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Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments

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Abstract

Background: The Canadian Network for Mood and Anxiety Treatments (CANMAT) conducted a revision of the 2009 guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of psychiatrists and other mental health professionals.

Methods: Using the question-answer format, we conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Neurostimulation Treatments" is the fourth of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 31 questions for 6 neurostimulation modalities: 1) transcranial direct current stimulation (tDCS), 2) repetitive transcranial magnetic stimulation (rTMS), 3) electroconvulsive therapy (ECT), 4) magnetic seizure therapy (MST), 5) vagus nerve stimulation (VNS), and 6) deep brain stimulation (DBS). Most of the neurostimulation treatments have been investigated in patients with varying degrees of treatment resistance.

Conclusions: There is increasing evidence for efficacy, tolerability, and safety of neurostimulation treatments. rTMS is now a first-line recommendation for patients with MDD who have failed at least 1 antidepressant. ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line. Third-line recommendations include tDCS and VNS. MST and DBS are still considered investigational treatments.

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In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders.[1] CANMAT has updated these guidelines in 2016 to reflect new evidence in the field.

The scope of these guidelines remains the management of adults with unipolar major depressive disorder (MDD). CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2] This section on "Neurostimulation Treatments" is 1 of 6 guidelines articles; other sections of the guidelines will expand on disease burden and principles of care, psychological treatments, pharmacological treatments, complementary and alternative medicine treatments, and special populations. These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

Neurostimulation, or neuromodulation, is an expanding area of research and clinical interest, driven in part by the increasing knowledge base on the neurocircuitry of depression. Neurostimulation treatments use electrical or magnetic stimulation targeting specific brain regions with noninvasive techniques, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST), as well as invasive surgical techniques, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Most of these neurostimulation treatments have been studied and are used in patients with treatment-resistant depression (TRD) who have failed to respond to standard treatments.

Methods

The full methods have been previously described,[3] but in summary, relevant studies in English published from January 1, 2009, to December 31, 2015, were identified using computerized searches of electronic databases (PubMed, PsychInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other guidelines and major reports. Each recommendation includes the level of evidence for each graded line of treatment, using specified criteria (Table 1). The level of evidence criteria now reflect the primacy of meta-analysis because of its increasing use in the evaluation of evidence.

Table 2 presents the overall neurostimulation treatment recommendations. More details for each modality are presented in the following questions. Because there is no consensus definition for TRD, we have specified the degree of treatment resistance whenever possible.

Transcranial Direct Current Stimulation (tDCS)

4.1. What Is tDCS and How Is It Delivered?

tDCS is a form of brain stimulation that delivers a continuous low-amplitude electrical current to a specified cortical region using scalp electrodes. *Anodal* stimulation over the cortex increases cortical excitability through depolarization of neuronal membrane potential. By contrast, *cathodal* stimulation decreases cortical excitability through hyperpolarization of the membrane potential.[4] Repeated use of tDCS may lead to neuroplasticity effects similar to long-term potentiation and/or long-term depression, perhaps mediated via N-methyl-D-aspartate receptor-dependent mechanisms.[4] Potential advantages of tDCS include ease of use, low cost, portability and potential for home-based use, ability for combination use with other treatments, and low potential for adverse effects.

4.2. What Are the Delivery Parameters for tDCS?

There is no cohesive summary evaluating the optimal stimulus parameters, frequency, or duration of tDCS for the treatment of MDD. Studies to date have used an electrode montage consisting of anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) with the cathode used as a ground over a noncortical region or a montage combining left DLPFC anodal stimulation with right DLPFC cathodal stimulation.[5] The exact frequency and duration of stimulation have not been established, but it seems that a minimum stimulation with 2 milliamperes (mA) for at least 30 minutes per day for 2 weeks is necessary to observe an antidepressant effect.[6] The largest randomized-controlled trial (RCT) to date ($N = 120$ in 4 conditions) using these parameters found higher remission rates at 6 weeks when combining tDCS with sertraline (47%) compared to tDCS (40%) or sertraline alone (30%),[7] which suggests that tDCS may have an additive or enhancing effect to other antidepressant treatments.[8] Furthermore, preliminary data suggest that tDCS may also enhance psychotherapeutic modalities.[9]

4.3. How Effective Is tDCS in Acute and Maintenance Treatment of MDD?

Studies evaluating the efficacy of tDCS have demonstrated mixed results. One meta-analysis (6 trials, $N = 200$) found no significant differences with tDCS compared to sham treatments,[10] while a subsequent meta-analysis (7 trials, $N = 269$) demonstrated modest differences between active and sham conditions with a small overall effect size of 0.37.[6] An individual patient-level meta-analysis (6 trials, $N = 289$)

Table 1. Criteria for Level of Evidence and Line of Treatment.

	Criteria
Level of evidence[a]	
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series *or* high-quality retrospective studies
4	Expert opinion/consensus
Line of treatment	
First line	Level 1 or Level 2 Evidence, plus clinical support[b]
Second line	Level 3 Evidence or higher, plus clinical support[b]
Third line	Level 4 Evidence or higher, plus clinical support[b]

RCT, randomized controlled trial.

[a]Note that Level 1 and 2 Evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgement of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence.

[b]Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.

found a similar effect size ($\beta = 0.347$).[11] The most recent meta-analysis (10 trials, $N = 393$) also found superiority for tDCS over sham conditions with a small but significant effect size ($g = 0.30$).[5] There are no controlled studies of tDCS for maintenance treatment or relapse prevention. History of treatment resistance has been associated with poorer responses to tDCS.[5,6,11]

tDCS is thus recommended as a third-line treatment for MDD. It has Level 2 Evidence for acute efficacy (Table 2), but given the small number of studies with heterogeneous methodologies and the inconsistent results from meta-analyses, further research is needed to establish the optimal parameters of stimulation and the efficacy of tDCS as monotherapy or combination therapy for acute treatment of MDD.

4.4. What Are the Side Effects Associated with tDCS?

Most studies have found that tDCS is well tolerated. Reddening of the skin, itching, burning, heat, and tingling sensations at the site of stimulation are the most common reported adverse events with tDCS in more than half of patients.[5,6] Headaches, blurred vision, ringing in the ears, brighter or illuminated vision, fatigue, nausea, mild euphoria, reduced concentration, disorientation, insomnia, and anxiety have also been reported but at low rates with minimal difference between active and sham stimulation.[5] In the RCT examining tDCS and sertraline 50 mg/d, hypomania (3 patients, 10%) and mania (2 patients, 7%) were reported with the combined treatment compared to tDCS and sertraline alone (both with hypomania reported in 1 patient, 3%).[7] Adverse effects have not led to differences in dropout rates ($\sim$3%) between active and sham conditions across the RCTs.[5,6] There are no studies examining safety and tolerability over long-term use.

Repetitive Transcranial Magnetic Stimulation (rTMS)

4.5. What Is rTMS and How Is It Delivered?

rTMS uses powerful (1.0-2.5 Tesla), focused magnetic field pulses to induce electrical currents in neural tissue noninvasively, via an inductor coil placed against the scalp.[12] Therapeutic rTMS is usually delivered by a trained technician or nurse, under physician supervision. Unlike ECT, no anaesthesia is required. The therapeutic mechanism of rTMS is still under investigation, with mechanisms proposed at both cell-molecular and network levels.[13]

Standard protocols deliver rTMS once daily, 5 days/week (Table 3). Three-times-weekly stimulation has been reported as similarly effective, albeit with slower improvement and a similar number of sessions required overall.[14] 'Accelerated' protocols with multiple daily sessions (2-10/days) are being explored to complete the course more rapidly.[15,16]

Repeated rTMS sessions can exert therapeutic effects lasting several months. Clinical trials and naturalistic studies have found maximal effects at 26 to 28 sessions.[17,18] Clinical experience concurs in suggesting 20 sessions before declaring treatment failure, with extension to 25 to 30 sessions if improvements occur. There is currently no validated biomarker for predicting rTMS outcome in individuals[19] and limited evidence for clinical features to suggest rTMS-responsive depression.

4.6. What Are the Delivery Parameters for rTMS?

rTMS parameters include stimulation intensity, frequency, pattern, and site (Table 3). Conventional figure-8 or circular rTMS coils can target brain regions 1 to 4 cm deep to the scalp; helmet-shaped 'deep' rTMS coils can stimulate slightly deeper structures. For coil navigation, magnetic resonance imaging (MRI) guidance is the most precise method; however, scalp-based navigation is most common. Stimulus intensity is based on individually determined resting motor threshold (RMT, minimum intensity to elicit muscle twitches at relaxed upper or lower extremities, by visual inspection or electromyography). The most common intensity in all trials to date is 110% RMT[20]; most recent large trials have employed 120% RMT. Stimulation above this level falls outside conventional safety guidelines.[21] Newer theta-burst stimulation (TBS) protocols are more commonly delivered at lower intensities (e.g., 70%-80% active motor threshold).

Table 2. Summary of Neurostimulation Treatment Recommendations for Major Depressive Disorder.

Neurostimulation	Overall Recommendation	Acute Efficacy	Maintenance Efficacy	Safety and Tolerability
rTMS	First line (for patients who have failed at least 1 antidepressant)	Level 1	Level 3	Level 1
ECT	Second line First line in some clinical situations (see Table 5)	Level 1	Level 1	Level 1
tDCS	Third line	Level 2	Level 3	Level 2
VNS	Third line	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3
MST	Investigational	Level 3	Not known	Level 3

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

Table 3. Summary of Treatment Parameters for Repetitive Transcranial Magnetic Stimulation (rTMS).

Intensity, frequency, and site
- Stimulate at 110%-120% of resting motor threshold (70%-80% for theta-burst stimulation) (Level 1)
- Select stimulation frequency and site (Table 4)

Treatment course
- Perform stimulation 5 times weekly (Level 1)
- Deliver initial course until symptom remission is achieved, up to 20 sessions (4 weeks) (Level 1)
- Extend course to 30 sessions (6 weeks) in responders who have not achieved symptom remission (Level 3)

Maintenance course
- Use rTMS as needed to maintain response (Level 3)

Table 4. Recommendation for rTMS Stimulation Protocols.

Recommendation	Level of Evidence
First line	
High-frequency rTMS to left DLPFC	Level 1
Low-frequency rTMS to right DLPFC	Level 1
Second line	
Bilateral rTMS to DLPFC (left high-frequency and right low-frequency)	Level 1
Low-frequency rTMS to right DLPFC (in nonresponders to high-frequency left DLPFC-rTMS) or high-frequency rTMS to left DLPFC (in nonresponders to low-frequency right DLPFC-rTMS)	Level 3
TBS protocols	Level 3
Intermittent TBS to left DLPFC	
Left intermittent and right continuous TBS to DLPFC	
Intermittent TBS to bilateral DMPFC	
Third line	
High-frequency rTMS to bilateral DMPFC	Level 3

DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation.

Different stimulation frequency and patterns exert different effects. Conventionally, high-frequency rTMS (5-20 Hz) is considered excitatory, while low-frequency stimulation (1-5 Hz) is inhibitory. Conventional stimulation is delivered in 2- to 10-second trains at 10- to 60-second intervals, in 15- to 45-minute sessions. TBS protocols require only 1 to 3 minutes of stimulation and may achieve comparable or stronger effects.[22] Intermittent TBS (iTBS) is considered excitatory and continuous TBS (cTBS) inhibitory.

4.7. How Effective Is rTMS as an Acute Antidepressant Therapy?

More than 30 systematic reviews and meta-analyses have been conducted on rTMS in depression, with most studies involving patients with some degree of treatment resistance (i.e., having failed at least 1 or 2 antidepressant trials). Overall, rTMS is considered a first-line treatment for MDD for patients who have failed at least 1 antidepressant treatment (Table 2). Table 4 lists recommendations for rTMS stimulation protocols.

Both high-frequency ($\geq$10 Hz) rTMS of the left DLPFC and low-frequency ($\leq$1 Hz) rTMS of the right DLPFC have demonstrated efficacy in numerous meta-analyses,[20,23-25] with no differences in outcomes between them.[20] Hence, both high-frequency left DLPFC and low-frequency right DLPFC are first-line rTMS protocol recommendations. Low-frequency rTMS has the advantage of shorter treatment time. Published studies also suggest that nonresponders to high-frequency left DLPFC rTMS may respond to low-frequency right DLPFC rTMS[17] and vice versa.[26] Hence, a second-line recommendation is to switch nonresponders to the other stimulation protocol.

Bilateral stimulation combines high-frequency left and low-frequency right DLPFC rTMS and has not shown superiority over unilateral rTMS in meta-analyses.[27-29] Because bilateral stimulation requires more intensive setup without efficacy or safety advantages, it is considered a second-line rTMS protocol.

The efficacy of rTMS is established even in patients with TRD defined by stringent criteria.[30] The most recent

meta-analysis of high-frequency left DLPFC rTMS for TRD (23 trials, $N = 1156$) found significant efficacy of rTMS over sham, with a weighted mean difference of 2.31 and an effect size of 0.33.[31] For left DLPFC rTMS, RCTs with adequate sessions (20-30) and treatment durations of 4 weeks or more achieved ~40% to 55% response and ~25% to 35% remission rates, and a real-world effectiveness study reported 58% response and 37% remission rates.[18] Similarly, a meta-analysis (8 trials, $N = 263$) found that low-frequency right DLPFC rTMS had superior remission rates compared to sham (35% vs. 10%, respectively, $P < 0.0001$).[32]

Excitatory rTMS of the dorsomedial prefrontal cortex (DMPFC) has shown antidepressant effects in a small sham-controlled trial ($N = 45$ in 3 conditions)[33] and several larger case series.[22,34,35] The sham-controlled RCT directly compared DMPFC- and DLPFC-rTMS, reporting slightly better outcomes for DMPFC-rTMS.[33] A large case series ($N = 98$) of open-label DMPFC-rTMS reported 50% response and 36% remission rates, not significantly different from iTBS ($N = 87$).[22] Based on this Level 3 Evidence, stimulation to bilateral DMPFC is recommended as a third-line rTMS protocol.

Randomized pilot studies of TBS protocols for DLPFC have shown superiority over sham for left iTBS[36] but not for right cTBS,[36,37] while bilateral stimulation (left iTBS and right cTBS) had positive results in one study[36] but not in another.[38] For TBS of bilateral DMPFC, a retrospective case series found that iTBS achieved equivalent outcomes to longer conventional 10-Hz rTMS protocols.[22] Randomized comparisons of conventional rTMS and TBS are in progress but have not yet been published. Hence, TBS protocols are recommended as second line with Level 3 Evidence (Table 4).

4.8. How Effective Is Maintenance Treatment Post-rTMS?

Without maintenance treatment, relapse is common following successful rTMS. One naturalistic study ($N = 204$) reported median relapse time at 120 days, with relapse rates of 25%, 40%, 57%, and 77% at 2, 3, 4, and 6 months, respectively.[39] With maintenance rTMS, long-term outcomes appear more favourable. In a naturalistic study ($N = 257$), maintenance rTMS sessions as needed over 12 months sustained remission in 71% of rTMS remitters and response in 63% of rTMS responders.[40] Another study found that without maintenance, 38% of rTMS responders relapsed within 24 weeks, at a mean of 109 days posttreatment.[41] With reintroduction of rTMS as needed, 73% met response and 60% met remission criteria at 24 weeks.[41]

Various rTMS maintenance schedules have been proposed. An observational study ($N = 59$) compared a 20-week gradual taper of maintenance rTMS (from 3 sessions/week down to 1 session/month) to no maintenance; relapse rates were 38% with maintenance versus 82% without maintenance.[42] Another study ($N = 35$) provided 5 'clustered' maintenance sessions over 3 days, once monthly, extending relapse times to a mean 10.8 months among the 25 patients who relapsed.[43] As yet, there is insufficient evidence to support any one particular schedule of maintenance sessions over another.

4.9. How does rTMS Compare to ECT?

rTMS and ECT differ in mechanism, tolerability, and acceptability by patients and may be best understood as complementary rather than competing techniques. That said, several meta-analyses[28,31,44-46] evaluating a similar number of studies have consistently found that rTMS is less effective than ECT, particularly in patients with psychosis.[44] The most comprehensive meta-analysis (9 trials, $N = 425$) found significant superiority of ECT over left DLPFC rTMS in response and remission rates but no significant difference in weighted mean difference, in contrast to the other meta-analyses that found large differences in favour of ECT for all outcomes.[28,31,45,46] Likewise, rTMS response rates are poor in patients where ECT has failed.[35] These findings indicate that rTMS should be considered prior to pursuing ECT and that patients who have not responded to ECT are unlikely to respond to rTMS.

4.10. What Are the Adverse Effects Associated with rTMS?

The most common adverse effects for rTMS are scalp pain during stimulation (~40%) and transient headache after stimulation (~30%), both of which diminish steadily over treatment, typically respond to over-the-counter analgesia, and result in low rates of discontinuation.[47,48]

The cognitive safety profile of rTMS appears benign. A systematic review (22 studies, $N = 659$) of cognitive performance with rTMS found no worsening in cognitive domains but also little evidence of improvement, with no differences in cognitive performance between active rTMS and sham conditions.[49]

The most serious rTMS adverse event is seizure induction. To date, fewer than 25 cases of rTMS-induced seizure have been reported worldwide.[50] Seizure incidence with rTMS is estimated at ~0.01% to 0.1% versus 0.1% to 0.6% on antidepressant medications and 0.07% to 0.09% spontaneous incidence in the general population. High-frequency rTMS is contraindicated in patients with a history of seizures. Safety of low-frequency rTMS has been demonstrated in patients with epilepsy,[21] but safety in patients with depression and seizures has not been formally established. Most rTMS practitioners currently consider a history of seizures an absolute contraindication.

Consensus safety guidelines for therapeutic rTMS[21] list metallic hardware (e.g., cochlear implants, brain stimulators or electrodes, aneurysm clips) anywhere in the head, except the mouth, as an absolute contraindication. Relative contraindications include the presence of a cardiac pacemaker,

implantable defibrillator, a history of epilepsy, or the presence of a brain lesion (vascular, traumatic, neoplastic, infectious, or metabolic).

4.11. Should rTMS be Combined with Other Antidepressant Medications?

Most rTMS studies have delivered rTMS as an add-on to the preexisting antidepressant regimen. There is no evidence that discontinuing antidepressants prior to rTMS will improve outcomes. However, a meta-analysis (6 trials, $N = 392$) found that starting a new antidepressant with rTMS resulted in higher response and remission rates than rTMS alone.[51]

Electroconvulsive Therapy (ECT)

4.12. What Is ECT and How Is It Delivered?

ECT is a therapeutic procedure that entails induction of a seizure by applying an electrical stimulus to the brain. It is an effective and well-established treatment method for depressive and other mental disorders. ECT is delivered in a controlled clinical setting, after induction of general anaesthesia and application of a muscle relaxant. There are no absolute contraindications for ECT. The following conditions may be associated with an increased safety risk: space-occupying cerebral lesion, increased intracranial pressure, recent myocardial infarction, recent cerebral haemorrhage, unstable vascular aneurysm or malformation, pheochromocytoma, and class 4 or 5 anaesthesia risk. The exact mechanism of action is still under investigation, but the main hypotheses include seizure-induced changes in neurotransmitters, neuroplasticity, and functional connectivity. For example, ECT can increase levels of brain-derived neurotrophic factor (BDNF), which may contribute to the antidepressant effect.[52]

ECT is generally recommended as a second-line treatment for MDD because of adverse effects (Table 2), but ECT can be considered a first-line treatment in some clinical situations (Table 5).

Table 6 summarizes the recommendations for delivery of ECT. Current treatment parameters for ECT include electrode position, electrical intensity, and pulse width. The most common electrode placements are bilateral, either bitemporal (BT) or bifrontal (BF), or right unilateral (RUL). The electrical intensity is based on the minimum intensity to produce a generalized seizure, called the seizure threshold (ST). Bilateral treatments (both BT and BF) most often use 1.5 to 2.0 times ST and RUL 5 to 6 or even 8 times ST. A meta-analysis (8 trials, $N = 617$) found that BT, BF, and RUL have the same efficacy but may adversely affect specific cognitive domains differently.[53] Both BF and RUL ECT are first-line recommendations, but BT is recommended as second line because of higher rates of short-term cognitive adverse effects.

ECT generally uses brief pulse (BP) width, but in the past decade, there has been clinical and research interest into ultrabrief pulse width (UBP, pulse width below 0.5 ms) RUL and bilateral treatments. UBP may be associated with less short-term cognitive impairment and specifically the loss of autobiographical memory.[54] However, UBP may have slower speed of improvement and require more treatments than BP.[55] A systematic review[56] concluded there was no advantage of UBP over BP in RUL or bilateral ECT, and a meta-analysis (6 trials, $N = 689$) found that BP RUL had a small efficacy advantage and required fewer treatments than UBP but led to more cognitive impairment after an acute course.[57] Hence, UBP RUL is recommended as a second-line ECT treatment, especially to minimize short-term cognitive impairment.

The number of ECT treatments required to achieve response and/or remission, referred to as the index course, ranges between 6 and 15. ECT is usually delivered 2 to 3 treatments per week during the index course. More than 3 treatments per week are not recommended, as they are associated with higher frequency of cognitive side effects. A meta-analysis (8 studies, $N = 214$) found that twice-weekly ECT had similar efficacy compared to thrice-weekly ECT but had longer duration of treatment.[58]

Table 5. Clinical Indications for Electroconvulsive Therapy as a First-Line Treatment for Major Depressive Disorder.

- Acute suicidal ideation (Level 1)
- Psychotic features (Level 1)
- Treatment-resistant depression (Level 1)
- Repeated medication intolerance (Level 3)
- Catatonic features (Level 3)
- Prior favourable response to ECT (Level 3)
- Rapidly deteriorating physical status (Level 3)
- During pregnancy, for any of the above indications (Level 3)
- Patient preference (Level 4)

Table 6. Recommendations for Delivery of Electroconvulsive Therapy.

Recommendation	Level of Evidence
First line	
BP RUL (at 5-6 times seizure threshold)	Level 1
BP BF (at 1.5-2.0 times seizure threshold)	Level 1
Second line	
UBP RUL (up to 8 times seizure threshold) or UBP BF (at 1.5-2.0 times seizure threshold)	Level 1
BP BT (at 1.5-2.0 times seizure threshold)	Level 1
Twice-weekly ECT sessions have similar efficacy to thrice-weekly but have longer duration of treatment	Level 2
If no response to RUL after 4 to 6 treatments, switch to bilateral ECT (BT or BF)	Level 3
For maintenance pharmacotherapy post-ECT, use an antidepressant that has not been tried prior to ECT *or* nortriptyline plus lithium *or* venlafaxine plus lithium	Level 2
Maintenance use of ECT is as effective as pharmacotherapy in preventing relapse/recurrence after an acute course of ECT	Level 2

BF, bifrontal; BP, brief pulse; BT, bitemporal; ECT, electroconvulsive therapy; RUL, right unilateral; UBP, ultrabrief pulse.

4.13. How Effective Is ECT as an Acute Treatment?

ECT is one of the most effective treatments for MDD. Response rates can reach 70% to 80%, with remission rates 40% to 50% or higher, depending on the patient population and type of stimulus used. For example, 1 multicentre RCT ($N = 230$) reported remission rates of 55% for RUL, 61% for BF, and 64% for BT in a mixed sample of patients with unipolar (77%) and bipolar (23%) depression.[59] The strongest predictor of nonresponse to ECT is the degree of resistance to previous treatments. In patients with greater degrees of resistance to pharmacological and psychological treatments, response rates with ECT approximate 50%, compared to 65% in patients without a previous treatment failure.[60] Highest response rates have also been observed when patients are older, have psychotic features, have a shorter episode duration, and, possibly, have lesser depressive severity.[61]

The relapse/recurrence rate following an acute course of ECT, with or without maintenance treatment, is also high. A meta-analysis of 32 studies from 1962 to 2013 ($N = 1706$ patients) that assessed relapse rates following successful treatment with ECT reported that relapse rates are highest within the first 6 months post-ECT (37.7%).[62] Even in those receiving maintenance treatment post-ECT, relapse rates of 51.1% and 50.4% have been observed at 1 and 2 years, respectively. Baseline medication resistance is not associated with relapse, but lower relapse rates have been observed in cohorts with a greater percentage of psychotic patients and older patients.[62]

4.14. How Effective Is Maintenance Treatment Post-ECT?

Medications are most commonly used for maintenance after an acute treatment course of ECT. The use of antidepressant medication post-ECT reduced relapse rates by approximately half (relative risk of relapse on medication = 0.56).[62] However, there has been little study of specific medication strategies to minimize post-ECT relapse, and there is no clear evidence of the superiority of a specific antidepressant or class of medication. In RCTs, the combination of nortriptyline and lithium was superior to both nortriptyline monotherapy and placebo in reducing relapse rates,[63] and the combination of venlafaxine and lithium was found to be equally efficacious as nortriptyline and lithium.[64] In summary, the recommendation for pharmacotherapy post-ECT is to use an antidepressant that has not been tried prior to ECT, or nortriptyline plus lithium, or venlafaxine plus lithium.

Continuation/maintenance ECT (c/mECT) is also a safe and effective strategy to reduce relapse/recurrence.[65,66] Studies in which continuation ECT was used yielded comparable relapse-prevention results at 6 months as studies of pharmacological strategies (relapse rates: 37.2% vs. 37.7%, respectively).[62] This has also been demonstrated in a prospective RCT of continuation ECT versus continuation pharmacotherapy with nortriptyline and lithium.[67] Hence, maintenance ECT also can be used as a relapse-prevention strategy after an acute course of ECT. There are no studies investigating optimal frequency of c/mECT, so the schedule should be adjusted to the needs of an individual patient. The most commonly used schedule in studies of c/mECT involves weekly treatments for 4 weeks, then biweekly for 8 weeks, and then monthly. If signs of relapse occur, more frequent sessions are usually provided.

There has been a paucity of evidence regarding psychotherapeutic strategies to prevent post-ECT relapse.[68] A small RCT found that cognitive-behavioural group therapy plus continuation medication ($n = 17$) demonstrated a lower relapse rate at 6 and 12 months compared to continuation of UBP ECT plus medication ($n = 25$) and continuation of medication alone ($n = 18$).[69] There is insufficient evidence to recommend psychotherapy for maintenance treatment post-ECT.

4.15. What Are the Adverse Effects Associated with ECT?

The use of general anaesthesia, muscle relaxants, oxygenation, and monitoring has minimized the risks associated with ECT, and the mortality rate has been estimated to be less than 1 death per 73,440 treatments.[70] No clinical studies have demonstrated damage to the brain structures related to the administration of ECT. The most common adverse effects occur during a treatment course, are transient, and can be treated symptomatically: headaches (45%), muscle soreness (20%), and nausea (1%-25%). In a small number (7%), there can be a switch into a manic or mixed state.

Subjective and objective cognitive impairment are the adverse effects that have received the greatest attention. Cognitive effects include transient disorientation when recovering from an ECT session (in part due to postictal confusion and effects of general anaesthesia), retrograde amnesia (difficulty recalling information learned before a course of ECT, such as autobiographical memories), and anterograde amnesia (difficulty in retaining learned information after a course of ECT). There is mild, short-term impairment in memory and other cognitive domains during and immediately following a course of ECT. Clinical factors, including preexisting cognitive impairment, older age, and use of BT ECT, are associated with greater cognitive impairment, while use of UBP RUL ECT is associated with less impairment. However, these impairments are usually transient, with recovery of cognitive functioning occurring within weeks and months after an acute course of ECT, and no eventual cognitive differences between ECT parameters, including electrode placement and pulse width.[71,72] For example, 1 meta-analysis (84 studies, $N = 2981$) examined 24 cognitive variables (including processing speed, working memory, anterograde memory, and executive function) and found recovery or improvement in all neuropsychological

Table 7. Factors Associated with Higher Rates of Short-Term Adverse Cognitive Effects of Electroconvulsive Therapy Versus Those Associated with Lower Rates.

Factors	Level of Evidence
Bitemporal electrode placement versus bifrontal or unilateral placement	Level 1
Brief pulse width (1.0-1.5 ms) versus ultrabrief pulse width (0.3-0.5 ms)	Level 2
Suprathreshold stimulation versus lower electrical dose	Level 2
Treatment 3 times a week versus twice a week	Level 2
Concomitant use of lithium or agents with independent adverse cognitive effects versus reducing doses or discontinuing these agents	Level 3
Use of high doses of anaesthetic medications versus lower doses	Level 4

measures within 3 to 15 days after completing ECT.[72] There is less consistent information about retrograde amnesia, with some studies suggesting persistent effects, while a systematic review (15 studies, $N = 1128$) found that objective tests of autobiographical memory did not show effects beyond 6 months post-ECT.[73] Patient self-reports indicate some persistent cognitive dysfunction, especially retrograde amnesia, but self-reports of cognitive dysfunction are usually highly correlated with persistent depressive symptoms and are not correlated with objective testing.[73,74] Table 7 lists some of the factors that are associated with higher or lower rates of short-term adverse cognitive effects.

4.16. Should ECT Be Combined with Other Antidepressant Treatments?

Lower relapse rates have been reported in studies where concurrent antidepressant medication was permitted during the course of ECT compared to studies where maintenance pharmacotherapy was begun following the course of ECT (29.2% vs. 41.6%, respectively), suggesting that improved long-term outcomes are achieved with the use of concurrent, rather than sequential, use of ECT and medication.[62]

There is some evidence that concomitant use of lithium and ECT may increase cognitive side effects, encephalopathy, and spontaneous seizures, whereas benzodiazepines and anticonvulsants may raise the seizure threshold and decrease seizure efficacy, although lamotrigine may be less problematic than other anticonvulsants.[75]

Magnetic Seizure Therapy (MST)

4.17. What Is MST and How Is It Delivered?

MST is a noninvasive convulsive neurostimulation therapy that relies on the principle of electromagnetic induction to induce an electric field in the brain strong enough to elicit a generalized tonic-clonic seizure. Currently, MST is being investigated as an alternative to ECT. Like ECT, the seizure is elicited under general anaesthesia with assisted ventilation and EEG monitoring, but MST has the potential for fewer side effects such as cognitive dysfunction.[76]

The equipment used in MST consists of a neurostimulator and coil that is placed in direct contact with the skull. When electrical current passes through the coil, a strong focal magnetic field is generated (in the order of 2 Tesla). This magnetic field crosses the skull and soft tissue unimpeded to reach brain tissue, inducing an electrical current that causes neuronal depolarization and eventually triggering a generalized seizure.

4.18. What Are the Delivery Parameters of MST?

The optimal delivery parameters for MST are still being investigated. Most studies have used a coil placement at the vertex (i.e., Cz in 10-20 electroencephalogram [EEG] system) with a frequency of stimulation of 100 Hz, pulse width of 0.2 to 0.4 ms, and stimulation duration of 10 seconds. A summary of MST parameters used in studies is listed in Supplemental Table S1. MST has been given on a similar schedule as ECT, usually 2 to 3 times per week, with an index course of 12 treatments.

4.19. How Effective Is MST Compared to ECT?

There are no studies comparing MST versus sham stimulation. One small RCT ($N = 20$) comparing MST to RUL ECT found no significant differences in response rates (60% vs. 40%, respectively) or remission rates (30% vs. 40%, respectively).[77] In addition, the largest MST case series ($N = 26$, which included the 10 patients who received MST in the randomized trial) reported an overall response rate of 69% and remission rate of 46%,[78] which would be similar to those obtained with ECT. There are no studies of relapse following MST or of relapse prevention strategies. As a result, MST is recommended as an investigational treatment alternative for ECT based on Level 3 Evidence (Table 2).

4.20. What Are the Adverse Effects Associated with MST Compared to ECT?

MST seems to be associated with lower rates of headaches and muscle aches than ECT. In addition, MST has not shown a significant impact on anterograde or retrograde amnesia, and reorientation time (the time it takes after the seizure and emergence from anaesthesia to be fully oriented to person, place, and time) appears to be significantly shorter in patients receiving MST compared to ECT (2-7 minutes vs. 7-26 minutes, respectively).[76] However, the 1 randomized comparison of MST versus RUL ECT ($N = 20$) found no significant differences in neuropsychological testing after 12 treatments.[77]

Vagus Nerve Stimulation (VNS)

4.21. What Is VNS and How Is It Delivered?

VNS is an implantable neurostimulation technology originally approved in 1997 for the treatment of drug-resistant

epilepsy. The VNS system comprises an implantable pulse generator (IPG), which is surgically inserted underneath the skin of the chest, connected to an electrode placed in one of the vagus nerves in the neck. The vagus nerve is a cranial nerve that largely consists of fibers that transmit nerve impulses from the periphery to the brain. Electrical stimulation of the vagus nerve provides stimulation to the nucleus tractus solitarius, which in turn is able to modulate multiple regions of the brain via its neuronal connections to anatomically distributed subcortical and cortical regions of the brain.[79]

4.22. What Are the Delivery Parameters for VNS?

Optimal treatment parameters for VNS remain a research question. In an RCT of open-label VNS ($N = 331$) comparing low (0.25 mA current, 130 ms pulse width), medium (0.5-1.0 mA, 250 ms), or high (1.25-1.5 mA, 250 ms) electrical outputs, higher electrical charges were correlated with better improvement in depressive symptoms.[80] More sustained antidepressant responses and less frequent suicide attempts were reported in the medium- and high-stimulation groups than the low-dose group.

4.23. How Effective Is VNS in Acute Treatment?

VNS was approved by the Food and Drug Administration (FDA) in the United States in 2005 for the adjunct long-term treatment of chronic or recurrent depression for adult patients experiencing a major depressive episode who had failed to respond to 4 or more adequate antidepressant treatments. A meta-analysis of open-label studies (7 studies, $N = 426$) found a response rate of 31.8%.[81] However, only 1 RCT ($N = 235$) has evaluated the efficacy of VNS versus a sham-control condition, with no significant differences in efficacy between the conditions at 12 weeks.[82] Therefore, VNS is recommended as a third-line acute treatment with Level 3 Evidence for efficacy (Table 2).

4.24. How Effective Is VNS During Extended Treatment?

Recent systematic reviews and meta-analyses of open-label studies have suggested that the antidepressant effects of VNS may accrue over time. A patient-level meta-analysis (6 trials, $N = 1460$) of all randomized and open-label data with VNS found significantly higher odds ratios (ORs) for response (OR, 3.19) and remission (OR, 4.99) for VNS plus treatment as usual (TAU) compared to TAU alone.[83] However, absolute rates were low (e.g., remission rates for VNS plus TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14%, respectively, vs. 1%, 1%, 2%, and 4% for TAU alone).[83] The median time to response with VNS was estimated to be 9 months in 1 study.[84] In another VNS study ($N = 74$), only 35% of patients had achieved a response by 3 months, but 61.5% and 50% of these 3-month responders maintained response at 12 months and 24 months, respectively.[85] Hence, the longer term results with VNS appear encouraging, and VNS can be considered for patients with chronic depression, particularly in situations where treatment adherence may be an issue.

4.25. What Are the Adverse Effects Associated with VNS?

Most patients with VNS are also on antidepressant medications, so adverse effects are for the combined treatment. The most commonly reported adverse effects after 1 year of VNS for TRD are voice alteration (69.3%), dyspnea (30.1%), pain (28.4%), and increased cough (26.4%).[83] Voice alteration and increased cough are often direct effects of VNS being actively delivered and can immediately improve by turning the stimulation off. The tolerability of VNS appears to improve over time with diminishing rates of adverse events reported by patients during their long-term treatment with VNS.[83] The reported rates of serious adverse psychiatric events have included suicide or attempted suicide (4.6%) and treatment-emergent hypomania or mania (2.7%).[80] A lower all-cause mortality rate, including suicide, has been observed in patients with TRD treated with adjunctive VNS compared to TAU.[86]

Deep Brain Stimulation (DBS)

4.26. What Is DBS and How Is It Delivered?

DBS is an invasive neurosurgical procedure involving the implantation of electrodes under MRI guidance into discrete brain targets. The electrodes are internalized and connected to an IPG that is typically implanted into the chest below the right clavicle. Similar to cardiac pacemakers and VNS, the IPG in DBS can be accessed using a handheld device, allowing the stimulation parameters to be monitored and/or programmed remotely. Modifiable DBS parameters include pulse width, frequency, and amplitude (voltage or current), which can be programmed by the treating physician and titrated to clinical effect. Currently, the most common indications for DBS are movement disorders (most specifically Parkinson's disease),[87] but DBS for difficult-to-treat psychiatric disorders, including TRD, is a growing research field.

4.27. How Effective Is DBS as an Acute Treatment in TRD?

DBS is still considered an experimental treatment, with Level 3 Evidence supporting efficacy (Table 2). Evidence for effectiveness of DBS has been based on nonrandomized, open-label trials with small sample sizes (fewer than 20 patients each) of patients with antidepressant-, psychotherapy-, and, often, ECT-refractory depression. The main anatomical targets for TRD are subcallosal cingulate (SCC) white matter, ventral capsule/ventral striatum

(VC/VS), nucleus accumbens, and medial forebrain bundle (MFB), with the majority of reports focused on the SCC.[88] The optimal stimulation parameters for various brain targets remain unknown. Generally, studies of DBS with these targets in highly refractory patients have reported response rates between 30% and 60% and remission rates between 20% and 40% at 3 or 6 months,[89,90] but a small study ($N = 7$) of open-label DBS of the MFB reported a response rate of 85.7% and a remission rate of 57.1%.[91]

The results from these open-label reports stand in contrast to the 2 multicentre, sham-controlled RCTs conducted to date, both of which were discontinued early because of lack of an efficacy signal. A study of VC/VS DBS ($N = 30$) found no differences between active and sham stimulation after the 16-week randomized phase, with response rates of 20% and 14.3%, respectively.[90] An open-label continuation phase showed response rates of 20%, 26.7%, and 23.3% at 12, 18, and 24 months, respectively. A multicentre, sham-controlled trial of SCC DBS ($N = 75$) was recently discontinued because of an interim futility analysis showing low probability of significant efficacy at 6 months.[88]

4.28. How Effective Is DBS During Extended Treatment?

Long-term data for DBS involves SCC DBS. A meta-analysis (4 open-label studies, $N = 66$) of SCC DBS for TRD revealed that depression severity was significantly reduced after 12 months (Hedges's $g = -1.89$, $P < 0.0001$).[89] At 3, 6, and 12 months, the pooled response rates were 36.6%, 53.9%, and 39.9%, respectively, while the pooled remission rates were 16.7%, 24.1%, and 26.3%, respectively.[89]

Higher rates of response have been observed in open studies beyond 1 year with SCC DBS. In 1 study ($N = 17$), the response rates were 36% and 92% at 1 and 2 years, respectively, and remission rates were 58% at 2 years.[92] In a long-term open study ($N = 20$) with follow-up to 6 years, response rates were 62.5%, 46.2%, and 75% at 1, 2, and 3 years, respectively, and remission rates were 20% and 40% at 2 and 3 years, respectively.[93] Improvements in health-related quality of life have also been reported with both long-term SCC and MFB DBS.[93,94]

In summary, the existing data from open-label studies are consistent with the premise that the antidepressant effects of SCC DBS continue to accrue over months and years of chronic stimulation, with improved rates of clinical and functional outcomes observed beyond 1 year postsurgery. However, the data from sham-controlled RCTs have yet to demonstrate efficacy of VC/VS and SCC DBS in acute treatment of TRD.

4.29. How Effective Is Maintenance Treatment Post-DBS?

Only 1 study has specifically addressed relapse prevention with DBS. Five patients were treated with SCC DBS to remission and randomized to on/off or off/on stimulation in blocks of 3 months.[95] At the end of active DBS, depression was remitted in 4 of 5 patients, and none of them had experienced a relapse, whereas at the end of sham stimulation, only 2 remained in remission, suggesting that ongoing DBS was required to maintain remission.

4.30. What Are the Adverse Effects Associated with DBS?

Adverse effects observed in longitudinal studies of DBS for TRD may be secondary to a multitude of factors, including those related to the surgical procedure itself (e.g., intracranial haemorrhage), perioperative risks (e.g., wound infection), factors unrelated to the DBS treatment, effects of stimulation on discrete brain regions, or changes in the DBS parameters. DBS has generally been well tolerated by patients, despite the inherent risks associated with an invasive neurosurgical procedure. The pooled dropout rate after 1 year of SCC DBS ($N = 63$) has been estimated to be 10.8% (95% CI, 4.3% to 24.4%).[89] There has been no evidence of worsening in neuropsychological performance with DBS, irrespective of the brain target,[94,96-98] and some studies report improvements in cognitive performance.

Reported psychiatric adverse events have included the emergence of psychosis and hypomania associated with a change in the stimulation parameters in patients receiving nucleus accumbens DBS.[99] These symptoms were transient and reversible with a change in DBS parameters. No episodes of hypomania have been reported with SCC DBS, including its use in patients with bipolar disorder.[92]

Oculomotor adverse events, including blurred vision and strabismus, have been reported with MFB DBS.[93] These effects were seen in all patients at higher amplitude settings. Suicidality and completed suicide have been reported,[92,93,99] although there was no evidence that these adverse events were secondary to device-related factors. The risk factors for suicidality with DBS are unclear but may be increased in those with a history of pre-DBS suicide or major concurrent psychosocial stressors.[92,93,99]

4.31. Should DBS Be Combined with Other Antidepressant Treatments?

To date, DBS has largely been used as an augmentation strategy to antidepressant medication, with very few patients receiving no psychotropic medication at the time of implantation. However, the optimal means of combining pharmacological, psychological, and other brain stimulation treatments with DBS remains unknown.

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