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Advances in the Management of Treatment-Resistant Depression

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Abstract

Treatment-resistant depression (TRD) is a prevalent, disabling, and costly condition affecting 1%–4% of the U.S. population. Current approaches to managing TRD include medication augmentation (with lithium, thyroid hormone, buspirone, atypical antipsychotics, or various antidepressant medications), psychotherapy, and ECT. Advances in understanding the neurobiology of mood regulation and depression have led to a number of new potential approaches to managing TRD, including medications with novel mechanisms of action and focal brain stimulation techniques. This review will define and discuss the epidemiology of TRD, review the current approaches to its management, and then provide an overview of several developing interventions.

Treatment-Resistant Depression: Definition and Epidemiology

Major depressive disorder is a widespread and costly illness, with a 1-year U.S. prevalence of about 7% (1). A variety of antidepressant treatments are available, but many patients fail to achieve sustained symptomatic remission. Continued depressive symptoms are associated with ongoing functional impairment (2), increased usage of health care resources (3), a greater risk of suicide (4–6), and overall increased mortality, especially associated with cardiovascular disease (7–10).

Despite the growing recognition of the public health importance of treatment-resistant depression (TRD), a consensus definition for this condition does not exist. Various approaches to stages of treatment resistance have been developed, including the Thase-Rush (11), Massachusetts General Hospital (12), and Maudsley systems (13). It has been conservatively estimated that >10% of depressed patients will not respond to multiple, adequate interventions (including medications, psychotherapy, and ECT) (14), and data from a large, community-based sequential treatment study (STAR*D) suggest that up to 33% of patients may fail to achieve full symptomatic remission despite multiple medication attempts (15). Studies of TRD have varied widely in the operational criteria used, but failure of at least two antidepressant treatments (of adequate dose and duration) from two distinct classes is one of the most consistent definitions in the literature (16). This definition also has predictive validity. In STAR*D, remission rates with the first two treatments were quite

similar (36.8% in the first level and 30.6% in the second) but decreased significantly after a failure of two treatments (13.7% in the third level and 13.0% in the fourth) (15).

Considering these various definitions of TRD, the estimated prevalence ranges from 10% to 60% of all depressed patients (12, 14, 15), resulting in a U.S. prevalence of about 1%–4%, equal to or greater than the prevalence of schizophrenia, obsessive-compulsive disorder (OCD), or Alzheimer's dementia. And, for those patients who do eventually respond after multiple treatments, relapse is quite high (up to 80%) (17–19), emphasizing the fact that better strategies are needed to both treat and prevent depressive episodes.

Current Approaches for Managing TRD

Establishing the Correct Diagnosis

When a patient presents with TRD, the first step is to confirm the primary diagnosis, assess for the presence of psychiatric and medical comorbidity, and verify the adequacy of prior treatments through a careful patient interview (with collateral information if available) and review of medical records (20). More than 10% of patients with the initial diagnosis of major depression may ultimately meet the criteria for bipolar disorder (21) and may require a modified treatment approach. Psychiatric comorbidity is common in depression and TRD (primarily anxiety, personality, and substance use disorders) (22, 23), and failure to achieve remission may be associated with inadequate treatment of these other conditions. Similarly, certain comorbid medical illnesses (e.g., sleep apnea, anemia, thyroid disease, hypogonadism, and others), as well as nonpsychiatric medications (e.g., corticosteroids, interferon alfa, and chemotherapy), may be associated with symptoms and side effects that overlap with those of depression. Finally, many patients with depression labeled as “treatment-resistant” may not have actually achieved adequate doses of prior medications for a sufficient duration (12, 14), such that a first step in management often includes increasing and potentially maximizing dose and duration of a current or prior treatment.

Medication Augmentation

For patients with documented treatment resistance to one or more medications, augmentation is a typical approach. Accepted augmentation agents for TRD include lithium, thyroid hormone, buspirone, and atypical antipsychotics. Combining antidepressant medications is also quite common. Table 1 provides a summary of these approaches, including the highest level of support for each.

Lithium—Lithium augmentation (typically at doses 600 mg/day) currently has the most extensive evidence base with reported response rates between 40% and 50% (in depression studies, response is typically defined as a decrease in depression severity of at least 50% compared with baseline) (24). However, it should be noted that the majority of these studies combined lithium with a tricyclic antidepressant (TCA) or monoamine oxidase inhibitor (MAOI). The efficacy of lithium augmentation of newer antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), is less clear (25). It is notable that lithium probably acts in part through modulation of the serotonin neurotransmitter system (26), such that it may be less mechanistically distinct from many newer medications compared with the older

agents. In STAR*D, lithium was added after two failed treatment attempts that included bupropion, citalopram plus bupropion, citalopram plus buspirone, sertraline, or venlafaxine (27). Lithium augmentation was compared with triiodothyronine (T₃) augmentation (results for T₃ are described below). Lithium augmentation was associated with a 16% remission rate and a 16% response rate; 23% of patients dropped out due to side effects.

Thyroid hormone—Augmentation with 25–50 µg of T₃ also has an extensive database in medication-refractory depression (again with most studies adding this agent to a TCA). One meta-analysis found mixed results but generally confirmed a statistically significant advantage for T₃ augmentation of TCAs, with an overall response rate of 57% (a 23% improvement over placebo) (28). Another meta-analysis identified a statistically significant benefit for T₃ in accelerating the response to TCAs (29). In STAR*D, patients were randomly assigned to augmentation with either T₃ or lithium after two failed treatments (see above for details). T₃ augmentation was associated with a 25% remission rate and a 23% response rate (response was defined using a different scale than that used to define remission; in addition, it is possible that some patients achieved remission without having a 50% decrease in depression severity because of a partial response in the previous STAR*D levels); 10% of patients dropped out due to side effects. The numerical advantage of T₃ over lithium augmentation was not statistically significant.

Buspirone—Buspirone augmentation (at doses ranging from 10 to 60 mg/day) has a mixed database supporting antidepressant efficacy (largely comprising open-label studies). One placebo-controlled trial (N=119) found no statistically significant benefit for buspirone augmentation in patients not responding to an SSRI (30). A second placebo-controlled trial (N=102) also found no overall augmentation benefit for buspirone but did identify statistically significantly greater antidepressant effects in patients with severe depression (31). Buspirone augmentation was used in the second level of STAR*D (for patients not achieving remission with citalopram) and compared with bupropion augmentation. Remission rates were virtually identical with the two agents (roughly 30%), although bupropion was associated with a greater reduction in self-rated depression severity and a lower dropout rate due to side effects.

Atypical antipsychotics—Atypical antipsychotic medications have previously shown benefit as augmentation agents for a number of SSRI-resistant nonpsychotic anxiety disorders (32–36). A recent meta-analysis of placebo-controlled trials found that atypical antipsychotic augmentation of an antidepressant medication was associated with statistically significantly greater response and remission rates, with a pooled response rate of 44% compared with 30% for placebo (37). Discontinuation due to side effects was greater for the antipsychotics compared with placebo. Aripiprazole is currently U.S. Food and Drug Administration (FDA)-approved for the treatment of depression not responding to an SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI). Quetiapine monotherapy and the combination agent olanzapine/fluoxetine have each received FDA approval for the treatment of bipolar depression.

Combining antidepressants—The most common combination of antidepressants is the addition of bupropion to an SSRI or SNRI (38, 39), despite a limited database with no placebo-controlled studies (40). As described above, bupropion augmentation of citalopram had a remission rate similar to that of buspirone augmentation in STAR*D, although there was some evidence for greater antidepressant effectiveness of bupropion overall. The efficacy of adding mirtazapine to an SSRI/SNRI is supported by a small database including at least one placebo-controlled trial (41, 42). The combination of an SSRI/SNRI with a TCA is somewhat supported by a limited dataset (43–46).

Psychotherapy

Psychotherapy is a mainstay in the treatment of depression, and it is generally accepted that structured, evidence-based psychotherapies such as behavioral activation, cognitive behavior therapy, and interpersonal psychotherapy are as effective as antidepressant medications, even in moderate and severe depression (47–50). These therapies may also be effective in medication-resistant depression (48, 51, 52). Short-term psychodynamic therapies have also shown benefit for depression (53–56). The combination of psychotherapy with an antidepressant medication may be more effective than medication alone (49, 54, 57). Finally, psychotherapy may help prevent relapse, possibly to a greater degree than continued pharmacotherapy (58, 59). One challenge in managing patients with psychotherapy is that efficacy probably correlates with therapist skill and expertise (50), and some patients may not have ready or affordable access to an appropriate psychotherapist.

ECT

ECT was introduced in 1938 as a treatment for “schizophrenia” (60), yet has proved to be the most effective acute treatment for a major depressive episode (61, 62), with remission rates of more than 40%, even in patients with TRD (63–65). The efficacy of ECT has been validated in a number of open and blinded controlled trials, including comparisons with medication, sham ECT, and transcranial magnetic stimulation (62, 66–68). Cognitive side effects, especially retrograde amnesia, are common with ECT, and may be persistent (61, 69, 70). In addition, despite its acute efficacy, depressive relapse after a successful ECT course is still common, even when continuation ECT (ECT treatments delivered at an increasing time interval beyond the acute course) or optimal medication management is used (18, 63). Despite these limitations, ECT remains the best validated acute treatment for a major depressive episode, even when standard medication and psychotherapeutic interventions have not been effective.

Ablative surgery

The first antidepressant medications were developed in the 1950s (71–73). Before this, treatments for patients with severe depression unresponsive to ECT were limited and often invasive [such as the prefrontal leucotomy (74)]. After the advent of pharmacotherapy for depression, neurosurgery remained an option for a small group of patients with severe and treatment-resistant depression, facilitated by the development of stereotactic neurosurgical techniques that allowed more focal ablation (75, 76). Ablative procedures in use today include capsulotomy (a lesion in the anterior limb of the internal capsule), cingulotomy (a

lesion in the dorsal anterior cingulate), subcaudate tractotomy (a lesion in thalamocortical white matter tracts inferior to the anterior striatum), and limbic leucotomy (which combines a subcaudate tractotomy with a cingulotomy) (77). In TRD, the efficacy for these procedures in open-label, naturalistic studies has been judged to be between 22% and 75% (78, 79); side effects include epilepsy, cognitive abnormalities, and personality changes (78–80).

Advances in the Management of TRD

Two main approaches have defined the search for improved strategies for managing depression and TRD. The first has focused on development of novel medications. Although some of these continue to rely on modulation of monoaminergic neurotransmitter systems, the majority are based on targets in neuromodulatory systems beyond the monoamines. The second approach has focused on development and refinement of focal brain stimulation techniques, in which a focal electrical current is introduced in neural tissue with the goal of modulating activity locally and within a broader network of connected brain regions. This review will focus on medications and brain stimulation approaches for which published clinical data are available (see Table 2 for a summary).

Novel Pharmacological Targets

Dopamine agonists—Dopamine receptor agonists (pramipexole and ropinirole) are accepted treatments for Parkinson's disease (81). Data in TRD are limited, although two placebo-controlled trials in treatment-resistant bipolar depression (82, 83) and two open-label studies in treatment-resistant unipolar depression support potential efficacy (84, 85). A long-term (48-week) extension of an open-label study of pramipexole in unipolar TRD showed that 36% of patients achieving remission relapsed; the absence of a comparison group limits the interpretation of this finding (86). Larger, placebo-controlled trials of both pramipexole and ropinirole as augmentation agents in TRD have been initiated and/or completed (<http://www.clinicaltrials.gov>), but results have not been published.

Modulators of hypothalamic-pituitary-adrenal axis function—It is well-recognized that emotional or physical stress predisposes an individual to developing depression. Corticotrophin-releasing factor (CRF), a neuropeptide produced in the hypothalamus and released after a stressful event to initiate the stress hormone cascade, has been implicated in the pathophysiology of depression, largely through its actions at the CRF-1 receptor (87–90). Several CRF-1 receptor antagonists possess anxiolytic- and antidepressant-like effects in animal models (88). However, the early clinical data on these agents are mixed (91, 92), although several agents are currently in phase II/III studies (93).

Another strategy for modulating the hypothalamic-pituitary-adrenal axis involves interfering with the synthesis or action of glucocorticoids. Several medications (e.g., ketoconazole, aminoglutethimide, and metyrapone) decrease cortisol synthesis and have demonstrated antidepressant effects, although poor tolerability has hampered use and further development of these agents (94). The glucocorticoid 2 receptor antagonist mifepristone has shown antidepressant efficacy for chronic depression in a single case series (95), and overall clinical efficacy for psychotic depression in one open (96) and one blinded placebo-

controlled study (97). In the latter, effects were greater for psychotic than depressive symptoms.

Substance P (NK-1) antagonists—Neurokinins are neuropeptides known to help mediate the neural processing of pain. The neurokinin substance P has been associated with the mammalian response to stressful stimuli (98, 99), and blocking its action can decrease the physiological and behavioral reactions to stress (100, 101). Substance P has also been implicated in the stress response in patients with major depression (102), and successful antidepressant treatment has been associated with decreased serum substance P levels (103). Agents that block a major substance P receptor (NK-1) have shown antidepressant-like effects in animal models. One NK-1 receptor antagonist, aprepitant, demonstrated antidepressant efficacy in a placebo-controlled study (100), but these results were not confirmed in a larger, phase III trial (104). Antidepressant effects have been seen with two other agents in early pilot studies (105, 106), but these findings await replication.

Glutamatergic modulation—Glutamate is the primary excitatory neurotransmitter in the brain that binds to both ionotropic [*N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainate) and metabotropic (G protein-coupled) receptors. Glutamatergic function is implicated in the neurobiology of depression (107–110). NMDA antagonists have shown antidepressant-like properties in animal studies (111, 112). Amantadine, an orally administered NMDA receptor antagonist, has shown antidepressant-like effects as an augmentation agent in preclinical and clinical studies (113).

More recently, placebo-controlled trials have demonstrated very rapid (within a few hours) and significant antidepressant effects with a single intravenous infusion of ketamine in patients with treatment-resistant unipolar (114) and bipolar (115) depression. Unfortunately, these effects were time-limited, and depressive relapse occurred within days to weeks. An open-label study found that six repeated ketamine infusions were safe and generally well-tolerated in a group of 10 patients with TRD (116). Of the nine patients who received repeated infusions, all responded and eight achieved remission. One patient remained generally well for more than 3 months, but the other eight relapsed within 2 months (with a mean time to relapse of 19 days).

The antidepressant effects of ketamine may be mediated by a family history of alcoholism as suggested in an open-label study (117). Further, although memantine, an orally administered NMDA antagonist, did not have statistically significant antidepressant effects in a double-blind, placebo-controlled trial (118), it did show antidepressant effects equivalent to those of escitalopram in patients with major depression and alcohol dependence (119).

Riluzole is a medication with a complex and largely unknown mechanism of action that may involve inhibition of glutamate release. Open-label studies in treatment-resistant unipolar and bipolar depression suggest antidepressant efficacy for riluzole (120–122). However, riluzole failed to prevent relapse after successful antidepressant treatment with ketamine (123).

Scopolamine—Based on a database suggesting a role for the cholinergic system in the neurobiology of depression and antidepressant treatment, the antimuscarinic agent scopolamine was tested and demonstrated rapid (within days) antidepressant effects in a series of small, placebo-controlled trials (124, 125). No data on relapse were presented in these reports, so the duration of these effects is unknown.

S-Adenosylmethionine—S-Adenosylmethionine (SAME) is a molecule involved in the transfer of methyl groups across a variety of biological substrates. A number of controlled studies have demonstrated antidepressant effects for intravenous or intramuscular SAME (126). A recent double-blind, placebo-controlled trial of oral SAME augmentation in patients not responding to an SSRI showed statistically significant antidepressant effects (127).

Focal Brain Stimulation

The emergence of focal brain stimulation therapies over the past few decades has been jointly facilitated by major advances in neuroimaging and the technical ability to acutely and chronically stimulate a discrete neural target. Neuroimaging studies have helped map out a network of brain regions involved in the pathophysiology of depression and the neurobiological mechanisms of various treatments (128, 129); this work has helped postulate critical nodes within this network that might reasonably serve as targets for direct modulation. Such focal neuromodulation is now possible via noninvasive acute stimulation techniques [e.g., transcranial magnetic stimulation (TMS) and transcranial DC stimulation (tDCS)] as well as methods that allow for chronic stimulation but require surgery [e.g., vagus nerve stimulation (VNS), direct cortical stimulation (DCS), and deep brain stimulation (DBS)]. Two of these procedures (VNS and TMS) are currently approved by the FDA for the treatment of depression.

VNS—VNS involves stimulating the vagus nerve via an electrode that is surgically attached to the nerve where it courses through the neck. A subcutaneously implanted pulse generator (IPG) controls stimulation and serves as the power supply for the system. Common treatment parameters include chronic but intermittent stimulation (e.g., 30 seconds on every 5 minutes). In 1997, VNS was approved by the FDA for the treatment of medication-resistant epilepsy. Observations of positive mood effects in some patients with epilepsy led to testing in medication-resistant depression. A double-blind, sham-controlled trial (on versus off stimulation) showed no statistically significant antidepressant effects for 10 weeks of active VNS, with a response of 15% for active VNS versus a 10% response rate with sham VNS (130). However, open-label data suggest increasing antidepressant efficacy over a year of stimulation [in combination with treatment-as-usual (TAU)] in patients in whom between two and six adequate treatments in the current episode have failed, with reported response rates of 27%–53% and remission rates of 16%–33% (131–133). Response and remission rates appear to either remain stable or may continue to increase with 2 years of stimulation (134, 135).

In a nonrandomized comparison with patients with TRD receiving only TAU, 1-year response rates were statistically significantly higher in the VNS + TAU group (27% versus 13%). In addition, VNS + TAU only showed a 23%–35% relapse rate over an additional

year of stimulation (136) compared with a 62% relapse rate in the TAU-only group over an equivalent time period (137). However, a European study suggested that only 44% of patients receiving VNS sustain a response over an additional year of stimulation (133).

Risks of VNS surgery are minor, and adverse effects associated with acute and chronic stimulation include voice changes, coughing, and difficulty swallowing. In general, VNS appears to be cognitively safe, although stimulation intensity may be associated with some modest cognitive impairments (80, 138). The published data suggest that more than 80% of patients receiving VNS choose to continue stimulation even in the absence of an antidepressant response, suggesting that the treatment is generally well-tolerated.

TMS—TMS uses an electromagnetic coil placed on the head to generate a depolarizing electrical current in the underlying cortex. Repetitive TMS (rTMS) delivers a train of stimuli at a set frequency, with “high-frequency” denoting 5 Hz stimulation and “low-frequency” denoting 1 Hz stimulation. A series of stimulation trains are given during each treatment session, and a typical treatment course involves daily sessions (each lasting about 1 hour) for 3–6 weeks. Patients are awake during treatment, and no anesthesia is required.

The types of rTMS most commonly studied for the treatment of depression include high-frequency rTMS (generally 5–20 Hz) applied to the left dorsolateral prefrontal cortex (DLPFC) and low-frequency rTMS (generally 1 Hz) applied to the right DLPFC. Safety and efficacy have been demonstrated for both approaches through a number of relatively small open-label and sham-controlled studies (139–144). Although effect sizes in favor of active rTMS have been moderately strong, absolute response rates have been relatively low (generally between 20% and 40% in sham-controlled studies).

Higher stimulation intensity and total number of pulses delivered (i.e., longer treatment sessions and more sessions over time) are associated with better antidepressant effects (145). High-frequency rTMS seems to be less effective in psychotic versus nonpsychotic depressed patients (67) and those with a longer versus shorter (<5 years) duration of the current episode (146). One study suggests lower efficacy in patients with late-life depression (147), although it is noted that this study probably did not use optimal treatment parameters, and the efficacy of rTMS may be lower if stimulation intensity is not adjusted upward to account for prefrontal cortical atrophy (148, 149), which was not done in this study of older patients.

Two multicenter, randomized, sham-controlled studies have helped clarify the safety and efficacy of rTMS as a monotherapy for medication-resistant depression. In an industry-sponsored study of medication-free patients who had not responded to at least one antidepressant medication, 4–6 weeks of high-frequency left DLPFC rTMS was associated with statistically significant antidepressant effects compared to sham rTMS, including higher response (24% versus 12%) and remission rates (14% versus 6%) after 6 weeks of treatment (150). However, a secondary analysis showed that the difference in antidepressant efficacy between active and sham rTMS was only statistically significant in those patients in whom no more than one medication (of adequate dose and duration) had failed in the current episode (151). A four-site National Institute of Mental Health-funded study using stimulation parameters and eligibility criteria similar to the industry-sponsored study also

showed statistically significant antidepressant effects for active rTMS with remission rates similar to those in the industry study (152). These data also suggested that rTMS was more effective in patients with a lower degree of medication resistance. The long-term efficacy of rTMS is largely unknown, with studies suggesting relapse rates similar to those seen after ECT (153, 154). Repeated rTMS courses may be beneficial in helping to maintain benefit over time (155).

Although rTMS can result in seizures, this is highly unlikely when stimulation parameters are maintained within suggested safety guidelines (156). Common side effects of rTMS include pain at the site of stimulation and headaches, although most patients tolerate treatments very well (150, 152). There are no cognitive side effects associated with rTMS for depression (80). A potential disadvantage of rTMS as currently administered is the need for daily treatments over several weeks. However, in a recent open-label study testing accelerated rTMS (in which 15 treatment sessions were delivered over 2 days in an inpatient setting) (157), response and remission rates immediately after treatment were 43% and 29%, respectively, and were largely maintained over the next 6 weeks; side effects were similar to and no more severe than those seen with daily rTMS.

Magnetic seizure therapy—More focal ECT administration is associated with fewer cognitive side effects but equivalent efficacy compared with less focal techniques (158, 159). Based on this finding, it was hypothesized that if seizures could be generated using very focal stimulation (i.e., with TMS), then efficacy approaching that of ECT could be achieved with an even better cognitive side effect profile. Similar to ECT, magnetic seizure therapy (MST) is performed under general anesthesia and involves the serial induction of seizures over several weeks. Preliminary data suggest that MST has antidepressant effects and may result in fewer cognitive side effects than ECT (160–162). Larger trials are currently underway.

tDCS—tDCS is a noninvasive technique that modulates cortical excitatory tone (rather than causing neuronal depolarization) via a weak electrical current generated by two scalp electrodes. Five sessions of tDCS applied to the left DLPFC have shown mixed antidepressant efficacy in sham-controlled studies with one study finding a statistically significant antidepressant benefit (163) but another failing to replicate this (164). A third sham-controlled study using 10 sessions demonstrated antidepressant efficacy for active tDCS (165). In general, tDCS is very well-tolerated with no known cognitive side effects.

DCS—Direct cortical stimulation involves electrical stimulation of the cortex via one or more electrodes surgically placed in either the epidural or subdural space. Similar to VNS, stimulation is driven by an IPG connected to the electrodes via subcutaneous wires. In a small pilot study of DCS of the medial and lateral prefrontal cortices, three of five patients with TRD achieved remission after 7 months of chronic, intermittent stimulation (in these patients at least four adequate treatments had failed in the current episode) (166). DCS was very well tolerated, although one patient required explantation due to a scalp infection.

DBS—DBS is achieved by placing a thin electrode through a burr hole in the skull into a specific brain region using imaging-guided stereotactic neurosurgical techniques. Electrodes

can be placed in essentially any brain region and can be implanted unilaterally or bilaterally. Each electrode typically contains several distinct contacts that can be used to provide monopolar or bipolar stimulation. As with VNS and DCS, the electrodes are connected via subcutaneous wires to an IPG that controls stimulation.

DBS is an established treatment for patients with severe, treatment-resistant Parkinson's disease, essential tremor, and dystonia. DBS has largely replaced ablative surgery in these conditions because it can be adjusted to achieve maximal benefit with a minimum of side effects and can be turned off or completely removed in the case of severe, unwanted side effects. DBS of the anterior internal capsule [as a potential replacement for capsulotomy; this target is also referred to as the ventral capsule/ventral striatum (VC/VS)] has shown potential safety and efficacy for patients with severe treatment-refractory OCD based on a multicenter open-label case series of 26 patients (167). This intervention is now FDA-approved via a Humanitarian Device Exemption. DBS of the subthalamic nucleus has also shown efficacy for OCD in a 6-month sham-controlled study (168).

Based on a converging neuroanatomical database suggesting a critical role for Brodmann area 25 in a neural network involved in depression and antidepressant response, Mayberg and colleagues (169, 170) demonstrated that open-label subcallosal cingulate DBS was associated with antidepressant effects in a cohort of 20 patients with severe TRD in whom at least four treatments had failed in the current episode. After 6 months of chronic stimulation, 60% of patients achieved response and 35% achieved remission; these effects were largely maintained over an additional 6 months with 72% of 6-month re-responders still meeting the response criteria at 12 months (and three additional patients achieving response by 12 months). Adverse events related to the procedure included skin infection (leading to explantation in two patients) and perioperative pain/headache related to surgery. There were no negative effects associated with acute or chronic DBS, and no negative cognitive effects (171).

In studies of VC/VS DBS for OCD, it was noted that many patients experienced significant improvement in comorbid depression (167), leading to testing of VC/VS DBS for TRD without comorbid OCD. After 6 months of chronic stimulation in 15 patients with TRD enrolled in a three-center open-label pilot study, 40% of patients achieved response and 27% achieved remission (172). At the last follow-up (an average of 24 ± 15 months after onset of stimulation, with a range of 6–51 months), there was a 53% response rate and a 33% remission rate. Adverse effects related to surgery and/or the device included perioperative pain and a DBS electrode break. Adverse effects of stimulation included hypomania, anxiety, perseverative speech, autonomic symptoms, and involuntary facial movements; these were mostly reversible with a stimulation parameter change. No cognitive side effects were described.

The most ventral aspect of the VC/VS DBS target includes the nucleus accumbens, a region implicated in reward processing. This region was targeted for DBS in a cohort of 10 patients with TRD in an open-label pilot study, with 50% of patients achieving an antidepressant response after 6 months of chronic stimulation (173). Case reports have described potential antidepressant efficacy of DBS of the inferior thalamic peduncle (which contains

thalamocortical projection fibers) (174) and the habenula (which is involved in modulation of monoaminergic neurotransmission) (175).

Summary and conclusions

TRD is a prevalent and disabling condition with few evidence-based treatments available. Several medication augmentation or combination strategies currently exist, but the supporting database is limited and overall response and remission rates are relatively low in patients with TRD. Psychotherapy has shown significant potential as a treatment for depression and TRD but it is relatively understudied, and patient access can be limited. ECT is highly effective, even in TRD, for getting a patient out of a depressed episode, but relapse rates are high. A general algorithm for approaching the patient with TRD is given in Figure 1.

Advances in the management of TRD include the development of a number of novel pharmacological agents, many of which target systems outside the monoamines, as well as several focal neuromodulation techniques. Overall, there is optimism that these strategies will lead to antidepressant treatments to help achieve and sustain remission in a greater number of depressed patients. However, progress to date has been limited: despite encouraging preliminary results, none of the novel drugs are yet established for clinical use; the two FDA-approved brain stimulation therapies (VNS and TMS) are associated with relatively low response and remission rates, and neither has shown efficacy in those patients with the most extreme forms of treatment-resistant depression (i.e., more than six treatment failures in the current episode); and data on the remaining brain stimulation approaches are far too preliminary to draw meaningful conclusions regarding safety and efficacy. Still, the efforts of the past decade herald a new era of antidepressant treatment development, and it is highly likely that this work will eventually result in new and more powerful antidepressant therapies.

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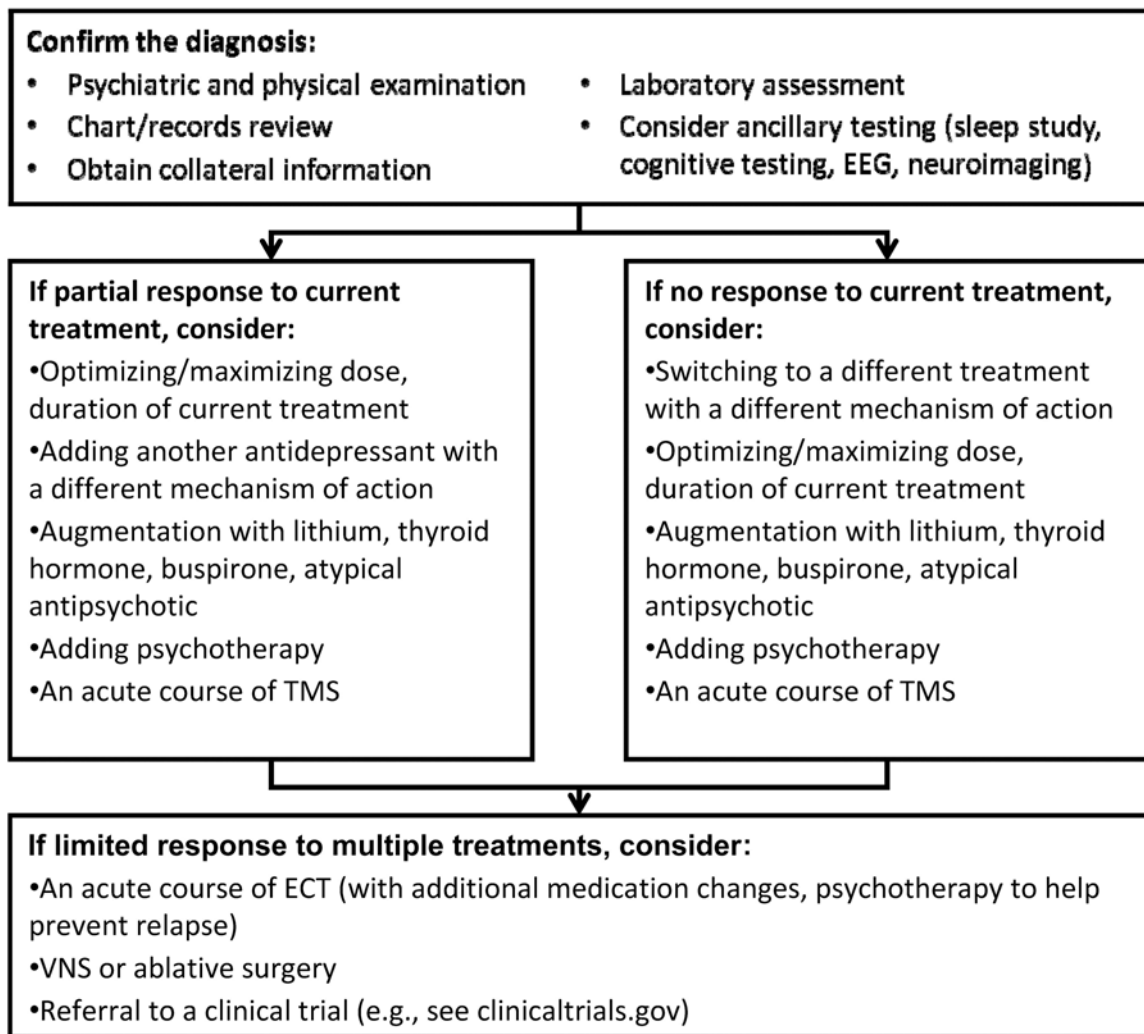


Figure 1.
A Proposed General Algorithm for Approaching and Managing a Patient with TRD. EEG, Electroencephalography.

Table 1
Common, Evidence-Based Medication Augmentation Approaches for TRD

Approach	Highest Level of Support	Comments
Lithium	Several placebo-controlled RCTs	Best data are from studies using TCAs or MAOIs; limited data with newer antidepressant medications
Thyroid hormone (T ₃)	Several placebo-controlled RCTs	Best data are from studies using TCAs; limited data with newer antidepressant medications
Bupirone	Two placebo-controlled RCTs	One RCT was positive for patients with severe depression (but was not positive overall), the other was negative
Atypical antipsychotics	Several placebo-controlled RCTs for various agents	
Additional antidepressants		
Bupropion	Open-label studies	Most common approach in clinical practice
Mirtazapine	One placebo-controlled RCT	
TCA + SSRI/SNRI	Open-label studies	

RCT, randomized controlled trial.

Table 2
Developing Treatment Options for TRD

Approach	Highest Level of Support	Comments
Dopamine agonists	Two placebo-controlled RCTs	
CRF-1 receptor antagonists	Open-label data	One negative placebo-controlled RCT has been published
Glucocorticoid receptor antagonists	One placebo-controlled RCT for mifepristone	Study was done in patients with psychotic depression; benefits were greater for psychotic than depressive symptoms
Substance P receptor antagonists	Two placebo-controlled RCTs for aprepitant Open-label data for 2 other agents	The smaller RCT was positive, but the larger phase III study was negative
Ketamine	Two placebo-controlled RCTs	Effects are acute (within a few hours), but relapse generally occurs within a few days
Riluzole	Open-label studies	
Scopolamine	Two placebo-controlled RCTs	
SAMe	One placebo-controlled RCT	
VNS	Three long-term open-label studies	A 10-week sham-controlled RCT was negative; data from one long-term open-label study were compared with those from a nonrandomized, treatment-as-usual group followed for a similar period of time
TMS	Several sham-controlled RCTs	Data from a large, industry-sponsored RCT suggest no statistically significant antidepressant effect for TMS in patients in whom more than one adequate antidepressant medication has failed
MST	Open-label comparisons to ECT	One study suggested greater antidepressant efficacy for ECT over MST
tDCS	Three sham-controlled RCTs	Two of the three RCTs were positive; one was negative
DCS	One open-label study	
DBS	One open-label study for each of 3 targets (SCC, VC/VS, and NAcc)Single case reports for 2 other targets (ITP and habenula)	

RCT, randomized controlled trial; SCC, subcallosal cingulate; VC/VS, ventral capsule/ventral striatum; NAcc, nucleus accumbens; ITP, inferior thalamic peduncle.