Medical Devices: Evidence and Research

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REVIEW

Neuromodulation therapies and treatment-resistant depression

This article was published in the following Dove Press journal:
Medical Devices: Evidence and Research
12 July 2012
Number of times this article has been viewed

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Background: Patients with treatment-resistant depression (TRD) who showed partial response to pharmacological and psychotherapeutic interventions need a trial of neuromodulation therapies (NTs).

Objective: This paper aims to review evidence-based data on the use of NTs in TRD.

Method: Using keywords and combined-word strategy, multiple computer searches of PubMed, Google Scholar, Quertle(R), and Medline were conducted for retrieving relevant articles published in English-language peer-reviewed journals (2000–2012). Those papers that addressed NTs in TRD were retained for extensive review.

Results: Despite methodological challenges, a range of 30%–93% of TRD patients showed substantial improvement to one of the NTs. One hundred–percent improvement was reported in two single-case studies on deep brain stimulation. Some studies reported no benefits from transcranial direct current stimulation. NTs were reported to have good clinical efficacy, better safety margin, and benign side-effect profile. Data are limited regarding randomized clinical trials, long-term efficacy, and cost-effectiveness of these approaches. Both modified electroconvulsive therapy and magnetic seizure therapy were associated with reversible but disturbing neurocognitive adverse effects. Besides clinical utility, NTs including approaches on the horizon may unlock the biological basis underlying mood disorders including TRD.

Conclusion: NTs are promising in patients with TRD, as the majority of them show good clinical response measured by standardized depression scales. NTs need further technological refinements and optimization together with continuing well-designed studies that recruit larger numbers of participants with TRD.

Keywords: treatment-resistant depression, neuromodulation therapies, modified electroconvulsive therapy, deep brain stimulation, transcranial direct current stimulation, magnetic seizure therapy

Introduction

It is estimated that depression afflicts about 121 million people worldwide. Major depression (MD) is the main cause of disability and the fourth-leading contributor to the global burden of disease. By the year 2020, MD is projected to reach second place in the ranking of disability-adjusted life years. Trials of available antidepressant medications alone or combined with psychotherapies are effective for 60%–80% of those affected with MD.[1] Conversely, up to 40% of patients with MD do not show satisfactory improvement attributable to multiple biopsychosocial factors. At its worst, MD can lead to suicide, and as a consequence about 850,000 lives are lost every year.[2]

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Treatment-resistant depression (TRD) evades universal definition; however, a poor response to two adequate (optimal dosage and 6–12 weeks duration) trials of two different classes of antidepressants has been proposed as its operational characterization.[3] Researchers have categorized TRD in accordance to antidepressant trials: stage 0, has not had a single adequate trial of medication; stage 1, failure of an adequate trial of one class of an antidepressant that is monotherapy; stage 2, failure of adequate trials of two distinctly different classes – that is, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants – of antidepressant, involving two monotherapy trials; stage 3, stage 2 plus failure to respond to one augmentation strategy of lithium or thyroid augmentation of one of the monotherapies; stage 4, stage 3 plus a failure to a second augmentation strategy in terms of monoamine oxidase inhibitors; and stage 5, stage 4 plus failure of an adequate course of ECT.[4] There are other staging methods of TRD.[5] These staging methods help researchers and clinicians to understand TRD patients and accordingly plan interventions for enhancing the response, remission rate, and quality of life. However, TRD continues to challenge mental health care providers despite the understanding of psychosocial and biological markers and psychopharmacology of mood disorders and also the availability of multiple therapeutic options including optimization, switching, and combination of antidepressants. Notably, currently there is an increasing interest in the utilization of several neuromodulation therapies (NTs) in the management of patients with TRD.[6] This is because psychopharmacological therapy exposes the entire body to a potentially therapeutic substance in order to treat a relatively small region of the brain, whereas NTs are designed to target specific brain circuits that are important in the pathogenesis of MD. Additionally, NTs are not systemic and, therefore, the side-effect profile is limited and different from medications, and there are minimal, if any, drug interactions.[7] Furthermore, evidence-based data has been emerging continuously about FDA-approved and yet-to-be-approved NTs in the TRD population over the past decade. This paper summarizes these data on the role of NTs in TRD patients.

Search method

Multiple computer searches were conducted using PubMed, Google Scholar, Quertle(R), and Medline databases for the years 2000–2012. A number of keywords were used: treatment-resistant depression, treatment-refractory depression, partial-response depression, nonresponse depression, neuromodulation techniques, neurostimulation approaches, and somatic therapies. These words were combined with modified electroconvulsive therapy (mECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), magnetic seizure therapy (MST), deep brain stimulation (DBS), transcranial direct current stimulation, cranial electric stimulation (CES), epidural cortical stimulation (ECS), focused ultrasound (FUS), near-infrared light therapy (NIR), low-field magnetic stimulation (LFMS), and optogenetic stimulation (OS) for a second round of computer searches. A third round of searches included words such as mechanisms, brain areas involved, and outcomes combined with aforesaid therapies. As a corollary, relevant articles published in English-language peer-reviewed journals were retrieved. Only clinical trials, systematic reviews, and meta-analyses that addressed TRD and NTs were retained for extensive review and inclusion in this study. Some exceptions were made with regard to some unique case reports, open and controlled studies, and small and large case series describing usefulness of NTs in patients with TRD and MD. Studies addressing non-TRD populations were excluded from this review. Similarly, studies focusing on neurosurgical ablation approaches in TRD populations were not considered for inclusion. References of selected articles were also reviewed for identifying relevant TRD trials, which were also included in this review. A couple of important TRD studies conducted prior to 2000 were also included.

Categorization of NTs

NTs for neuropsychiatric disorders including MD are categorized into the following: (1) seizure therapies, including mECT and MST, (2) noninvasive therapies, including rTMS, TDCS, and CES, (3) neurosurgical approaches, including VNS, ECS, and DBS, and (4) new approaches on the horizon, including FUS, NIR, LFMS, and OS.[8] Another category represents neurosurgical ablation therapies, including cingulotomy and limbic leucotomy used in TRD. Such technical details as invasiveness, anesthesia needed, seizures induced, target related to deep brain structures, contactness, stimulation being focal or generalized and form of stimulation of each neuromodulation therapy are presented in Table 1.

Mechanisms of action of NTs

There is an increasing focus on exploring biomarkers underlying the pathogenesis of mood disorders[9] that help in the development of new drugs and NTs. In several related studies, overactive subcallosal cingulate gyrus (SCG) glucose metabolism has been reported in MD that is reduced with successful antidepressant therapies.[10] Interestingly, DBS is

Table 1 Technical information of neuromodulation therapies

Somatic therapy	Surgical	Anesthesia	Seizures	Deep brain	Contactness	Focal	Form of stimulation
ECT	No	Yes	Yes	Yes	No	No	Electrical/AC
MST	No	Yes	Yes	No	Yes	Yes	Magnetic
rTMS	No	No	No	No*	Yes	Yes	Magnetic
TDCS	No	No	No	No*	No	No*	Electrical/DC
CES	No	No	No	No*	No	No*	Electrical/AC
DBS	Yes	Yes	No	Yes	No	Yes	Electrical/AC
VNS	Yes	Yes	No	Yes**	No	No**	Electrical/AC
ECS	Yes	Yes	No	No	No	Yes	Electrical/AC
FUS	No	No	No	Yes	Yes	Yes	Ultrasound
LFMS	No	No	No	Yes	Yes	No	Magnetic
NIR	Yes	Yes	No	No	Yes	Yes	Optical
OS	Yes	Yes	No	Yes	Yes	Yes	Optical

Notes: *Function of coil type or electrode array; **left vagal afferents.
Abbreviations: ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; TDCS, transcranial direct current stimulation; CES, cranial electric stimulation; DBS, deep brain stimulation; VNS, vagus nerve stimulation; ECS, epidural cortical stimulation; FUS, focused ultrasound; LFMS, low-field magnetic stimulation; NIR, near-infrared light therapy; OS, optogenetic stimulation.

reported to modulate neural pathways linked with SCG in relieving MD.[8,11,12] According to some studies, antidepressant effects were also found when DBS targeted ventral capsule/ventral striatum (VC/VS) in patients with severe obsessive-compulsive disorder (OCD) and MD.[13,14] In a study of single patients with dystonia suffering from depression, DBS of globus pallidus internus (GPI) showed improvement in dystonia but also showed antidepressant effects through modulation of mesolimbic dopamine pathways.[15] In another study, also of single patients with tardive dyskinesia (TD) and MD, DBS brought about improvement in depressive mood.[16] Other studies have also reported improvement in both depression and TD after DBS of the inferior thalamic peduncle (ITP), which modulates orbitofrontal cortex hyperactivity.[17,18] Bewernick and colleagues reported that DBS of the nucleus accumbens (NAc) was associated with decreased ratings of depression and anxiety in TRD patients.[19]

Rush and colleagues[20] noticed antidepressant effects when VNS was used for epilepsy. VNS modulates neural pathways associated with mood regulation: the nucleus tractus solitaries, raphe nucleus, and locus ceruleus.[21] In fact, the VNS device stimulates left cervical vagus nerve containing afferent neurons tracking through the brain stem to cortical and subcortical networks.[20–23] Furthermore, some neurobiological studies reported disruptions in right and left dorsolateral prefrontal cortex (R/LDLPFC) in mood disorders. Also, rTMS of R/LDLPFC results in antidepressive effects coupled with increasing cerebral blood supply to this brain areas.[23–25] Certainly, NTs target more specific, localized regions in the brain, which are somehow dysfunctional in MD. It remains uncertain how the depression is relieved; this is yet to be understood well, and hence basic neurobiological studies are needed. Similarly with regard to ECT, though no exact mechanism is known, debate and research continues in this field.[26–30]

Electroconvulsive therapy

Modified ECT has been used extensively in psychotic depression, schizophrenia, mania, and other mental disorders. It requires light anesthesia and is a recognized mode of treatment for TRD.[31,32] It remains the most effective therapy in TRD patients with a response rate of 50%–70%, though the strength of recommendation of ECT is C.[33,34] It targets nonspecific, broad regions of the cortex, and its mechanism of action is elusive. Notably, high post-ECT relapse rate and safety profile are of great concern for TRD patients and health providers as well. In a study of patients with nonpsychotic MD that tested whether pre-ECT medication resistance is associated with post-ECT relapse rates, it was observed that 34.6% of nonmedication-resistant patients who were not exposed to at least one antidepressant medication trial relapsed, while 50.0% of medication-resistant patients relapsed, a difference that was not statistically significant but clinically relevant.[35] Furthermore, in the first week after acute remission, 9.8% of patients not having at least one antidepressant medication trial met relapse criteria, while 31.4% of medication-resistant patients met relapse criteria, a difference that was statistically significant. It was concluded that MD patients who have had at least one adequate antidepressant medication trial or no such trial before ECT may be especially prone to early relapse after successful acute remission with mECT.[35] Research is needed to develop strategies in order to prevent

relapse following successful ECT in MD, which may be maintenance ECT and a combination of pharmacotherapy and mECT.

Furthermore, it is also important to identify the predictors of nonresponse to mECT. In a large sample of patients with TRD, mECT was effective in 66% of patients. mECT nonresponse was associated with bipolar subtype, mixed features, slightly less severe depressive symptoms, and longer duration of the depressive episode.[36] In another study that aimed to investigate whether the clinical course of TRD patients following a course of mECT might be associated with changes of plasma brain-derived neurotrophic factor (BDNF) concentrations, it was shown that at baseline, plasma BDNF levels of patients were significantly lower than those of control subjects, and those after ECT were significantly increased in parallel with the decrease of the Hamilton Depression Rating Scale (HDRS) total score. Only remitter patients who showed higher baseline BDNF levels than nonremitters reached normalized BDNF levels after mECT. These findings suggested the potential usefulness of baseline plasma BDNF levels as predictors of response to mECT in TRD patients.[37] In an earlier study of 18 patients with TRD, levels of BDNF and 3-methoxy-4-hydroxyphenylglycol but not homovanillic acid were increased following mECT in responders, which suggested that dopamine and BDNF might be involved in the mechanism of action of mECT.[38] In a recent study of adolescents with TRD, both continuation and maintenance of mECT were useful and safe for selected adolescents with severe TRD, and symptom remission was achieved without experiencing cognitive impairment;[39] the latter is a surprising finding and needs replication studies. Interestingly, in another development, data support the use of ketamine as anesthetic agent prior to ECT for increasing its antidepressant effect as compared to propofol. In a related study, 31 inpatients with TRD underwent eight mECT sessions for 4 weeks. The HDRS was used to evaluate these patients before ECT and after the completion of the second, fourth, sixth, and eighth ECT sessions. The HDRS scores improved earlier in the ketamine group, with decreases in HDRS scores that were significantly greater in the ketamine group. The implication of this finding is that the symptoms of MD might be alleviated rapidly if ketamine anesthesia is used in TRD patients during ECT.[40]

A retrospective evaluation of 5482 ECT treatments in 455 patients with TRD found therapeutic advantages in combination therapies versus ECT. A total of 18.2% of treatments were ECT monotherapy, 8.87% were done with one antidepressant. Results revealed that seizure duration was unaffected by most antidepressants, but SSRI caused a lengthened seizure activity. Postictal suppression was lower in mirtazapine and higher in SSRI and SNRI-treated patients. A significant enhancement of therapeutic effectiveness was seen in the patient group receiving tricyclics, SSRI, or mirtazapine, with no serious adverse events. This study supported the use of mirtazapine in enhancing the therapeutic effectiveness of ECT. Baghai and colleagues suggested that controlled studies are necessary to investigate further the possible advantages of ECT and pharmacotherapy combinations, especially the use of modern dual-acting antidepressants, which also have proven their efficacy in TRD.[41] Although mECT is effective in TRD, it significantly produces transient confusion, anterograde amnesia, and retrograde amnesia. Therefore, scientists have focused attention on technological refinements in ECT and also developing techniques that do not cause cognitive impairment and at the same time remain effective in MD and TRD.[42–46]

Repetitive transcranial magnetic stimulation

The FDA has approved rTMS for the treatment of MD and TRD in adolescents and adults. It is a noninvasive technique with good efficacy in TDR. Its other indications include chronic pain, movement disorders, stroke, epilepsy, tinnitus, and other psychiatric disorders. Notably, rTMS is safer on long-term use and acts more selectively than mECT on brain areas implicated in the pathogenesis of MD.[47,48] The rTMS has two forms: high-frequency rapid (HFR) (>1 Hz) and low-frequency slow (LFS) (≤1 Hz). Furthermore, HFR rTMS is preferred over LFS sychronized TMS, as the former was associated with more antidepressant effects in depressed patients as reflected by significant increases in blood supply to prefrontal cortical and limbic regions.[23] A sequential bilateral rTMS (LF right [LFR] then HF left [HFL]) is also effective in TRD patients but not more effective than unilateral HFL rTMS.[49,50]

In an open-label study, 21 patients who failed two antidepressant trials were given rTMS (HF, 10 Hz and intensity of 110%) for 4 weeks, keeping the dose of preexisting antidepressants unchanged. The majority of patients (n = 19) completed the 4-week study and were assessed. In intention-to-treat analysis, the mean HDRS scores were reduced from 30.80 ± 5.00 to 19.00 ± 6.37. No patient discontinued rTMS due to adverse effects, including headache, which was reported by 16% of patients. The study indicated the potential utility of rTMS as an augmenting agent in TRD.[51] Like LFR then HFL sequential bilateral rTMS, HFL and LFR unilateral

rTMS are also efficacious in TRD. In a 6-week double-blind, randomized, sham-controlled trial in 50 patients with TRD, three trains of LF rTMS to the right prefrontal cortex of 140 seconds' duration at 1 Hz were applied daily, followed immediately by 15 trains of 5 seconds' duration of HFL rTMS at 10 Hz. Sham stimulation was applied with the coil angled at 45° from the scalp. The primary outcome variable was the score on the Montgomery–Åsberg Depression Rating Scale (MADRS). According to this study, there was a significantly greater response to active than sham stimulation at 2 weeks and across the full duration of the study. A significant proportion of the study group receiving active treatment met response (44%) or remission (36%) criteria by study end compared to the sham stimulation group (8%), and none remitted (0%). It was noted that sequentially applying both HFL rTMS and LFR rTMS to the right prefrontal cortex resulted in substantial improvement in patients with TRD. Furthermore, the treatment response accumulated to a clinically meaningful level over 4–6 weeks of active treatment.[23] In another controlled investigation, patients with TRD were randomized to receive 15 sessions of active or sham rTMS delivered to the LDLPFC at 110% the estimated prefrontal cortex threshold. Each session consisted of 32 trains of 10-Hz rTMS delivered in 5-second trains. The results showed response rate (≥50% decrease in HDRS score) for the rTMS group was 30.6%, significantly greater than the 6.1% rate in the sham group. The remission rate (an HDRS score $<$ 8) for the rTMS group was 20%, significantly greater than the 3% rate in the sham group. The authors concluded that rTMS to LDLPFC can produce statistically and clinically significant antidepressant effects in patients with TRD.[25]

In another study, subjects between the ages of 18 and 85 years were recruited from a tertiary care university hospital. Seventy-four subjects with TRD and an HDRS score $>$ 21 were randomized to receive unilateral, bilateral, or sham rTMS. According to this study, the remission rate was significantly higher in the bilateral group than the sham group, but the remission rate in the unilateral group did not differ from either group. These findings warrant larger controlled studies that compare the efficacy of sequential bilateral rTMS and HFL/LFR rTMS in MD and TRD.[50,52] From a safety perspective, rTMS can rarely induce accidental seizures, especially among patients with brain insult and on medications that reduce seizure threshold. However, this major side effect could be curtailed if expert guidelines are followed.[53,54] Over the past 10 years, a number of meta-analyses of rTMS efficacy studies were conducted and the summary of these studies is as follows: a minimum of five to a maximum of 33 studies included; almost all included studies except one focused on depression rather than TRD; rTMS was more effective than sham rTMS; quality of studies improved successively; and rTMS designs also improved and effect size of rTMS was comparable to antidepressant drugs.[55–60] Finally, Moreines and colleagues[61] have reviewed the neuropsychological effects of somatic therapies including rTMS that were associated with reversible mild reductions in sustained attention, spatial planning, and verbal retention.

Vagus nerve stimulation

The FDA approved the use of VNS in patients with MD and TRD in 2005.[62,63] VNS principally stimulates the left cervical vagus nerve with a programmable neurostimulator. Observations of mood elevation during VNS for resistant epilepsy have suggested its potential role in TRD.[21,22,64] VNS targets the nucleus tractus solitarius, frontolimbic network, the locus ceruleus, and dorsal raphe nucleus, which regulate mood. Notably, initial studies on VNS reported inconsistent findings regarding reduced metabolism and blood flow in targeted brain networks with no putative antidepressant mechanism.[21,63,65] Similarly, a multicenter study on VNS found no significant reductions in depression scores for the experimental group as a whole, but antidepressant responses were observed among 40% of 30 recruited patients with TRD.[20] However, subsequent studies on VNS reported positive results. In a naturalistic, 1-year, follow-up study of 30 TRD patients who received VNS, the results were as follows: response rate of 40%–46% was sustained and the remission rate significantly increased, from 17% to 29% with an additional 9 months of long-term VNS. It was concluded that long-term VNS was associated with sustained benefit linked with good functional status.[66] Another naturalistic study with 2 years' follow-up of 74 European patients with TRD showed a significant reduction at all the three time points, ie, 3, 12, and 24 months of VNS in the HDRS scores. After 2 years, 53.1% of the patients responded well, and 38.9% fulfilled the remission criteria. The proportion of patients with remission remained constant as the duration of VNS increased, with no concomitant antidepressant medication significant impact. This 2-year open-label trial of VNS suggested a clinical response and a benign adverse-effect profile among patients with TRD.[67] In a recent study of 15 consecutive outpatients with TRD, VNS significantly decreased Beck Depression Inventory (BDI) scores compared to baseline at 6 and 12 months, from a mean of 37.8 ± 7.8 before VNS activation to a mean of 24.6 ± 11.4 at 12 months. By 1 year, 28.6% of patients responded to VNS and 7.1% remitted.

HDRS showed similar improvement at 1 year, with a 43% response rate and 14.3% remission rate. Reported side effects of VNS in decreasing frequency were hoarseness, dyspnea, nausea, pain, and anxiety, and no patient terminated treatment due to side effects. According to this study, a substantial minority of patients with TRD benefited from VNS.[68] VNS also induces cough, neck or jaw pain, and rarely infection. But it has no adverse neuropsychological effects.[61] In a study of single patients, VNS produced good results, with cost savings over mECT.[69] According to a systematic review, VNS examined in four clinical trials with 355 patients demonstrated steadily increasing improvement with full benefit after 6–12 months, sustained up to 2 years. But the primary results of the only controlled trial were negative and attributed to small sample size. Further controlled studies with large sample size are warranted to establish its efficacy and tolerability in future.[62,70] The issue of predictors of response to VNS is addressed sparsely. In an open-label study of TRD, the predictors of response to VNS were history of resistant depression, mild to moderate resistant depression, not-severe resistant depression, and no history of use of ECT.[71] Trials of VNS in combination with pharmacotherapy are also needed in TRD populations.

Transcranial direct current stimulation

Transcranial direct current stimulation, a noninvasive technique with no FDA approval, has been used in patients with MD with mixed results. TDCS of the prefrontal cortex has been proposed as a therapeutic intervention in MD.[72,73] In a parallel-group, double-blind clinical trial, 40 patients with MD who were medication-free were randomized into three groups. They were assessed by a blind rater using HDRS and BDI after ten sessions of TDCS during a 2-week period. According to this investigation, significantly larger reductions in depression scores after DLPFC TDCS were observed as compared to occipital and sham TDCS. Moreover, the beneficial effects of TDCS in the DLPFC group persisted for 1 month after the end of treatment. The authors suggested further investigation on the effects of TDCS for the treatment of MD.[72] Another double-blind, randomized study tested TDCS in 40 depressed participants and used the following parameters: 1-mA current strength, five treatment sessions, active or sham, and given on alternate days. Anodal stimulation was centered over the left DLPFC, with the cathode placed on the lateral aspect of the contralateral orbit. TDCS was continued up to a total of ten active sessions per participant. Overall, depression scores improved significantly over ten TDCS treatments, but there was no between-group difference in the five-session, sham-controlled phase. According to this study,[73] TDCS was found to be safe, with no adverse effects on a variety of assessed neuropsychological functions.[61] It was recommended that the efficacy of TDCS in MD be further evaluated over a longer treatment period, using enhanced stimulation parameters.[73]

In another study, 22 patients with TRD were randomly assigned to a crossover protocol comparing TDCS and placebo stimulation add-on to a stable antidepressant medication. The parameters of active TDCS were 1 or 2 mA for 20 minutes/day, anode over the left DLPFC, and cathode over the contralateral supraorbital region. Active and placebo TDCS were applied for 2 weeks using indistinguishable DC stimulators. The results showed that there was no significant difference in depression scores after 2 weeks of real compared with 2 weeks of sham TDCS. In contrast, subjective mood ratings showed an increase in positive emotions after real TDCS compared with sham TDCS. Anodal TDCS, applied for 2 weeks, was not superior to placebo stimulation in patients with TRD. The authors suggested that modified and improved TDCS protocols should be carried out in controlled trials to develop TDCS with better efficacy in TRD.[74] All aforementioned studies except one[74] addressed the usefulness of TDCS in MD, and hence more controlled trials are needed in TRD patients.

Deep brain stimulation

Deep brain stimulation, yet to be approved by the FDA, is a reversible invasive technique that involves stereotactical implantation of electrodes powered by a pulse generator into the specific dysfunctional brain regions implicated in mood disorders, Parkinson's disease, Alzheimer's disease, movement disorders, and other neuropsychiatric disorders. High frequency DBS of motor, mood, and cognitive neuronal circuits is reported to improve these conditions.[75] DBS therapy, dose- and site-dependent, is a less invasive and less extreme alternative to ablative psychosurgeries.[76] Research data supports DBS that targets cortico-striatal-pallido-thalamocortical loop, the VC/VS, and other neuronal networks in patients with MD, TRD, OCD, and Tourette's syndrome.[77–81] Additionally, NAc that contains dopamine, a reward system and involved in the pathogenesis of MD, is a promising target for DBS. In a study, ten patients with severe TRD were implanted with bilateral DBS electrodes in the NAc. Twelve months later, five patients reached 50% reduction of the HDRS score, with significantly increased pleasure activities. Furthermore, the [^{18}F]-2-fluoro-2-deoxy-D-glucose positron emission

tomography data revealed that DBS decreased metabolism in the SCG, orbital prefrontal cortex, and amygdala. This study supported antidepressant and antianhedonic effects of DBS in patients with TRD. However, the small sample size limits the interpretation of results, and further research recruiting larger samples is needed.[82] In a multicenter study of 21 TRD patients who received DBS, it was found that patients treated with SCG DBS had variable response with time: 57% at 1 month, 48% at 6 months, and 29% at 12 months. The response rate after 12 months of DBS increased to 62% when redefined as a reduction in the baseline HRSD of 40% or more. Additionally, reductions in depressive symptoms were associated with amelioration in disease severity in patients who responded to surgery. Overall, this study corroborated the results of other research that the outcome of SCG DBS may be replicated across multiple centers.[83]

In two influential review articles, researchers have provided greater details of somatic treatments in terms of target structures, motivation, response rates, mechanism of action, and technical issues.[8,9] Accordingly, somatic therapies targeted SCG, VC/VS, left cervical vagus nerve, R/L DLPFC, GPI, lateral habenula, and ITP in MD and TRD patients, and improvement reported ranged from 30.6% to 66.7%.[8,10,12,14] (Table 2).

Furthermore, an improvement of 100% was reported in two DBS studies that included one patient with dystonia and TRD and another patient with MD and tardive dyskinesia.[16,17] On a long-term basis (≤6 years), DBS is safe and effective in patients with TRD, as substantiated by recent data.[87–89] According to these studies,[87–89] chronic DBS SCG was effective in TRD and bipolar patients and well tolerated with minor hemorrhagic events,[86,90,91] but no neurocognitive impairment was reported[61] (Table 3). As a mechanism of action, overactive SCG glucose metabolism seen in MD is reduced with antidepressant therapies and DBS.[10,11]

Magnetic seizure therapy

Magnetic seizure therapy, also known as magnetic convulsion therapy and yet to be approved by the FDA, has antidepressant effects. It uses magnetic fields to induce therapeutic seizures. It has a better side-effect profile than modified ECT. Studies conducted in humans and primates suggest that cognitive side effects of MST are more benign than those of mECT. Notably, postictal orientation recovery time is short and rapid with MST.[61,92,93] Furthermore, several studies have corroborated improved cognitive outcomes with MST as compared to mECT. However, neither therapy causes structural changes, ie, volume, total number, or numerical density in neurons or glia in the frontal cortex, hippocampus, and their subregions in human and nonhuman brain.[94–96] Overall, magnetic seizures with benign side-effect profile are therapeutically better than mECT seizures. Other than adverse neurocognitive effects, ECT is also associated with reversible bradycardia and tachycardia immediate post-ECT and ictal and postictal stages, respectively. In nonhuman studies of MST, these effects were minimal, reflecting a more superficial cortical site of action with less impact on deep brain structures, which are implicated in sympathetic and parasympathetic nervous system control, relative to ECT.[97] Both antidepressant activity and cognitive side-effect profile of MST were further addressed in an open-label study, which tested whether it is associated with clinically significant antidepressant effects in TRD as an add-on therapy to controlled pharmacotherapy.[85] Twenty patients with TRD were randomly assigned to receive either MST or ECT for more than 2 years. The primary outcome measure was antidepressant response assessed by MADRS, and secondary outcome measures included HDRS, Hamilton Anxiety Scale, BDI, and 90-Item Symptom Checklist. Antidepressant response as defined by 50% improvement in MADRS ratings was statistically significant and of similar size in both treatment groups with no cognitive side effects. Characteristics in MST- and ECT-induced seizures were comparable, especially regarding ictal activity and postictal suppression. Kayser and colleagues suggested that MST may be a potential alternative to ECT if efficacy and safety are validated in larger clinical trials.[85] MST is reported to result in minimal retrograde and anterograde amnesia.[61] In summary, more studies are needed to further substantiate the efficacy of MST in mood disorder, including TRD patients.

Notably, there is converging evidence that NTs have a lower risk of neurocognitive side effects compared to mECT, which are benign.[61] (Table 4). By and large, short- and long-term research is needed to establish the efficacy, safety, and cost-effectiveness of neurostimulation therapies.[98] In addition, these therapies in general need proper selection of patients in line with tailored treatment guidelines.[99] Also, treatment teams should strictly follow ethical guidelines, especially those concerning autonomy, voluntary consent, beneficence, and nonmaleficence prior to using NTs in individual patients.[48,80,100]

There are other NTs, including CES and ECS, used uncommonly for a variety of disorders, such as anxiety, headaches, pain, stroke recovery, movement disorders, insomnia, and depression, but the data are largely limited in TRD patients.[101,102] In a systematic review, Rosa and Lisanby have described the technical details of all NTs, including indications, safety, and effectiveness of ECS and CES.[8]

Table 2 Summary of treatment-resistant depression studies

Study	Target	Underlying concept	Stimulation type	n	Response	Mechanism
Mayberg et al[11,12] and Lozano et al[10]	SCG	Overactive SCG glucose metabolism in MD reduced by antidepressant therapies[10]	DBS, continuous, constant voltage, monophasic	6 20	66.7% 60%	Modulates neural network[10]
Malone et al[14]	VC/VS	Antidepressant effects seen from VC/VS stimulation in OCD[13]	DBS, continuous, constant voltage, biphasic	15	40%	Modulates neural network coupled with OCD and depression[14]
George et al,[22] Rush et al,[20] Goodman and Insel[64]	Left CVN	Antidepressant effects seen from VNS in epilepsy[20]	VNS, intermittent, constant I, monophasic	30	55%[66]	Modulates neural networks coupled with mood regulation via the nucleus tractus solitaries[21]
Klein et al[84]	RDLPFC	PFC functions are disrupted in depression and sTMS of right DLPFC has antidepressive effects[23]	sTMS, 2 weeks and 10 sessions	35	49%	Modulates right PFC activity coupled with mood regulation
Speer et al,[24] Avery et al[25]	LDLPFC	PFC functions are disrupted in depression and rTMS of left DLPFC has antidepressive effects[23]	rTMS, 4 weeks and 15 sessions	35 25	30.6%,[25] 44%[23]	Modulates left PFC activity and increases cerebral blood[24]
Halbig et al,[15] Kosel et al[16]	GPI	Some antidepressant effects seen from GPI stimulation for dystonia[15,16]	DBS, continuous, constant voltage, monophasic	1 case study	100%	Modulates mesolimbic DA pathways[16]
Jimenez et al,[17] Velasco et al[18]	ITP	ITP stimulation may modulate dysfunctional thalamo-orbitofrontal system activity[19]	DBS, continuous, constant voltage, biphasic	1 case study	100%[18]	Modulates orbitofrontal cortical hyperactivity[19]
Kayser et al[85]	Cortex	ECT effectiveness in depression and TRD patients	MST/ECT, anesthesia	20	MST 60%, ECT 40%	Superficial cortex mainly modulated
Bewernick et al[82]	NAc	Dopamine pathways are disturbed in depression	Bilateral DBS	10	50%	NAc DBS, decreased metabolism in SCG and orbital prefrontal cortex
Jhanwar et al[51]	LDLPFC	PFC functions are disrupted in depression	HF rTMS	21	90%	Modulates left PFC activity and increases cerebral blood
Blumberger et al[50]	L/R DLPFC	PFC functions are disrupted in depression	HFL vs sequential bilateral rTMS	74	Both equally effective	Modulates L/R PFC activity and increases cerebral blood
Bajbouj et al[67]	LVN	Antidepressant effects seen from VNS in epilepsy[20]	VNS	74	53.1%	Modulates neural networks coupled with mood regulation
Cristancho et al[68]	LVN	Antidepressant effects seen from VNS in epilepsy[20]	VNS	15	28.6%, 43%	Modulates neural networks coupled with mood regulation
Palm et al[74]	Left DLPFC	PFC functions are disrupted in depression	TDCS	22	No benefits	Modulates left PFC activity
Blomstedt et al[86]	NAc, SCG, VC/VS	Overactive SCG glucose metabolism in MD reduced by antidepressant therapies	DBS bilateral	59	36% (NAc), 40% (VC/VS) to 52% (SCG)	Mood regulatory pathways
Fitzgerald et al[49]		PFC functions are disrupted in depression	L/R rTMS vs HFL rTMS	67	Both equally effective	Modulates L/RDLPF cortex that regulate mood
Holtzheimer et al[87]	SCG	Overactive SCG glucose metabolism in MD reduced by antidepressant therapies	DBS bilateral	10 MD, 7 BD	92% after 2 years	Modulates neural network Modulates neural network[10]

Abbreviations: SCG, subcallosal cingulate gyrus; DBS, deep brain stimulation; VC/VS, ventral capsule/ventral striatum; OCD, obsessive-compulsive disorder; CVN, cervical vagus nerve; VNS, vagus nerve stimulation; R/LDLPFC, right/left dorsolateral prefrontal cortex; s/rTMS, synchronized/repetitive transcranial magnetic stimulation; GPI, globus pallidus internus; ECT, electroconvulsive therapy; TRD, treatment-resistant depression; MST, magnetic seizure therapy; NAc, nucleus accumbens; HFL, high-frequency left; LVN, left vagus nerve; TDCS, transcranial direct current stimulation; MD, major depression; BD, Bipolar disorder.

Table 3 Side effects of deep brain stimulation

Physical effects	Psychological effects	Positive effects	Neurocognitive effects
Swollen eye, erythema, sweating, paresthesia, headache, lead dislodgment, dysphagia, pain, disequilibrium, muscle cramps, infections, affection of vision, perioperative pain, seizure 20%, intracranial hemorrhage (1%–2%) but not severe	Anxiety increase, hypomania, agitation, psychotic symptoms, worsening of mood, hypomanic episode, depression and suicide ideation	Clinical effects can be achieved without irreversible lesioning Electrodes can be completely removed if necessary Brain activity can be changed in a direct, controlled manner Opportunity to continuously adjust stimulation variables for each patient individually The patient can turn off stimulation immediately if side effects occur Allows blinded studies for therapy control No extrapyramidal effects No weight gain No long-time side effects as in antidepressant treatments are reported	*SCG*: No neurocognitive impairment in general intellectual ability, language, processing speed, executive functioning, learning, or memory; possible improvement in verbal learning (not apparently associated with mood improvement) *VC/VS*: No neurocognitive impairment in general intellectual ability, language, processing speed, executive functioning, learning, or memory; possible improvement in verbal learning (not apparently associated with mood improvement) *NAc*: No neurocognitive impairment in general intellectual ability, language, processing speed, executive functioning, learning, or memory *ITP*: No changes in visual attention, visuoconstructive perception, verbal fluency or abstraction; possible improvements in manual praxis and verbal/nonverbal memory *LHb*: No data available

Abbreviations: SCG, subcallosal cingulate gyrus; VC/VS, ventral capsule/ventral striatum; NAc, nucleus accumbens; ITP, inferior thalamic peduncle; LHb, lateral habenula.

At the neurophysiological level, CES is quite different from tDCS.[103] In one study, with ECS that used prefrontal cortical modulation, an average 55% improvement in depression scores was demonstrated.[104] CES is associated with headache and nausea followed by skin irritation.[105] Unlike DBS, epidural cortical stimulation has fewer side effects.[8]

Table 4 Neurocognitive effects of somatic therapies*

Somatic therapies	Neurocognitive effects
ECT*	Retrograde amnesia, anterograde amnesia, postictal disorientation
rTMS**	Mixed reports, with most studies reporting no impairments, but some studies finding mild reductions in sustained attention, spatial planning, and verbal retention; possible improvements in global cognitive awareness, manual motor speed, simple reaction time, verbal learning, attention, processing speed, verbal fluency, autobiographical memory, visual learning, working memory, and executive functioning
VNS***	No neurocognitive impairment in attention, psychomotor speed, verbal fluency, memory, or executive functioning; possible improvement in psychomotor speed, language, and executive functioning and potentially associated with mood improvement
MST	Minimal retrograde amnesia, minimal anterograde amnesia, rapid postictal reorientation
TDCS	No neurocognitive impairment in psychomotor speed, working memory, attention, recognition memory, or executive functioning; possible improvement in working memory

Notes: From multiple sources[26–30,35,68] and NIH Public Access.[61] These are mostly acute effects of somatic therapies, but their long-term use and consequent effects are yet to be explored. *Higher post-ECT relapse; **induced seizures; ***hoarseness of voice, dyspnea, nausea, anxiety, cough, neck or jaw pain and infections.
Abbreviations: ECT, electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; VNS, vagus nerve stimulation; MST, magnetic seizure therapy; TDCS, magnetic seizure therapy.

Newer neurostimulation therapies

There are other neuromodulation therapies on the horizon, which include FUs, LFMS, and NIR.[106–109] The data about these approaches are limited and need further research, especially concerning their role in mood disorders, including TRD populations. With regard to OS, microbial light-sensitive proteins called opsins are introduced into neurons and function as ion channels that open or close according to light exposure. Channelrhodopsin-2 is one that allows Na+ ions to enter the cell following exposure to ~470 nm blue light.[110] According to Rosa and Lisanby,[8] the advent of this technique has multiple implications: targeting specific fiber tracts that overlap in space; selectively activating or inactivating specific projection neurons to the same target; being a contactless form of stimulation relying on photoactivation; and its potential use in treating mood disorders. Like DBS, OS will also require surgical implantation of the light-emitting electrode; however, OS certainly has other advantages over DBS.[8] In one nonhuman study, antidepressant effects of OS of medial prefrontal cortex have already been reported in a chronic social defeat stress model in rodents.[111] More studies on newer NTs are needed in human subjects with MD and TRD.

Discussion

This is a qualitative review of literature on somatic therapies used in the management of MD and refractory depression.

About 30% of patients with TRD not responding to several intervention approaches, including optimization, augmentation and a combination of antidepressant drugs, are the principle candidates for NTs.[5–9] Among these therapies, mECT is most extensively and effectively used in severe depression and TRD but associated with serious neurocognitive adverse effects because of nonspecific, broad excitation of cortical and deeper structures of the brain, and its mechanism of action is continuingly debatable.[26–33] Other noninvasive somatic treatments such as rTMS, tDCS, MST, and CES target more specific neuronal networks in the brain that are dysfunctional in MD, TRD, and other neuropsychiatric disorders, and reported to have fairly good safety and clinical profiles with more benign neuropsychological side effects.[8,9,23–25,48–61,72–74,85] Invasive NTs, ie, VNS, DBS, and ECS with nonserious adverse effect profile, are also reported to be effective in patients with MD and TRD.[8–10,12–22,61,104] New NTs on the horizon are also promising in patients with MD and TRD. Although short- and long-term evidence-based comparative-effectiveness data on the role of NTs in adult patients TRD is emerging at a rapid pace,[112] further research on their technical optimization, mechanisms of action, efficacy, side effect profile, and cost-effectiveness in larger populations of TRD patients are warranted in future.

Conclusion

There is converging evidence that up to 40% patients with MD fail to respond to an initial antidepressant therapy. Modified ECT has a definite place in the management of patients with TRD; however, it carries well-known potential for neurocognitive impairment. Like ECT, MST also has neuropsychological adverse effects but of a milder nature. The role of other neuromodulation methods, including VNS, rTMS, DBS, and tDCS, in TRD patients is expanding with greater efficacy and fewer side effects. These neuromodulatory approaches rather tend to improve neurocognitive functions. These treatment modalities could be used alone or in combination with antidepressant therapy and/or psychotherapy. Besides their therapeutic utility, neuromodulation techniques can further open windows into the biological basis of disordered neurocircuits related to MD and TRD.

Recommendations

1. Most studies on somatic therapies are of small sample size and hence reflect less reliable and valid results. Therefore, collaborative, multisite and/or multicountry studies that use the same protocols and also recruit larger samples with TRD are urgently needed.
2. Another observation is that multiple hypotheses were tested in most neuromodulatory intervention trials. This methodological dilemma could be circumvented by determining a hypothesis a priori and others as exploratory.
3. Most importantly, TRD evades a universally accepted definition, and hence tools to measure refractoriness of depression and strict eligibility criteria need to be developed.
4. Evidently, poor results of recent MD and TRD trials indicate the heterogeneous nature of depression and TRD as well. Therefore, treatment trials of somatic therapies should target more specific subpopulations together with the detection of endophenotypes to predict their response
5. Another challenge is blinding, which is vulnerable, and both the use of external raters and avoiding contact between subjects will solve this problem.
6. Additionally, open-label studies, especially of VNS and DBS, tend to produce weak results, and therefore alternative designs including partial crossover and comparison against waiting list are needed.
7. There is a relative lack of follow-up studies on somatic therapies, and hence more naturalistic studies are required in future.
8. It is observed that the optimal parameters of somatic therapies are not defined, which could be managed by the use of adaptive designs and collaborative networks.
9. Finally, unlike nonpharmacologic research in adults with TRD,[112] there is a relative lack of direct comparison with antidepressant drugs, and hence comparative research is needed. Most of these recommendations were constructed closely matching the challenges reported in the literature on NTs, MD, and TRD populations.[8,72,113]

Disclosure

The authors disclose no conflicts of interest in this manuscript.

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