

Treatment Strategies and Tactics for Treatment-resistant Depression

a report by

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Treatment-resistant depression (TRD)—depression that does not remit after one or more adequately delivered treatments^{1,2}—is a major and increasing public health burden due to its high prevalence, chronic and recurrent course, substantial morbidity, and significant direct and indirect costs.³⁻⁵ Treatment for this condition needs to be aimed at effecting full remission (e.g. absence of symptoms) rather than response, since anything short of remission is likely to result in relapse, recurrence, and future treatment resistance.⁶⁻⁸

The recent National Institute of Mental Health (NIMH)-funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study showed that remission rates are modest even after two state-of-the-art, diligently delivered treatment steps with the support of depression-care specialists.⁹⁻¹¹ Even following four steps, a large percentage of patients who do not benefit remains.⁸

Available treatment strategies, as currently implemented, are relatively ineffective for patients in later stages of TRD, for example those who have not achieved remission despite several adequately delivered treatments.^{8,12-14} Specifically, current research on TRD fails to guide practicing physicians about which treatment sequences are the most effective, with even greater uncertainty about which specific treatment sequence is most effective for individual patients. Given that there is considerable response heterogeneity among individuals, and insufficient understanding of who responds to what treatment, the treatment process is often little more than trial and error until an appropriate treatment is found. There is a clear need for empirically based information to identify effective treatments and use them earlier—thereby reducing the steps needed to achieve remission—and to determine how to individualize and tailor treatment for a particular patient. The fact that 60–70% of all patients with major depressive disorder (MDD) meet criteria for TRD underscores the need for systematic development of innovative treatments for TRD.¹⁵⁻¹⁷

Treatment-resistant Depression

Treatment-resistant depression is a common problem in the treatment of MDD, yet little agreement exists about either the definition of TRD or evidence-based options for treatment. There is likely a continuum of treatment resistance, with modest resistance referring to failure to fully respond to one adequate treatment trial, and greater resistance referring to failure to respond to two or more adequate treatment trials or one trial of augmentation.^{11,18}

Remission as the Goal of Treatment

There is considerable evidence that, even with treatment, residual symptoms often persist, leading to psychosocial dysfunction,^{5-7,19} and the

longer a patient remains symptomatic, the lower the chances of a complete recovery.²⁰ Furthermore, the occurrence of both MDD and substance abuse, or other comorbidities, intensifies the degree of medical and psychosocial impairment, resulting in significant suffering and degradation in global function.

Tactics and Treatment Strategies for Treatment-resistant Depression

Pharmacological Strategies

Over time, many different strategies have been developed in an effort to overcome the problem of partial or non-response to treatment. These include augmentation strategies, switching agents, combining antidepressants (two medications or medication and psychotherapy), and dual-action agents.

In terms of sequential treatment approaches, as yet there are no randomized studies suggesting the best specific treatment sequence, and further studies are needed to evaluate the comparative efficacy and tolerability of different approaches. Adaptive strategies to date rely primarily on consensus-based, clinical decision-making rather than on innovative study designs that address the identification of the best sequence for individual or groups of patients. Traditional approaches have considered each step in the sequence as a new trial, but we now know that each treatment step builds on the previous treatment, and that resistance to one step increases the chances of resistance to



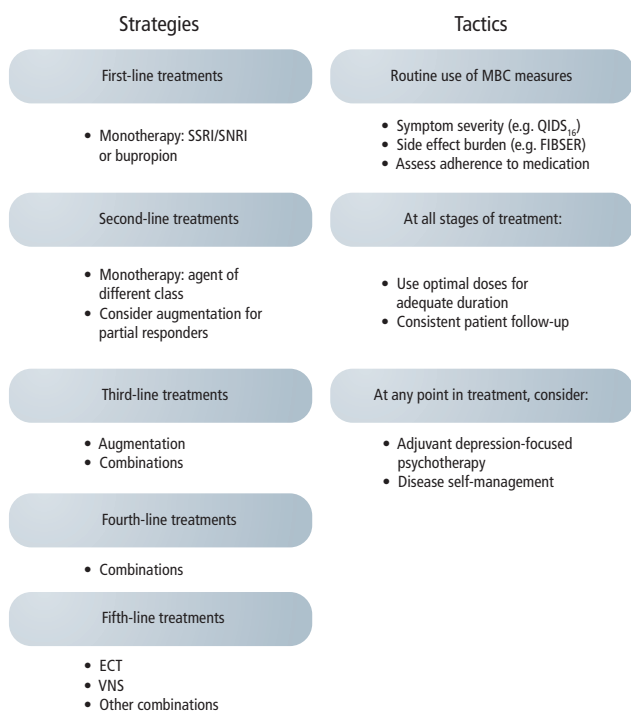
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Figure 1: Approaches to the Management of Treatment-resistant Depression



ECT = electroconvulsive therapy; FIBSER = Frequency, Intensity, and Burden of Side Effects Rating Scale; MBC = measurement-based care; QIDS₁₆ = 16-item Quick Inventory of Depressive Symptomatology; SNRI = selective noradrenergic re-uptake inhibitor; SSRI = selective serotonergic re-uptake inhibitor; VNS = vagus nerve stimulation.

subsequent steps. In addition, despite patient and provider education, suboptimal medication dosing and duration of exposure remain the norm.²¹⁻²⁴ These difficulties herald the need for a paradigm shift in how clinical decision-making is incorporated into clinical practice and research study designs.

Switching, Augmentation, and Combination Strategies

There is increasing evidence that augmentation and switching are effective strategies after failure of an adequate antidepressant treatment trial. In general, augmentation is the preferred clinical choice when the patient is showing at least a partial response to the primary antidepressant and the primary medication is well tolerated. In contrast, switching is preferred when the patient has shown no response to the initial antidepressant. In determining the choice of the switching agent, clinical consensus suggests a trial with an antidepressant of a different class from the first medication. However, there is now evidence that switching from one selective serotonin re-uptake inhibitor (SSRI) to another SSRI may be a reasonable strategy.⁹ Furthermore, switching from a medication to a depression-focused psychotherapy, or vice versa, appears to produce comparable outcomes.²⁵ In terms of augmentation, many agents have been investigated with variable evidence of efficacy, including lithium,²⁶⁻²⁹ triiodothyronine (T3),^{30,31} buspirone,^{11,32} atypical antipsychotics,^{33,34} lamotrigine,^{35,36} dopaminergic agonists,^{37,38} pindolol,^{39,40} and psychostimulants,^{41,42} as well as antidepressants with a different neurochemical profile from the primary agent. Despite the widespread use of these strategies, further supporting

evidence from placebo-controlled trials is still lacking.⁴³ Other novel targets are also being investigated, including melatonin receptor agonists, N-methyl d-aspartate (NMDA), glucocorticoid, omega-3 fatty acids, novel monoamine oxidase inhibitors, substance P, and triple re-uptake inhibitors.⁴⁴

Non-pharmacological Strategies

Non-pharmacological treatments have also been evaluated in terms of their potential as treatment options in patients not responding to antidepressants.

Somatic Treatments

There has been growing interest in the potential application of vagus nerve stimulation (VNS) in the non-pharmacological treatment of TRD.⁴⁵⁻⁵¹ In July 2005, the US Food and Drug Administration (FDA) approved VNS with an indication for the adjunctive long-term treatment of chronic or recurrent depression for adults refractory to antidepressant drugs (with the recommendation that patients should have failed at least four traditional therapies before using VNS).

Similarly, repetitive transcranial magnetic stimulation (rTMS) has been studied as an adjunctive treatment for drug-resistant major depressive disorder.⁵²⁻⁵⁴ However, results so far have been conflicting, a fact that may be related to variability in stimulation parameters, small sample sizes, and heterogeneity of concomitant drug treatments. Larger trials are ongoing. Other novel neurostimulation treatments with preliminary evidence of efficacy for TRD include deep brain stimulation^{55,56} and magnetic seizure therapy.^{57,58}

There remains controversy within the field in terms of the efficacy and safety of electroconvulsive therapy (ECT) as a treatment modality. Following a meta-analysis, a group of researchers in the UK recently found that ECT is an effective short-term treatment for depression, with some evidence suggesting that ECT is more effective than pharmacotherapy.⁵⁹ However, another group looked at ECT versus pharmacotherapy as a treatment for relapse prevention, finding that both treatments had limited efficacy with more than half of patients experiencing disease relapse or dropping out of the study.⁶⁰

Psychotherapy

Cognitive, interpersonal, and behavioral psychotherapy have all been shown to be effective in the treatment of depression, with results comparable to those found with antidepressant medications in randomized, controlled trials.⁶¹⁻⁶³ Specifically, cognitive behavioral therapy (CBT) appears to reduce residual symptoms in depression and ultimately reduces the risk of relapse.⁶⁴⁻⁶⁷ It has also been suggested that combined treatment with antidepressant medication and psychotherapy may be more effective than either strategy alone.^{68,69} However, others caution that the advantage of combined treatment may be limited to treatment of patients with more complex depressive disorders, including characteristics such as comorbidity, chronicity, treatment resistance, frequency, and severity.⁷⁰

Measurement-based Treatment of Depression

Even in guideline-driven practice, clinical treatment of depression is often associated with wide variations among practitioners. Clinicians often change from one antidepressant to another too quickly or, conversely, conduct an unnecessarily prolonged treatment trial with an obviously unsuccessful medication or psychotherapy.^{10,71} Practitioners also differ in

how they assess the outcomes of treatment (symptoms, function, side effect frequency, and burden), with global judgments often used instead of specific symptom assessments, even though the former are less accurate.⁷² These differences lead to wide variability in treatment implementation and likely also result in wide variations in outcomes in typical practice.

Other chronic medical conditions—such as diabetes mellitus—utilize laboratory as well as symptom and function measures in research settings that are readily usable in clinical practice. However, to our knowledge no system to provide specific feedback or prompts related to symptoms, side effects, and recommended tactics (i.e. when and by how much to change the dose) during treatment has been successfully used in a large clinical trial for patients with psychiatric disorders. It is now clear that measurement-based care (MBC) is an essential component to any adaptive decision support system, allowing the physician to individualize decisions about care for the patient based on his or her progress and ability to tolerate the medication.^{10,73} The medication algorithms developed by our group (see *Figure 1*) allow for sequential adaptive MBC treatment approaches, including switching or augmenting antidepressant treatment in the case of patients who do not fully remit following an adequate trial (at an adequate dose and duration) of an antidepressant.^{2,10,74} Both the Texas Medication Algorithm Project (TMAP) and STAR*D trials were performed in real-world clinical settings and emphasized the importance of an MBC approach, wherein the physician routinely assessed depression symptom severity, adherence to treatment, and side effects at each visit and used this information when following the medication treatment protocol.¹⁰

Complicated Depression

Depression commonly occurs in the context of chronic medical illness.⁷⁵ Patients with chronic medical illness and clinical depression experience enhanced morbidity, a poorer prognosis, and even increased mortality from the medical condition.^{76,77} Additionally, patients with comorbid depression and chronic medical illness often go untreated because of the diagnostic challenge resulting from the presence of shared symptoms, as well as the assumption that depression is an expected and unavoidable consequence of serious illness, or that adequate control of the medical condition supersedes concerns for mental illness.⁷⁶ Similarly, there is evidence suggesting that comorbid psychiatric disorders have a negative impact on MDD,^{78–80} and that patients with comorbid disorders do not respond as well to therapy, have a more protracted course of illness, and experience less positive treatment outcomes.⁸⁰

Despite evidence of the efficacy of antidepressants and psychotherapy in the treatment of depression in medically ill patients, this evidence has not

resulted in improved care.⁷⁶ Given that comorbid medical and psychiatric illness are known to further increase the challenge of getting the patient to remission, other non-pharmacological options may be indicated in this patient population. For example, in patients who have not responded to multiple trials of antidepressants, psychotherapy, and ECT, or who have comorbid conditions, a disease self-management approach may be appropriate. A growing body of evidence suggests that more comprehensive, multifaceted innovations that simultaneously address healthcare provider practice, patient education, and patient self-management tend to have more compelling results.^{81,82}

Conclusion

TRD is a major and increasing public health burden. Current research on TRD fails to guide practicing physicians about specific treatment options, so the treatment process is often little more than trial and error until an appropriate treatment is found. In choosing treatment options, clinicians should be guided by evidence-based research in order to bring about the desired goal of full remission. Certain augmentation strategies have been shown to be effective in this area, but there is still a need for more well-designed, randomized, controlled trials to elucidate which agents or strategies are superior to others.

It is also increasingly apparent that there is a need to tailor treatment for individual patients by introducing routine measurements of symptoms and side effects in clinical practice. In addition, other interventions apart from pharmacological, psychotherapeutic, and somatic approaches should be considered, including those focusing on the chronic illness model, such as disease self-management. This is an exciting time in terms of depression research as higher standards are set for treatment and management with the goal of reducing long-term disability and human suffering. ■

Statement of Interest

Dr Trivedi has been a consultant for Akzo (Organon Pharmaceuticals Inc.), Bristol-Myers Squibb, Cyberonics, Inc., Eli Lilly and Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica Products, LP, Johnson & Johnson, Organon, Pfizer, Pharmacia & Upjohn, Sepracor, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals. He has also received grant support from Abbott Laboratories, Inc., Akzo (Organon) Pharmaceuticals Inc., Bayer, Bristol-Myers Squibb, Cephalon, Inc. Corcept Therapeutics, Inc., Eli Lilly and Company, Forest Pharmaceuticals, Inc., GlaxoSmithKline, Janssen Pharmaceutica, Johnson & Johnson PRD, Meade Johnson, the National Alliance for Research in Schizophrenia and Depression, the National Institute of Mental Health, Parke-Davis Pharmaceuticals, Pfizer, Inc., Pharmacia & Upjohn, Predix Pharmaceuticals, Solvay Pharmaceuticals, Inc., and Wyeth Pharmaceuticals.

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