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The Trillion Dollar Question:

Why Treatment Resistant Depression clinical trials commonly fail to meet endpoints and how to minimize this risk.

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Depression Medication

Treatment-resistant depression (TRD) is a major public health concern that affects millions of individuals worldwide.

TRD is characterized by a lack of response to at least two different antidepressant therapies, leading to a persistent and debilitating depressive state. According to the World Health Organization (WHO), depression is a leading cause of disability worldwide and affects more than 264 million people globally[1]. The prevalence of treatment-resistant depression (TRD) in the general population is estimated to be around 3.3%[2]. Developing effective treatments for TRD 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 TRD and offer suggestions to overcome these challenges.

A systematic review of clinical trials for antidepressant medications found that approximately 50% of trials conducted in the 1990s failed to demonstrate a significant difference between the active treatment and placebo arms of the study[3].

More recent studies have also reported high failure rates for clinical trials in depression, with one analysis of clinical trials for antidepressant medications finding that over half of the studies conducted between 2007 and 2016 failed to meet their primary endpoint[4].

The reasons for these high failure rates can be multifactorial and may include high placebo response rates, heterogeneity of patient populations, inadequate study design, and other factors. It is worth noting that failure of a clinical trial does not necessarily mean that the intervention being tested is ineffective, as there may be other factors contributing to the lack of a significant treatment effect.

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Most common failure points of TRD trials

Heterogeneity of the patient population:	TRD is a highly heterogeneous disorder, with patients presenting various symptoms, disease severities, and comorbidities. This diversity can make it difficult to establish a clear treatment effect within the studied population.
Inadequate sample size:	Clinical trials with too few participants may lack the statistical power needed to detect meaningful treatment effects, leading to inconclusive results.
Insufficient treatment duration or dosage:	If the treatment duration or dosage is not sufficient to produce a significant effect, the trial may fail to meet its primary endpoint.
Inadequate outcome measures:	The use of subjective self-report measures in TRD trials can introduce biases and make it difficult to accurately assess treatment efficacy.
High dropout rates:	High dropout rates can lead to a loss of statistical power, making it difficult to detect significant treatment effects.
Placebo effect:	Depression trials are often prone to a strong placebo effect, which can make it difficult to differentiate between the true treatment effect and the placebo response.

Recently failed TRD Drug candidates:

As new drugs are developed, some potential treatments fail to proceed past the clinical trial stage. Below are some recent examples:

R-ketamine:

R-ketamine is an enantiomer of ketamine that was being developed as a potential antidepressant medication. However, a Phase III clinical trial of R-ketamine for TRD was terminated early due to lack of efficacy[5].

Rislenemdaz (CERC-301):

CERC-301 is a selective kappa opioid receptor antagonist that was being developed as a potential antidepressant medication. However, a Phase II clinical trial of CERC-301 in patients with TRD failed to meet its primary endpoint[6].

Vortioxetine (Lu AA21004):

Lu AA21004 is a multimodal antidepressant medication that targets multiple neurotransmitter systems. However, a Phase III clinical trial of Lu AA21004 in patients with TRD failed to meet its primary endpoint[7].

1 World Health Organization. Depression. Accessed October 19, 2021. https://www.who.int/news-room/fact-sheets/detail/depression.
2 Papakostas GI, Fava M, Thase ME. Treatment-resistant depression: a clinical term in need of clinical understanding. Eur Neuropsychopharmacol. 2012;22 Suppl 3:S391-S398. doi:10.1016/S0924-977X(12)70241-2.
3 Khan A, Faucett J, Lichtenberg P, et al. A systematic review of comparative efficacy of treatments and controls for depression. PLoS One. 2012;7(7):e41778. doi:10.1371/journal.pone.0041778
4 Jakobsen JC, Gluud C, Kirsch I. Should antidepressants be used for major depressive disorder? Cochrane Database Syst Rev. 2019;4(4):CD008726. doi:10.1002/14651858.CD008726.pub3
5 https://www.businesswire.com/news/home/20210305005126/en/Xenon-Pharmaceuticals-Announces-Results-of-Phase-3-Trial-of-XEN496-in-Adults-with-Focal-Epilepsy
6 https://www.businesswire.com/news/home/20180813005207/en/Cerecor-Announces-Top-Line-Results-from-a-Phase-2-Trial-of-CERC-301-in-Depression
7 https://www.nature.com/articles/nrd.2018.76

Precision Medicine and Biomarker-Based Stratification

One of the main challenges in TRD clinical trials is the heterogeneity of the disorder. To overcome this issue, researchers can adopt a precision medicine approach that incorporates genetic, biochemical, and other biomarkers to stratify patients into more homogeneous subgroups. As an example, One study of ketamine for TRD found that patients who did not respond to ketamine had higher levels of anxiety and anhedonia at baseline compared to responders[8].

This can be used to identify subgroups of patients who are more likely to benefit from a particular treatment.

For example, in the context of depression, certain genetic biomarkers may be associated with a better response to specific antidepressant medications. By identifying patients who are more likely to respond to a particular treatment, clinicians can improve treatment outcomes and reduce the risk of adverse events.

Biomarker-based stratification can also help to identify patients who are at increased risk for adverse events. For example, genetic biomarkers may be associated with an increased risk of side effects from a particular medication.

By identifying patients who are at increased risk, clinicians can adjust treatment plans or select alternative treatments to reduce the risk of adverse events and improving the likelihood of patients and participants completing the trial in safe manner, while also providing high-quality data to the study.

A review of clinical trials for antidepressant medications found that placebo response rates in depression trials ranged from 30% to 50%, on average.

Reducing the Placebo Effect

A review of clinical trials for antidepressant medications found that placebo response rates in depression trials ranged from 30% to 50%, on average[9].

To minimize the impact of the placebo effect on trial outcomes, researchers can implement strategies such as using an active comparator, conducting a placebo run-in period, or employing innovative placebo-controlled designs like the sequential parallel comparison design (SPCD). These approaches can help in distinguishing true treatment effects from placebo responses.

Novel Trial Designs

Adaptive trial designs can enhance the efficiency and success of TRD clinical trials. These designs allow for modifications during the trial based on accumulating data, enabling researchers to optimize sample sizes, adjust treatment arms, or alter randomization ratios. This approach can improve the chances of detecting treatment effects and reduce the number of patients exposed to ineffective treatments.

Creating a bespoke plan for trial design requires sourcing partners and collaborators with the experience and understanding of the space. By leveraging this knowledge, the trial design can address the risk factors while also providing data in a format that can be contrasted and compared to established data sets, as well as submitted to the required regulatory body.

Incorporating Digital Health Technologies

Digital health technologies, such as smartphone apps, wearables, and remote monitoring systems, can provide objective and continuous data on patient symptoms and functioning. By incorporating these technologies into clinical trials, researchers can obtain more reliable and accurate outcome measures, reducing the reliance on subjective self-report measures that may be prone to biases.

The time-frame for the data to be entered into the system can also be shortened, and in some cases may allow for almost real-time external monitoring, increasing transparency and improving data integrity of the trial.

"Maximizing the Signal-to-Noise ratio is the hidden secret to using small trials to show impactful efficacy outcomes."

-Dr Sud Agarwal

Enhancing Patient Retention and Engagement

High dropout rates are a common challenge in TRD clinical trials. To improve patient retention and engagement, researchers can implement strategies such as providing personalized support, offering flexible treatment schedules, and utilizing telemedicine for remote visits. These efforts can help to maintain patient adherence and improve the overall success of the trial.

Multi-site Collaboration and Data Sharing

Collaboration between research institutions and data sharing can help to increase sample sizes and improve the generalizability of trial results. By pooling resources and expertise, researchers can enhance the statistical power of their studies, increasing the likelihood of detecting meaningful treatment effects.

Early-Phase Proof-of-Concept Trials

Conducting early-phase, proof-of-concept trials can help to identify promising interventions and provide valuable information on their safety, tolerability, and potential efficacy. This approach allows researchers to prioritize the most promising treatments for larger, confirmatory trials, thereby increasing the overall success rate of clinical trials in TRD.

8 Cusin C, Ionescu DF, Pavone KJ, et al. Ketamine augmentation for outpatients with treatment-resistant depression: Preliminary evidence for two-step intravenous dose escalation. Aust N Z J Psychiatry. 2017;51(1):55-64. doi:10.1177/0004867416633039

9 Khan A, Faucett J, Lichtenberg P, et al. A systematic review of comparative efficacy of treatments and controls for depression. PLoS One. 2012;7(7):e41778. doi:10.1371/journal.pone.0041778

Many research organizations are looking for potential treatments for TRD. 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 TRD:

Promising TRD Drug Candidates:

Brexanolone (Zulresso):

Brexanolone is a synthetic form of the neurosteroid allopregnanolone, which modulates the gamma-aminobutyric acid (GABA) receptor. It has been approved by the FDA for postpartum depression, and its potential for TRD is being investigated.

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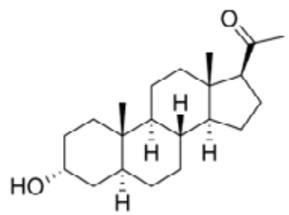

Dextromethorphan (DM) and Bupropion (AXS-05):

AXS-05 is a combination of dextromethorphan, an NMDA receptor antagonist, and quinidine, which increases dextromethorphan's bioavailability. This combination is being investigated for TRD due to its potential synergistic effects on glutamate modulation.

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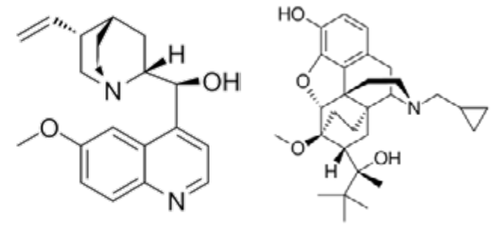

Psilocybin:

Psilocybin, the active compound found in "magic mushrooms," is being investigated for its potential in treating TRD. Research has shown that psilocybin can produce rapid and sustained antidepressant effects, possibly by modulating the serotonin system. Several clinical trials are underway to evaluate its safety and efficacy.

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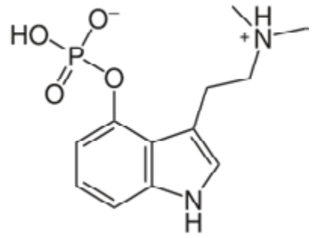
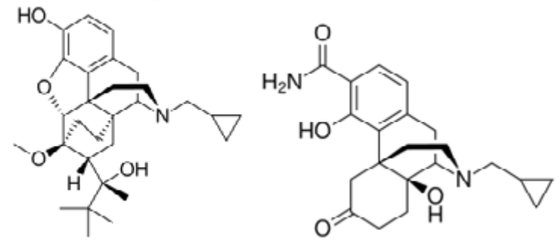


ALKS-5461:

ALKS-5461 is a combination of buprenorphine, a partial agonist of the mu-opioid receptor, and samidorphan, an antagonist of the same receptor. This combination is thought to modulate the opioid system, which is involved in mood regulation. ALKS-5461 has shown promise in some clinical trials for TRD, though it has encountered regulatory hurdles.

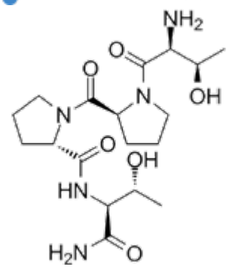
Alkermes



Rapastinel:

Rapastinel is an investigational drug that acts as an NMDA receptor modulator, similar to ketamine but with a different mechanism of action. It has shown promise in preclinical studies and early-phase clinical trials for TRD, with rapid and sustained antidepressant effects and a favorable safety profile.

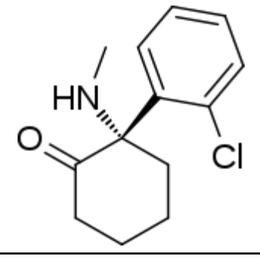
Allergan



Esketamine:

Esketamine, an enantiomer of ketamine, has been approved by the FDA for TRD under the brand name Spravato and was developed by Janssen Neuroscience. It is administered as a nasal spray and works by antagonizing the N-methyl-D-aspartate (NMDA) receptor. Esketamine has shown rapid antidepressant effects, making it a promising option for further development with a greater number of TRD patients.

Janssen | Pharmaceutical Companies of Johnson & Johnson



These are just a few examples of the many drug candidates under investigation for TRD, and the companies investigating them. Some have already received approval for therapeutic use with other conditions, so final approval is highly probable. The field of depression research is rapidly evolving, and new drug candidates and treatment approaches continue to emerge.

Conclusion:

Overcoming the high failure rates in treatment-resistant depression clinical trials requires innovative solutions and strategic approaches.

By embracing **precision medicine**, addressing the **placebo effect**, incorporating **novel trial designs**, leveraging **digital health technologies**, undertaking **Multi-site Collaboration and Data Sharing**, conducting collaborative efforts to **retain patients and participants**, and where possible commissioning **proof-of-concept trials**, researchers can enhance the efficiency and success rate of clinical trials in TRD.

These strategies have the potential to accelerate the development of effective treatments, ultimately improving the lives of millions of individuals suffering from this debilitating disorder.

Overall, the field of psychedelic research is still in its early stages, and more research is needed to determine the optimal treatment protocols and to identify which patient populations are most likely to benefit from these treatments.

Many of these risks can be minimized by selecting an appropriate partner to help guide you through the process, and acting as a safe pair of hands to ensure the resulting data is accurate, accessible and actionable.

iNGENŪ are a hands-on partner ready and able to help you take your investigational product through the clinical trial process, quickly, cost-effectively, and to a high standard of quality.

The authors of this paper:

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"Correct Clinical Trial design—which will include enrichment strategies and preferential selection of sub-populations—will provide the best return on investment."

-Dr Sud Agarwal

DR. ROB JENNY
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"With Clinical Trials being a significant investment for pharmaceutical companies, creating a strategy to maximize the chances of reaching endpoints is a business critical activity."

-Dr. Rob Jenny

Thank you for taking the time to read our document.

If you would like further information on how iNGENū CRO can assist you to conduct your Clinical Trial, please contact our representative on these details:

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