



REVIEW

# Recent Advances in the Treatment of Treatment-Resistant Depression: A Narrative Review of Literature Published from 2018 to 2023

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## Abstract

**Purpose of Review** We review recent advances in the treatment of treatment-resistant depression (TRD), a disorder with very limited treatment options until recently. We examine advances in psychotherapeutic, psychopharmacologic, and interventional psychiatry approaches to treatment of TRD. We also highlight various definitions of TRD in recent scientific literature.

**Recent Findings** Recent evidence suggests some forms of psychotherapy can be effective as adjunctive treatments for TRD, but not as monotherapies alone. Little recent evidence supports the use of adjunctive non-antidepressant pharmacotherapies such as buprenorphine and antipsychotics for the treatment of TRD; side effects and increased medication discontinuation rates may outweigh the benefits of these adjunctive pharmacotherapies. Finally, a wealth of recent evidence supports the use of interventional approaches such as electroconvulsive therapy, ketamine/esketamine, and transcranial magnetic stimulation for TRD.

**Summary** Recent advances in our understanding of how to treat TRD have largely expanded our knowledge of best practices in, and efficacy of, interventional psychiatric approaches. Recent research has used a variety of TRD definitions for study inclusion criteria; research on TRD should adhere to inclusion criteria based on internationally defined guidelines for more meaningfully generalizable results.

**Keywords** Treatment-resistant depression (TRD) · Major depressive disorder (MDD) · Electroconvulsive therapy (ECT) · Transcranial magnetic stimulation (TMS) · Ketamine · Esketamine · Pharmacotherapy

## Introduction

While there is no universally accepted definition, treatment-resistant depression (TRD) often refers to a condition of those with major depressive disorder (MDD) whose

depression fails to respond to at least two trials of antidepressants [1, 2, 3••]. TRD is highly prevalent in the US with a yearly incidence of 2.8 million people, 30.9% of those 8.9 million treated for MDD [4]. Treating TRD poses a challenge, with risk factors of TRD including many psychiatric comorbidities, greater depression severity, and older age [5–7]. Patients with TRD have higher rates of psychiatric comorbidities, have more severe depression, and exhibit substantially higher rates of suicide risk relative to those with non-resistant MDD, stressing the need for more effective treatments [8–11]. Moreover, those with TRD cost health systems more per-patient compared to those with non-resistant MDD, reflecting higher rates of hospitalizations and multiple medication trials [12–14]. The need to develop novel treatments for TRD is thus both an epidemiological and financial imperative [15].

Treatments for TRD have historically relied on pharmacotherapy employing strategies of optimization, combination, switching, and augmentation, each on an individual basis [16]. Optimization consists of adjusting antidepressant (AD) dose or duration length to seek a clinical response,

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