Psychedelic Clinical Trials: Regulatory Considerations from the FDA

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Acknowledgments

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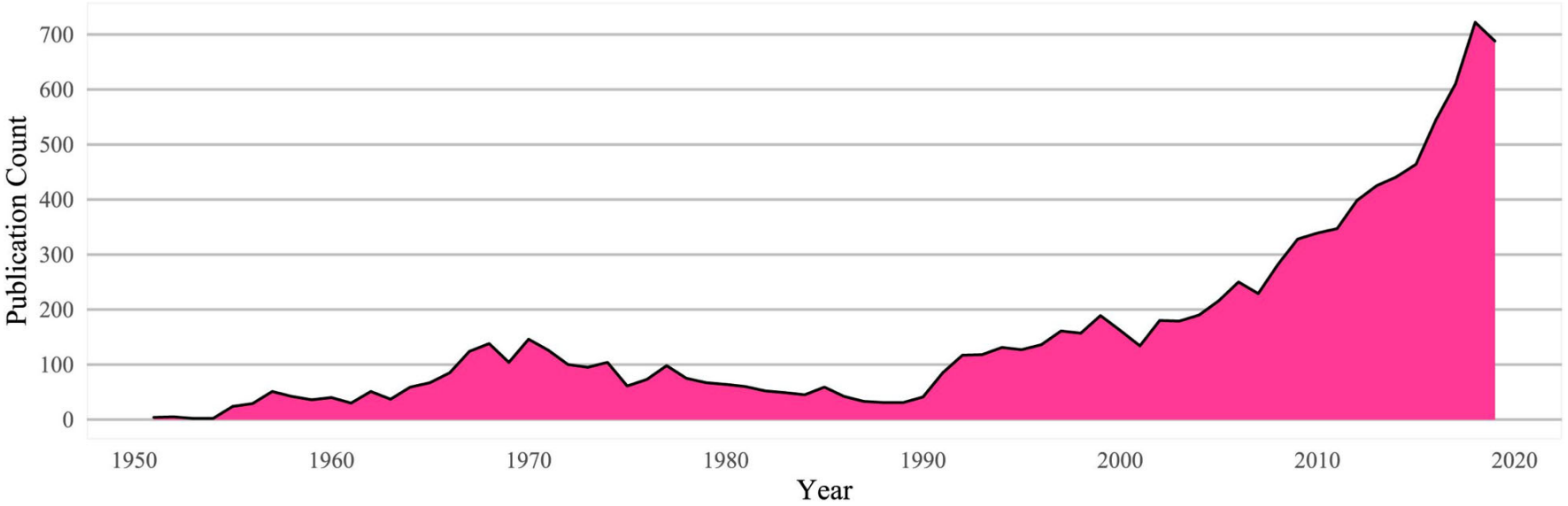
Overview

- The evolving landscape of psychedelic research
- High-level regulatory background
- Unique challenges
  - Complicators of efficacy assessment
  - Psychotherapy
  - Set and setting
  - Making valid comparisons and minimizing biases
  - Additional challenges

The Evolving Landscape of Psychedelic Research

Psychedelic Scientific Publications by Year



Petranker, R., et al. (2020). Psychedelic research and the need for transparency: Polishing Alice's Looking Glass. *Frontiers in psychology*, *11*, 1681.

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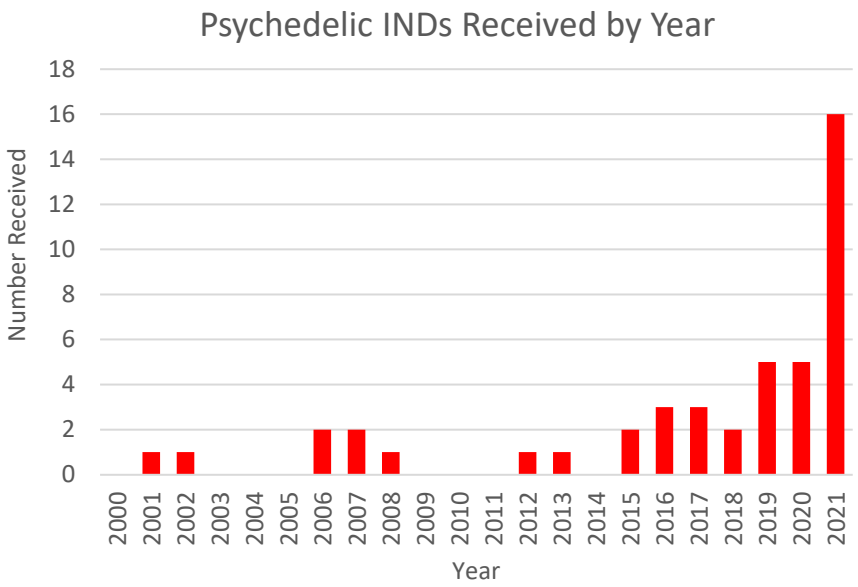
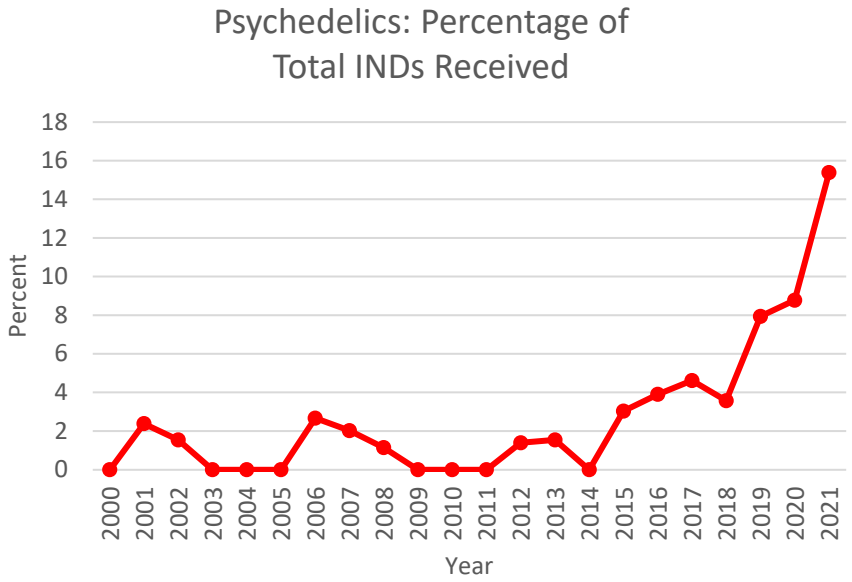
Psychedelic therapy could 'reset' depressed brain

By Rachel Schraer
Health reporter

Current FDA Landscape

New IND Applications to DP: 2000 to 2021





Unpublished internal analysis; includes research and commercial INDs
Psychedelics included: ayahuasca, DMT, LSD, MDMA, psilocybin

Reviews and Overviews

Full Access

Psychedelics and Psychedelic-Assisted Psychotherapy

Collin M. Reiff, M.D., Elon E. Richman, M.D., Charles B. Nemeroff, M.D., Ph.D., Linda L. Carpenter, M.D., Alik S. Widge, M.D., Ph.D., Carolyn I. Rodriguez, M.D., Ph.D., Ned H. Kalin, M.D., William M. McDonald, M.D., and the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research

Published Online: 26 Feb 2020 | https://doi.org/10.1176/appi.ajp.2019.19010035

- Provides an evidenced-based summary of the literature on the clinical application of psychedelic drugs in psychiatric disorders.
- The most significant database exists for MDMA and psilocybin
- RCTs support the efficacy of MDMA in the treatment of PTSD and psilocybin in the treatment of depression and cancer-related anxiety
- Database is insufficient for FDA approval of any psychedelic compound for routine clinical use in psychiatric disorders at this time, but continued research is warranted.

Reiff, C. M., et al. (2019) Psychedelics and psychedelic-assisted psychotherapy. American Journal of Psychiatry, 177(5), 391-410.

Regulatory Background

FDA Drug Approval

- When reviewing New Drug Applications, the FDA considers the treatment indication, available treatment options, and evidence for both the effectiveness and safety of the proposed new drug.

- If the drug is assessed to be effective and the safety concerns can be adequately managed, the favorable benefit-risk balance supports marketing approval

21 U.S. Code §355(d)

21 CFR 314.126

- Relevant features of an adequate and well-controlled trial:
  - The study uses a design that permits a **valid comparison** with a control to provide a quantitative assessment of drug effect.
  - Adequate measures are taken to **minimize bias** on the part of the **subjects, observers**, and analysts of the data.
  - The methods of assessment of subjects' response are **well-defined** and **reliable**.

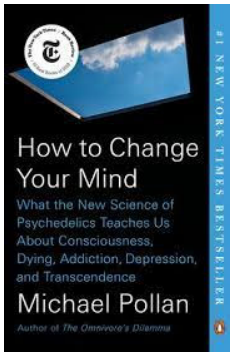
Unique Challenges of Psychedelic Trials

Complicators of Efficacy Assessment

Engaged practitioner

Patient expectations

Griffiths et al., 2006; Metzner et al., 1965



Elaborate Intervention

Hypersuggestibility

de Rios, Grob, 1994

Dramatic Functional Unblinding

Unique Challenges of Psychedelic Trials:

Psychotherapy

Example Psychedelic Psychotherapy Components

Preparatory Psychotherapy	Drug Treatment Session	Integrative Psychotherapy
• Series of meetings (e.g., 4 x 2-hour sessions in month prior to drug treatment) between patients and monitors/therapists • Discuss meaningful life experiences, beliefs, goals	• Monitors/therapists offer gentle guidance, support, and reassurance as needed • Encouragement to "trust, let go, be open" to experience • Instrumental music, eyeshades to block distractions	• Series of meetings (e.g., next-day session + 2 additional sessions over 6 months) between patients and monitors/therapists • Discuss novel thoughts and feelings that arose during drug treatment session
Goal: Prepare patient for drug treatment, build trust/rapport establish intentions/goals	Goal: Reduce adverse psychological reactions, facilitate therapeutic session	Goal: Ensure psychological stability, process and integrate experience

Johnson, Richards, & Griffiths. *Journal of Psychopharmacology* (2008)

The Practice of Medicine Exception

21 USC §396: “Nothing … shall be construed to limit or interfere with the authority of a health care practitioner to prescribe and or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”

- FDA has long maintained that it does not regulate the practice of medicine, which is generally defined as 1) diagnosing a disease, condition, or injury and 2) prescribing, administering, or providing a treatment for that disease, condition, or injury

- The FDA does not restrict physicians from prescribing FDA-approved drugs in an off-label manner.

Labeling Approaches

- The FDA regulates product labeling to ensure that it contains the essential scientific information needed for the safe and effective use of the drug (21 CFR 201.56).

- Labeling regulations allow for specification that a drug should be used only in conjunction with another mode of therapy:

> 21 CFR 201.57(c)(2)(i)(A): If the drug is used for an **indication only in conjunction with a primary mode of therapy** (e.g., diet, surgery, behavior changes, or some other drug), **a statement that the drug is indicated as an adjunct to that mode of therapy**.

Psychotherapy-Relevant Labeling Precedents

Drug and Indication	Label Section	Text
Naltrexone extended-release injectable suspension for alcohol and opioid dependence	Indications and Usage	"Treatment … **should be part of a comprehensive management program that includes psychosocial support**."
Bupropion hydrochloride extended-release tablets for smoking cessation	Dosage and Administration	"It is important that patients continue to receive **counseling and support throughout treatment … and for a period of time thereafter**."
Buprenorphine sublingual tablets for opioid dependence	Clinical Studies	"All trials used **buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program**. There were no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment."

Risk Evaluation and Mitigation Strategies (REMS)

- Implemented if necessary to ensure that the benefits outweigh the risks of the drug

- Requires "**elements to assure safe use**," such as provider training or certification, patient monitoring, or dispensing of drug only in specific settings or safe-use conditions

- **Must not be "unduly burdensome** on patient access to the drug" and, to the extent practicable, must "**minimize the burden** on the health care delivery system"

21 U.S. Code §355–1

Unique Challenges of Psychedelic Trials:

Set and Setting

“Set and Setting”

- Optimal set and setting can have a positive treatment effect without a pharmacological intervention[1]
- What are the minimum requirements?
- How do we communicate this on a label?

[1]Hartogsohn, I. (2016). Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology*, *30*(12), 1259-1267.

- The Agency is aware of the unique risks that may be associated with the nature of these treatments, including the possible risk of sexual misconduct, and we work closely with sponsors to include appropriate patient protection provisions for these and all risks in the investigations we regulate

Unique Challenges of Psychedelic Trials:

Making Valid Comparisons and Minimizing Biases

Selection of Appropriate Controls

- “Inactive” placebo
  - Nocebo?
- “Active” placebo
  - Other psychoactive drugs
  - Subperceptual doses of psychedelic drugs
- To help overcome the limitations of any single approach, and NDA could use different comparators in different studies

Recommendations for Reducing Potential Biases

- Use of a blinding questionnaire can be informative
- Use of video and central raters, blinded to treatment and visit number
- Have the post-treatment therapist be different than in-session monitor
- Dose-response Trial
  - 21 CFR 314.126(b)(2)
    - "(ii) Dose-comparison concurrent control. At least two doses of the drug are compared. A dose-comparison study may include additional treatment groups, such as placebo control or active control."
  - Guidance for Industry: Exposure-Response Relationships Study Design, Data Analysis, and Regulatory Applications https://www.fda.gov/media/71277/download

Additional challenges

- Poorly understood dose-response relationship[1]
- Generalizability to target patient population
- Need to understand parameters for retreatment
- Need for nonclinical safety database up to current standards[1]
  - 5HT2B agonism and valvulopathy?
- Need for formal studies on abuse potential[1, 2]

[1]Sellers, E et al (2018). Studies with psychedelic drugs in human volunteers. *Neuropharmacology*, 142, 116-134.
[2]Calderon, S. et al (2018). A regulatory perspective on the evaluation of hallucinogen drugs for human use. *Neuropharmacology*, *142*, 135-142.

Summary

- Preliminary evidence is suggestive that psychedelic drugs could be effective against a range of various psychiatric conditions; however, safety and efficacy need to be established in large, adequate and well-controlled trials
- Psychotherapy and “set and setting” pose unique regulatory challenges
- Appropriate treatment comparators are difficult; multiple approaches may be appropriate
- Additional challenges (e.g., generalizability, understanding dose-response relationship, retreatment parameters)