Regulatory Perspectives on Psychotherapy in Psychedelic Drug Development

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Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development

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THE TEN LESSONS OF PSYCHEDELIC PSYCHOTHERAPY, REDISCOVERED

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FDA

The Experimental Use of Psychedelic (LSD) Psychotherapy

Walter N. Pahnke, MD, PhD; Albert A. Kurland, MD; Sanford Unger, PhD; Charles Savage, MD; and Stanislav Grof, MD

Psilocybin: Psychotherapy or drug?

Guy M Goodwin

Psychedelic Psychotherapy: Insights From 25 Years of Research

Psilocybin-assisted psychotherapy for dying cancer patients – aiding the final trip

David Spiegel

William A. Richards[1]

Psilocybin with psychological support for treatment-resistant depression: six-month follow-up

R. L. Carhart-Harris[1] · M. Bolstridge[1,2] · C. M. J. Day[1,2] · J. Rucker[1,3,4] · R. Watts[1] · D. E. Erritzoe[1] · M. Kaelen[1] · B. Giribaldi[1] · M. Bloomfield[5] · S. Pilling[6] · J. A. Rickard[7] · B. Forbes[8] · A. Feilding[9] · D. Taylor[10] · H. V. Curran[6,11] · D. J. Nutt[1]

Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin

R. L. Carhart-Harris, R. Leech, T. M. Williams, D. Erritzoe, N. Abbasi, T. Bargiotas, P. Hobden, D. J. Sharp, J. Evans, A. Feilding, R. G. Wise and D. J. Nutt

What is psychotherapy?

What is psychedelic psychotherapy?

"Psychotherapy is the informed and intentional application of clinical methods and interpersonal stances derived from established psychological principles for the purpose of assisting people to modify their behaviors, cognitions, emotions, and/or other personal characteristics in directions that the participants deem desirable".

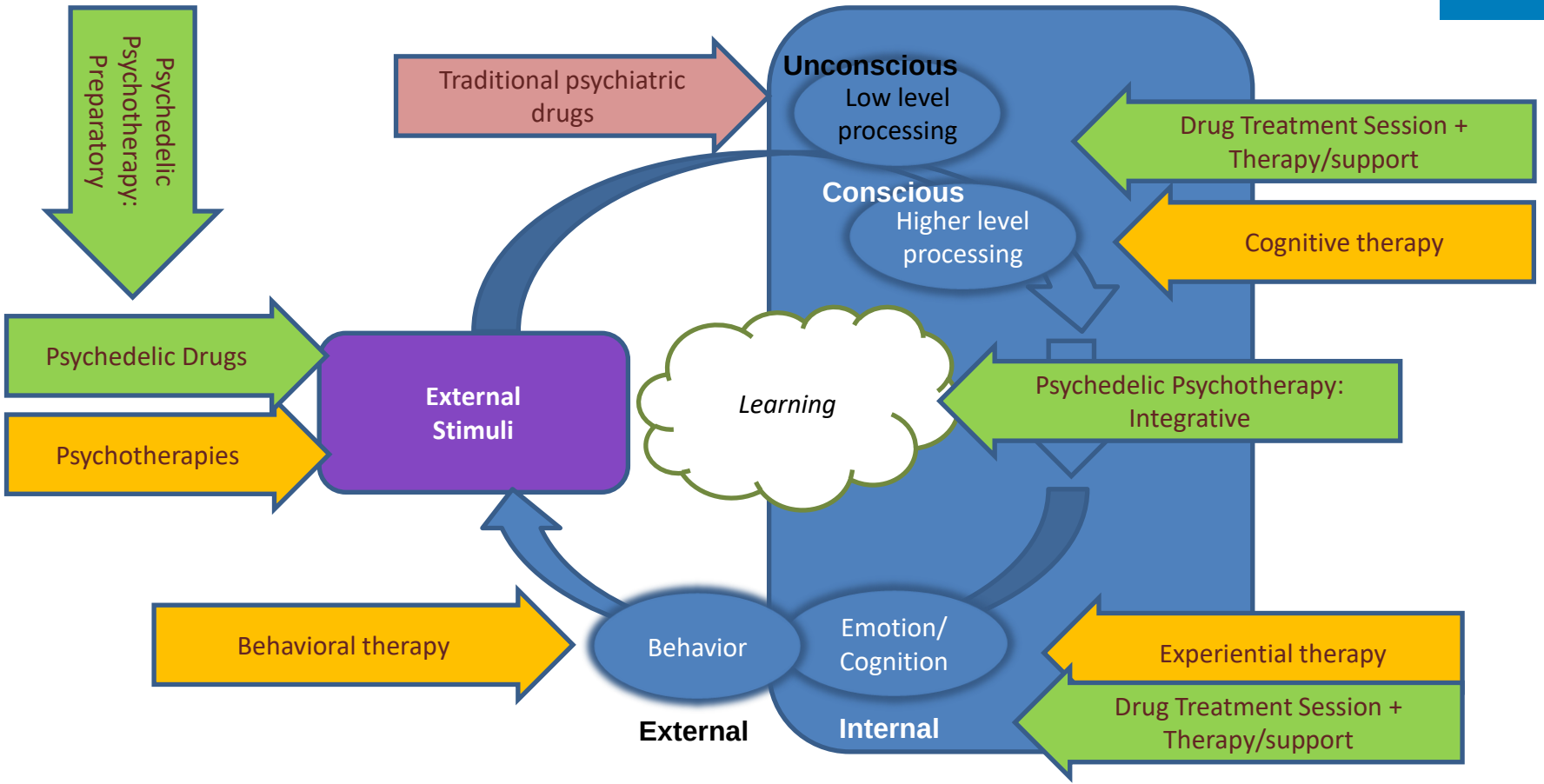
Campbell at al. *Psychotherapy* (2013)

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)

Psychiatric Disorders and Treatment Paradigms



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)

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 for 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
- May require “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

Psychotherapy Considerations: Safety

- The summative experience of decades of early psychedelic research found that interpersonal support during psychedelic treatment reduced the risk for psychological adverse reactions
- DP has required the use of a trained sitter/monitor in addition to a licensed mental healthcare provider administering in session support during clinical trials of psychedelic drug treatment sessions to protect subject safety.
- Support/monitoring for psychedelic psychotherapy providers could be considered an element to assure safe use if a psychedelic drug was approved for marketing.
- The appropriate extent of support/monitoring needs to be determined.

Figure 1 The living room-like session room used in the Johns Hopkins hallucinogen research studies. Aesthetically pleasing environments such as this, free of extraneous medical or research equipment, in combination with careful volunteer screening, volunteer preparation and interpersonal support from two or more trained monitors, may help to minimize the probability of acute psychological distress during hallucinogen studies.

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

Psychotherapy Considerations: Efficacy

- For most existing drugs approved for the treatment of depression and anxiety disorders, registration studies either prohibited concurrent psychotherapy or allowed only chronic psychotherapy with no expected changes during the study.

- Accordingly, most antidepressant labels do not mention psychotherapy, although clinical trial evidence and practice guidelines support a combined pharmacotherapy/psychotherapy approach.

Table 3 Direct comparisons between psychotherapy, pharmacotherapy, combined psychotherapy and pharmacotherapy, and placebo in anxiety and depressive disorders (Hedges' g)

	Ncomp	g	95% CI	I^2	95% CI	NNT
Combined vs. placebo	11	0.74	0.48-1.01	65	33-82	2.50
Pharmacotherapy vs. combined	11	0.37	0.12-0.63	43	0-72	4.85
Pharmacotherapy vs. placebo	11	0.35	0.21-0.49	0	0-60	5.10
Psychotherapy vs. combined	11	0.38	0.16-0.59	53	8-76	4.72
Psychotherapy vs. placebo	11	0.37	0.11-0.64	68	41-83	4.85

Ncomp - number of comparisons, NNT – number needed to treat

Cuijpers P…Reynolds CF, *World Psychiatry* (2014)

Assessing the role of psychotherapy and psychedelic drug in treatment efficacy

Study Arms

Psychotherapy Control + Placebo	Psychotherapy Active + Placebo
Psychotherapy Control + Psychedelic	Psychotherapy Active + Psychedelic

- 2x2 factorial design ideal, but logistically challenging and not a regulatory requirement
- Certain components of psychotherapy (i.e., use of a sitter/monitor during the drug treatment session) would be required for safety, but the contribution of, e.g., preparatory + integrative psychotherapy could be assessed

- If the intended drug indication is specifically to facilitate psychotherapy, clinical studies should demonstrate an add-on effect of the drug to psychotherapy

Take Home Messages

- Combination psychedelic + psychotherapy is a treatment paradigm studied for 50+ years that may potentially reduce safety risks and increase therapeutic benefits associated with psychedelic drug therapy

- FDA does not regulate the practice of medicine or psychotherapy

- The development program will need to establish the efficacy of the drug and meet the relevant regulatory standards. If the drug is to be used only in conjunction with another mode of therapy, studies should include that mode of therapy, and provide rigorous evidence of an add-on effect of the drug to the mode of therapy

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