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Treatment Resistant Depression—Advances in Somatic Therapies

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Background. *The failure to achieve remission for patients with Major Depressive Disorder (MDD) represents a major public health concern. Inadequately treated depression is associated with higher rates of relapse, poorer quality of life, deleterious personal and societal economic ramifications, as well as increased mortality rates. Unfortunately, only a minority of patients achieves this goal with initial antidepressant treatment and by convention, failure to achieve response after two adequate trials of antidepressant therapy defines "Treatment Resistant Depression" (TRD). Furthermore, results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) group of studies suggest that approximately 50% of "real world" patients who meet criteria for MDD fail to achieve remission, even after four carefully monitored sequenced treatments.*

Methods. *Given these limitations of existing antidepressant medications alone and in combination, together with improved understanding of the neural circuitry of depression, it is not surprising that there is a renewed interest in neuromodulation strategies for TRD.*

Results. *The purpose of this article is to review the evidence for the inclusion of various non-pharmacological, neuromodulatory strategies for TRD. Specifically, information regarding the mechanism, tolerability and efficacy of electroconvulsive therapy (ECT), magnetic seizure therapy (MST), repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and deep brain stimulation (DBS) in ameliorating TRD will be presented.*

Conclusions. *Although these treatments are at various stages of clinical development, they represent a new frontier in expanding the treatment options available for individuals with TRD, as well as contributing to a better understanding the neurobiology of depressive disorders.*

Keywords Deep brain stimulation, Vagal nerve stimulation, Transcranial magnetic stimulation, Electroconvulsive therapy

INTRODUCTION

Approximately 50% of patients fail to achieve an adequate response to the first antidepressant treatment, and over half of those fail to respond to a second pharmacotherapy approach (1). Phamacotherapies are the mainstay of treatment, although various neuromodulatory somatic treatments have risen in prominence as evidence-based alternatives. The purpose of this review is to provide an update on these advances in the somatic approaches to Treatment Resistant Depression (TRD).

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Definition and Pharmacotherapy Approaches

TRD is a relative concept. Several definitions have been proposed, ranging from the generic "inadequate response following adequate antidepressant therapy" (1) to the more operationally specific "failure to respond to two adequate trials of different classes of antidepressants" (2). Others have suggested staging levels of resistance, with a recommendation that treatment with first line antidepressants from SSRI and SNRI classes should precede trials of tricyclic and monoamine oxidase inhibitor antidepressants before moving to electroconvulsive therapy (3).

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) series of studies evaluated the response to switching, augmentation and combination options across increasingly treatment-resistant patients. Even after four sequential trials, almost

50% of patients had failed to achieve remission and would qualify for a diagnosis of TRD (4). This sequential trial did not evaluate the role of atypical antipsychotic agents or any somatic therapies including Electroconvulsive Therapy (ECT).

Neurocircuitry Models of Depression: Implications for TRD

Neurocircuitry models of depression hypothesize that depressive symptoms are reflective of a failure in homeostatic processes. Attempts to compensate for endogenous or exogeneous stressors set in motion changes at a molecular level aimed at re-establishing a euthymic mood state (5). These circuit dysregulations are represented in functional neuroimaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) techniques.

The mode of action of existing treatments for depression, namely psychotherapy, pharmacotherapy and various forms of neuromodulation, can be similarly evaluated within the same circuitry framework. Different treatment modalities may modulate distinct neural targets in both a "top-down" and a "bottom-up" fashion to restore homeostasis. Patients with TRD represent the subset of depressed individuals for whom these resetting techniques have failed. These patients are candidates for somatic treatments such as electroconvulsive therapy (ECT), magnetic seizure therapy (MST), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) or deep brain stimulation (DBS), in order to "kick start" the cascade of adaptive processes necessary to compensate for a depressive mood state. The primary focus of this review is to evaluate the rationale and therapeutic potential for each of these somatic therapies in TRD (see Table 1).

Electroconvulsive Therapy

Despite a half century of progress in the pharmacotherapy of affective illnesses, ECT remains an important therapeutic modality, particularly for TRD. However, the stigma associated with this treatment and the burgeoning range of pharmacotherapy and psychotherapy options have contributed to the frequently held view that ECT is seen as "a treatment of last resort" (6). The presence of acute suicidal ideation, delusions or catatonia are generally indications for the use of ECT (7–9). The polarity of a depressive episode does not appear to influence outcome (10). Currently, ECT is most likely to be offered to the elderly, the medically ill and pharmacotherapy resistant or intolerant populations (11,12).

The strongest predictor of favorable response to ECT is a prior history of resistance to antidepressant medication. Over 50% of patients who have failed to respond to one or more adequate antidepressant medication trials, respond to ECT (13). Other predictors of poor response to ECT include chronicity and comorbid personality disorders (14). While the evidence to support the use of ECT as a first line treatment in patients who received inadequate trials of antidepressant medication is limited, response rates in the 80%–90% range have been reported (8).

Meta-analyses have revealed that ECT is superior to sham ECT, placebo or antidepressant medications (15,16). In one meta-analysis, the likelihood of responding to ECT was almost 4 times greater than to antidepressants (16). The antidepressant effects of ECT are usually apparent earlier than with antidepressant medications (17). A report from the Consortium for Research in ECT (CORE) (18) revealed that over half of the subjects demonstrated an improvement within the first week and that 65% had achieved remission after 10 treatments. Evidence from preclinical studies on the effects of various antidepressant therapies, including electroconvulsive shock, on hippocampal neurogenesis may help to explain the more rapid action of ECT compared to antidepressant medications (19).

There is robust evidence that the antidepressant efficacy of ECT is related to its stimulation parameters. In an influential double blind randomized study, Sackeim and colleagues evaluated the antidepressant effects of right unilateral (RUL) ECT at 1.5, 2.5 and 6 times seizure threshold (20). Efficacy of RUL treatment was associated with the dose relative to seizure threshold rather than the absolute dose administered. RUL ECT at 6 times seizure threshold was also found to have comparable efficacy, but less cognitive side-effects than bifronto-temporal ECT at 1.5 times seizure threshold. In contrast to the dose-response relationship between antidepressant efficacy and stimulus dose for RUL ECT, the efficacy of bilateral fronto-temporal ECT has been described as a step-function with optimal efficacy achieved at marginally supra-seizure threshold stimuli (6,21). An average course of ECT consists of 6–8 treatments, although some individuals may require more treatments to optimize the antidepressant response.

Relapse Prevention Following Electroconvulsive Therapy

Although the acute antidepressant properties of ECT are unequivocal, at least 50% of patients will relapse within the first year in the absence of medication prophylaxis and 90% of those relapses will occur in the first 6 months (20). There is no evidence that ECT can "energize" an antidepressant to which the patient has previously failed to respond (22). In one of the few reports to evaluate relapse prevention following ECT, the combination of nortriptyline and lithium carbonate reduced the rate of relapse during the 6 months following ECT (23). Unfortunately, there are no data at this point to compare the efficacy of maintenance ECT and medication management.

Cognitive side-effects associated with ECT have limited its widespread use. These include an acute confusional state lasting minutes to hours associated with both the post-ictal state and recovery from the general anesthetic; anterograde amnesia which resolves within weeks of cessation of treatment and retrograde amnesia, the rarest yet most important adverse cognitive effect of ECT. Emerging somatic techniques represent an attempt to disentangle and fine-tune the robust antidepressant

Table 1 Comparison of Brain Stimulation Techniques for the Treatment of TRD

	Advantages	Disadvantages	Outstanding Clinical Questions
Electro-convulsive Therapy	• Largest body of evidence to support its efficacy in TRD • Efficacy across multiple subtypes of depressive episodes, including psychotic depression • Demonstrated to decrease rates of suicide in individuals with depression • Ability to modify the laterality of the stimulation and amount of energy delivered • Widely available in most clinical settings	• Cognitive dysfunction can be prominent. • Rapid recidivism of depressive symptoms has been observed following the discontinuation of the treatment.	• Can the cognitive side-effects be dissociated from its efficacy in the treatment of depression? • The clinical usefulness of alternative electrode placements e.g. bifrontal • Is maintenance ECT superior to pharmacotherapy to prevent relapse following treatment of the acute episode?
Transcranial Magnetic Stimulation	• Non-convulsive stimulation of the brain • Does not require general anesthesia for its administration • Ability to modify the location and frequency of the stimulation applied to the brain • Both stimulation and inhibition of neurons possible. • Effective in animal models of depression.	• Not as effective as ECT for severe depressive episodes • Limited date regarding long-term efficacy • Unable to directly stimulate subcortical structures	• Determining the optimal stimulation parameters.
Magnetic Seizure Therapy	• Seizure produced by stimulation of the brain with Transcranial Magnetic Stimulation device requires decreased doses of anesthetic agents • Decreased cognitive side-effects compared to ECT. • Animal data supporting its safety.	• Difficult to reliably elicit a seizure with current Transcranial Magnetic Stimulation devices • Limited availability.	• No controlled trials to date demonstrating its clinical efficacy in the treatment of depression
Vagus Nerve Stimulation	• Large body of clinical evidence regarding the safety and tolerability of VNS from its use in the treatment of epilepsy • Growing literature regarding mechanisms of action • May have increasing benefit over time. • Well tolerated. • Effective in animal models of depression.	• Limited efficacy in the treatment of depression in the short-term • Less effective in individuals with greater degrees of treatment-resistance • Invasiveness. Requires a surgical procedure for implantation of the device	• No controlled trials to date demonstrating clinical efficacy in the treatment of depression
Deep Brain Stimulation	• Large body of clinical evidence regarding the safety and tolerability of DBS from its use in the treatment of movement disorders and OCD. • ++ anatomical specificity. Ability to target both cortical and subcortical structures • ++ flexibility i.e. provides potential to provide stimulation from multiple sites along the electrode. Ability to modify stimulation parameters • Reversible. • Evidence from an open trial demonstrating both acute and sustained antidepressant response in TRD.	• Invasiveness. Requires a neurosurgical procedure for implantation • Limited availability.	• No controlled trials to date demonstrating clinical efficacy in the treatment of depression. • Determining the optimal stimulation parameters and anatomical location for treatment of depression.

effects seen with ECT without incurring the unwanted cognitive side-effects.

Magnetic Seizure Therapy

Magnetic Seizure therapy (MST) is a proposed refinement of ECT, which aims to induce a seizure through magnetic stimulation of the cortex rather than by electrical stimulation (24,25). Currently the treatment is considered investigational and is available only in the context of research protocols. Repetitive trains of stimulation are delivered to the frontal cortex through a transcranial magnetic stimulation (TMS) device used to generate magnetic fields of up to 2 Tesla in magnitude (26). When repetitive trains of TMS (rTMS) are applied to the scalp, action potentials can be induced in cortical neurons. If sufficient stimulation is generated, a generalized tonic-clonic seizure can be elicited. Compared to ECT, where much of the exogenously applied electrical stimulus is prevented from exerting its effects on the brain due to high skull impedance, magnetic fields are able to penetrate the scalp and skull with no resistance, offering the promise of greater control over the location and extent of cortical stimulation than can be achieved with ECT (24). However, seizures have not been reliably provoked with current rTMS devices even at maximal energy output settings (27), suggesting that modifications to conventional rTMS devices are necessary to ensure that a seizure is generated.

MST has the potential to become a more precise method of seizure induction by focusing the stimulation on selected cortical structures thought to be essential for antidepressant efficacy, while minimizing spread of the effects to medial temporal regions implicated in the cognitive side effects of ECT (28,29). Cognitive side effects of MST, including post-ictal recovery time, attention and some measures of anterograde and retrograde amnesia are more benign than with ECT (29,30).

Primate models of MST suggest that MST-induced seizures differ from seizures induced by electrical convulsive stimulation (ECS) in their effects on the hippocampus. Specifically, MST results in less marked anatomical changes in the dentate gyrus than ECS (28) and does not increase mossy fibre sprouting, as occurs with ECS (30). This relative sparing of the hippocampus may underlie the superior cognitive profile of MST.

While the cognitive side-effect profile of MST is more benign than that of ECT, the antidepressant efficacy of MST remains to be established. Other than case reports (24,31) and a small case series (27), the antidepressant effect of MST awaits further verification.

Transcranial Magnetic Stimulation

In contrast to MST, TMS involves repeated subconvulsive magnetic stimulation to the brain. This treatment is more generally available and has a larger database of evidence to evaluate compared to MST. It is also less invasive than other neuromodulatory interventions. The first report of the antidepressant effects of rTMS in 1993 was by Hoflich who performed the procedure on two patients with TRD (32). The frequency of stimulation determines whether the activity of the stimulated neural structures is inhibited or enhanced. Slow TMS, defined as a frequency ≤ 1 Hz, and fast TMS with a frequency ≥ 1Hz, exert opposite effects. Slow TMS over the frontal cortex in depressed patients has been reported to decrease cerebral blood flow, while fast TMS increases blood flow to this region (33).

For both practical and theoretical reasons the dorsolateral prefrontal cortex (DLPFC) has been the primary target for rTMS. Since the strength of the magnetic field generated by TMS decays exponentially with distance, only superficial cortical structures such as the DLPFC can be directly modulated by TMS (34) and direct stimulation of deeper subcortical structures such as the cingulate and limbic cortices is precluded. There is also theoretical support for DLPFC stimulation, as reduced activity is frequently observed in the DLPFC of depressed patients in neuroimaging studies (35). Most commonly, fast TMS to the left DLPFC has been employed as the preferred antidepressant strategy, based on the rationale that stimulating this region will normalize the hypoactivity, although the putative antidepressant effect of slow rTMS over the right PFC has also been investigated (36). Several meta-analyses of the acute antidepressant effects of left DLPFC rTMS have been reported, with effect sizes ranging from 0.35 to 0.89 (37,38).

In the studies directly comparing rTMS to ECT, rTMS has similar antidepressant efficacy to ECT in non-psychotic depressed patients, but is clearly inferior to ECT in the treatment of psychotic depression (39,40). rTMS has been associated with a better cognitive side-effect profile than ECT (41) and is generally well tolerated (42). Common side-effects include tinnitus, headaches and facial twitches, but they are mild and respond to analgesics (43). Rarely, more serious side-effects including switches to mania (44) and the induction of a seizure have been reported. The incidence of seizures with TMS has been estimated to be less than 1% and may be lower with lower frequency rTMS (45).

Negative predictors of clinical response to rTMS in TRD include older age (46), greater prefrontal atrophy (47), history of refractoriness to antidepressant pharmacotherapy, longer duration of the index depressive episode (48) and depression with psychotic (40) or melancholic features (49).

Vagus Nerve Stimulation

The genesis of the idea for studying the role of vagus nerve stimulation (VNS) in the treatment of TRD stemmed from the observation of mood improvement, independent of seizure control, in patients who were receiving this therapy for epilepsy (50,51). Additionally, PET imaging in individuals receiving VNS for refractory epilepsy demonstrated reductions

in the metabolic activity of the amygdala, hippocampus, and cingulate gyrus (52); structures that have been implicated in the neurocircuitry of mood (53–56). VNS has been approved in the US and Europe for medication-resistant epilepsy and is now approved in the US for TRD, although expense and limited availability currently preclude general access to this treatment option.

Treatment with VNS requires the implantation of a generator, similar in size to a cardiac pacemaker, in the chest under the skin just below the clavicle. An incision is made in the lower neck to expose the left vagus nerve. Electrodes are then wrapped around the vagus nerve and subcutaneously connected to the battery generator, which delivers intermittent-pulsed electrical signals to the vagus nerve. The left vagus nerve is chosen, since it has limited effects on cardiac physiology (57). The stimulation parameters, including the intensity, frequency and timing of stimulation can be programmed remotely by a telemetric wand (58,59).

The vagus nerve consists largely of afferent fibers, which transmit sensory information from the head, neck and abdomen to the brain stem (58). The fibers of the vagus nerve then terminate in the nucleus tractus solitarius, which serves as a relay station to other brain regions including those involved in the neurocircuitry of pain and emotion (59). Thus, it has been hypothesized that stimulation of the vagus nerve may provide a means to alter activity in widely distributed brain regions in a bottom-up manner.

In general, VNS has been well tolerated. The most common side-effect is hoarseness of voice, which is experienced as a benign irritant by virtually everyone receiving this therapy (60). VNS has been associated with switches into mania in patients with and without a known history of Bipolar Disorder, although manic symptoms were short-lived (1–3 days) and were successfully managed by changes in the stimulation parameters and psychotropic medications (61,62). VNS has not been associated with neuropsychological impairment, and in fact may improve cognitive function in some individuals (63,64).

Convergent lines of evidence from preclinical and clinical investigations of VNS support common mechanisms of action shared by VNS and other antidepressant treatments (65,66). Stimulation of the vagus nerve in rats increased firing rates of neurons in the locus coeruleus (LC) and the dorsal raphe nucleus (DRN), which are important in noradrenergic and serotonergic neurotransmission respectively (67). Furthermore, in this study the firing rates of both the LC and DRN neurons increased as the length of treatment was prolonged, suggesting that VNS may be capable of initiating or facilitating a cumulative long-term process of neural adaptation.

This neurobiological finding supports consistent clinical observations that the antidepressant efficacy of VNS demonstrates an extended latency before becoming clinically effective. Initial pilot studies of the acute antidepressant effect of VNS reported response and remission rates of 30% and 15% respectively after 12 weeks of VNS therapy (68,69), with a mean time to response just under 50 days. In a follow-up sham-controlled trial, acute effects of active VNS treatment for TRD were modest, with a response rate of 15% in the active treatment group compared to 10% in the sham stimulation group (70), although these rates increased after the initial 3 months of treatment with VNS (62,71,72). However, it is unclear whether the long-term benefits should be attributed to VNS or to the concomitant medication changes that were permitted during the follow-up period in these studies.

The finding that VNS combined with pharmacotherapy may have long-term benefits in TRD, has been replicated (73). In a group of 11 patients with TRD, there was one responder at 3 months (9%), two at 6 months (18%) and 6 at 1 year (54%) of VNS treatment. Changes in medications were permitted after 3 months post-implantation. At the end of 1 year, three patients were in remission (27%), defined in this study as a score on the 24-item HRSD of less than 10.

Further work needs to be done with respect to predictors of response to VNS in TRD. It appears that the degree of previous resistance to antidepressant pharmacotherapy is inversely correlated with the likelihood of responding to VNS (69). Given that VNS does not appear to have robust acute antidepressant effects, the most appropriate place of VNS in the therapeutic armamentarium of depression remains to be determined. Data regarding its high tolerability and potential for long-term benefit to accrue when used in combination with pharmacotherapy suggest that VNS may find a role as an adjunctive or augmentation strategy in TRD. It may also have a role in relapse prevention following ECT, although this awaits further examination (58).

THE EMERGENCE OF DEEP BRAIN STIMULATION FOR TRD

Rationale

Informed by over a decade of experience in the use of DBS for several neurological conditions including Parkinson's disease (PD), and by advances in functional neuroimaging to guide the selection of appropriate stimulation targets, DBS represents a unique targeted intervention for treatment-resistant psychiatric populations, including TRD. At this stage however, it remains an investigational treatment within clinical research settings and will remain so until its effectiveness is established in larger clinical populations.

The selection of target sites has been driven by clinical observations of mood benefit in other neuropsychiatric conditions. Support for stimulation of Brodmann Area 25 (BA 25) is hypothesis driven. Converging lines of evidence to support the role of BA 25 in the modulation of mood states have been advanced by Mayberg and colleagues in several studies that used Positron Emission Tomography (PET) to evaluate regional cerebral activity in different mood states (74). Increased metabolic activity in BA 25 was evident in healthy

volunteers during induction of transient sadness, while reductions in the same region were observed in fluoxetine responsive depressed patients. Similarly, depressed patients who achieved remission with venlafaxine showed a significantly higher level of metabolism in BA 25 compared to non-depressed controls at baseline and experienced a significant decrease in metabolic activity during treatment (75). These findings resonate with evidence from the initial evaluation of DBS for TRD in which four of six highly refractory depressed patients had a positive response and showed similar reductions in BA 25 activity (76). A subsequent report on 12 patients from this protocol suggests that similar rates of response have been maintained (77).

Other possible anatomical sites, where stimulation may improve depressive symptoms including the nucleus accumbens, have been suggested (78,79).

Technique of DBS

Two electrodes, each with four active stimulation sites, are bilaterally implanted under stereotactic guidance and local anesthesia through burr holes in the skull. Following implantation and intraoperative microelectrode recording to confirm placement of the electrodes, they are then connected to a pacemaker implanted under the pectoralis muscle through lead wires channeled subcutaneously under the scalp. Following successful implantation of the device, the stimulator is turned on and remains active 24 hours a day. The stimulation parameters can be adjusted, as needed, via a telemetric wand.

Psychiatric Management

Given the complexity of this treatment, DBS for TRD is ideally performed by a multidisciplinary team comprised of psychiatrists, neurosurgeons, neurologists, neuropsychologists, and other allied health professionals. Although this procedure for TRD is still in its infancy, selection of appropriate candidates assumes great importance, given the nature of the intervention.

The ability of an individual to provide informed consent for the procedure is a critical component in assessing the candidate's suitability for DBS (80). The presence of a strong social support network is also important during the preoperative assessment period and following the surgery. Regarding illness characteristics which may predict a favorable response to DBS in BA25, preliminary observations from our group suggest that patients with melancholic rather than atypical features respond better (77); however these findings require replication in a larger sample.

Beyond patient selection, the psychiatrist plays a primary role in the ongoing management of what amounts to "triple therapy," dealing with stimulator, medication and psychosocial interventions. Particularly in the early stages following DBS implantation, ongoing psychiatric management directed at exploring the patient's expectations for recovery, and challenging catastrophic thinking should be part of the management strategy. With continued improvement, the psychotherapeutic emphasis shifts to optimizing functional capacity.

Patients selected for DBS in the Toronto series have typically maintained the preoperative antidepressant regimen in the post operative phase, although most patients have undergone dose reductions and in some cases drug discontinuations. This observation suggests that DBS may be working synergistically with medications, and/or increasing the sensitivity of the CNS to the effects of these medications.

The surgical procedure has been well tolerated, with limited adverse neurological or psychiatric sequelae. One patient from our initial report developed an infection at the site of implantation, which necessitated removal and subsequent re implantation of the device (76).

No clear guidelines yet exist to inform the programming of DBS parameters for TRD, as they do for DBS in PD (81). Initial observations however suggest that stimulation parameters for TRD may approximate those in PD. The mean stimulation parameters used in our group for BA25 DBS in TRD are 4.0 Volts, 60 msec pulse widths, and a frequency of 130 Hz. (82). Each of these variables may be adjusted independently, allowing for an infinite array of possible combinations, although the higher the voltage setting, the shorter the battery life of the stimulator (83). It appears that once the appropriate electrode and stimulation parameters are achieved, the antidepressant effect is sustained without requiring alteration in DBS or pharmacotherapy.

Future Directions for the Management of TRD

Lack of confidence in the diagnostic homogeneity of major depressive disorder, incomplete descriptions of symptom profiles and inadequate consideration of psychiatric and medical comorbidities all substantially limit conclusions about treatment efficacy and treatment resistance (84). Nevertheless, the progress over the last decade in exploring and evaluating new somatic therapies that act as neuromodulators of selected brain regions represents a promising advance in managing TRD. Beyond the limited evidence of effectiveness or efficacy for these novel neuromodulation therapies, few centers are able to provide a full range of neuromodulatory treatments.

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