Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies

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A B S T R A C T

Background: In 2001, the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. A revision of these guidelines was undertaken by CANMAT in 2008–2009 to reflect advances in the field. There is renewed interest in refined approaches to brain stimulation, particularly for treatment resistant major depressive disorder (MDD).

Methods: The CANMAT guidelines are based on a question–answer format to enhance accessibility to clinicians. An evidence-based format was used with updated systematic reviews of the literature and recommendations were graded according to Level of Evidence using pre-defined criteria. Lines of Treatment were identified based on criteria that included evidence and expert clinical support.

This section on “Neurostimulation Therapies” is one of 5 guidelines articles.

Results: Among the four forms of neurostimulation reviewed in this section, electroconvulsive therapy (ECT) has the most extensive evidence, spanning seven decades. Repetitive transcranial magnetic (rTMS) and vagus nerve stimulation (VNS) have been approved to treat depressed adults in both Canada and the United States with a much smaller evidence base. There is also emerging evidence that deep brain stimulation (DBS) is effective for otherwise treatment resistant depression, but this is an investigational approach in 2009.

Limitations: Compared to other modalities for the treatment of MDD, the data based is limited by the relatively small numbers of randomized controlled trials (RCTs) and small sample sizes.

Conclusions: There is most evidence to support ECT as a first-line treatment under specific circumstances and rTMS as a second-line treatment. Evidence to support VNS is less robust and DBS remains an investigational treatment.

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Keywords: Electroconvulsive therapy, Repetitive transcranial magnetic stimulation, Vagus nerve stimulation, Deep brain stimulation

1. Introduction

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, collaborated on the publication in 2001 of evidence-based clinical guidelines for the treatment of depressive disorders (Kennedy et al., 2001). A revision of these guidelines was undertaken by CANMAT in 2008–2009 to update the recommendations based on new evidence. The scope of these guidelines encompasses the management of adults with unipolar major depressive disorder (MDD). This section on Neurostimulation is one of 5 guidelines articles. There are separate CANMAT guidelines for Bipolar Disorder (Yatham et al., 2009).

Neurostimulation involves the delivery of a physical intervention either through electric current or a magnetic
field to target selective or generalized brain regions. ECT represents the prototypic form of neurostimulation, that has been used since the 1930s although it only received the Food and Drug Administration’s (FDA) approval in 1979. Despite favourable rates of outcome, failure to sustain antidepressant response and adverse cognitive effects have been the main limitations of ECT. rTMS relies on electromagnetic induction to generate a superficial current in the dorsolateral prefrontal cortex (DLPFC) which may be of high intensity or low intensity. This treatment is devoid of adverse neurocognitive effects and continues to be refined in the treatment of MDD. VNS and DBS are more invasive forms of neurostimulation that have been approved for the treatment of neurological disorders prior to being investigated for treatment resistant depression (TRD). The VNS device received approval for adjunctive long-term use for chronic or recurrent MDD and relays a mild electrical pulsed stimulus to the left vagus nerve which activates limbic structures. The efficacy of this procedure is still being evaluated, although it has a good safety profile. DBS is the most invasive form of neurostimulation and requires direct neurosurgical implantation of electrodes to targeted brain regions. In both VNS and DBS, patients require an implantable pulse generator (IPG), usually inserted subclavicularly to maintain pulsatile or continuous current. Although early reports suggest promising results in open-label trials, DBS requires RCT evidence before it can be recommended in routine clinical practice. A summary of evidence and recommendations is contained in Table 1. However, the recommendations are presented as guidance for clinicians who should consider them in the context of individual patients, and not as standards of care.

Methods

The full methods have been described elsewhere (Kennedy et al., 2009) but, in summary, relevant studies of English language publications from January 1, 2000 to December 31, 2008 were identified using computerized searches of electronic databases (PubMed, PsycInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other guidelines and major reports. The previous question–answer format has been retained based on feedback from clinicians. Recommendations for each Line of

<table>
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<td>Second-line for otherwise treatment resistant or medication intolerant populations</td>
<td>Level 1</td>
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<tr>
<td>rTMS</td>
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<td>DBS</td>
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<td>Level 3</td>
<td>Level 3</td>
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**Table 2** Criteria for Level of Evidence a and Line of Treatment. b

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<th>Line of Treatment</th>
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<tr>
<td>First-line</td>
<td>Level 1 or 2 evidence, plus clinical support c</td>
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<tr>
<td>Second-line</td>
<td>Level 3 evidence or higher, plus clinical support c</td>
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<tr>
<td>Third-line</td>
<td>Level 4 evidence or higher, plus clinical support c</td>
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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, hence the highest Level of Evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgment of the strength of evidence from various data sources, and therefore are primarily Level 4 evidence.

b A first-line treatment represents a balance of efficacy, tolerability and clinical support. Second-line and third-line treatments are reserved for situations where first-line treatments are not indicated or cannot be used, or where first-line treatments have not worked.

c Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are realistic in clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower Lines of Treatment due to clinical issues such as side effect or safety profile.

Treatment are based on the Level of Evidence and clinical support (Table 2).

3. Electroconvulsive therapy (ECT)

4.1. What is ECT and how is it delivered?

ECT involves the induction of a convulsion (seizure) by the application of electrical current to the brain. The stimulus parameters are: current (usually 500 to 800 mA); frequency (20 to 120 Hz); pulse width (0.25 to 2 ms) and duration (0.5 to 8 or more seconds). The charge of electricity delivered is measured in millicoulombs (below 600 mC for machines sold in Canada and USA but somewhat higher for other markets) and the energy is measured in joules. The minimum charge to induce a seizure is known as the seizure threshold. The electrodes can be placed bilaterally (either bitemporal or bifrontal) or unilaterally (typically, on the right side − RUL). Markedly suprathreshold ECT is the goal for unilateral placement and entails applying a stimulus dose up to 6 times above seizure threshold. In contrast, moderately suprathreshold ECT is the goal for bilateral placement, which implies 1.5 to 2.5 times threshold. Barely suprathreshold brief-pulse unilateral ECT is remarkably ineffective (Sackeim et al., 1987). Response rates of 80% or higher have been reported with ECT although there are very few comparisons between ECT and first-line antidepressants.

There is consistent evidence that the antidepressant efficacy of ECT is related to its stimulation parameters. Bitemporal placement is generally regarded as faster in improving depressive symptoms and more effective than unilateral, at a lower dose of electrical stimulus. However, bitemporal placement is associated with more cognitive side effects (Stoppé et al., 2006). There is evidence that the right unilateral stimulus at suprathreshold dose is as effective as bilateral stimulation.
and is associated with fewer side effects (Sackeim et al., 1999, 2000). Meta-analyses suggest that ECT delivered bitemporally is associated with greater acute cognitive side effects compared to RUL (The UK ECT Review Group, 2003). There is also evidence that the less frequently evaluated, bifrontal placement of electrodes is as effective as bitemporal or right unilateral, and is also associated with fewer cognitive side effects (Balline et al., 2000; Eschweiler et al., 2007). In addition, shorter pulse width and lower pulse frequency may have lower seizure thresholds (Kotresh et al., 2004; Sackeim, 2004; Sackeim et al., 2008).

4.2. What is the recommended frequency and duration of a course of ECT?

ECT is typically delivered two or three times per week under monitored conditions. The need for a rapid onset of antidepressant effects must be weighed against the deleterious effects of more frequent ECT treatments. Some studies (Shapira et al., 2000), but not all (The UK ECT Review Group, 2003), support a faster onset of action when patients receive the treatment 3 times per week. On the other hand, patients receiving a twice weekly regimen have decreased frequency and intensity of cognitive side effects compared to those on a three times weekly schedule (The UK ECT Review Group, 2003) (Table 3).

4.3. How effective is ECT as an acute antidepressant therapy?

When ECT is prescribed as a first-line treatment (Table 4) or in individuals with a history of antidepressant medication trials of inadequate dose or duration, response rates in the 80%–90% range have been reported (Petrides et al., 2001). Several meta-analyses have concluded that ECT is a superior acute antidepressant compared to pharmacotherapy (Kho et al., 2003; Pagnin et al., 2004; The UK ECT Review Group, 2003), although there are very few direct comparisons between ECT and the first-line antidepressants as mono-therapies used alone or in combination. In most countries the use of ECT is reserved for a major depressive episode that has proved “treatment resistant” to adequate trials of two or more pharmacotherapies, including combination medications and/or cognitive therapy. When used in patients who have failed to respond to one or more adequate antidepressant medication trials, ECT response rates have traditionally been estimated to be 50–60% (Prudic et al., 1996).

4.4. How effective is ECT as a relapse prevention therapy?

Although the antidepressant benefits of ECT tend to be acute, they may not persist without some form of maintenance treatment. Results from two large multi-site collaborations – the Consortium for Research in ECT (CORE) (Kellner et al., 2006) and Columbia University Consortium (CUC) (Sackeim et al., 2001a,b,c) support the combination of nortriptyline plus lithium for relapse prevention in patients who responded to ECT. The CORE study reported that both continuation pharmacotherapy and maintenance ECT were equally effective for relapse prevention during the first 6 months after responding to ECT (Kellner et al., 2006). Maintenance ECT ranging from one per week to one per month is associated with low rates of cognitive side effects (Vothnecht et al., 2003). However, there is insufficient evidence to recommend one frequency over another for maintenance ECT. Maintenance treatments should be reviewed every 6 months.

4.5. Which patients respond best to ECT?

ECT is a first-line treatment under certain clinical circumstances (see Table 4). Evidence exists that ECT is effective for all subtypes of MDD, including atypical depression (Husain et al., 2008), and bipolar depression (Grunhaus et al., 2002), but may be especially effective for psychotic depression (Petrides et al., 2001) and depression with prominent suicidal ideation (Kellner et al., 2005). A recent report from the Consortium for Research in ECT (CORE) concluded that antidepressant medication treatment failure does not predict lower remission with ECT (Rasmussen et al., 2007).

4.6. What are the adverse effects associated with ECT?

ECT is a safe procedure with a very low mortality rate (0.2 per 100,000 treatments), approximating the risk of general anaesthesia (Kramer, 1999). Patients who have myocardial ischemia, cardiac arrhythmias, or abdominal aortic aneurysms carry higher morbidity and mortality risks.

The most frequently reported short-term side effects are nausea, headache, muscle pain, oral lacerations, dental injuries, and persistent myalgia (Wijeratne et al., 1999). Although improvements in depression-related cognitive dysfunction have been reported with ECT (Stoudemire et al., 1998), cognitive side effects are of most concern to patients and their families, particularly acute confusional states, anterograde and retrograde amnesia, word finding difficulties, and deficits in autobiographical memory. There is evidence to show impairment in verbal learning after three treatments (Porter et al., 2008), although this did not correlate with long-term memory function. In addition, there were no differences in retrograde memory loss between patients who received unilateral followed by bilateral stimulation, compared to those who received

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### Table 3

**Recommendations for delivery of ECT.**

- Start with either high dose (e.g., 6 times seizure threshold) right unilateral or low dose (e.g., 2 times seizure threshold) bitemporal treatment [Level 1].
- If improvement (at least 20% reduction in a standardized rating scale) after 4–6 sessions, continue to 8–10 sessions [Level 3].
- If no response after 6 treatments, switch to bitemporal treatment up to 12 sessions [bifrontal placement represents an alternative option] [Level 3].

### Table 4

**Indications for ECT as a first-line treatment.**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Level</th>
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<td>Acute suicidal ideation</td>
<td>1</td>
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<tr>
<td>MDE with psychotic features</td>
<td>1</td>
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<tr>
<td>Treatment resistant depression</td>
<td>1</td>
</tr>
<tr>
<td>Catatonia</td>
<td>3</td>
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<tr>
<td>Prior favourable response</td>
<td>3</td>
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<tr>
<td>Repeated medication intolerance</td>
<td>3</td>
</tr>
<tr>
<td>Rapidly deteriorating physical status</td>
<td>3</td>
</tr>
<tr>
<td>During pregnancy, for any of the above indications</td>
<td>3</td>
</tr>
<tr>
<td>Patient choice</td>
<td>4</td>
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*MDE = Major Depressive Disorder.*
only unilateral stimulation (O’Connor et al., 2008). Others have found persistent retrograde amnesia at 2 months post-ECT for bilateral ECT compared to unilateral ECT (Lisanby et al., 2000).

Reducing the frequency of treatments (from 3 to 2 per week), the use of brief pulse rather than sine wave ECT machines, right unilateral or bifrontal positioning of the electrodes (instead of bitemporal) and lower dose stimuli should reduce the frequency and intensity of cognitive side effects (Sackeim et al., 2007).

Claims that ECT may result in structural brain damage are unsubstantiated (Devanand et al., 1994; Zachrisson et al., 2000). In fact, consistent with evidence about various antidepressant treatments, ECT stimulates neurotrophic growth factors including brain derived neurotrophic factor (BDNF), causing migration and growth of new neurons in the hippocampus (Marano et al., 2007), and this may contribute to the antidepressant effect.

4.7. Should ECT be combined with other antidepressant treatments?

Although it has been generally accepted that combining ECT and antidepressant medication does not increase therapeutic effects (Flint and Rifat, 1998), there is recent evidence to suggest that continuation of nortriptyline during ECT increases the remission rate compared to ECT plus placebo (Sackeim et al., 2009) [Level 2]. If replicated, these results have the potential to alter clinical practice.

Because of reports that lithium may increase post-ictal confusion and delirium, many practitioners omit one or two doses prior to each ECT session. The use of benzodiazepines and anticonvulsants may interfere with the seizure duration and are best avoided (Rabheru and Persad, 1997) [Level 3]. In practice, patients who are receiving ECT and taking anticonvulsants/mood stabilizers are generally required to avoid medication on the days of treatment.

4. Repetitive transcranial magnetic stimulation (rTMS)

4.8. What is rTMS and how is it delivered?

Repetitive transcranial magnetic stimulation (rTMS) involves a non-invasive, superficial, powerful magnetic stimulation of the brain. A magnetic field (1.5–2.5 T), generated when current is passed through a coil (electromagnetic induction), is delivered through the skull. In the brain, the magnetic field induces electric currents affecting neuronal function (see George et al., 2007 for a detailed review).

The TMS coil is usually round or figure-eight (butterfly) in shape. The latter produces a stronger and more focal field than the circular coil, and is widely used to deliver repetitive (rTMS) stimuli. There are two types: (i) low-frequency rTMS (at or below 5 Hz) which appears to produce a transient reduction in cortical excitability and (ii) high-frequency rTMS (usually over 5 Hz) which seems to increase excitability (Fitzgerald et al., 2006a). Almost all studies have applied a standard procedure to position the coil, identifying the motor cortical site for optimal stimulation of abductor pollicis brevis, and measuring 5 cm anteriorly along the skull surface and in a parasagittal line. An alternative method of MRI based neuro-navigation to target the left DLPFC between BA 9 and BA 46 has also been evaluated (Fitzgerald et al., 2009).

rTMS is delivered in trains, lasting several seconds, followed by inter-train intervals. Several trains can be delivered per session and usually five sessions are delivered per week. Early reports evaluated the effect of rTMS over 2 weeks (10 sessions), but subsequent trials have been 4–6 weeks in duration (O’Reardon et al., 2007). Variations in the frequency of sessions range from two sessions per day (Loo et al., 2006), to one session every second or every third day (Schutter, 2008).

The intensity of the stimulus is based on the individual motor threshold (the minimal intensity required to produce muscle twitches), and usually is between 90% and 120% of this threshold. Target areas to be stimulated are left or right DLPFC. There is most evidence to support high-frequency rTMS applied to the left DLPFC, but positive results have also been reported with low-frequency right DLPFC (Fitzgerald et al., 2006b), simultaneous combined high-frequency left DLPFC with low-frequency right-DLPFC stimulation, and sequential low frequency to the right hemisphere followed by high frequency to the left (Fitzgerald et al., 2006b) (Table 5).

4.9. How effective is rTMS as an acute antidepressant therapy?

rTMS has been approved for use in Canada since 2002, and received approval in the United States in 2008 to treat depressed adults who failed to respond to at least one antidepressant. Since the first case reports in 1993 (Hollch et al., 1993), there have been many open label and RCTs, evaluating the effect of rTMS for the treatment of depression (O’Reardon et al., 2007). Direct comparisons among rTMS studies are limited by variations in study design, dosing and frequency parameters, and site of stimulation. The authors of two meta-analyses (Couturier, 2005; Martin et al., 2003) concluded that there was insufficient evidence to support claims that high-frequency left sided rTMS was superior to low-frequency right sided rTMS. Subsequent reports (Schutter, 2008) have reached the opposite conclusion. A meta-analysis in 2007 concluded that the efficacy of rTMS was higher in studies published after 2005 (Gross et al., 2007). The best support for rTMS to date is an RCT involving 301 medication free patients showing the active TMS was significantly better than sham, but only after a post hoc correction for inequality of baseline severity between groups (O’Reardon et al., 2007). This study accounts for one third of the entire sample reviewed in a subsequent meta-analysis (Daskalakis et al., 2008).

A meta-analysis of rTMS for TRD reported response and remission rates, respectively, of 25% and 17% for active treatment compared to 9% and 6% for sham treatment. Although these rates are lower than those reported in studies of other interventions for TRD, the differences between active and sham treatments were significant for both response and remission rates (Lam et al., 2008). Enhanced response to

<table>
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<th>Table 5</th>
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<tr>
<td></td>
<td>Start with high-frequency rTMS to the left DLPFC. [Level 1]</td>
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<tr>
<td></td>
<td>Superior outcome for 20 vs 10 sessions. [Level 2]</td>
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<tr>
<td></td>
<td>Minimal evidence for maintenance and relapse prevention effect. [Level 3]</td>
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</table>
rTMS has been reported when an MRI based neuro-navigation technique is used to target the specific site on the DLPFC for administration (Fitzgerald et al., 2009).

There is no evidence to support superiority of rTMS over ECT. In fact, comparisons suggest either equal efficacy (Rosa et al., 2006) or some advantage for ECT (Eranti et al., 2007), although rTMS and ECT are equally cost-effective (Knapp et al., 2008).

4.10. How effective is rTMS as a relapse prevention therapy?

To date, there is only one open-label case series supporting maintenance rTMS to left DLPFC at 100% motor threshold delivered on average 1 to 2 times per week for up to 6 years (O’Reardon et al., 2005). This is a major gap in the evidence base for rTMS.

4.11. Which patients respond best to rTMS?

There is inadequate evidence to characterize a prototypic responder to rTMS although this procedure has been evaluated for the treatment of major depressive episodes in both MDD and bipolar disorder. Predictors of positive treatment outcomes with high-frequency left-DLPFC rTMS include shorter duration of current depressive episode, and the absence of anxiety disorder comorbidity (Lisanby et al., 2009). The majority of evidence supports the superiority of ECT compared to rTMS in depressed patients with psychotic symptoms (Gershon et al., 2003), although there are conflicting data regarding the efficacy of rTMS in TRD (Brakemeier et al., 2007; Lisanby et al., 2009; Loo et al., 2008). Superior efficacy has also been reported in more severe depression (Fitzgerald and Daskalakis, 2008).

There are also preliminary reports that rTMS is effective in various medical populations with comorbid MDD, including patients who have comorbid Parkinson’s Disease (PD) (Fregni et al., 2006), vascular depression (Jorge et al., 2008) and pain in the context of depression (Avery et al., 2007). Results from a Canadian open trial and large case series suggest efficacy in late-life depression (Abraham et al., 2007; Milev et al., 2009), contrary to earlier findings (Mosimann et al., 2004). A preliminary report suggests that the response to rTMS correlates with serotonergic gene polymorphisms (Zanardi et al., 2007).

4.12. What are the adverse effects associated with rTMS?

In general, rTMS is a safe and well-tolerated treatment. Common short-term side effects include headaches and scalp pain usually responding well to symptomatic treatments. Because of concerns about hearing loss (due to the clicking noise of the apparatus), both patients and staff should use ear plugs with 30 dB protection during the treatment process. rTMS does not involve general anaesthesia or seizure induction and is not associated with adverse cognitive effects.

There is no evidence of cognitive impairment with rTMS. In a sham-controlled rTMS study, patients who received active rTMS displayed improvements in measures of executive functioning (Moser et al., 2002). In a head to head comparison of rTMS vs ECT, cognitive performance remained constant or improved and memory complaints were alleviated in the rTMS group (Schulze-Rauschenbach et al., 2005).

There have been 12 case reports of seizures occurring during rTMS (Loo et al., 2008) [Level 3]. In the majority of cases, pre-existing neurological disorders or sleep deprivation were noted. Patients should be screened for these conditions before they receive rTMS (Keel et al., 2000). The effects of rTMS on the fetus are not known at this stage, so this treatment is not recommended during pregnancy.

To date, there have been no systematic long-term safety evaluations of rTMS, although open-label reports on maintenance rTMS suggest that it is safe in the long term (O’Reardon et al., 2005) [Level 3]. Absolute contraindications include seizures, the presence of ferromagnetic material anywhere in the head (excluding the mouth) such as cochlear implants, brain stimulators or electrodes, aneurysm clips, plates, etc. Cardiac pacemakers are also a contraindication. Increased intracranial pressure, severe cardiovascular disease, epilepsy and other serious medical conditions are also contraindications (Nahas et al., 2008).

4.13. Should rTMS be combined with other antidepressant treatments?

There is growing evidence that the combined use of rTMS with antidepressant medication accelerates response under sham-controlled conditions (Bretlau et al., 2008; Rossini et al., 2005; Rumi et al., 2005), although initial advantages are not always sustained (Poulet et al., 2004; Rossini et al., 2005) [Level 1]. Adding open-label mirtazapine also increased the response to rTMS monotherapy (Schule et al., 2003) [Level 3].

Vagus nerve stimulation (VNS)

4.14. What is VNS and how is it delivered?

VNS is an approved treatment in the USA and Canada for refractory epilepsy. The clinical observation of mood improvement during VNS therapy for epilepsy provided the rationale to evaluate its potential use in TRD. The US FDA approved the use of the VNS for refractory depression in 2005 and Health Canada approved its use for TRD in 2001.

VNS involves implantation of a bipolar electrode around the left vagus nerve, accessed through a small incision in the lower neck. This wire is connected to a subclavicular pulse generator, which delivers intermittent electrical signals to the left vagus nerve. Signal frequency and intensity can be controlled remotely using a telemetric wand linked to a palmtop computer. The left vagus nerve is chosen for VNS due to its limited cardiac effects. The most commonly used stimulation parameters are: a frequency of 20–30 Hz, an intensity 0.25 mA, and a pulse width of 250–500 ms with a cycle of 30 s of stimulation every 5 min. Battery life of the device is 6–8 years; hence its status needs to be checked during the course of clinical follow-up until it is ultimately replaced (Rado and Janicak, 2007).

The mechanism of action of VNS is not fully understood although emerging data suggest that VNS therapy modulates the function of neural structures implicated in depression and also influences monoaminergic neurotransmission (Nemeroff et al., 2006).
4.15. How effective is VNS as an acute antidepressant therapy?

In a randomized sham-controlled trial, VNS only showed a modest effect with a response rate of 15% compared to 10% with sham treatment (implantation but device not activated) during a 10 week trial and thus failed to demonstrate significant acute antidepressant effects (Rush et al., 2005a). Results from four open-label studies showed a response rate of 30% and remission rate of 15% during 10–12 weeks of adjunctive VNS therapy (Rush et al., 2000; Sackeim et al., 2001c; Corcoran et al., 2006; Schlaepfer et al., 2008b).

4.16. How effective is VNS during extended therapy?

When patients were followed for 1–2 year extension phases, response rates ranged from 27% to 46% and remission rates from 16% to 29% (Marangell et al., 2002; George et al., 2005; Nahas et al., 2005; Rush et al., 2005a,b; Nierenberg et al., 2008). In one of these studies, a parallel non-randomized design was used to compare VNS plus treatment as usual with treatment as usual only and response rates at 12 months were 27% for VNS and 13% for treatment as usual (George et al., 2005). One explanation is that VNS may deliver a delayed antidepressant effect with an increasing clinical improvement over time, although changes in concurrent antidepressant medications during the extension trials cannot be excluded as an explanation for the increased rates of response and remission. Given the lack of substantial evidence for short-term and long-term efficacies in acute severe depression, the appropriate place of VNS in the treatment algorithm for TRD remains to be determined.

4.17. How effective is VNS as a relapse prevention therapy?

Given the evidence of a slowly progressive therapeutic effect in extension studies, adjunctive VNS therapy may have a role in long-term maintenance treatment for less severe TRD [Level 3], although further RCT evidence is required.

4.18. Which patients respond best to VNS?

Results from an acute phase pilot study of 59 TRD participants suggest that patients with chronic or recurrent, TRD may show long-term benefit when treated with VNS (Nahas et al., 2005). In practice, it would be reasonable to consider patients who have failed at least 4 prior treatments at adequate dose and duration for the current episode. Failure to respond to ECT is not a prerequisite.

4.19. What are the adverse effects associated with VNS?

Overall, VNS has a favourable side effect profile, however, the common acute side effects are voice alteration, neck pain, headache, cough, dysphagia and dyspnoea (Table 6). They are related to the stimulation parameters and can be minimized by reducing the intensity of the stimulation being delivered. The rate of psychiatric adverse events have been reported as follows: hypomania (3.3%), mania (1.2%), and suicide attempt (3.5%). No cognitive side effects have been reported (Sackeim et al., 2001b).

4.20. Should VNS be combined with other antidepressant treatments?

As with other neurostimulation treatments, most patients in VNS trials have continued on their pre-trial antidepressant medications. Evidence of greater antidepressant effects accruing over time with concurrent medication changes in patients receiving VNS suggests that these two antidepressant modalities may work synergistically [Level 3]. However, there is insufficient evidence to recommend any specific combination of VNS and antidepressant medication.

Deep brain stimulation (DBS)

4.21. What is DBS and how is it delivered?

DBS involves the stereotactic neurosurgical implantation of electrodes under MRI guidance to distinct brain regions. These electrodes are connected to a stimulator implanted in the chest wall (similar to VNS) that provides continuous electrical stimulation. After several decades of evaluation as a treatment for Parkinson’s Disease, where stimulation of the subthalamic nucleus results in acute and sustained relief of tremor and rigidity, there is emerging evidence to support DBS as an experimental intervention for patients with treatment-refractory depression.

There is no consensus on the most effective target brain region for implantation, although three regions have been explored. To date, the subcallosal cingulate gyrus (SCG) (approximately Brodmann Area 25) has been evaluated most (Lozano et al., 2008; Mayberg et al., 2005; Neimat et al., 2008). The rationale for this site comes from evidence that healthy volunteers experiencing sadness during functional neuroimaging display increased activity in BA 25 and depressed patients responding to antidepressant medications demonstrate a reduction (Mayberg, 2003). Two additional sites in close proximity to one another have also been examined: the nucleus accumbens (Schlaepfer et al., 2008a) and the ventral caudate/ventral striatum region (Malone et al., 2009), on the basis that anhedonia, a core depressive symptom, is modulated through dopaminergic pathways involving these regions.

Following surgery, which may be carried out in the awake state, patients wait approximately 7–14 days before the device is switched on. This allows localized edema to resolve and inspection of both the scalp and subclavicular wound sites. Typical settings within a range of 3.5–5.0 V, 130 Hz and 90 ms have been reported (Lozano et al., 2008).

4.22. How effective is DBS as an acute antidepressant therapy?

To date, there are no large RCTs, on which to judge efficacy. In the largest open trial reported so far, 20 patients with

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<td>Profile of adverse events with VNS.</td>
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<table>
<thead>
<tr>
<th>Side effect</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoarseness</td>
<td>54%–68% [Level 2]</td>
</tr>
<tr>
<td>Cough</td>
<td>6%–29% [Level 2]</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>15–23% [Level 2]</td>
</tr>
<tr>
<td>Neck pain</td>
<td>13–21% [Level 2]</td>
</tr>
<tr>
<td>Headache</td>
<td>4–22% [Level 2]</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>4–21% [Level 2]</td>
</tr>
</tbody>
</table>

Modified from O’Reardon et al. (2006).
treatment resistant MDD were followed for one year after surgery (Lozano et al., 2008). Six months post-surgery, 60% of patients met response criteria and 35% achieved remission. The improvements in depressive symptomatology remained stable for the remainder of the 12 month period, with 55% of patients (13/20) meeting criteria for response: results similar to those in the original report on 6 patients with TRD (Mayberg et al., 2005) and in a more recent report that noted a 50% response rate (Malone et al., 2009).

4.23. How effective is DBS as a relapse prevention therapy?

Patients who responded early to SCG DBS were more likely to maintain their response, although late responders (response after 6 months of DBS) were also observed. There are currently no relapse prevention studies, but anecdotal case reports suggest relapse when the device has been inadvertently switched off or the battery has failed, with a return to symptom improvement when the device is reactivated.

4.24. Which patients respond best to DBS?

To date, no demographic factors or illness characteristics have been identified to predict response to DBS. Larger sample sizes are required to establish definition of factors associated with antidepressant response with DBS.

4.25. What are the adverse effects associated with DBS?

Post-operative pain, or discomfort, intracranial or subcutaneous hemorrhage, and wound infection at the intracranial or subclavicular site, have been reported in some depressed patients who have received DBS (Lozano et al., 2008). Emergent symptoms of hypomania have been reported in a limited number of patients, including those with and without a history of bipolar disorder (Malone et al., 2009). Follow-up of 6 patients with neuropsychological testing revealed no evidence of cognitive impairment after 12 months of SCG DBS (McNeely et al., 2008) [Level 3]. Adverse events associated with DBS for PD, essential tremor and dystonia have been reported in a meta-analysis of ten years experience (Appleby et al., 2007). These authors conclude that the prevalence of depression was lower (2–4%) than in PD patients who have not received DBS, but that the rate of completed suicide appears to be elevated compared to both the general population and PD patients who did not receive DBS (Appleby et al., 2007). While the adverse events reported in the small number of TRD patients compare favourably to those reported in the much larger sample included in this ten year meta-analysis among DBS-PD patients, and may be explained by the different anatomical sites for stimulation and the neurodegenerative nature of PD, caution is required at this early stage in the evaluation of DBS for TRD.

4.26. Should DBS be combined with other antidepressant treatments?

To date, the open-label studies of DBS for TRD have aimed to minimize concurrent changes to antidepressant medications. There is no published evidence on the relative effectiveness of DBS with or without concurrent antidepressant medications. In the largest study of DBS for TRD to date, it was noted that one year post-DBS, antidepressant medications were either decreased in dose or discontinued in half of the patients (Lozano et al., 2008). Therefore, there is insufficient evidence to recommend DBS in the absence of concurrent antidepressant medication [Level 3].

7. Conclusion

There have been important advances in neuromodulation techniques since the previous CANMAT guideline publication for MDD in 2001. These changes reflect advances in theoretical models for depression, paired with emerging technologies to deliver continuous or intermittent electrical stimulation and experience from the application of these techniques in other disease states. At this stage, only ECT has a robust evidence base for its recommendation.

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Conflict of interest

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Research report

Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. V. Complementary and alternative medicine treatments

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Complimentary and Alternative Medicine
Light therapy
Exercise therapy
Nutraceutical therapies

ABSTRACT

Background: In 2001, the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. A revision of these guidelines was undertaken by CANMAT in 2008–2009 to reflect advances in the field. There is widespread interest in complementary and alternative medicine (CAM) therapies in the treatment of major depressive disorder (MDD).

Methods: The CANMAT guidelines are based on a question-answer format to enhance accessibility to clinicians. An evidence-based format was used with updated systematic reviews of the literature and recommendations were graded according to Level of Evidence using pre-defined criteria. Lines of Treatment were identified based on criteria that included evidence and expert clinical support.

Results: There is Level 1 evidence to support light therapy in seasonal MDD and St. John's wort in mild to moderate MDD. There is also some evidence for the use of exercise, yoga and sleep deprivation, as well as for omega-3 fatty acids and SAM-e. Support for other natural health products and therapies is still limited.

Limitations: The evidence base remains limited and studies often have methodological problems, including small samples, variability in dose, short duration of treatment, unknown quality of the agent and limited long-term data. Safety data are also sparse with little information about drug interactions.

Conclusions: Some CAM treatments have evidence of benefit in MDD. However, problems with standardization and safety concerns may limit their applicability in clinical practice.

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Introduction

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, collaborated on the publication in 2001 of evidence-based clinical guidelines for the treatment of depressive disorders (Kennedy et al., 2001).

A revision of these guidelines was undertaken by CANMAT in 2008–2009 to update the recommendations based on new evidence. The scope of this guideline encompasses the management of adults with unipolar major depressive disorder (MDD). Guidelines for bipolar depression are included in the CANMAT guidelines for bipolar disorder (Yatham et al., 2009).

Complementary and alternative medicine (CAM) treatments (such as light therapy, acupuncture, yoga, dietary and herbal supplements, etc.) are commonly used by people with depression and other psychiatric conditions, in part because of a
prevalent belief that “natural is better” (Tindle et al., 2005). There are also intuitive reasons to support the use of light, sleep deprivation and exercise in the treatment of MDD. In a survey of primary care patients, about 11% of people with depression and anxiety reported using a CAM therapy (Roy-Byrne et al., 2005), which is similar to the proportion of people with MDD who use antidepressants (Mojtabai and Olfson, 2008). There is also a bias towards certain forms of CAM in different parts of the world, e.g., yoga in India, and St. John’s wort in Germany and other parts of Europe. In this section, guidance is provided for the use of physical therapies and natural health products for MDD. As with all guidelines, recommendations must be customized within the context of an individual patient and should not be considered as standards of care.

Due to the large number of publications in this area, these guidelines are restricted to the more common and more evidence-based therapies. As such, certain other CAMs, including aromatherapy, qi gong and massage therapy, have not been reviewed.

Methods

The full methods have been described elsewhere (Kennedy et al., 2009) but, in summary, relevant English language studies published from January 1, 2000 to December 31, 2008 were identified using computerized searches of electronic databases (PubMed, PsychInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and reviews of other guidelines and major reports. The question–answer format of the previous guidelines has been retained based on feedback from clinicians. Recommendations include the Level of Evidence for each graded Line of Treatment, using specified criteria (Table 1). Note that this article does not provide comprehensive citations or references, but the evidence tables are posted on the CANMAT web site (www.canmat.org).

5.1. What are general caveats and limitations to the evaluation and clinical use of CAM treatments?

Because CAM therapies are not regulated like pharmaceuticals, the evidence supporting many of these therapies is often anecdotal. Nutraceuticals and herbal remedies (called dietary supplements in the U.S. and other countries) are regulated by Health Canada under the Natural Health Product Regulations, which stipulate a pre-market approval process that includes the review of evidence of both safety and efficacy, albeit with lower rigor for efficacy in conjunction with the claims. Licensed products are assigned a natural product number and only products with such a number are recommended for use.

There are an increasing number of randomized controlled trials (RCTs) for CAM treatments. The quality of many RCTs remains an issue, with variability in diagnostic criteria, small sample sizes, limitations of blinding and placebo controls, and few systematic evaluations of side effects. Even for those treatments with reasonable evidence of efficacy, there are variations and lack of standardization in dosage, potency, and concentration, all of which make it difficult for clinicians and patients to be confident they are using the same doses as described in clinical studies. There is, on balance, greater evidence and clinical experience with traditional treatments (pharmacotherapy and psychotherapy) and few studies directly compare these with novel treatments like neurostimulation or CAM.

Because of these issues, first-line psychotherapy (Parikh et al., 2009) or pharmacotherapy (Lam et al., 2009) recommendations should usually be considered before CAM treatment, especially as monotherapy. Adjunctive use of CAM therapies as an add-on treatment to evidence-based psychotherapy or pharmacotherapy can be considered, but clinicians must still be cautious because there is very little information about interactions of CAM therapies with medications.

Physical Therapies

5.2. What is light therapy? Is it effective in treating depression?

Light therapy consists of daily exposure to bright light, usually administered at home with a fluorescent light box. The standard “dose” of light is 10,000 lux (intensity) for 30 min per day given in the early morning. Response usually occurs within 1–3 weeks. Other light devices that have shown efficacy, in small studies, include those using light-emitting diodes (LEDs) (Desan et al., 2007; Glickman et al., 2006). The mechanism of action of light therapy is still under debate, with correction of disturbed circadian rhythms and modulation of serotonin and catecholamine systems being among the theories proposed (Sohn and Lam, 2005).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Criteria for Levels of Evidence and Lines of Treatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Evidence</td>
<td>Criteria</td>
</tr>
<tr>
<td>1</td>
<td>At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals</td>
</tr>
<tr>
<td>2</td>
<td>At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals.</td>
</tr>
<tr>
<td>3</td>
<td>Non-randomized, controlled prospective studies or case series or high quality retrospective studies.</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion/consensus.</td>
</tr>
<tr>
<td>Line of Treatment</td>
<td>Criteria</td>
</tr>
<tr>
<td>First-line</td>
<td>Level 1 or Level 2 evidence plus clinical support</td>
</tr>
<tr>
<td>Second-line</td>
<td>Level 3 evidence or higher plus clinical support</td>
</tr>
<tr>
<td>Third-line</td>
<td>Level 4 evidence or higher plus clinical support</td>
</tr>
</tbody>
</table>

* Levels of evidence do not assume positive or negative or equivocal results; they merely represent the quality and nature of the studies that have been conducted.
* A first-line treatment represents a balance of efficacy, tolerability and clinical support. Second-line and third-line treatments are reserved for situations where first line treatments are not indicated or cannot be used, or when first line treatments have not worked.
* Clinical practice refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are realistic and applicable for clinical practice, in order to enhance the utility of the guidance for clinicians. Therefore, treatments with higher levels of evidence may be downgraded to lower Lines of Treatment due to clinical issues such as side effect or safety profile.