illness). M-TMS is a course that begins after the end of C-TMS and is intended to prevent recurrence of an episode (a new episode). The only published controlled trial to date of continuation TMS was performed in the Brainsway multicenter trial. MDD patients ($N = 212$) were randomized to sham or active TMS during the acute 4-week treatment phase followed by a continuation phase of 2 treatments a week for an additional 12 weeks [8]. At the end of the continuation phase (week 16), the difference in response rates between Deep TMS (44.3%) and the sham group (25.6%) was significant ($p < 0.001$) but the remission rates between TMS (31.8%) and sham (22.2%) were not significant ($p = 0.15$). 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 continuation phase.

In a feasibility study, Harel and colleagues studied 29 MDD patients who did not respond to at least one antidepressant medication or who did not tolerate at least two medication trials. They were treated with the Brainsway H1 coil as an add-on to medications and treated in an acute phase with 5 sessions per week for 4-weeks, followed by a C-TMS phase for 8 weeks, at 2 sessions per week and then for an additional 10-weeks, at one session per week [20]. Response at the end of the 4-week acute phase was 46% and 27% met remission criteria (all remitters are also included as responders). Response and remission rates after the additional 18 weeks of C-TMS (at week 22) were both 31% (i.e. all responders also met remission criteria). 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 continuation of Deep TMS treatment over 18 weeks.

Most recently, Neuronetics sponsored a multi-site study involving 49 antidepressant free treatment resistant depressed patients who responded or remitted to a 6-week acute course of treatment. Subjects were randomized to receive one TMS treatment session per month, regardless of symptoms, or to be monitored. Both groups received rescue TMS if their symptoms worsened. There was a mathematical difference in favor of scheduled TMS in terms of delaying time to relapse, although this was not statistically significant. There was a high rate of re-response to TMS if it was needed again (78%) [37].

Naturalistic outcomes study in community practices

Neuronetics sponsored a naturalistic, multisite, clinical outcomes study (Clinicaltrials.gov listing: NCT001114477) evaluating the effectiveness of the NeuroStar TMS Therapy System in routine clinical practice [13,14]. 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 over 15 meta-analyses and numerous systematic reviews of TMS for depression. Among these, five of the more recent meta-analyses included the results of one or both of the acute TMS therapy, randomized, controlled trials using the Neuronetics' research device in their synthesis of the evidence supporting TMS for depression (Agency for Healthcare Research and Quality, 2012) [23,38–43]; see Table 1). 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.

Society endorsements

TMS for the treatment of depression has also received positive endorsements by specialty societies and technology assessment entities, including the American Psychiatric Association [44], the World Federation of Societies for Biological Psychiatry [45], the Canadian Network for Mood and Anxiety Disorders [46], the Royal Australia and New Zealand College of Psychiatrists (Position Statement #79, Oct. 2013), and the Agency for Healthcare Research and Quality (2012) [47].

Thus, 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 became available in January 2012 CPT Code Book (AMA CPT Editorial Panel, 2012). The codes are summarized in Table 2 and the reader is referred to the AMA Code Book for further information.

Overall conclusions and summary of the literature review

Three large, randomized controlled studies support TMS therapy for 4–6 weeks as an effective treatment for patients with MDD (single or recurrent course of illness) who have not benefitted from prior antidepressant medication (+/– psychotherapy?). 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 [6,7] (one of which was conducted independent of industry involvement) [7] and one large, multisite trial that used Deep TMS [8]. All three studies are consistent in their conclusions. These RCT results are also supported by the results of large, multisite, observational studies of TMS as applied in routine clinical practice settings [13,14,28,48]. Finally, several professional organizations have included TMS in their guidelines as a recommended acute treatment for major depression.

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

Recommended clinical 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 device training provided by industry regarding their specific TMS machines.

Training

Peer-to-peer and graduate medical education have an important role in physician and staff training. In addition to industry-sponsored training that is device specific, we recommend that TMS providers complete additional training either through a university affiliated or industry independent Continuous Medical Education (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.

We also advise 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 cTMSs 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 of TMS, which involves a medical device, is ultimately responsible for the overall daily management of the TMS treatment team [49]. We recommend that the prescribing physician to 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 or another physician in the practice should perform the initial motor threshold determination and identify the appropriate coil location for subsequent treatments. 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. In this circumstance, 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 [50]. 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. We recommend that all TMS clinical staff maintain appropriate training to support their role as first responders to potential medical emergencies.

The society further recommends that the TMS operator have cardiopulmonary (CPR) or basic life support (BLS) training; and in the

US, Health Insurance Portability and Accountability act (HIPAA) competency and compliance. Non-physician operators should also undergo manufacturers' training prior to independently performing treatments. TMS is a medically complex treatment, and therefore emergency medical services must be accessible at all times. The operator should provide updates, progress notes or both every day that should be monitored by the prescribing physician. We strongly encourage the use of repeated ratings with mood scales to document depression changes.

Establishing a treatment plan

The standard treatment regimen recommended in the TMS depression clinical development studies involved a specified parameter set of high frequency, left prefrontal rTMS that showed gradual and continued benefit after five daily treatments over 4–6 weeks. Some patients who respond slowly to TMS may benefit from 1–4 additional weeks of treatment [15,17]. The Brainsway study demonstrated that an additional 12 weeks of twice weekly continuation 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 that the patient has a thorough, accurate, and informative presentation of what a course of TMS will entail. 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 starting. A variety of visual aids should be provided with the product documentation, including 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 [51,52]. 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 [12]. Adherence to recommendations endorsed by International Federation for Clinical Neurophysiology can help minimize this risk [52,53]. 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 must be trained as first responders to provide appropriate initial management of 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 5000 patients with the Brainsway coil (User Manual, Brainsway, Israel) [54]. All seizures to date have been self-limited and 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.

Vasovagal syncope has also occurred with TMS, particularly in initial sessions. Management here is largely reassurance to the patient, and protection from harm if they fall.

During a TMS session, the magnetic pulse produces an audible clicking sound, which varies with different coil designs and intensity [55,56]. Therefore, an additional standard safety precaution for all TMS treatments is the use of earplugs or other hearing protection capable of at least 30 dB sound reduction [57]. Such a precaution eliminates the risk of changes in auditory threshold with treatment for either the patient or the treatment provider. Of note, the Dhamne review concluded that for short exposure of a session, the sound pressure level does not exceed Occupational Safety Hazard permissible thresholds [35].

The TMS treatment can produce scalp discomfort [35,58,59]. This is location and intensity dependent, and patients generally develop tolerance to this over the first two weeks. As a result, in patients that are highly sensitive, many clinicians use a gradually escalating dose of TMS over the first week.

Outcome evaluation

We recommend that objective documentation of clinical benefit be obtained as a routine practice in a TMS service in order to document changes and provide data for making clinical decisions. This is important for ongoing clinical care and may be required by payers for insurance approval. Several validated patient-reported outcome measures of depression symptoms are available in the public domain, along with their methods of scoring. A majority of cTMSs members use either the Patient Health Questionnaire, 9-Item scale (PHQ-9; 49; http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/), the Inventory of Depression Scale – Self Rated (IDS-SR) [60] or the Beck Depression Inventory [61].

Post-treatment planning

Once a determination of maximum benefit is made, the TMS treatments should be tapered and a continuation and then maintenance regimen developed for the patient. In the Neuronetics and OPT-TMS clinical studies, patients were discontinued from treatment slowly over a 3-week interval (3/week, then 2/week, then 1 on the last week), while maintenance antidepressant medications were started. Following the Neuronetics trial, patients were restricted to a single antidepressant medication only, but were permitted to re-access to TMS upon symptom re-emergence [16].

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:

Moderate to severe treatment resistance in the current treatment episode – Patients had received 1–4 adequate antidepressant medication attempts and a range of 1–23 total antidepressant attempts. Among all of these treatment attempts, a patient had

received 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 clinical TMS society members reported that a "sufficient trial" means one with adequate dose and duration of at least 6–8 weeks and antidepressant failure from an adequate trial or intolerance of antidepressants provided over a shorter duration.

The OPT-TMS trial and the Brainsway Deep TMS trial also included patients who were treatment intolerant (i.e. had tried antidepressant medications but were unable to receive a full dose due to emergent side effects). The total lifetime number of antidepressant medication treatment exposures was not limited in these clinical studies.

A recurrent course of illness – More than 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 and about 30% 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. 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 clinical considerations for a specific 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. [6] [Level 1b – Individual RCT]; George et al. [7] [Level 1b – Individual RCT]; Levkovitz et al. [8] [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 4–6 weeks, it is reasonable to continue treatment beyond 6 weeks in specific circumstances. For example:
  - In patients who experience only partial improvement and the clinician believes that a clear plateau of benefit has not 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 the course of acute treatment beyond 6 weeks may be indicated, but with likely low probability of success.
- These considerations are further justified by the absence of any known cumulative toxicity with extended exposure to TMS [12,19,62,63] and because of open-label data supporting the potential for late response in some patients. In clinical TMS practice and in one case series [15], 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 option in patients who previously benefited from an acute treatment course and are experiencing a recurrence of their illness (continuation or maintenance).**

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 with 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. Early studies used measurement based approaches to placing the coil relative to the motor cortex. These were found to miss the target in about 30% of patients. More recent studies use placement strategies that adjust for the patient's skull size [64]. There are intriguing research leads but no strong clinical data to suggest that neuronavigation from MRI improves outcome [65–71]. The standard parameter set described in the product labeling was studied in three Level 1 randomized controlled trials and has demonstrated clinical benefit in treatment courses up to six weeks in duration. Controlled studies of longer duration or using alternative treatment parameters are not clearly established.

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

Principal Supporting Evidence: Level 1b [6–8]

Additional Expert Consensus Comments: The cTMSs 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 TMS therapy experience:

- Extended treatment course: (see above following recommendation #1)

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-5 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 or other psychotropic medications. There are currently no data from controlled trials supporting the use of medications with TMS, but there is currently no evidence of an increased risk 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 are no significant changes in this parameter.

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

Principal Supporting Evidence: Carpenter et al. [13] [Level 2b – individual cohort study]

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. A majority of members recommend continuing extant medications during TMS therapy. Most members refrained from medication taper during the acute TMS course.

Recommendation 4: **TMS therapy can be used as a continuation or maintenance 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 continuation 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 psychotherapy, considering continuation or maintenance TMS therapy when other established methods of maintenance antidepressant therapy 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 continuation or maintenance TMS therapy are based on current expert consensus opinion and are discussed below.

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

Supporting Evidence: Levkovitz et al. [8] [Level 1b studies]

Additional Expert Consensus Comments: The cTMSs guideline committee considers the following comments clinically appropriate considerations as additional guidance in the application of this recommendation. In terms of avoiding relapse, the majority of cTMSs members use maintenance medications and psychotherapy. Some members consider continuation or maintenance TMS or both when a patient has a history of frequent relapse (two or more in one year). cTMSs members reported that they typically administer continuation or maintenance treatments, one session at a time either monthly, biweekly or weekly; or they titrate the frequency to the patient's response.

Recommendation 5: **TMS therapy can be reintroduced in patients who are relapsing into depression after initially responding to TMS treatment.**

Statement of specific recommendation for use: Should relapse occur in patients who benefitted from an acute TMS course, it is recommended that TMS should be reintroduced until remission is reachieved. The first study that assessed TMS reintroduction involved the 24-week naturalistic follow-up study [16] that recruited (n = 99) partial responders to acute TMS (i.e. 25% decrease from the baseline HAMD17) in the first Neuronetics-sponsored multicenter trial [6]. These patients were tapered off TMS, started on maintenance antidepressant monotherapy, and followed for a 6-month period. During this period, 10% (10/99) (Kaplan–Meier survival estimate = 12.9%) of patients relapsed (mean time ~23.5 weeks) and another 38.4% (38/99) (Kaplan–Meier survival estimate = 40%) patients met criteria for symptom worsening (at least 1-point decrease in Clinical Global Impression scale over 2 weeks). The latter group received adjunctive TMS and 32/38 (84.2%) re-achieved symptomatic benefits. The mean time for first TMS reintroduction was 109 (±5) days and the mean number of sessions was 14.3 (SD = 9.3). The more recent study by Phillips found high rates of response in previous TMS responders or remitters (78% in those getting scheduled TMS, and 63% in those in the watch and wait group) [37].

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

Principal Supporting Evidence: Janicak et al. [12] [Level 2b – open label study]

Additional Expert Consensus Comments: Most (90%) of cTMSs members reintroduce TMS during early relapse when symptoms worsen beyond mild severity while only a few (10%) wait until full relapse occurs. Most cTMSs members provided 3–5 treatments per week until response or remission is reestablished. The length of TMS introduction was brief (1–3 weeks) if TMS was reintroduced early in relapse. Most cTMSs members rechecked the motor threshold and location prior to TMS reintroduction.

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. A smaller percentage of members ceased treatment immediately after six weeks. 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 the patient is a partial responder who has not yet achieved maximum benefit.

Remission and tapering

Most cTMSs members (over 90%) surveyed reported that they typically first observe remission in patients between four and six weeks of treatment. When terminating treatment after remission, the majority of cTMSs members (78%) taper treatments over three weeks as was done in the Neuronetics and OPT-TMS trial [6].

Summary and conclusions

Left prefrontal rTMS repeated daily for 4–6 weeks is an effective and safe treatment in adult patients with unipolar MDD that have failed one or more antidepressant trials. These conclusions and guidelines should help the field continue to improve and progress.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.brs.2016.03.010.

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