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<p>Major depressive disorder is characterized by depressed mood and/or anhedonia with neurovegetative symptoms and neurocognitive changes affecting an individual's functioning in multiple aspects of life. Treatment outcomes with commonly used antidepressants remain suboptimal. Treatment-resistant depression (TRD) should be considered after inadequate improvement with two or more antidepressant treatments of adequate dose and duration. TRD has been associated with increased disease burden including higher associated costs (both socially and financially) affecting both the individual and society. Additional research is needed to better understand the long-term burden of TRD to both the individual and society.</p>	
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<p>Measurement-based care (MBC) is the systematic screening and ongoing assessment of symptoms, side effects, and adherence to adjust treatments as needed based on these factors. Studies show MBC leads to improved outcomes for depression and treatment-resistant depression (TRD). In fact, MBC may reduce the chances of developing TRD, as it leads to optimized treatment strategies based on symptom changes and compliance. There are many rating scales available for monitoring depressive symptoms, side effects, and adherence. These rating scales can be used in a variety of clinical settings to help guide treatment decisions, including depression treatment decisions.</p>	
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<p>Major depressive disorder is a chronic and recurrent illness that affects 20% of adults during their lifetime and is one of the leading causes of suicide in the United States. A systematic measurement-based care approach is the essential first step in the diagnosis and management of treatment-resistant depression (TRD) by promptly identifying individuals with depression and avoiding delays in treatment initiation. As comorbidities may be associated with poorer outcomes to commonly used antidepressants and increase risk of drug-drug interactions, their recognition and treatment is an essential component of management of TRD.</p>	

Pharmacotherapy for Treatment-Resistant Depression: Antidepressants and Atypical Antipsychotics

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Treatment-resistant depression (TRD) affects one in three patients with major depressive disorder and is associated with increased risk of all-cause mortality. Studies of real-world practices suggest that antidepressant monotherapy continues to be the most widely used treatment after inadequate response to a first-line treatment. However, rates of remission with antidepressants in TRD are suboptimal. Atypical antipsychotics are the most widely studied augmentation agent and aripiprazole, brexpiprazole, cariprazine, quetiapine extended-release, and olanzapine-fluoxetine combination are approved for depression. Benefits of using atypical antipsychotics for TRD has to be weighted against their potential adverse events, such as weight gain, akathisia, and tardive dyskinesia.

Pharmacotherapy: Ketamine and Esketamine

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Anna Feeney and George I. Papakostas

Ketamine and esketamine have rapid-onset antidepressant effects and may be considered for the management of treatment-resistant depression. Intranasal esketamine has regulatory approval in the United States and European Union. Intravenous ketamine is often administered off-label as an antidepressant, though no standard operating procedures exist. Repeated administrations and the use of a concurrent standard antidepressant may maintain antidepressant effects of ketamine/esketamine. Possible adverse effects of ketamine and esketamine include psychiatric, cardiovascular, neurologic and genitourinary effects, and the potential for abuse. The long-term safety and efficacy of ketamine/esketamine as antidepressants require further study.

Role of Psychedelics in Treatment-Resistant Depression

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Shubham Kamal, Manish Kumar Jha, and Rajiv Radhakrishnan

There is increasing interest in exploring the therapeutic potential of psychedelics in treatment-resistant depression (TRD). Classic psychedelics (such as psilocybin, LSD, ayahuasca/DMT), and atypical psychedelics (such as ketamine) have been studied in TRD. The evidence for the classic psychedelics TRD is limited at the present time; early studies however show promising results. There is also recognition that psychedelic research may be subject to a “hype bubble” at the present time. Future studies focused on delineating necessary ingredients of psychedelic treatments and the neurobiological basis of their effects, will help pave the way for the clinical use of these compounds.

Noninvasive Brain Stimulation Techniques for Treatment-Resistant Depression: Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation

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Transcranial magnetic stimulation is a safe, effective, and well-tolerated intervention for depression; it is currently approved for treatment-resistant depression. This article summarizes the mechanism of action,

evidence of clinical efficacy, and the clinical aspects of this intervention, including patient evaluation, stimulation parameters selection, and safety considerations. Transcranial direct current stimulation is another neuromodulation treatment for depression; although promising, the technique is not currently approved for clinical use in the United States. The final section outlines the open challenges and future directions of the field.

Photobiomodulation: An Emerging Treatment Modality for Depression

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Major depressive disorder (MDD) is considered a global crisis. Conventional treatments for MDD consist of pharmacotherapy and psychotherapy, although a significant number of patients with depression respond poorly to conventional treatments and are diagnosed with treatment-resistant depression (TRD). Transcranial photobiomodulation (t-PBM) therapy uses near-infrared light, delivered transcranially, to modulate the brain cortex. The aim of this review was to revisit the antidepressant effects of t-PBM, with a special emphasis on individuals with TRD. A search on PubMed and ClinicalTrials.gov tracked clinical studies using t-PBM for the treatment of patients diagnosed with MDD and TRD.

The Role of Psychotherapy in the Management of Treatment-Resistant Depression

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Taylor Rogan and Samuel T. Wilkinson

This article reviews the role of psychotherapy in management of treatment-resistant depression (TRD). Meta-analyses of randomized trials show that psychotherapy has a positive therapeutic benefit in TRD. There is less evidence that one type of psychotherapy approach is superior to another. However, more trials have examined cognitive-based therapies than other forms of psychotherapy. Also reviewed is the potential combination of psychotherapy modalities and medication/somatic therapies as an approach to TRD. There is significant interest in ways that psychotherapy modalities could be combined with medication/somatic therapies to harness a state of enhanced neural plasticity and improve longer-term outcomes in mood disorders.

Special Populations: Treatment-Resistant Depression in Children and Adolescents

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Emine Rabia Ayvaci and Paul E. Croarkin

Major depressive disorder is a substantial public health challenge impacting at least 3 million adolescents annually in the United States. Depressive symptoms do not improve in approximately 30% of adolescents who receive evidence-based treatments. Treatment-resistant depression in adolescents is broadly defined as a depressive disorder that does not respond to a 2-month course of an antidepressant medication at a dose equivalent of 40 mg of fluoxetine daily or 8 to 16 sessions of a cognitive behavioral or interpersonal therapy. This article reviews historical work, recent literature on classification, current evidence-based approaches, and emerging interventional research.

Treatment-Resistant Late-Life Depression: A Review of Clinical Features, Neuropsychology, Neurobiology, and Treatment

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Major depression is common in older adults (≥ 60 years of age), termed late-life depression (LLD). Up to 30% of these patients will have treatment-resistant late-life depression (TRLLD), defined as depression that persists despite two adequate antidepressant trials. TRLLD is challenging for clinicians, given several etiological factors (eg, neurocognitive conditions, medical comorbidities, anxiety, and sleep disruption). Proper assessment and management is critical, as individuals with TRLLD often present in medical settings and suffer from cognitive decline and other marks of accelerated aging. This article serves as an evidence-based guide for medical practitioners who encounter TRLLD in their practice.

Brain Features of Treatment-Resistant Depression: A Review of Structural and Functional Connectivity Magnetic Resonance Imaging Studies

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Increased awareness of the growing disease burden of treatment resistant depression (TRD), in combination with technological advances in MRI, affords the unique opportunity to research biomarkers that characterize TRD. We provide a narrative review of MRI studies investigating brain features associated with treatment-resistance and treatment outcome in those with TRD. Despite heterogeneity in methods and outcomes, relatively consistent findings include reduced gray matter volume in cortical regions and reduced white matter structural integrity in those with TRD. Alterations in resting state functional connectivity of the default mode network were also found. Larger studies with prospective designs are warranted.

Immune Dysregulation in Treatment-Resistant Depression: Precision Approaches to Treatment Selection and Development of Novel Treatments

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Owing to the link between immune dysfunction and treatment-resistant depression (TRD) and the overwhelming evidence that the immune dysregulation and major depressive disorder (MDD) are associated with each other, using immune profiles to identify the biological distinct subgroup may be the step forward to understanding MDD and TRD. This report aims to briefly review the role of inflammation in the pathophysiology of depression (and TRD in particular), the role of immune dysfunction to guide precision medicine, tools used to understand immune function, and novel statistical techniques.