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Review

Treatment-resistant depression: Definitions, review of the evidence, and algorithmic approach

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ABSTRACT

Background: Most adults with major depressive disorder (MDD) fail to achieve remission with index pharmacological treatment. Moreover, at least half will not achieve and sustain remission following multiple pharmacological approaches. Herein, we succinctly review treatment modalities proven effective in treatment-resistant depression (TRD).

Methods: We conducted a review of computerized databases (PubMed, Google Scholar) from 1980 to April 2013. Articles selected for review were based on author consensus, adequacy of sample size, the use of a standardized experimental procedure, validated assessment measures and overall manuscript quality.

Results: The evidence base supporting augmentation of conventional antidepressants with atypical antipsychotics (i.e., aripiprazole, quetiapine, and olanzapine) is the most extensive and rigorous of all pharmacological approaches in TRD. Emerging evidence supports the use of some psychostimulants (i.e., lisdexamfetamine) as well as aerobic exercise. In addition, treatments informed by pathogenetic disease models provide preliminary evidence for the efficacy of immune-inflammatory based therapies and metabolic interventions. Manual based psychotherapies remain a treatment option, with the most compelling evidence for cognitive behavioral therapy. Disparate neurostimulation strategies are also available for individuals insufficiently responsive to pharmacotherapy and/or psychosocial interventions.

Limitations: Compared to non-treatment-resistant depression, TRD has been less studied. Most clinical studies on TRD have focused on pharmacotherapy-resistant depression, with relatively fewer studies evaluating "next choice" treatments in individuals who do not initially respond to psychosocial and/or neurostimulatory treatments.

Conclusion: The pathoetiological heterogeneity of MDD/TRD invites the need for mechanistically dissimilar, and empirically validated, treatment approaches for TRD.

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1. Introduction

Major depressive disorder (MDD) is a multidimensional common, often severe mental disorder with an age of onset below the age of 30 in most affected individuals (Kessler et al., 2012). Major depressive disorder is associated with a high rate of non-recovery and recurrence, with chronicity rates estimated at approximately 20% (van Randenborgh et al., 2012). The estimated annual costs attributable to MDD are approximately $83 billion, with indirect costs due to decreased psychosocial function (notably workforce performance) being a major contributor (Greenberg et al., 2003). For example, it is estimated that MDD is associated with an annual loss of 27.2 workdays per ill worker (Kessler et al., 2006). The significant illness burden attributable to MDD in the general population is disproportionately accounted for by individuals who have not exhibited recovery from illness.

Consensus exists that symptomatic remission increases the probability for recovery in MDD. Available evidence indicates that the majority of individuals with MDD receiving guideline-concordant and measurement-based care do not achieve and sustain a fully remitted state with index antidepressant treatment. Results from the STAR-D study indicate that remission rates decrease, and subsequent relapse rates increase, as a function of the number of failed acute therapies. For example, the overall remission rates reported in STAR-D for the medication options were 28%, 25%, 18%, and 10% at steps 1, 2, 3, and 4, respectively. Taken together, the burden of illness attributable to MDD, the high rates of non-remission with most first-line treatment strategies, and the increasing availability of mechanistically dissimilar agents (e.g., psychosocial interventions, neurostimulatory approaches and an expanding array of complementary and alternative medicines [CAM]) provide the impetus for refining therapeutic objectives in MDD, defining treatment-resistant depression (TRD) and providing evidence-based sequential treatment strategies capable of achieving symptomatic remission (Kennedy et al., 2009a, 2009b). This narrative review broadly aims to define TRD and succinctly review the evidence supporting treatment strategies in TRD.

2. Method

We conducted a review of computerized databases (PubMed, Google Scholar) from 1980 to April 2013. "Major Depressive Disorder" was cross-referenced with treatment-resistant depression, combination, augmentation, cognition, cognitive dysfunction, cognitive deficits, dementia, memory, learning, and functional outcome. The search was augmented with a manual review of relevant article reference lists. Articles selected for review were based on author consensus, adequacy of sample size, the use of standardized experimental procedures, validated assessment measures and overall manuscript quality.

3. Results

Available modalities for TRD are outlined in Table 1.

3.1. Treatment-resistant depression: definition

Operationalizing TRD begins with defining the therapeutic objectives in MDD. Broadly speaking, the overarching aim in treating MDD is to achieve a fully recovered state with the affected individual no longer experiencing clinically significant symptomatology and/or functional impairment (e.g., at work, personal and family life). Replicated evidence indicates that achieving a "remitted" state significantly increases the probability of recovery in MDD when compared to the categorical outcome of "response with residual depressive symptomatology" (Kennedy et al., 2009a, 2009b; McIntyre and Donovan, 2004).

A universally accepted definition for TRD does not currently exist. Notwithstanding, it has been proposed that failure to achieve

Table 1
Available modalities for treatment-resistant depression.

Atypical antipsychotics	Aripiprazole Quetiapine Olanzapine
Combination antidepressants	
Psychostimulants	
Lithium	
Thyroid Hormone	
Buspirone	
Glutamatergic	Ketamine Scopolamine
Complementary alternative medicine (CAM)/ nutraceuticals	L-methylfolate S-adenosyl-methionine (SAMe)
Inflammatory-immune based	Infliximab, NSAIDs
Psychotherapy	Cognitive behavioral therapy (CBT)
Neuromodulatory	ECT, rTMS, DBS
Aerobic exercise	

DBS=deep brain stimulation; ETC=electroconvulsive therapy; NSAIDs=non-steroidal anti-inflammatory; and rTMS=repetitive transcranial magnetic stimulation.