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Psychedelic Clinical Trials: Methods and Mystique

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Psychedelics are in the spotlight once again for their potential in treating mental health conditions like post-traumatic stress disorder (PTSD), depression, and substance abuse. Compounds such as psilocybin, LSD, and MDMA are being investigated with new scientific rigor. But with this resurgence comes a mix of excitement, myth, and significant scientific challenges. To truly evaluate the potential of psychedelics, we have to separate the potential benefits from myths and miraculous expectations—and that's where scientific methods come into play.

Why Methodology Matters

Methodological rigor is the foundation of science, enabling us to distinguish scientific truth from opinion. In research intended to gain regulatory approvals, cultural narratives and personal experiences have no weight unless backed by data. Regulators, as well as good clinicians, know that opinions—especially ones formed from isolated clinical experiences—can be misleading. This problem is amplified in the case of psychedelics, which come with decades of cultural baggage, hope-filled anecdotes, and taboos.

The bottom line is that psychedelic compounds, despite all ballyhoo about their unique effects, must be held to the same standards as other drugs. Proper evaluation of their medical potential requires the same rigor and transparency we expect from all other classes of pharmaceuticals.

The Biomedicalization Imaginary: A Useful Framework for Psychedelic Development

Claudia Schwarz-Plaschg's[1] work on socio-psychedelic imaginaries provides a useful framework for those who ponder alternatives to the biomedical development pathway. Viewing through this lens facilitates a comparison of the risks and benefits of biomedicalization to other imaginaries, such as continued legal prohibition, or decriminalization without pursuit of approval for specific medical indications, the

"biomedicalization imaginary." By studying psychedelics as pharmacological agents, we approach them with the objectivity and scientific rigor. This path not only frees society from the influence of idealizations and myth, but it also provides practitioners and patients with the reliable information needed to weigh risks and benefits associated with therapeutic use.

The biomedical approach isn't just about changing public perceptions of psychedelics; it's also a practical approach. By focusing on psychedelics as regulated medical compounds, we design controlled trials and engage in systematic inquiry that tests the safety and efficacy of these drugs. This imaginary, adopted by the collective vision of public policy, will ground psychedelic research in a medical context, and if results merit, enable integration into healthcare systems.

The Challenge of Functional Unblinding in Psychedelic Trials

But even with a strong methodological framework, psychedelic research faces some significant hurdles. These include public awareness of the hype around psychedelics and the high potential for functional unblinding. Both can raise expectation and bias.

These twin problems are formidable but not unique to psychedelic drugs lessons learned with compounds in other classes as applicable.

Key strategies for addressing these problems include careful communication of the study value proposition, rigorous training for study staff in placebo response mitigation techniques, use of blinded central raters, and engagement of participants and their supports as research collaborators as distinct from ordinary clinical practice. By thoroughly educating everyone involved on the range of potential experiences in both active and placebo conditions, researchers can help manage expectations and reduce bias. This type of training helps raters evaluate outcomes with greater objectivity and keeps participants aware of the possibility of receiving a placebo. Beyond improving blinding, such preparation strengthens the overall integrity of the study by mitigating the influence of expectancy bias on trial results.

Another strategy borrowed from clinical trials with non-nonpsychedelic drugs is the use of active placebos—substances that mimic some of the physiological or psychological effects of psychedelics without providing their full therapeutic impact. Ultra-low-dose psychedelics, antihistamines like diphenhydramine, or mild stimulants such as niacin have been explored as active placebo comparators to enhance blinding integrity.

Alternative study designs can also mitigate unblinding risks. Crossover designs, where participants receive both the placebo and active drug at different time points, may control individual expectancy effects. Additionally, microdosing studies, which involve

administering repeated low doses over time, may avoid the perceptual distinctiveness of the intervention and thus help maintain blinding. Some trials also incorporate non-psychedelic control groups, such as those receiving meditation or psychotherapy-only interventions, to distinguish expectancy effects from true pharmacological outcomes.

Bringing Psychedelics from Myth to Medicine

For psychedelic research to succeed in delivering a fair test of investigational products, the field has to temper public enthusiasm with scientific caution. The biomedicalization imaginary can help the field stay grounded, framing psychedelics as medical tools that should be studied with the same rigor as other pharmaceuticals. While psychedelics may have an aura of mystery, they should be seen as medical compounds to be tested, not as miracle cures to be accepted uncritically.

In the end, rigorous methodology is the foundation upon which the future of psychedelic therapy will stand—or fall. Placebo effects and unblinding challenges won't disappear, but they can be managed with well-designed trials and innovative research methods. Robust longitudinal data is essential to substantiate sustained benefits, while effectively mitigating safety risks. By studying psychedelics with appropriate respect and scrutiny, we can separate myth from reality and determine the place of these promising compounds in modern medicine.

Learn more about Signant's approach and discover solutions to optimize your psychedelic trial. Placebo response mitigation

About the Authors

Gary Sachs, PhD, is a Therapeutic Area Leader in bipolar disease and mood disorders and Clinical Vice President at Signant Health. He is a recognized expert in clinical trial methodologies. He founded the Bipolar Clinic at Massachusetts General Hospital and is an Associate Professor of Psychiatry at Harvard Medical School. With over 200 publications, Dr. Sachs also serves on the Scientific Advisory Boards of the National Alliance on Mental Illness and the Depression and Bipolar Support Alliance.

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Sayaka Machizawa, Psy.D., is an Associate Director of Clinical Science at Signant Health, bringing over 18 years of expertise in neurodegenerative and psychiatric diseases. She has played a key role in supporting large-scale global clinical trials across a wide range of indications. Fluent in both Japanese and English, Sayaka has led rater training sessions at numerous Investigator Meetings worldwide.

With a Doctorate in Clinical Psychology, she has also dedicated 12 years to academia, teaching graduate-level Psychology courses, and conducting neuropsychological evaluations for diverse populations. Her extensive experience bridges clinical research, education, and applied neuropsychology, making her a valuable contributor to advancing scientific rigor in clinical trials.

References

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