Prevalence and Management of Treatment-Resistant Depression

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Treatment-resistant depression (TRD) is a major public health problem in terms of its prevalence and in terms of individual suffering and cost to society. Best estimates indicate 12-month prevalence rates of ~3% for Stage 1 TRD (failure to respond to 1 adequate trial of an antidepressant) and ~2% for Stage 2 TRD (failure to respond to 2 adequate trials). The current article provides a brief review of the definitions, prevalence, and various treatment options for TRD, including switching, augmentation, and combination therapies and use of nonpharmacologic treatments. Given the public health importance of TRD, the relative absence of adequately powered, double-blind trials is striking. *(J Clin Psychiatry 2007;68[suppl 8]:17–25)*

The traditional definition of *treatment-resistant depression* (TRD) requires an inadequate response to an adequate course of treatment in a patient meeting criteria for major depressive disorder (MDD). In the past decade, almost all parts of this traditional definition have been subjected to scrutiny and have had empirical criteria applied to them. *Inadequate response* has been operationalized by applying specific criteria for treatment response or, alternatively, remission. The magnitude of TRD increases substantially if failure to achieve remission is used as the qualifying criterion. However, although remission is the gold standard outcome for antidepressant treatment, failure to achieve remission is not typically required for a patient to meet criteria for TRD.

What constitutes *an adequate course of treatment* has been operationalized relatively recently by delineating a TRD staging system (Table 1).[1] Criteria for Stage 1 and 2 TRD require failure to respond, respectively, to 1 or 2 adequate antidepressant trials. Each trial must comprise antidepressants of distinctly different classes. Stage 3 requires a third trial which must include a course of treatment with a tricyclic antidepressant, if this class was not used in Stage 1 or 2. Stage 4 TRD requires failure to respond to at least 4 different classes of antidepressants, one of which must be a monoamine oxidase inhibitor. Stage 5 TRD requires meeting all Stage 4 criteria, in addition to which a patient must have failed an adequate course of electroconvulsive therapy (ECT).

Treatment-resistant depression typically is limited to patients who meet criteria only for unipolar MDD. There is no consensus as to whether patients with extensive and/or severe Axis I comorbidity should be categorized as having TRD. Additional research is needed to characterize the extent to which TRD might be secondary to untreated comorbid disorders such as anxiety syndromes or other Axis I disorders, Axis II diagnoses, or medical illness.

More research is also needed to refine the TRD staging system, which, at this point, continues to be largely a proposed schema. Issues which need to be addressed include (1) Is response, remission, or complete recovery a more clinically useful outcome criterion? (2) Should each antidepressant treatment have a different mechanism of action? (3) Should combined therapies or treatment augmentation be including in staging? (4) Should newer treatments (e.g., vagal nerve stimulation) be included in the staging schema? (5) How should Axis I comorbidity be handled? (6) Are all symptom response or remission criteria (e.g., using HAM-D ≤ 6) created equal? In other words, taking remission as an example, does the presence of single symptoms rated as "severe" (such as insomnia or hopelessness/suicidality) have the same prognostic significance as multiple symptoms rated as "mild"?

Another important question is whether Stage 4 or 5 TRD might not constitute a unique depressive subtype.[2] It would not be surprising if failure to respond to multiple adequate antidepressant trials, which typically target monoaminergic neurotransmitters, might define a unique pathophysiologic subgroup. Pharmacogenomic and functional imaging studies are needed to clarify this issue.

PREVALENCE OF TRD

Given the lack of consensus criteria, it is perhaps not surprising that no agreed-upon estimates of the prevalence of TRD exist. It follows from the TRD staging schema, summarized above, that the prevalence of TRD is not a unitary phenomenon. Instead, different prevalence rates will be associated with each TRD stage. Estimates of TRD prevalence also vary greatly depending on the treatment setting in which

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Table 1. Thase-Rush Treatment-Resistant Depression (TRD) Staging Method[a]

TRD Stage	Criteria
Stage 1	Failure of an adequate trial of 1 class of major antidepressant
Stage 2	Failure of adequate trials of 2 distinctly different classes of antidepressants
Stage 3	Stage 2 plus failure of a third class of antidepressant, including a tricyclic antidepressant
Stage 4	Stage 3 plus failure of an adequate trial of a monoamine oxidase inhibitor
Stage 5	Stage 4 plus failure of an adequate course of electroconvulsive therapy

[a]Adapted with permission from Thase and Rush.[1]

the estimate is made, with the lowest rates expected in primary care settings, and progressively higher rates occurring in outpatient psychiatry settings, inpatient psychiatric settings, and academic/tertiary care settings.

On the basis of data from randomized controlled trials (RCTs) conducted in a research setting, Stage 1 TRD has been reported to have a prevalence of ~50% when "response" is used as the criterion outcome and at least 60% when "remission" is used.[3,4] Studies conducted in clinical practice settings have reported even lower remission rates, in the range of 15% to 35%.[5,6] In the National Institute of Mental Health (NIMH)–sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which was conducted in both psychiatric and primary care practice settings, patients with nonpsychotic major depression (N = 2876) were treated in Stage 1 for 12 weeks with citalopram at a mean final daily dose of 55 mg. Stage 1 response rates were 47% and remission rates were 28%.[7] These findings would suggest a prevalence for Stage 1 TRD of ~50% using response criteria and of ~70% using remission criteria.

Recent STAR*D data reported response rates of 26% to 28% when switching to a second antidepressant (sustained-release bupropion [N = 239], sertraline [N = 238], or venlafaxine-XR [N = 250]) after failure to achieve remission (or intolerance) with initial citalopram treatment.[8] Alternatively, combination of an SSRI with sustained-release bupropion (N = 279) was associated with a 32% response rate.[9] If one extrapolates from STAR*D data, then Stage 2 TRD (failure to achieve response criteria after 2 courses of adequate treatment) may be estimated to occur in approximately 35% of patients. Given a 12-month MDD prevalence estimated at 6.6%,[10] then the total 12-month prevalence estimates are ~3% for Stage 1 TRD and ~2% for Stage 2 TRD. Adequately powered and well-controlled trials of TRD in Stages 3 to 5 in clinical practice settings have not been reported, and thus no estimates are available.

An alternative TRD staging model has been proposed that uses a scoring system in which points are assigned depending on the type of adequate trial(s) that the patient has failed to respond to, and that takes into account whether the trials have been optimized in terms of higher doses and/or longer durations and/or use of augmentation.[11] A retrospective chart review of the treatment histories of 115 patients diagnosed with MDD found the alternative TRD scoring system and the STAR*D scoring system to be highly correlated, although the former had higher predictive validity.[12]

COSTS AND BURDEN OF TRD

Treatment-resistant depression is a costly illness that is associated with a significant increase in both medical and psychiatric health care costs. Compared to non-TRD, TRD patients have been reported to have significantly higher outpatient medical costs and to be approximately twice as likely to be hospitalized, either medically or psychiatrically.[12,13] Patients with TRD who were hospitalized had a 6-fold increase in overall medical costs compared to non-TRD patients ($42,344 vs. $6512).[12]

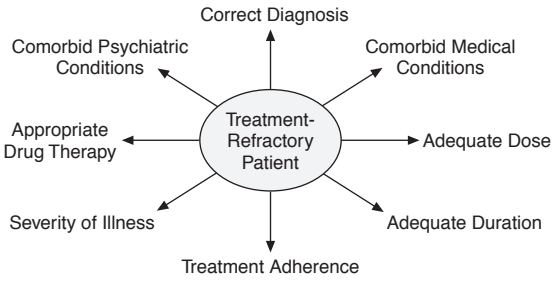
Treatment-resistant depression also is thought to be associated with a significant increase in indirect costs (e.g., lost work and decreased productivity) for both identified patients and family members. However, accurate estimates of TRD-related indirect costs are not available. For non-TRD, the proportion of the total cost burden contributed by indirect costs is approximately 2-times the proportion contributed by direct medical costs.[14]

CORRELATES AND PREDICTORS OF TRD

Although various clinical and demographic factors have been identified that are associated with an increased risk of treatment nonresponse (see below), it is important to note that more than half of treatment nonresponse in MDD appears to be due to 2 factors: (1) poor adherence to prescribed treatments and (2) poor tolerability. Poor tolerability may result in nonadherence, but is only one of several causes.

The extent to which poor adherence and/or poor tolerability contribute to treatment-resistance is uncertain, especially because the tolerability and adherence rates in classic placebo-controlled efficacy trials do not generalize well to "real world" clinical settings.[15] Overall, it has been estimated that up to 20% of TRD might be attributable to nonadherence.[16] However, this is likely to be a significant underestimate, because usual care data from primary care settings indicate that only ~40% of patients take adequate antidepressant dosages during the first 6 months of treatment.[6] Nonadherence has been most commonly associated with younger age and intolerance of adverse events.[17] In the STAR*D program, maximum side effect intensity was rated as "severe-intolerable" after a course of acute treatment by 10% of patients who achieved remission and by 18% of patients who did not.[7] Among successful remitters, the likelihood that treatment will be continued, and remission maintained, over many months is unlikely in the presence of severe-intolerable side effects.

Figure 1. Factors to Consider in Patients Failing First Trial of Antidepressant Monotherapy



FAILURE AFTER 1 COURSE OF TREATMENT: DIFFERENTIAL DIAGNOSIS OF TRD STAGE 1

More than one third of patients who complete an initial course of antidepressant treatment will not achieve a satisfactory response, and at least two thirds will not achieve remission. These patients qualify for Stage 1 TRD. The likelihood that they will progress to Stage 2 TRD may be reduced substantially by systematically reviewing the common reasons for treatment failure (Figure 1).

First, it is important to confirm that the prescribed dose of antidepressant was adequate and was taken for a sufficient duration. The overall dose-response curve is relatively flat for SSRIs within their therapeutic dosing range, but some patients clearly benefit from taking higher doses. Other classes of antidepressants (e.g., tricyclics, and perhaps serotonin-norepinephrine reuptake inhibitors [SNRIs]) exhibit a more significant dose-response curve.[18] Similarly, 6 weeks of treatment appears to be an adequate duration for the majority of patients, but there is a subgroup of patients who may benefit from a longer course of treatment. The following variables have been identified as risk factors for delayed remission: chronicity (both duration of the current episode and number of previous episodes), older age, the presence of psychiatric and medical comorbidity, and symptom severity.[1,19,20] Treatment optimization (higher doses and/or additional weeks of treatment) is one option, especially when the treatment response is suboptimal, i.e., insufficient to qualify as remission.

A second important consideration, as noted in the previous section, is whether the patient has been compliant with the prescribed regimen. Studies suggest that approximately one third of patients are nonadherent to prescribed antidepressant regimens.[15] If medication nonadherence is due to poor tolerability, then alternative antidepressants may need to be prescribed.

A third important consideration is to review the diagnosis—both the primary diagnosis and the presence of comorbid diagnoses. Does the patient suffer from a subtype of MDD (e.g., bipolar, psychotic, atypical) that might benefit from use of another class of antidepressant, or some combination therapy, or ECT? The article by Rush in the current issue[21] reviews the treatment implications of depression subtypes.

In addition to MDD subtype, it is important to evaluate whether the diagnosis of MDD is complicated by comorbid medical or psychiatric illnesses. In the STAR*D program, significant medical comorbidity was present in 53% of patients and was more likely to occur in older patients, in patients with lower socioeconomic and educational status, and in patients with no family history of depression.[22] All patients, particularly those with TRD, should be evaluated for comorbid medical illness (or medication treatment) that might be contributing to the depression, or interfering with its successful treatment.

Clinically relevant comorbid psychiatric illness is also very common and is also likely to contribute to treatment resistance. Psychiatric comorbidity in MDD is significantly higher if the patient is younger, female, and of lower socioeconomic status.[23] In a multivariate regression model, the STAR*D program identified obsessive-compulsive disorder (odds ratio [OR], 0.71) and posttraumatic stress disorder (OR, 0.63) as the only significant independent predictors of incomplete treatment response.[7] In univariate logistic regression analyses, incomplete response was also predicted by generalized anxiety disorder (0.80), panic disorder (0.62), agoraphobia (0.64), and somatoform disorder (0.40). Interestingly, alcohol and substance dependence/abuse were not negative predictors of response; nor was social anxiety disorder or bulimia. Current comorbidity was relatively common between MDD and generalized anxiety disorder (24%), obsessive-compulsive disorder (14%), panic disorder (13%), and posttraumatic stress disorder (21%). Overall, 76% of patients had at least 1 current comorbid disorder, and 38% had 2 or more. The odds of achieving a complete response progressively decreased as a function of the number of comorbidities, from 1 (OR, 0.83) to 4 or more (OR, 0.52).

If treatment nonresponders are suffering from concurrent Axis I comorbidity, then the specific comorbidity may be a useful guide in choosing which drug or combination of drugs might be most efficacious. Despite the appeal of this approach, there are surprisingly few double-blind RCTs that compare the effectiveness of 2 antidepressants, or combination therapy, in treating MDD with current Axis I comorbidity.

MANAGEMENT OPTIONS FOR TRD

Switching

In the past 5 years, the great majority of patients diagnosed with MDD receive either a selective serotonin reuptake inhibitor (SSRI) or SNRI antidepressant as their first course of treatment. If the first trial fails to achieve an adequate response, and no specific reason can be identified and corrected (as summarized above), then switching to a second antidepressant is the most common next step.

A large number of open-label trials[24–33] and a few double-blind, controlled trials[34–38] suggest that such switching is effective in achieving a response in approximately 40% to 60% of cases. It is frequently recommended that patients who fail one class of antidepressant be switched to a class of antidepressant with a different mechanism of action. Even though the recommendation appears to have merit, to date, there is no good evidence that between-class switching increases the likelihood of achieving either response or remission compared to within-class switching.

Recently reported results from the STAR*D also do not support any advantage for between-class switching.[8] Patients who failed to respond to citalopram had similar response rates after within-class switching to sertraline (27%) when compared to between-class switching to either sustained-release bupropion (26%) or extended-release venlafaxine (28%). The relatively low rates of treatment response for all 3 second-line treatments are somewhat disappointing, especially for venlafaxine-XR with its dual serotonin and norepinephrine reuptake inhibiting action. Of interest, within-class switching to sertraline was well-tolerated, even in the subgroup of patients who reported poor tolerability to their initial course of treatment with citalopram. It is important to note that although citalopram and sertraline share the property of blockade of serotonin reuptake, they also have unique pharmacologic properties. Thus, sertraline is a relatively potent dopamine reuptake inhibitor.[39]

Monoamine oxidase inhibitor (MAOI) antidepressants have long been considered a treatment option in patients with TRD,[40] and use of an MAOI is one of the treatment options in TRD staging.[1] Several clinical trials and retrospective chart reviews suggest that the classic MAO inhibitors (tranylcypromine and phenelzine) have efficacy in both early and late stage TRD.[34,35,41–48] The third conventional MAOI, isocarboxazid, has not been studied in this regard. The results of these studies suggest that approximately 50% of patients meeting criteria for TRD, including Stages 2 and 3, will respond to treatment with either tranylcypromine or phenelzine. Larger and more methodologically rigorous RCTs are needed to establish the place of MAOIs in the emerging TRD treatment algorithm.

Safety concerns with first-generation MAOIs, specifically the potential for a hypertensive crisis, have limited research on this class of drugs, as well as the willingness of physicians and patients to use the drugs in clinical practice, even among TRD patients. The greater safety of the new MAOI selegiline, administered transdermally, may reverse this reluctance; however, before this can happen, much research needs to be done to establish its efficacy in TRD.

Augmentation/Combination Therapy

A survey of prescribing practices found that raising the dose was the most common "next-step" when patients achieved a partial response, followed by augmentation.[49] This inclination to raise the dose is perhaps unfortunate, because surveys suggest that dose escalation as a treatment strategy may not be particularly effective in patients being treated with SSRIs.[49] For nonresponse, augmentation is the most common "next-step" after switching to a non-SSRI antidepressant.[49,50]

Table 2. Drugs Used for Augmentation in Treatment-Resistant Depression (TRD)[a]

Drug	Strength of Evidence of Efficacy in TRD
Lithium	A (with TCA) C (with SSRI)
Bupropion or mirtazapine combination therapy	B
Anticonvulsants (lamotrigine, divalproex sodium, carbamazepine)	B
Thyroid hormone (T_3)	B (with TCA) C (with SSRI)
Atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole)	B (olanzapine) C (other atypicals)
Dopamine agonists (pramipexole)	C
Pindolol	C
Stimulants	C
Buspirone	B
Modafinil	B/C
Testosterone, estrogen	C
Miscellaneous (buprenorphine, SAMe, inositol)	C

[a]Data from Thase.[111]
A: ≥ 2 adequately powered, double-blind, placebo-controlled trials.
B: ≥ 1 adequately powered, double-blind, placebo-controlled trial (or an equivalent weight of evidence from multiple smaller trials).
C: positive evidence from open-label trials and case series.
Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

A wide array of drugs have been used to augment the efficacy of antidepressants in patients with various stages of TRD (Table 2). Surveys suggest that choice of augmentation strategy among clinicians is fairly evenly divided among 4 categories: (1) bupropion, (2) dual-acting combinations (serotonin/norepinephrine), (3) lithium, and (4) miscellaneous agents including triiodothyronine (T_3), buspirone, pindolol, psychostimulants, etc.

Evidence for the benefit of bupropion in TRD rests upon uncontrolled case reports and pilot data,[51] and the recently reported STAR*D results.[8] In the STAR*D study, remission rates were modestly higher after augmentation with sustained-release bupropion (39%) compared to buspirone (33%). In addition, bupropion was better tolerated than buspirone, with significantly lower attrition due to adverse events (12% vs. 21%). This latter finding confirms the clinical practice perception of the favorable tolerability of bupropion in combination therapy. It should be noted that the STAR*D data examined early stage TRD. The efficacy of bupropion as an augmentation strategy in late stage TRD is unproven.

Use of dual-action antidepressants as an augmentation strategy may be accomplished by combining an SSRI with a noradrenergic reuptake inhibitor (atomoxetine, desipramine) or switching to (or adding) duloxetine or venlafaxine-XR. Alternatively, treatment with an SSRI or SNRI has been

augmented with α_2-adrenergic antagonists such as mirtazapine or mianserin (not available in the United States). As noted above, combining drugs to achieve a dual action is one of the most common augmentation strategies. Available studies that test this augmentation strategy show promising results,[52–54] but it is important to note that there are virtually no adequately powered, double-blind, placebo-controlled trials available in well-defined TRD. One of the largest double-blind trials tested the comparative efficacy of using a dual-action agent (venlafaxine) and simple switching to another SSRI (paroxetine) in TRD.[55] Treatment with venlafaxine resulted in significantly higher remission rates than paroxetine (N = 122; 42% vs. 20%).

Lithium and T_3 are 2 commonly used augmentation strategies that predate the introduction of SSRI and SNRI antidepressants. Meta-analyses of multiple studies, mostly poorly designed and notably underpowered, have found the use of T_3 augmentation to be associated with a significant increase in the likelihood of response and in the speed of response to antidepressants.[56,57] Only a small subsample of these patients met criteria for TRD. After almost 50 years of use of T_3 as an augmentation strategy in depression, the quality of the evidence for T_3 augmentation is poor, despite the promising nature of the results.

The use of lithium as an augmentation strategy in TRD is almost as venerable as T_3 use. A recent meta-analysis identified 27 studies with a total of 803 patients.[58] Once again, the majority of the studies were open-label and/or used no placebo control. TRD staging was imprecise and the antidepressant therapy that was being augmented was highly heterogeneous, even within a given study. Overall, 10 double-blind, placebo-controlled studies were identified, but all were notably underpowered, with sample sizes per treatment group ranging from N = 3 to a high of N = 30. In the placebo-controlled trials, the response rate was significantly higher with lithium augmentation (45%) than with placebo (18%).

A recently published STAR*D study[59] compared the efficacy of augmentation with lithium (N = 69; 900 mg/day) or T_3 (N = 73; up to 50 μg/day) in patients diagnosed with nonpsychotic MDD who had failed 12 weeks of prospective treatment with both citalopram and a second course of treatment that consisted of either switching to a second antidepressant class or augmentation with bupropion or buspirone. After 10 weeks of treatment, remission rates were 16% with lithium augmentation and 25% with T_3 augmentation. The efficacy advantage in favor of T_3 was not significant, although T_3 augmentation was significantly better tolerated.

Miscellaneous other augmentation strategies have been employed, including pindolol, atypical antipsychotics, anticonvulsants, dopaminergic agents, estrogen, testosterone, and multiple other agents (buprenorphine, SAMe, inositol).

Pindolol is a β-blocker with presynaptic 5-HT_{1A} antagonist activity that has shown promise as an agent for optimizing antidepressant response in non–treatment-resistant patients. However, a series of small controlled trials of its use as an augmentation strategy in TRD have been negative, although the doses employed may have been inadequate.[60–62]

Atypical antipsychotics have been suggested as augmentation agents in TRD because they act on a wide range of receptor targets that may have antidepressant effects, such as antagonist activity at 5-HT_{2A} receptors. A flurry of research studies have been published in the past 5 years that examine the use of atypical antipsychotics as an augmentation strategy in (nonpsychotic) TRD.[63–72] The results are very promising, although it should be noted that many of the available studies are open-label or underpowered double-blind trials. To date, only 2 large, double-blind trials[65,72] have been reported. In the first study,[65] similar response and remission rates, respectively, were reported after 8 weeks of double-blind treatment with combined olanzapine/fluoxetine (28%, 17%), compared to monotherapy with olanzapine (19%, 13%), fluoxetine (29%, 13%), or nortriptyline (30%, 18%). In the second study,[72] the long-term relapse prevention benefits were examined when risperidone was combined with citalopram in citalopram nonresponders who had shown an initial response to risperidone augmentation. Even though initial open-label augmentation was highly effective in achieving an initial response (63%), a double-blind comparison of continuation therapy with citalopram plus placebo versus citalopram plus risperidone found no additional relapse prevention benefit from combined use of risperidone on the primary outcome measure, though secondary outcome measures favored the combination.

Anticonvulsants, especially lamotrigine, have been used as augmentation agents, in both treatment-resistant unipolar and bipolar depression. Preliminary studies suggest potential benefit, but adequate controlled trials are not yet available.[73,74]

Various dopaminergic agents, including psychostimulants, bromocriptine, pergolide, ropinirole, and pramipexole, have been used to augment the efficacy of antidepressants. Psychostimulants, such as dextroamphetamine and methylphenidate, have been used clinically for many years. The antidepressant effects occur rapidly, but have been reported to be transient. Data on the potential benefits and risks of psychostimulants in TRD come exclusively from small case series and open-label studies.[75–79] No double-blind, placebo-controlled trials are available in TRD.

More recently, modafinil has been studied in patients with partial or nonresponse to SSRI or SNRI antidepressants. Modafinil is a stimulant-like medication with a novel mechanism of action that is not fully understood, but appears to differ from amphetamine-type drugs. Modafinil has shown promise as an augmentation agent in Stage I TRD by targeting unresponsive depressive symptoms such as fatigue, lack of energy, and poor concentration.[80–84]

Pramipexole is a novel $D_{2/3}$ agonist that has been suggested as a potential augmentation agent based on efficacy

results obtained in a series of pilot studies (some randomized and with a placebo control) of bipolar depression, including treatment-resistant patients.[85–89] Currently no RCTs of pramipexole are available that evaluate its efficacy of TRD.

Nonpharmacologic Therapy

Six somatic, nonpharmacologic treatments of TRD have been studied: ECT, vagus nerve stimulation, transcranial magnetic stimulation, deep brain stimulation, magnetic seizure therapy, and cognitive-behavioral therapy.

Electroconvulsive therapy is the best-studied and most effective single treatment for advanced TRD. Meta-analyses performed over the past 20 years consistently find ECT to have a larger effect size than other classes of antidepressants, including tricyclic antidepressants, MAO inhibitors, and SSRI and SNRI antidepressants.[90–92] The few studies that have directly compared the efficacy of ECT to pharmacologic treatment have found higher response rates with ECT.[93]

Vagus nerve stimulation (VNS) therapy is delivered by a pocket watch–sized device that is implanted in the left chest wall and that is connected to the left vagus nerve by electrodes in the neck. The VNS device is approved by the U.S. Food and Drug Administration for both refractory epilepsy and TRD. VNS is hypothesized to act, via ascending projections, by altering the activity of CNS regions implicated in MDD (e.g., orbital frontal cortex, insula, thalamus, hypothalamus, cingulate, and hippocampus).[94–96] VNS treatment has been shown to increase the CNS concentration of 5-HIAA, homovanillic acid, and GABA.[97] VNS has demonstrated significant efficacy in an open trial of TRD,[98] as well as in 2 short-term, double-blind trials, one evaluating VNS as a monotherapy, and one study evaluating VNS in combination with usual treatment with antidepressants.[99–101]

Repetitive transcranial magnetic stimulation (rTMS) is a neurostimulatory therapy in which a pulsed electromagnetic field is applied to the left prefrontal cortex. rTMS has shown modest-to-moderate efficacy in MDD.[102] Well-designed RCTs of rTMS employ a double-blind, sham rTMS control group. Active treatment consists of high-frequency rTMS (between 5–20 Hz) applied to the left dorsolateral prefrontal cortex.

Recently, 3 small but well-designed trials have all demonstrated significant antidepressant response to rTMS in patients meeting criteria for TRD.[103–105] Response rates for rTMS are ~30%, in the same range as reported for switching in the STAR*D program. These preliminary results strongly suggest a role for rTMS in the treatment of TRD, but confirmation of the potential benefit of rTMS awaits the publication of a large, well-controlled RCT.[106]

Magnetic seizure therapy uses the same machine as is used for rTMS therapy, but the pulsed magnetic field is used to produce focal stimulation sufficient to trigger a seizure. Thus, magnetic seizure therapy is a variant of ECT. It has been studied only in 1 pilot study and in a case series.[107,108] It appears to be better tolerated than ECT, but whether it will have comparable efficacy awaits the results of ongoing controlled trials.

A more recent neurostimulatory treatment approach uses deep brain stimulation to treat severe and intractable TRD. Deep brain stimulation has been reported to be effective in pilot studies, but controlled trials with adequate follow-up are needed.[107,109]

Finally, psychotherapy, especially cognitive-behavioral therapy, has been suggested as a nonpharmacologic approach to TRD, especially Stage 1 or Stage 2. While psychosocial problems are prominent complications of TRD, no large controlled trials of psychotherapy in TRD have been reported.[110]

CONCLUSIONS

This brief review of TRD highlights the importance of 2 specific issues. First, TRD is a major, and relatively neglected, public health issue, with an estimated 12-month prevalence of ~3% for Stage 1 resistance and ~2% for Stage 2. Second, given the prevalence of TRD and the magnitude of the public health problem it represents, what is striking about TRD is the relative dearth of adequately powered, randomized, double-blind treatment studies. Currently, there are more than 2 dozen TRD treatment strategies, all supported by (often multiple) open-label trials, case series, and small double-blind pilot studies. Promising pilot studies are rarely followed up by well-designed trials that rigorously test a candidate treatment.

Finally, the fascination with novel TRD treatment strategies appears to have distracted us from focusing on the prosaic fact that optimizing treatment adherence and careful diagnosis to identify and target medical and psychiatric illnesses that are comorbid with TRD may have as high a yield in overall response as the next novel drug.

Drug names: aripiprazole (Abilify), atomoxetine (Strattera), bromocriptine (Parlodel and others), buprenorphine (Buprenex, Subutex, and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Tegretol, Epitol, and others), citalopram (Celexa and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine, Dextrostat, and others), divalproex sodium (Depakote), duloxetine (Cymbalta), fluoxetine (Prozac and others), fluoxetine-olanzapine (Symbyax), isocarboxazid (Marplan), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Daytrana, Ritalin, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pergolide (Permax and others), phenelzine (Nardil), pindolol (Visken and others), pramipexole (Mirapex), risperidone (Risperdal), ropinirole (Requip), selegiline (Emsam, Eldepryl, and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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National Institute of Mental Health, Pfizer, and Wyeth-Ayerst; was a member of the speakers bureau for Abbott, GlaxoSmithKline, Janssen, and Pfizer; was a stock shareholder of Acadia Pharmaceuticals, Corcept Therapeutics, Cypress Bioscience, and NovaDel Pharma; was on the Board of Directors of The American Foundation for Suicide Prevention, American Psychiatric Institute for Research and Education, George West Mental Health Foundation, NovaDel Pharma, and National Foundation for Mental Health; holds a patent for a method and devices for transdermal delivery of lithium (US 6,375,999) and for a method to estimate serotonin; had a provisional filing (April 2001) for a method to estimate serotonin and norepinephrine transporter occupancy after drug treatment using patient or animal serum; and had equity in Reevax, BMC-JR LLC, and CeNeRx. Currently, Dr. Nemeroff is supported by grants from the National Institutes of Health, NARSAD, and the American Foundation for Suicide Prevention.

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