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Treatment-resistant depression: recent developments and future directions

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A significant proportion of patients with major depressive disorder (MDD) fail to achieve remission with standard antidepressant therapies, even when optimally delivered. These patients are classified as treatment-resistant depression (TRD), which is distinguished from “difficult-to-treat” depression,[1] defined as depression treated under circumstances that precludes the optimal delivery of a potentially beneficial treatment (e.g., subtherapeutic dosing, intolerable side effects, poor adherence, etc.) TRD is also distinguished from severe depression, as some patients with milder depressive symptoms are markedly treatment resistant, while others with profound, acute depressive symptoms are quite treatment responsive. Defining the boundaries of TRD is critical from a clinical, research, and public health perspective, as drug and device manufacturers seek new regulatory approvals for numerous indications in the TRD spectrum. This article reviews recent developments in TRD, with a focus on classification methods used for regulatory clinical trials; treatments currently approved in the US for TRD; how classification schemes and regulatory rules have limited understanding of their scope of effectiveness; and what changes are needed in research approaches to facilitate novel therapeutic discovery.

Challenges in the Classification of TRD

There is no validated consensus definition of TRD. At a minimum, TRD signifies depression that has failed to respond to at least one optimally administered therapy. Regulatory authorities such as the European Agency for the Evaluation of Medicinal Products have defined TRD as failure to respond to two products of different classes, used for a sufficient length of time at an adequate dose, without specification of an adequate dose or duration.[2] The US FDA does not define TRD. Rather, FDA approved devices or medication describe the specific patient population investigated in pivotal trials demonstrating safety and efficacy.

Several rating instruments and classification schemes for treatment resistance have been adopted for use in research studies of TRD, although none are routinely used in clinical settings. At a minimum, these instruments attempt to quantify the number of previous antidepressant trials (including augmentation strategies and ECT), assess the adequacy of trials by determining maximum dose and duration, and assess patients’ response to treatments.[3] While several instruments have shown reliability and validity in research settings, they have important limitations: (1) Four to six-week monotherapy trials of antidepressants may be categorized as adequate, despite evidence that longer trial durations may be required, particularly for chronic depressions; (2) Acceptable antidepressant doses in previous trials include the minimal approved dose, although drugs such as venlafaxine XR may require titration significantly higher than approved doses;[4] (3) Most critically, the

infrequent implementation of measurement-based care (MBC)[5] in clinical practice obstructs the accurate determination of response to previous therapies. Further, the lack of electronic medical records in most treatment settings hinders researchers' ability to obtain records in a timely and efficient manner prior to study enrollment. Even when obtained, medical records may be difficult to interpret due to incomplete documentation of response, side effects, adherence, and concurrent therapies (psychotherapy, phototherapy, etc). Salient clinical issues impacting outcome in MDD such as substance use and exercise may be unrecorded. Thus, the validity of TRD may ultimately hinge on the accuracy of patients' self-report of their complex treatment histories and clinical course.

Approved Therapies for TRD: Comparative Efficacy and Generalizability

Five treatments have received regulatory approval in the U.S. for TRD, including 3 devices [electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS)], one medication (the atypical antipsychotic aripiprazole), and one medicinal food (L-methylfolate). In addition, two industry-supported pivotal trials of deep brain stimulation (DBS) are ongoing, and several pharmacotherapies are expected to seek regulatory approval in the next few years. Although each of these treatments has been studied in patients who meet a broad categorical definition of TRD, the heterogeneity of the specific patient populations and study designs make it difficult to directly compare these therapies.

Most recently in October 2008, the Center for Devices and Radiological Health (CDRH) of the FDA approved the NeuroStar TMS system as monotherapy for MDD patients who failed to respond to one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. In 2007, aripiprazole was approved on the basis of two positive, 6-week placebo-controlled trials in MDD patients who showed an insufficient response to 2-4 courses of an antidepressant medication (of which one trial was conducted prospectively for 8 weeks). VNS was approved in 2005 for the adjunctive long-term treatment of chronic or recurrent depression in patients who showed inadequate response to four or more adequate antidepressant treatments. L-methylfolate, under the brand name Deplin, is classified as a FDA-approved medicinal food for antidepressant augmentation. Its FDA indication is for patients with low plasma and/or low red blood cell folate "with particular emphasis for those individuals who have a major depressive disorder that has not fully responded or may not fully respond to antidepressant therapy." [6] Finally, ECT has remained the gold standard acute treatment for TRD and severe depression for many years, with large effect sizes in controlled and active comparison studies with pharmacotherapy.[7] Among approved interventions, ECT is associated with the most rapid onset of action, although high relapse rates upon discontinuation and cognitive side effects are concerns.

Much of the rationale for investigating novel brain stimulation therapies for TRD has centered on their comparative efficacy relative to available pharmacotherapies. These comparisons are imprecise and potentially misleading. For example, a post hoc analysis of a recent multicenter sham-controlled acute efficacy trial of TMS reported larger effect sizes at 4 weeks in patients with one prior antidepressant medication failure, determined by the Antidepressant Treatment History Form, compared to patients with 2 or more treatment failures.[8] In terms of treatment resistance classification, the TMS group with one prior failed treatment resembled patients in Level 2 of the NIMH funded STAR*D study who prospectively failed to remit or were intolerant of open-label citalopram in Level 1. Approximately one in four patients in Level 2 of STAR*D went on to achieve remission with one of 3 different open-label augmentation strategies delivered for up to 14 weeks,[4] a remission rate similar to the TMS subgroup with one prior antidepressant failure. However, critical differences in almost every key aspect of study design (prospective versus

retrospective determination of treatment resistance; method of recruitment; trial duration; primary efficacy outcome; comorbidity, blinding, etc.) prohibit meaningful comparisons of efficacy. Similarly, significant design differences make it difficult to reasonably compare remission rates from the Level 2 STAR*D augmentation trial with remission rates from a 6-week trial of adjunctive aripiprazole in patients who failed to respond to a prospective 8-week trial of antidepressant medication.[9]

A related issue concerns the generalizability of FDA registration trials in TRD, the “efficacy-effectiveness gap.” Perhaps the most striking example of this gap in TRD research pertains to a study of ECT efficacy outcomes. In this prospective naturalistic study of 347 patients at seven hospitals in the U.S., remission rates following ECT were found to be substantially lower than in clinical trials, and even among remitters, approximately two-thirds experienced relapse during follow-up.[10] Registration trials in TRD have generally restricted participants to unipolar patients experiencing a current major depressive episode [a notable exception was the inclusion of bipolar I or II in VNS trials [11]], with a minimum severity threshold on rating scales such as the Hamilton Rating Scale for Depression (HRSD) and Montgomery Asberg Depression Rating Scale (MADRS). The inclusion of chronic forms of depression (> 2 years) has varied across TRD studies, with the most invasive interventions (e.g. DBS and VNS) requiring disorder chronicity.[11,12] A recent analysis of clinical factors associated with pharmacotherapy resistance in a sample of 702 patients with MDD found that comorbid anxiety disorder was the most powerful variable associated with TRD, with an odds ratio (OR) = 2.6.[3] Similarly, STAR*D participants who were switched from citalopram to another antidepressant monotherapy due to nonremission were less likely to remit if they had concurrent anxiety disorders.[13] Other factors highly associated with TRD were early age of onset (OR=2.0), and suicidal risk (OR=2.2).[3]

In pursuit of an efficacy signal, recent industry-supported registration trials in TRD may have failed to enroll those patients most representative of TRD. For example, patients with comorbid panic disorder or PTSD in the 12 months prior to screening were excluded from a recent trial of DBS of the subgenual cingulate cortex.[12] Patients with histories of atypical depression have also been excluded,[11,12] although these patients are more likely to have an early onset and chronic course of illness,[14] which are associated with TRD. Finally, patients with often vaguely defined suicidal risk are categorically excluded from regulatory clinical trials in TRD. It is an unfortunate irony that while the FDA has recently mandated prospective monitoring for emergent suicidality during the course of antidepressant trials, there is no mandate to enroll subgroups of patients with “suicidal risk” in clinical trials of TRD. Thus, TRD registration trials may have poor generalizability, which also characterizes phase 3 trials of antidepressant medications in non-resistant MDD.

STRATEGIES TO ADVANCE THERAPEUTIC DISCOVERY IN TRD

The identification of clinical and demographic predictors of response in TRD has been elusive, but may provide a more narrow TRD phenotype crucial for advancing therapeutic discovery. Despite numerous investigations, clinical characteristics such as course of illness and cross-sectional symptom presentation have failed to provide acceptable predictive value. The most reliable predictor of treatment response in TRD is the magnitude of previous treatment resistance. Antidepressant medication treatment resistance is strongly associated with poor response to subsequently administered somatic therapies, including VNS, TMS, ECT, and pharmacotherapy. Because of this robust relationship between treatment resistance and outcome, recent clinical trials in TRD have capped the degree of treatment resistance for study eligibility.[8,9,11]

Given that there are no reliable clinical predictors of response, biomarkers that identify subgroups of patients likely to respond, or highly unlikely to respond, would undoubtedly represent a breakthrough advance for the field. Numerous neuroimaging studies have been performed in MDD patients aimed at identifying neural markers of response. Pathological neural activity in subregions of the anterior cingulate cortex (ACC) has been identified as a critical node in a widely distributed mood circuit which includes projections to nucleus accumbens, amygdala, hypothalamus, and orbitofrontal cortex. The efficacy of subgenual DBS in TRD may be mediated by changes in functional connectivity through this widely distributed anatomical network.[15] Elevated baseline ACC activity detected with techniques such as positron emission tomography (PET), fMRI, EEG, and magnetoencephalography (MEG) has been associated with acute and longer-term outcome following several antidepressant therapies, including acute sleep deprivation, pharmacotherapy, and most recently, intravenous (IV) ketamine, a glutamate NMDA receptor antagonist associated with rapid improvements in depressive symptoms in TRD. [16,17]

Although promising biomarker candidates have been identified through these studies, neuroimaging studies in TRD have been limited by small sample sizes and exclusive focus on a single brain imaging or neurophysiological modality. To achieve substantial progress in biomarker development, prospective investigations in large patient cohorts using combination modalities (e.g. PET and MRI) that integrate structure and functional activity may be required. The Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private partnership funded by NIH, industry, and private foundations, suggests a viable model for biomarker research in TRD. The goal of ADNI is to develop validated neuroimaging biomarkers for Alzheimer's disease clinical trials and to identify biomarkers for the progression of mild cognitive impairment and early Alzheimer's disease, using serial MRI and PET imaging.[18] Prospective studies in large cohorts of well-characterized patients with MDD are necessary to empirically test staging schemes for TRD and assess the reliability of neural biomarkers. A significant methodological challenge concerns medication wash-out. Do imaging studies in medicated patients yield useful information? A recent review of this issue in bipolar disorder concluded that neuroimaging studies performed on medicated patients enhance generalizability by including severely ill patients who may be unable to safely discontinue medication.[19] In addition to prospective neuroimaging studies, large-scale collaborative initiatives can facilitate collection of peripheral biomarker samples such as serum brain derived neurotrophic factor, as well as samples for genomic and proteomic analyses. Candidate genes associated with pharmacotherapy resistance have recently been identified from the STAR*D study;[20] the identification of candidate genes related to response in brain stimulation trials is an intriguing future direction.

POINTING THE WAY TO THE FUTURE

The current trial-and-error approach to therapeutics in TRD is inefficient, costly, and associated with poor outcomes, despite the prevalent use of multiple medication combinations in clinical practice. A "magic bullet" therapeutic approach is unlikely to be successful for the heterogeneous patients classified as TRD. Although several therapies have shown acute benefit and now have regulatory approval for TRD, there is minimal guidance for practicing clinicians for the long-term management of these complex patients. Public-private partnerships that facilitate the establishment of TRD-focused networks are essential for progress, as seen in Alzheimer's disease. Critical objectives would include the development of empirically-derived classification schemes for TRD, prospective collection of outcome data, and the close integration of biomarker and genetic studies with clinical trials.

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Biography

Sanjay J. Mathew, M.D. Sanjay J. Mathew, M.D. is an Assistant Professor of Psychiatry, Director of the Mood and Anxiety Disorders Program, and director of psychopharmacology teaching for psychiatry residents at the Mount Sinai School of Medicine in New York. His research focuses on the development of novel therapeutic approaches and biomarkers for treatment-resistant depression (TRD) and anxiety disorders. Dr. Mathew is the recipient of a Career Development Award from the National Institute of Mental Health to study the neurochemistry of generalized anxiety disorder and depression using high field proton magnetic resonance spectroscopy, a brain imaging modality that quantifies regional brain amino acid neurotransmitters and markers of neuroplasticity. His group is testing additional neuroimaging and peripheral biomarkers in the course of clinical trials of plasticity-enhancing agents in TRD. He has been awarded grants from NARSAD and the American Foundation for Suicide Prevention, and has received research awards from the American College of Neuropsychopharmacology, the American Psychiatric Association, and the Anxiety Disorders Association of America.

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