Major Depressive Disorder (MDD):

An alarmingly high failure rate of efficacy endpoints in clinical trials

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Introduction

Major Depressive Disorder (MDD), often simply referred to as depression, is a common but serious mood disorder. MDD affects how an individual feels, thinks, and manages daily activities such as sleeping, eating, or working.

To be diagnosed with depression, the symptoms must be present for at least two weeks. Symptoms can range from persistent sadness, loss of interest or pleasure in activities, feelings of hopelessness or guilt, difficulty sleeping, fatigue, changes in appetite, and even thoughts of death or suicide.

Approximately 21.0 million adults residing in the United States experienced at least one significant episode of major depression, constituting **8.3%** of the entire adult population. Notably, the incidence of major depressive episodes **was more common among adult females (10.3%) than in males (6.2%).**

The underlying pathophysiology of MDD remains an area of active research, but it's thought to result from a combination of genetic, biological, environmental, and psychological factors. Neuroimaging studies suggest structural and functional changes in areas of the brain associated with mood regulation, although the exact cause-and-effect relationship remains elusive.

From a public health perspective, MDD carries significant morbidity and mortality. The World Health Organization ranks depression as **the leading cause of disability worldwide**. Therefore, the development of effective treatments for MDD is of paramount importance.

Developing effective treatments for MDD is a high priority, but clinical trials in this area **face unique challenges that can lead to failure points**. This article will discuss the main problems that arise in clinical trials for MDD and offer suggestions to overcome these challenges.

DSM-5 Criteria for MDD

Symptoms	Required Frequency
Depressed mood*	Most of the day, nearly every day
Markedly diminished interest or pleasure*	All or almost all activities most of the day, nearly every day
Significant weight loss or gain, or change in appetite	A change of 5% of body weight within a month
Insomnia or hypersomnia	Nearly every day
Psychomotor agitation or retardation	Nearly every day (observable by others, not merely subjective feelings)
Fatigue or loss of energy	Nearly every day
Feelings of worthlessness or excessive guilt	Nearly every day
Diminished ability to think or concentrate, or indecisiveness	Nearly every day (either subjective or observed)
Thoughts of death, suicidal ideation, or suicide attempts	Recurrent or persistent thoughts
Symptoms must cause clinically significant distress or impairment in important areas of functioning	
*At least one of either depressed mood or anhedonia must be present	

FDA-Approved Treatments for MDD

	Drug Name	Year of Approval	Number of Pivotal Studies	FDA Endpoints	Years of Effective Patent Life Remaining
MAOI	Phenelzine (Nardil)	1959	Limited	Improvement in depressive symptoms	No longer under patent protection
	Isocarboxazid (Marplan)	1959	Two	Improvement in HAM-D Score	No longer under patent protection
	Tranylcypromine (Parnate)	1961	Limited	Improvement in depressive symptoms	No longer under patent protection
	Selegiline Transdermal (Emsam)	2006	Two	Improvement in HAM-D Score	Patent protection until 2028
Tricyclics	Amitryptaline (Elavil)	1961	One	Improvement in depressive symptoms	No longer under patent protection
	Nortriptyline (Pamelor)	1964	One	Improvement in depressive symptoms	No longer under patent protection
	Doxepin (Sinequan)	1969	One	Improvement in depressive symptoms	No longer under patent protection
Atypical Agents	Bupropion (Wellbutrin)	1985	Multiple	Improvement in HAM-D score	Patent expired (2006)
	Mirtazapine (Remeron)	1996	Multiple	Improvement in HAM-D score	Patent expired (2011)
	Dextromethorphan/ bupropion (Auvelity)	2022	One	Improvement in MADRS score	Patent protection until 2034
Serotonin Modulator	Trazodone (Desyrel)	1981	Multiple	Improvement in HAM-D score	Patent expired (1999)
SSRI	Fluoxetine (Prozac)	1987	Multiple	Improvement in HAM-D score	Patent expired (2001)
	Sertraline (Zoloft)	1991	Multiple	Improvement in HAM-D score	Patent expired (2006)
	Paroxetine (Paxil)	1992	Multiple	Improvement in HAM-D score	Patent expired (2019)
	Citalopram (Celexa)	1998	Multiple	Improvement in HAM-D score	Patent expired (2003)
	Fluvoxamine (Luvox)	1994	Multiple	Improvement in HAM-D score	Patent expired (2002)
	Escitalopram (Lexapro)	2002	Multiple	Improvement in HAM-D score	Patent expired (2012)
SNRI	Venlafaxine (Effexor XR)	1993	Multiple	Improvement in HAM-D score	Patent expired (2017)
	Duloxetine (Cymbalta)	2004	Multiple	Improvement in HAM-D score	Patent expired (2013)
	Desvenlafaxine (Pristiq)	2008	Multiple	Improvement in HAM-D score	Patent expired (2022)
	Levomilnacipran (Fetzima)	2013	Multiple	Improvement in HAM-D score	Patent expired (2022)

FDA Pivotal Endpoints for MDD

When reviewing drug applications for MDD, the U.S. Food and Drug Administration (FDA) typically considers the following primary endpoints:

- Change from baseline in a depression severity score, often using scales like the Hamilton Depression Rating Scale (HDRS) or Montgomery-Åsberg Depression Rating Scale (MADRS).
- The proportion of patients achieving a response, typically defined as a 50% or greater reduction in the depression severity score from baseline.
- Remission rates, usually defined as a specific low score on a depression rating scale, indicating minimal to no symptoms.
- Duration of response or remission, commonly referred to as “durability” to ensure that the MDD remission is not short lived.

Most common failure points of MDD trials

Challenges	Description
Heterogeneity of MDD	MDD is a highly heterogeneous disorder with varying symptoms, severity levels, and comorbidities. This diversity makes it challenging to define clear inclusion and exclusion criteria, impacting patient recruitment and trial outcomes.
Stigma and Reluctance to Participate	The stigma associated with mental health issues, including MDD, can discourage individuals from openly discussing their condition or participating in clinical trials. Fear of judgment, discrimination, or privacy invasion may deter potential participants.
Suicidality and Safety Concerns	Suicidal ideation and behaviors are common in individuals with MDD. Addressing safety concerns and ensuring appropriate monitoring and support for participants at risk of self-harm during the trials is a key patient safety consideration.
Placebo Response and Expectancy Effect	MDD trials often involve placebo-controlled studies. However, the placebo response rate in MDD trials is often substantial, making it difficult to discern the true efficacy of the investigational treatment.
Long-Term Engagement and Dropout Rates	MDD trials typically require long-term engagement, and dropout rates can be high due to the chronic nature of the disorder, adverse effects, lack of perceived improvement, or personal circumstances. High dropout rates can compromise trial integrity and outcomes.
Comorbidities and Medication Interactions	Many individuals with MDD have comorbid conditions (e.g., anxiety disorders, chronic pain), and they often take multiple medications. Assessing interactions between these comorbidities, medications, and the investigational treatment can be complex.

Recently Failed MDD Drug Candidates

Zuranolone (Zurzuvae)

Perhaps the most recent example and an interesting case demonstrating that sometimes even an FDA approval isn't enough, Sage Therapeutics received an approval for Zuranolone for treating postpartum depression but failed to have the same therapeutic approved for MDD. Despite Zuranolone being the first and currently only oral treatment for postpartum depression, the inability to demonstrate significant efficacy data in MDD trials meant they missed out on a significantly bigger segment of the market. Investors reflected their disappointment with this missed target in Sage Therapeutics' stock price and the company has gone on to announce significant workforce cuts.

Alkermes' ALKS-5461 (Brexanolone)

ALKS-5461 is a combination of buprenorphine and samidorphan. The ALKS-5461 clinical trials were conducted to evaluate its efficacy and safety in treating major depressive disorder (MDD). Despite promising results in earlier trials, Phase 3 trials failed to demonstrate a statistically significant improvement in depressive symptoms compared to placebo leading to an FDA rejection and a Complete Response Letter requesting "additional clinical data to provide substantial evidence" of effectiveness.

AstraZeneca and Targacept's TC-5214

TC-5214 was a drug being investigated for the treatment of major depressive disorder via a collaboration between AstraZeneca and Targacept. Despite earlier promising results, numerous Phase 3 clinical trials did not show statistically significant improvements in depressive symptoms compared to placebo. This failure combined with the inability of some of Targacept's other drug candidates to similarly demonstrate efficacy led to AstraZeneca dissolving its collaboration with the company.

Key Strategies to Enhance MDD Trials

Major Depressive Disorder (MDD) trials aim to develop effective treatments for this complex mental health condition. Improving these trials and increasing their chance of success is crucial for advancing treatment options. Here are four key strategies to enhance MDD trials and bolster their success rates:

Enhance Trial Design and Methodology:

- Implement a robust trial design with clearly defined endpoints, inclusion and exclusion criteria, and randomized controlled trials (RCTs) that minimize bias.
- Utilize adaptive trial designs that allow for flexibility and adjustments based on interim data analyses, optimizing resources, and accelerating trial progression.

Enhance Patient Recruitment and Retention:

- Develop effective strategies to enhance patient recruitment, including community engagement, partnerships with patient advocacy groups, and leveraging social media and online platforms to raise awareness about the trial and encourage participation.
- Implement patient-centric trial designs and protocols that consider patient preferences, minimize burden, and improve retention rates, ultimately leading to a more representative and engaged participant pool.

Pick Your Patient Population:

- Patients who have not experienced a significant duration of depressive illness may not be appropriate candidates for inclusion in clinical trials as they are more likely to respond to placebo than those with longer disease durations. Enrolling patients who have experienced recurrent or enduring MDD alleviates this diagnostic risk.
- Enrolling patients with moderate to severe depression provides a greater opportunity for demonstrable improvement in efficacy endpoints when compared with those with mild disease.

Utilize Novel Technologies:

- Leverage digital health technologies, wearables, and smartphone applications to collect real-time patient data, enabling more precise monitoring of symptoms and treatment adherence. Additional functional or QoL data that informs clinically relevant secondary endpoints can help with differentiating the investigational medicinal product and open new avenues for exploration.

By implementing these strategies, MDD trials can be optimized to enhance their success rates, ultimately leading to the development of more effective and personalized treatments for individuals suffering from Major Depressive Disorder.

Promising Candidates

Many research organizations are looking for potential treatments for MDD. While pre-clinical data is positive, real-world clinical data is required for trials to progress to the point that a therapy can be brought to market. Below are some of the more promising candidates that may develop into useful treatments for MDD.

Neumora

Navacaprant (NMRA-140), an oral kappa opioid receptor antagonist and dopamine modulator, posted positive phase 2 results with improvement in depressive symptoms, particularly anhedonia, as well as a postive safety profile. Following a positive end of phase 2 meeting with the FDA, Neumora has been spurred on to a phase 3 development program commencing in the very near future.

ALTO NEUROSCIENCE

ALTO-100, utilizing an artificial intelligence (AI)-driven brain biomarker platform, is currently in the developmental stage for addressing post-traumatic stress disorder (PTSD) and major depressive disorder (MDD). Administered orally, this drug candidate operates by focusing on BDNF to alleviate these mental health conditions. While early in the pipeline, ALTO-100 has posted promising results in its first Phase 2 trial.

Intra-Cellular THERAPIES

Lumateperone sold under the brand name Caplyta, is a medication approved for the treatment of schizophrenia in adults. Studies re-tasking this therapeutic towards MDD with mixed features as well as bipolar depression have demonstrated promising improvements on the MADRS for both patient populations.

TONIX PHARMACEUTICALS

TNX-601 ER is a novel oral formulation of tianeptine hemioxalate being developed as a potential treatment for major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and neurocognitive dysfunction associated with corticosteroid use. TNX-601 ER includes tianeptine hemioxalate in an extended-release formulation and works by a novel mechanism, activating peroxisome proliferator-activated receptors. Tonix Pharmaceuticals recently announced the completion of the clinical component of their phase 2 trial, with the topline results expected in November 2023.

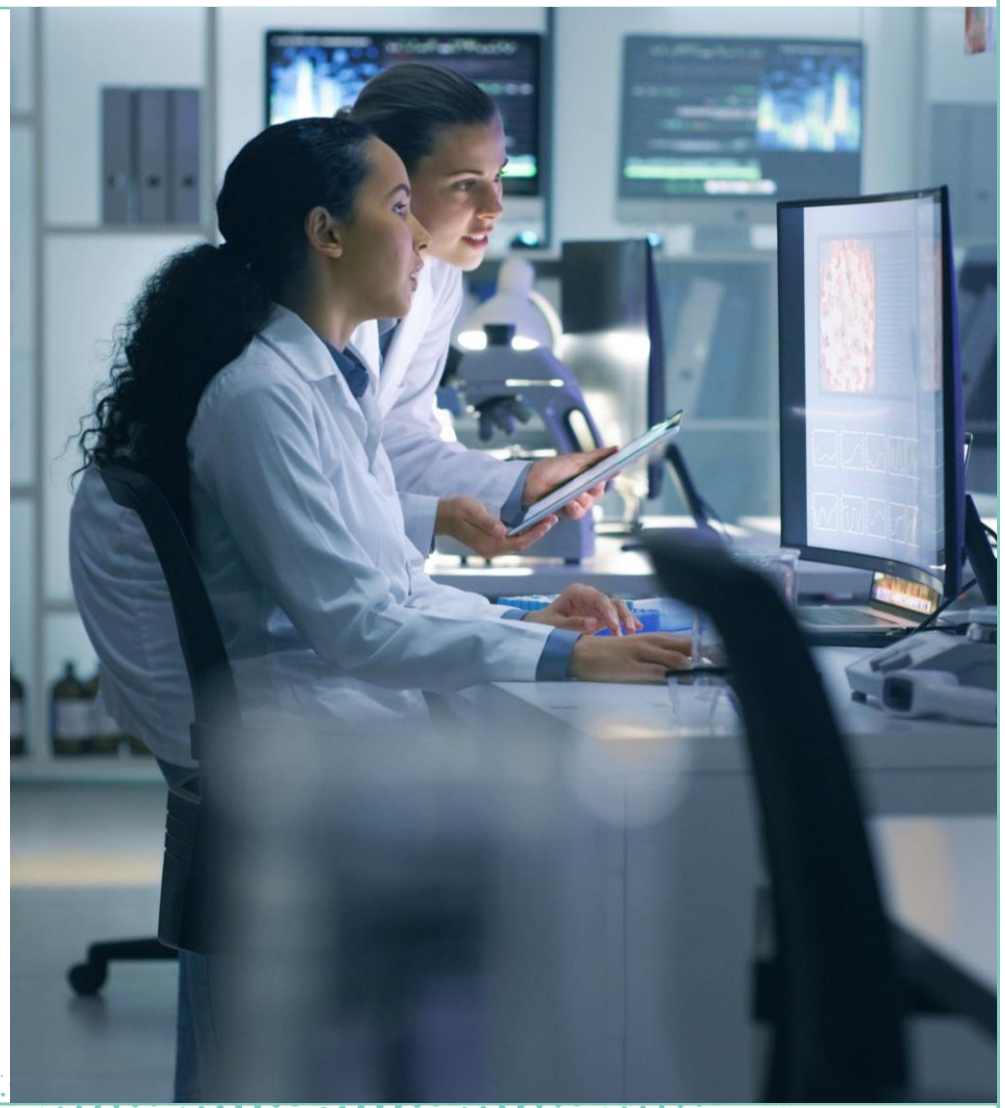
Relmada THERAPEUTICS

REL-1017 operates by blocking the NMDA receptor (NMDAR) channel, with a specific focus on inhibiting overactive GluN2D channels. NMDARs play a key role in normal neural plasticity, and disruptions in their function have been linked to various central nervous system (CNS) disorders, including Major Depressive Disorder (MDD). The primary factor contributing to MDD could be the heightened activity of a particular NMDAR subtype: the GluN1-GluN2D subtype. REL-1017 may modulate these receptors without affecting the normal functioning of other NMDARs.

Conclusion

Clinical trials for MDD face distinctive challenges, including lack of efficacy, patient recruitment and retention issues, safety concerns, high placebo response rates, and inadequacies in study design.

To enhance the success rates of MDD trials, crucial strategies include optimizing trial design and methodology, leveraging novel technologies, picking the best patient population, and improving patient recruitment and retention. By implementing these strategies, MDD trials can be refined, leading to the development of more effective and tailored treatments, ultimately offering hope to individuals grappling with Major Depressive Disorder.



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