



# Advancing Psychedelic Clinical Study Design

The meeting will begin shortly

Funding Disclosure: This activity is one part of a multi-part Foundation project related to substance use disorder.

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# Welcome

**Susan C. Winckler, RPh, Esq.**

Chief Executive Officer

Reagan-Udall Foundation for the FDA

# Thank you for joining



Due to the meeting size, your microphone and video will remain off during the meeting.



This public meeting is being recorded. The slides, transcript, and video recording will be available on the FDA Foundation website after the meeting.



While we won't have time to directly address audience questions during today's meeting, you may use the Zoom chat function for comments.

# Today's Agenda (Eastern Time)



- 10 a.m.** Welcome
- 10:10 a.m.** Session 5: Set and Setting
- 11:20 a.m.** Session 6: Overview of FDA Regulatory Authority
- 11:40 a.m.** Session 7: Considerations for Potential Psychedelic Use in the Real World
- 12:55 p.m.** Closing Remarks
- 1 p.m.** Adjourn

# Session 5: Set and Setting

## *Presenters:*

- **Ido Hartogsohn, PhD**, Bar-Ilan University
- **David Yaden, PhD**, Johns Hopkins University

## *Respondents:*

- **Brian Anderson, MD**, University of California, San Francisco
- **Javier Muniz, MD**, U.S. Food and Drug Administration

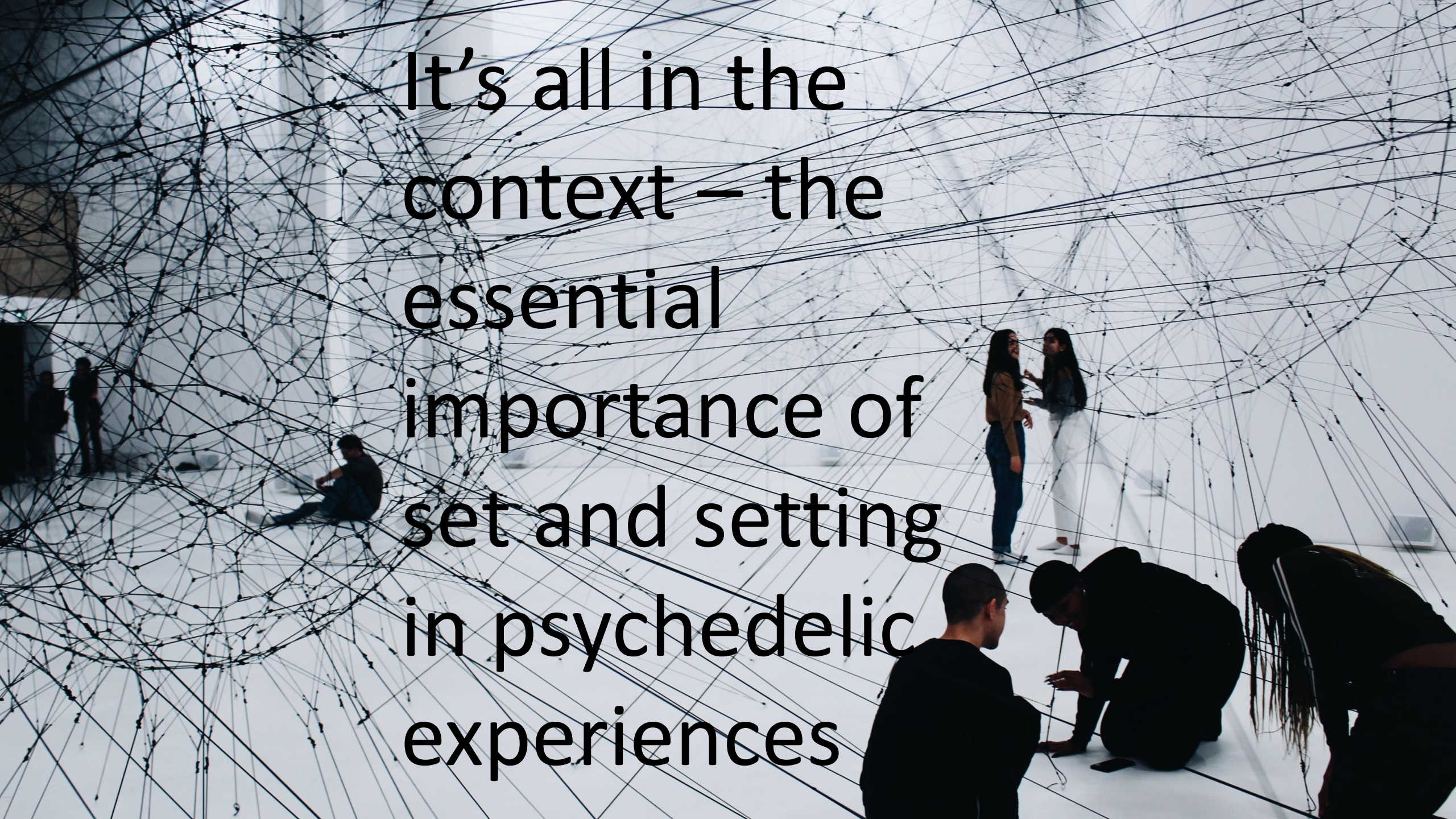
# Contextual considerations in clinical trials and applications

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Ido Hartogsohn

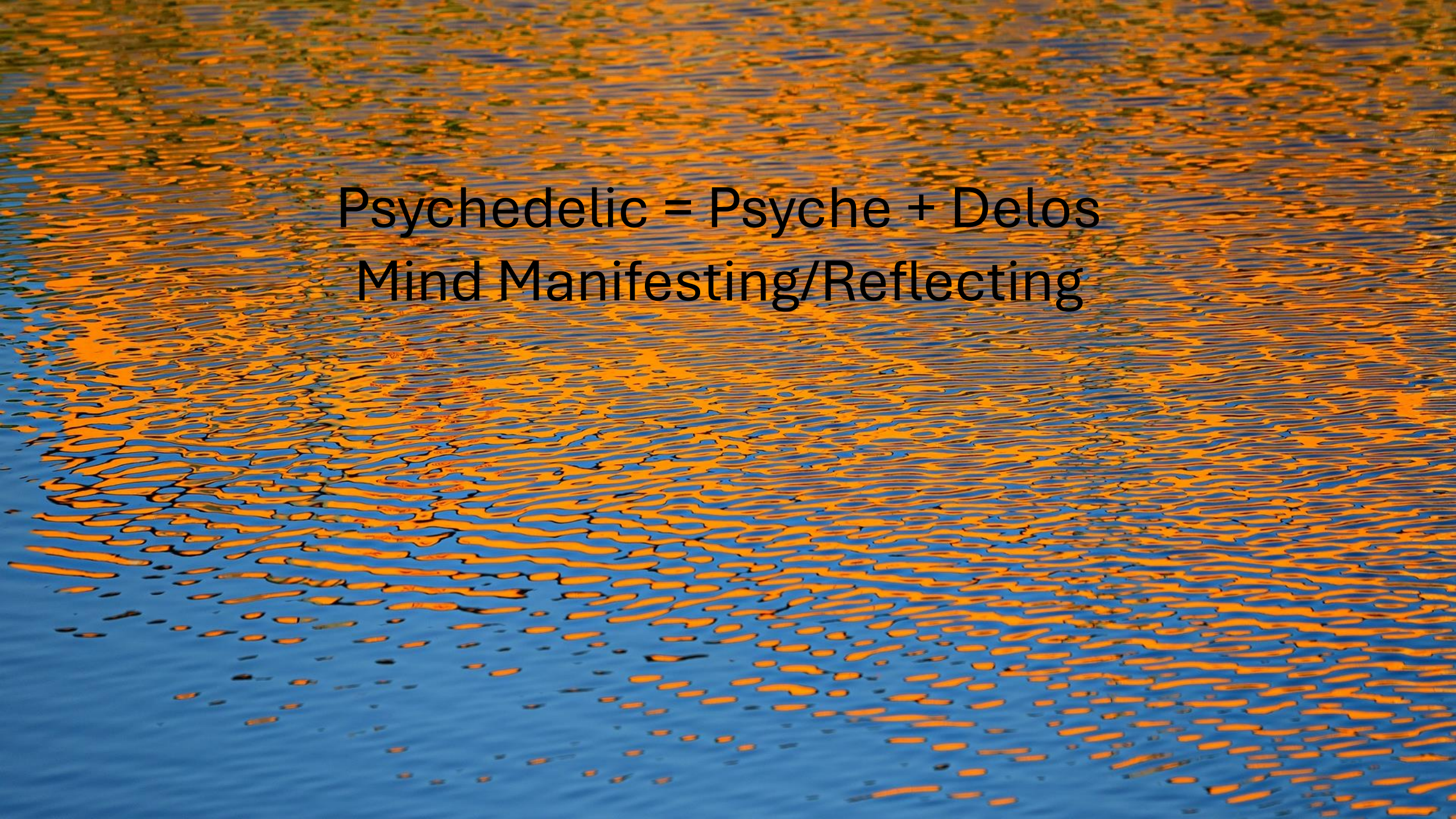
The Graduate Program in Science  
Technology and Society, Bar Ilan  
University

[idohartogsohn@gmail.com](mailto:idohartogsohn@gmail.com)



It's all in the  
context – the  
essential  
importance of  
set and setting  
in psychedelic  
experiences





Psychedelic = Psyche + Delos  
Mind Manifesting/Reflecting

# Elements of Set and Setting

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## Set

- Personality
- Expectancy
- Intention

Substance and dose  
(Fadiman, Zinberg)

Skillset  
(Godasi)

## Setting

- Physical (Sensory environment)
- Social
- Cultural

Session (Fadiman)

Integration/Matrix  
(altered states vs.  
Altered traits)

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# Current research on set and setting demonstrates the crucialness of context

- Clear intention is conducive to mystical type experiences
- Positive set decreased likelihood of challenging experiences
- Social connection in psychedelic ritual correlates with long term psychological well being
- Preparation before session increases mental health benefits
- Features of space correlate with frequency of difficult experiences.
- Musical selection mediates therapeutic efficacy



Why were the results of mid-20th-century hallucinogenic research contradictory?

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Do hallucinogens induce psychosis or heal the mind?

---

Do hallucinogens disrupt cognition or enhance creativity and innovation?

---

Are hallucinogenic experiences beatific or horrific?

---

# Incoherent experimental results can be explained by set and setting

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- Impersonal relationships vs. therapeutic alliances
- Sterile hospital setting vs. comfortable, cozy surroundings
- Extensive testing vs. freedom to explore
- Expecting insanity vs. expecting healing
- Therapeutic intention vs. no intention/choice
- etc. etc.

---

# Seven modalities of set and setting in the 1950s and 1960s

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- Psychotomimetic research
- Psychotherapeutic research
- Spiritual application
- Art and culture
- Technological innovation
- Military and special operations
- Peace building and political work

*Why are set and setting  
exceptionally potent in  
the case of psychedelics?*

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Psychedelics as  
experiential  
magnifiers



ALDOUS HUXLEY

Heaven

& Hell



Contemporary  
psychedelic  
research pays  
careful attention to  
set and setting to  
provide a  
psychologically safe  
environment,  
conducive to  
therapeutic results

- Pleasant room arrangement
- Soft lighting
- Able to lie down
- Privacy
- Musical selection
- Therapeutic alliance between therapist and client
- Therapeutic framework
- Preparatory session
- Integration sessions

Individual Set and Setting (2<sup>nd</sup> Level)

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Collective Set and Setting (1<sup>st</sup> Level)

# Reactions to Mescaline Dependent on Culture



Caucasians in clinical experiments:

- Extreme mood swings
- Sexual and aggressive disinhibition. Suspiciousness.
- Paranoia and feeling of meaninglessness



Native American peyotists

- No Mood swings
- Calm presence, awe and satisfaction.
- Higher sense of meaning and integration in the community.

Marlene Dobkin de Rios



# Hallucinogens

CROSS-  
CULTURAL  
PERSPECTIVES



# Hallucinogens and Culture

Peter T. Furst





# American Trip

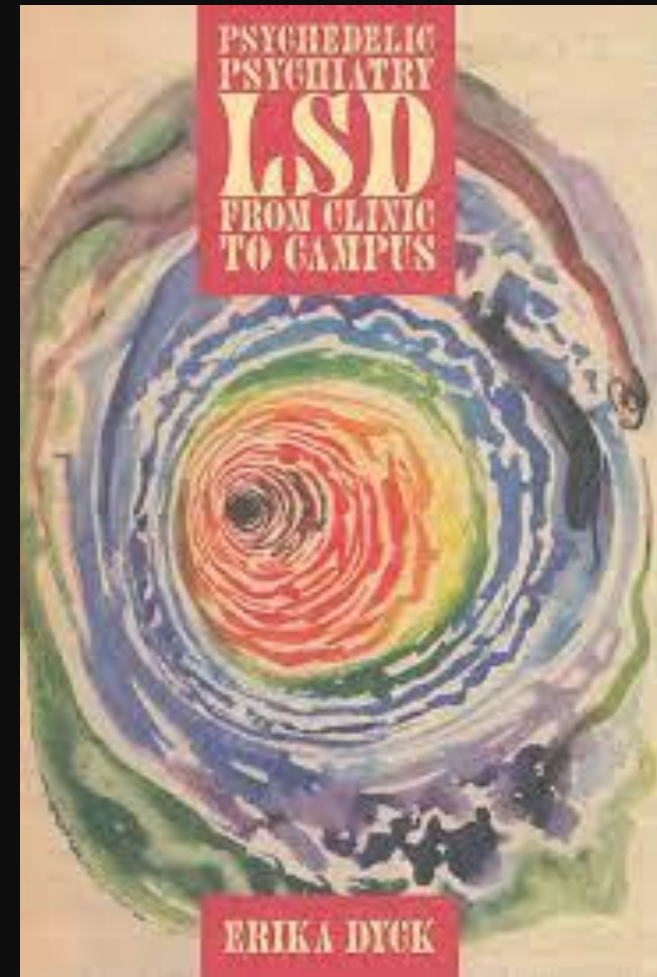
SET, SETTING, AND THE  
PSYCHEDELIC EXPERIENCE  
IN THE TWENTIETH  
CENTURY

**IDO HARTOGSOHN**

Values habitually associated with psychedelics can be recognized as culture-dependent when viewed through a cross-cultural and comparative-historical prism

*Contextual considerations in  
contemporary clinical trials and  
applications*

Rethinking objectivity:  
Humphry Osmond and  
the Canadian Addiction  
Research Foundation



“The quixotic attempt to eliminate the effects of participant-observation in the name of a misplaced pseudo-objectivity is fruitless, not so much because it is impossible but because it is unproductive. ... The question becomes not how to eliminate bias ... of participant observation, but how optimally to account for and exploit the effects of the participant observation transaction in terms of the purposes of the research.”

Tooley, Pratt. Letter to the editor. *Behav Sci* 9 (1964) 3:254-56.



## Race as a component of set and setting: How experiences of race can influence psychedelic experiences

LOGAN NEITZKE-SPRUILL\*

Department of Sociology and Criminal Justice, University of Delaware, Newark, DE, USA

(Received: April 12, 2019; accepted: August 7, 2019)

**Background and aims:** Set and setting function both as a concept that guides research and practice with psychedelic drugs and as a meme aimed at reducing harm among psychedelic users. Referring to non-pharmacological factors that shape drug experiences, the concept of set and setting was popularized in the West during the mid-20th century. However, little theoretical development has occurred regarding what falls under the umbrella of set and setting since its conception. **Methods:** By bridging set and setting theory with research from the fields of social psychology and sociology of medicine, this review calls attention to how race can contribute the set and setting for a psychedelic experience. **Results:** I argue that psychosocial factors influencing racial differences in mental health also constitute

## Making psychedelics into medicines: The politics and paradoxes of medicalization

TEHSEEN NOORANI\*

Department of Anthropology, Durham University, Durham, UK

(Received: April 30, 2019; accepted: July 10, 2019)

This commentary considers efforts to turn psychedelics into medications that can be administered through healthcare systems as examples of “medicalization.” I draw on ethnographic research both inside and outside of university-based clinical trials from 2014 to date, together with analogous examples from psychiatry and drug research and development. Rather than taking a normative stance on medicalization, I situate it in a wider political, economic, and cultural context to better understand its logics and effects. I begin by suggesting the resurgence of psychedelic science has been concerned with medicalization from the outset, recently prompting a crisis in the “psychedelics community” over its self-identity and values. Next, against the confident public messaging surrounding psychedelics, I consider how attempts to scale up and market psychedelic-assisted therapy could end up undermining the safety and efficacy of the therapy itself. I then outline the movements to decriminalize, legalize, and minimize the harms and risks of using psychedelics in their currently illicit therapeutic and recreational modalities. Finally, I explore how working toward psychedelic medicalization over the coming years may influence the movements toward decriminalizing and legalizing psychedelic use, focusing on the underarticulated ways in which medicalization may




AKADÉMIAI KIADÓ

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## Culture and psychedelic psychotherapy: Ethnic and racial themes from three Black women therapists

MONNICA T. WILLIAMS<sup>1,2,3\*</sup> , SARA REED<sup>1,2</sup> and JAMILAH GEORGE<sup>1</sup><sup>1</sup> Department of Psychological Sciences, University of Connecticut, Storrs, CT, USA<sup>2</sup> Behavioral Wellness Clinic, LLC, Tolland, CT, USA<sup>3</sup> School of Psychology, University of Ottawa, Ottawa, ON, CanadaReceived: March 29, 2020 • Accepted: July 5, 2020  
Published online: September 8, 2020

## THE CORPORADELIC SET AND SETTING

### On the Consequences of Psychedelic Commodification

IDO HARTOGSOHN

**Abstract:** The term “corporadelic” signifies “manifesting corporate structures, ethos, or logic within the context of the psychedelic landscape.” It points to a relatively novel phenomena in the history of psychedelics: the appropriation of these psychoactive agents by for-profit corporations and the integration of psychedelic use into corporate setting. Set and setting is a fundamental concept in the field of psychedelics and points to the crucial dependence of psychedelic effects on contextual factors, such as expectancy, intention, and environment. In recent years, the term has been extended to include an examination of sociocultural structures and their role in shaping experiences with

# Cultivating contextual literacy in psychedelic clinical trials and applications



Thank you

Ido Hartogsohn

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# Psychedelic Experiences & Psychological Support/Therapy

**David B. Yaden, PhD**

The Roland R. Griffiths Professor of Psychedelic Research

Center for Psychedelic and Consciousness Research

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SCHOOL *of* MEDICINE

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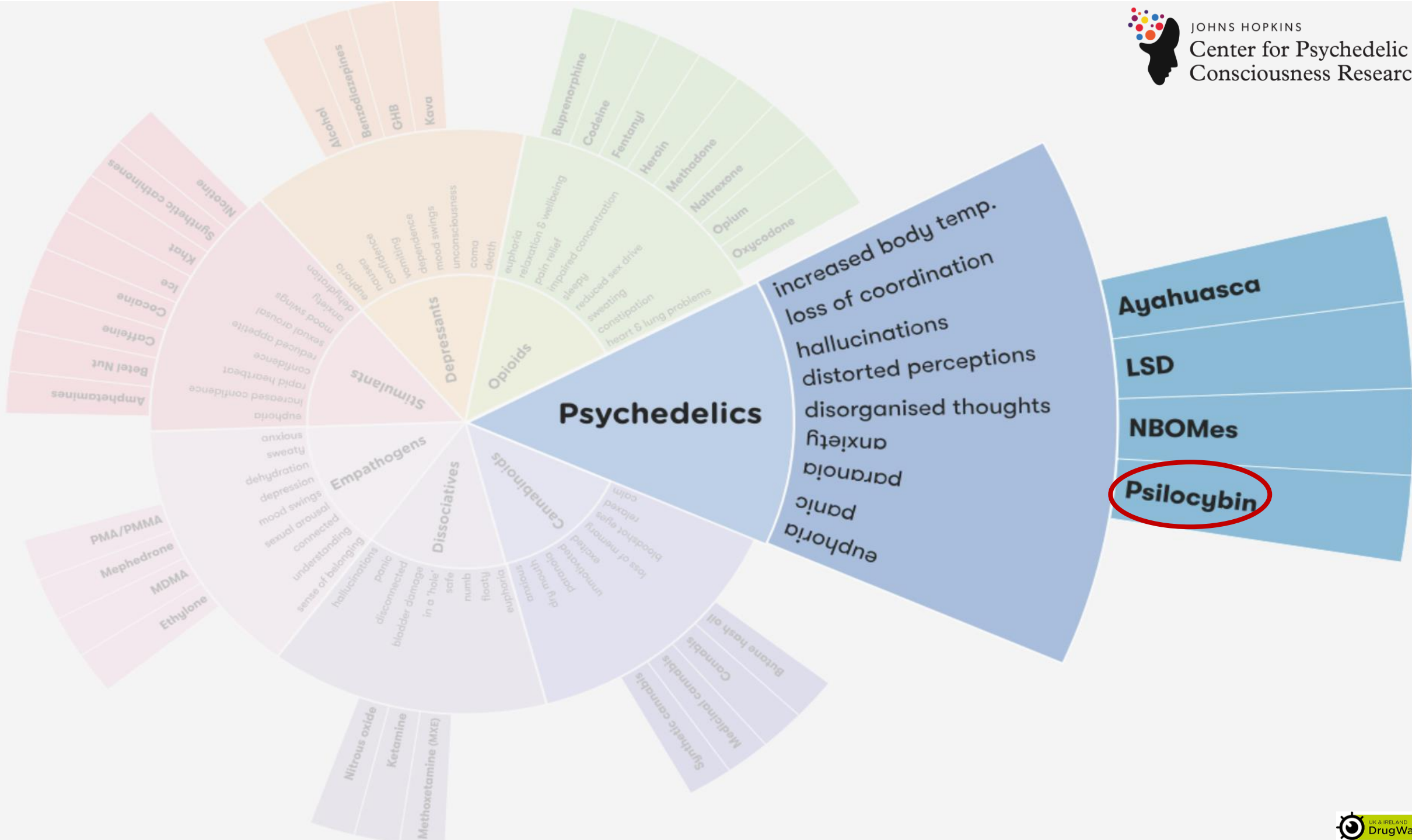
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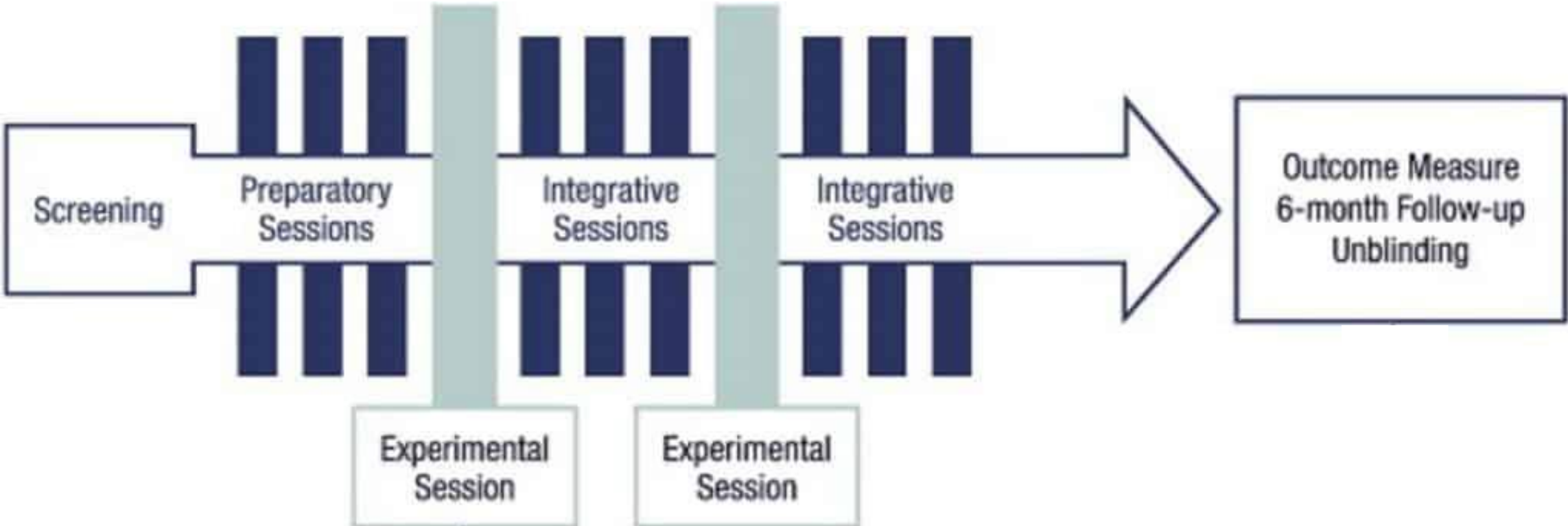


- Psychological Support in Psychedelic Research
- Concepts from Different Paradigms
- Support vs. Therapy



- **Psychological Support in Psychedelic Research**
- Concepts from Different Paradigms
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# Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default

*David B. Yaden<sup>1\*</sup>, Dylan Earp<sup>2</sup>, Marianna Graziosi<sup>3</sup>, Dara Friedman-Wheeler<sup>1</sup>,  
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- Psychological Support leaves open opportunities to draw from an eclectic array of concepts
- But standardization is ideal
- But which paradigm to use?



- Psychological Support in Psychedelic Research
- *Concepts from Different Paradigms*
- Support vs. Therapy



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- **But which paradigm to use?**
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  - ~~Draw from psychodynamic/psychoanalytic?~~
  - Draw from cognitive-behavioral approaches?

# Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default

Concept	Citations	Description	Relevance to psychedelic treatments
<b>Dosing session</b>			
<b>CBT</b>			
<i>Core beliefs and cognitive distortions</i>	Beck and Haigh, 2014	Beliefs and thoughts that address the self, one's future, and the world.	During dosing sessions, a participant may encounter core beliefs and cognitive distortions.
<i>Cognitive restructuring</i>	Beck and Haigh, 2014	Targeting dysfunctional or biased reasoning (including core beliefs and cognitive distortions) and to help clients evaluate them.	There is initial evidence to suggest that psychedelic therapy can change various beliefs. Training with this skill may facilitate this desired outcomes.
<i>Relaxation techniques</i>	Clark and Beck, 2010	These techniques include <i>progressive muscle relaxation (PMR, applied relaxation, and breathing retraining.</i>	If these are practiced in advance, session monitors could prompt clients to use techniques (functionally similar to therapeutic touch) to restore a sense of safety and empower participants to continue with the session, should anxiety or panic occur.
<b>Dosing session: DBT</b>			
<i>Mindfulness skills</i>	Linehan, 2015	The core mindfulness skills are the <i>what</i> (e.g., observe, describe, and participate) and <i>how</i> skills (e.g., non-judgmentally, one-mindfully, and do what works)	Training in mindfulness skills taught during preparation may help client to experience the session in a more engaged manner.
<i>Emotion regulation skills</i>	Linehan, 2015	Emotion regulation skills are often taught in DBT with the caveat that we cannot have total control over our emotions, but useful for modulating emotion.	In session, participants may be better to able to articulate and manage what emotions are coming up and thereby give session monitors a better sense of when to intervene and minimize unnecessary disruption

# Psychedelics and Psychotherapy: Cognitive-Behavioral Approaches as Default

Concept	Citations	Description	Relevance to psychedelic treatments
<i>Distress tolerance skills</i>	Linehan, 2015	<i>Crisis survival skills</i> (such as the relaxation techniques described in traditional CBT) and <i>reality acceptance skills</i> , which promote a conscious commitment to accept situations beyond one's control.	When challenging experiences arise in the session phase, participants can be encouraged to use the <i>Turning the Mind</i> skill, which is a stance cultivated through practice involving choosing to accept one's present experience.
<b>Dosing session: ACT</b>			
<i>Defusion</i>	Luoma et al., 2017, p. 99	Exercises and discussion to help participants to get a better sense of the nature of their unique process of thinking rather than getting caught up (or fused) with a particular thought, sensation, image, or memory.	May help clients be able to let go of the struggle with attempting to understand or more make sense of the psychedelic experience in the moment, to help them engage more fully therapy.
<i>Acceptance</i>	Hayes et al., 2012	Allow thoughts and feelings to come and go without trying to change them.	Helpful for navigating challenging experiences. Participants could be cued to engage in acceptance during difficult moments.
<i>Present moment awareness</i>	Harris, 2009, p. 156	Involves paying attention to one's moment by moment experience (internally and externally)	Helpful for clients who get caught up in repetitive thinking, catastrophic worry, or otherwise unable to return to the psychedelic experience.

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- Psychological Support in Psychedelic Research
- Concepts from Different Paradigms
- *Support vs. Therapy*







Guy Goodwin, MD  
Oxford, England



Max Wolff, PhD  
Berlin, Germany



Guy Goodwin, MD  
Compass Pathways



Max Wolff, PhD  
MIND Foundation

COI?



Evans, 2023



“There are other reasons to think of the clinical effects as being more related to the drug than the psychotherapy. And the first of these considerations is that drugs, unlike psychotherapy, have a very clear dose-response relationship. The higher the dose, the more the effect.”



## Synthetic Psilocybin

**25 mg**  
(N=79)

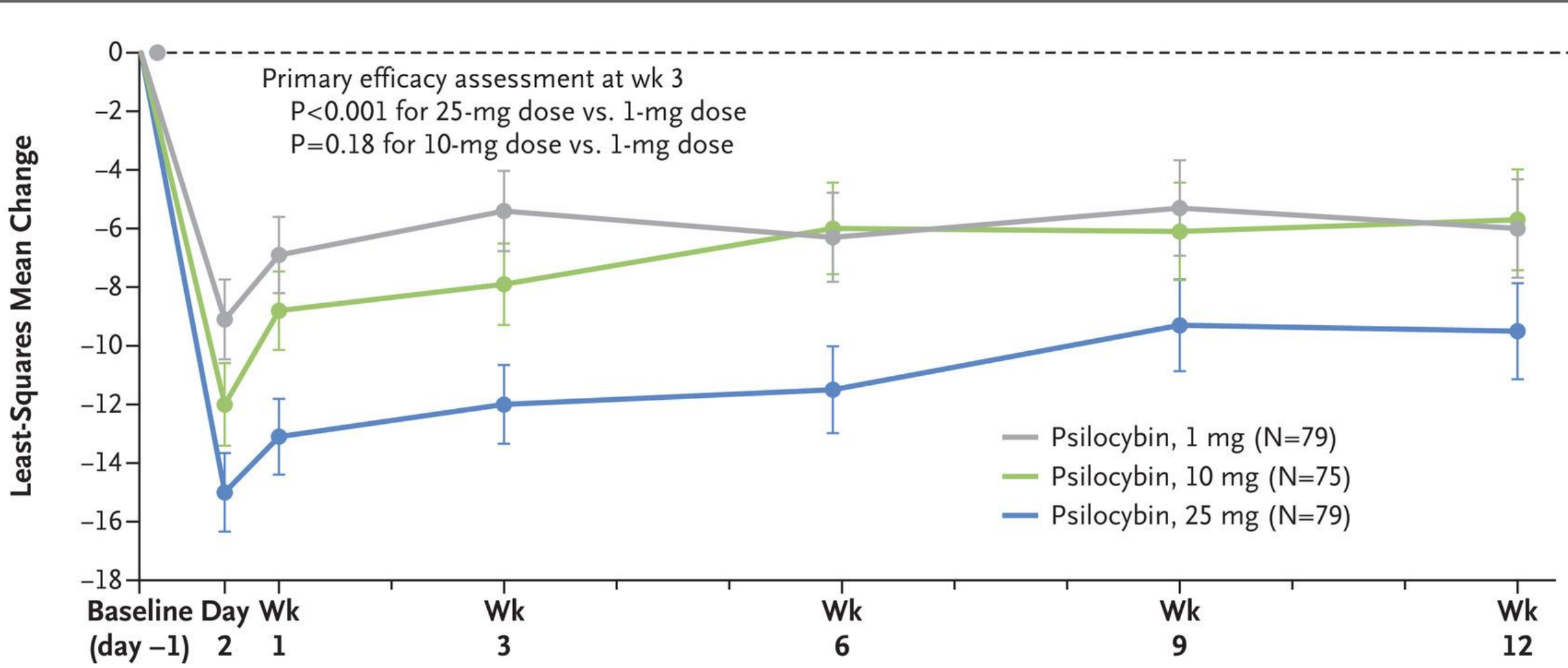


**10 mg**  
(N=75)



**1 mg**  
(N=79)

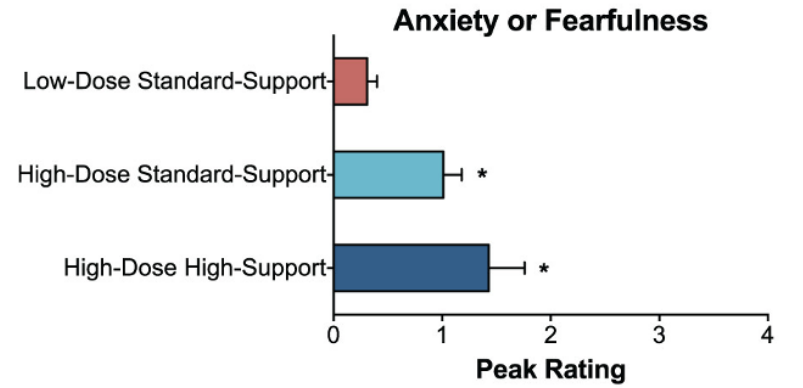
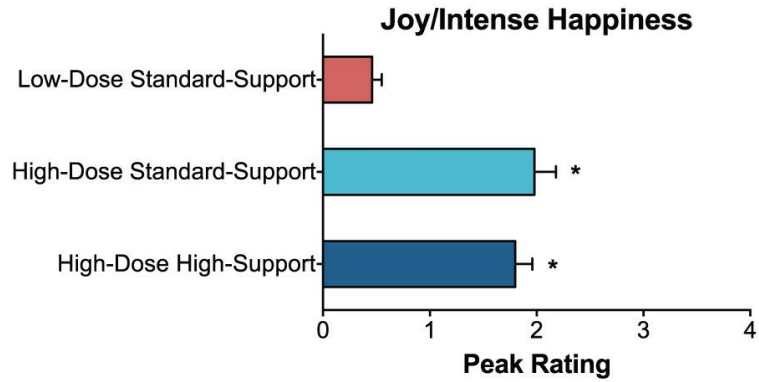
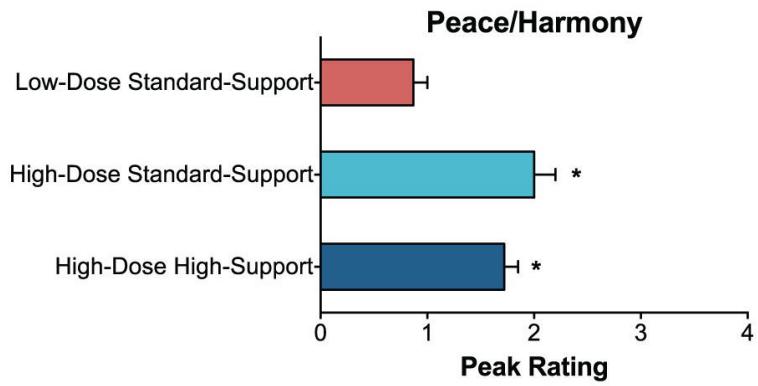




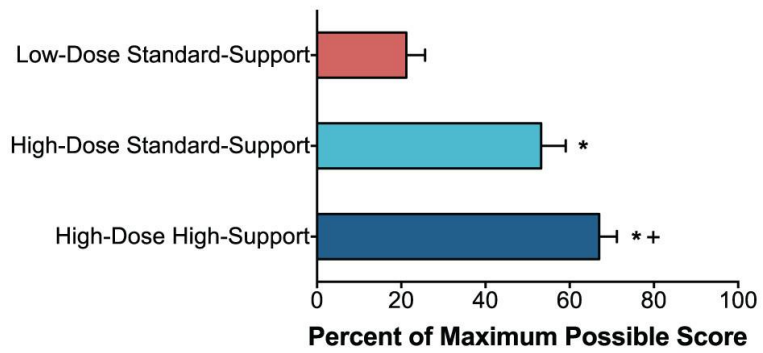


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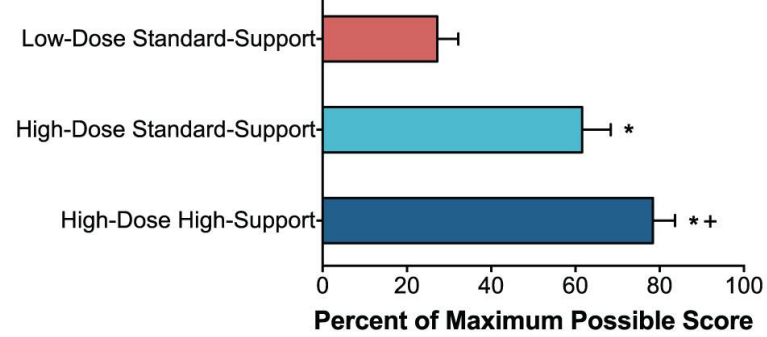
<b>Low-Dose</b>	<b>High-Dose</b>	<b>High-Dose</b>
<b>Standard-Support</b>	<b>Standard-Support</b>	<b>High-Support</b>
<b>(N=25)</b>	<b>(N=25)</b>	<b>(N=25)</b>
1 mg + 1 mg	20 mg + 30 mg	20 mg + 30 mg Journaling + Meditation



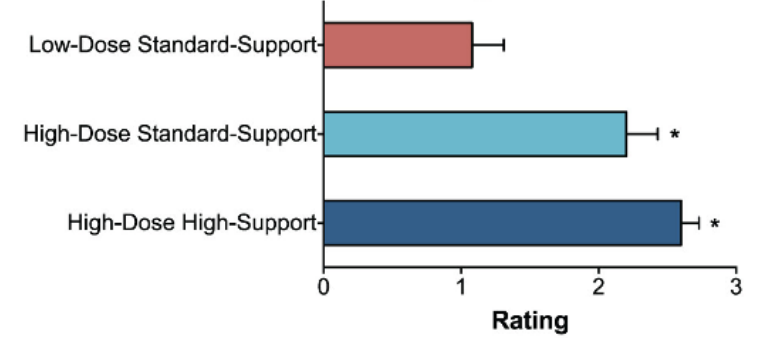
**Altruistic/Positive Social Effects**



**Positive Behavior Changes**



**Did the experience change your sense of well-being or life satisfaction?**





“I think the ‘psychedelic assisted psychotherapy’ is a too pervasive expression. And while we're far from understanding how serotonergic drugs work, we should use more neutral terminology and not anticipate the outcomes we may desire but cannot prove.”

“Dr Max Wolff, in response, argued that psychedelic treatments, good ones anyway, always do involve psychotherapy. He pointed out that Compass Pathways’ own trial protocol emphasized the importance of the ‘therapeutic process’ – it says:

*‘Participants are encouraged to describe and connect with the range of emotional, cognitive and physical experiences of the psilocybin session and relate to them to their personal narrative.’*

Dr Wolff concluded: “This sounds a lot like psychotherapy.””





There are any number of medical interventions, including throughout psychiatry, that don't *require* pairing psychotherapy.

...But psychotherapy almost always helps.

# Psychedelic Scientific and Ethical Exceptionalism (PSEE)?



Katherine Cheung  
*NYU*



Kyle Patch  
*NIH*



Brian Earp  
*University of Oxford*





# Psychedelic Scientific and Ethical Exceptionalism (PSEE)?

“Although we argue that some issues should not be treated as exceptional, in the sense of being categorically different or unique, they are nonetheless important and deserving of attention and caution.”

# Psychedelic Scientific and Ethical Exceptionalism (PSEE)?

“Instead of treating psychedelics in an exceptional manner, we can take the new era of psychedelic science as an opportunity to redouble our efforts on applying existing concepts, guidelines, and standards in psychedelic research and clinical applications.”

# Psychedelic Scientific and Ethical Exceptionalism (PSEE)?

“Instead of treating psychedelics in an exceptional manner, we can take the new era of psychedelic science as an opportunity to redouble our efforts on applying existing concepts, guidelines, and standards in psychedelic research and clinical applications.”



# Thank you!

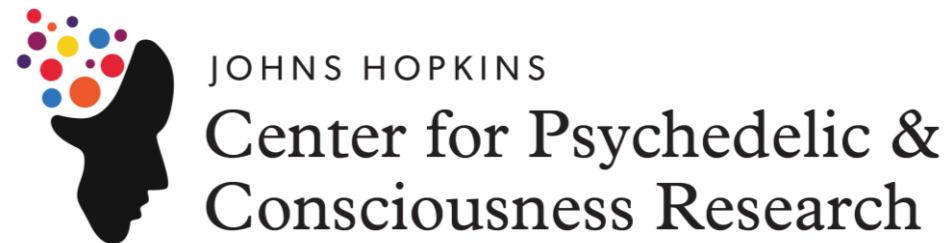
## MEET THE TEAM



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JOHNS HOPKINS  
SCHOOL of MEDICINE



# Session 5: Set and Setting

## *Presenters:*

- **Ido Hartogsohn, PhD**, Bar-Ilan University
- **David Yaden, PhD**, Johns Hopkins University

## *Respondents:*

- **Brian Anderson, MD**, University of California, San Francisco
- **Javier Muniz, MD**, U.S. Food and Drug Administration

# Session 6: Overview of FDA Regulatory Authority

- **Tiffany Farchione, MD**, U.S. Food and Drug Administration

# Limitations of FDA's Regulatory Authority

**Tiffany R. Farchione, MD\***  
Director, Division of Psychiatry  
Office of Neuroscience

February 1, 2024

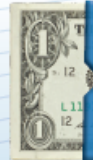
*\*No financial interests to disclose.*

## FDA REGULATED PRODUCTS AND FACILITIES

FDA oversees the safety of more than

**\$3.6 trillion**

worth of food, tobacco, and medical products produced in the U.S. and abroad.



FDA-regulated products account for about **21 cents** of every dollar spent by U.S. consumers.



There are over 20,000 prescription drug products approved for marketing.

About 82% of active pharmaceutical ingredient manufacturers are located outside of the U.S.

FDA oversees over 6,500 different medical device products.

About 47% of medical devices used in the U.S. are imports.

There are about 1,600 FDA-approved animal products.

About 8% of animal product sales are imports.

There are about 896 FDA-licensed biologics products.

About 80% of biologics sales are imports.



FDA regulates about 78% of the U.S. food supply; except meat, poultry, and some egg products.

About 60% of fresh fruit, 39% of vegetables, and 92% of seafood consumption by volume are imports.

FDA regulations cover about:

- 35,000 produce farms
- 300,000 restaurant food establishments
- 10,500 vending machine operators



FDA oversees over 100,000 tobacco products, not including ENDS.

About 4% of tobacco product sales are imports.

FDA-regulated products are manufactured or handled at nearly 280,000 registered facilities, more than half of which are outside of the U.S.

### FDA-Registered Facilities

Program	Domestic	Foreign	Total
Animal Drugs	985	720	1,705
Animal Food	17,969	8,204	26,173
Biologics	5,226	649	5,875
Human Drugs	4,577	3,843	8,420
Human Food	84,886	122,678	207,564
Medical Devices	13,010	12,891	25,901
Tobacco	1,559	0	1,559
<b>Total</b>	<b>128,212</b>	<b>148,985</b>	<b>277,197</b>

FDA-regulated products account for 14% of U.S. imports and 17% of exports.

### U.S. Imports and Exports by FDA Program

Program	Imports (Billions)	Exports (Billions)
Animal Food	\$4.50	\$7.24
Biologics	\$46.91	\$34.85
Human & Animal Drugs	\$107.90	\$34.26
Human Food & Cosmetics	\$217.10	\$151.20
Medical Devices	\$83.04	\$49.27
Tobacco	\$1.82	\$0.23
<b>FDA Total</b>	<b>\$461.27</b>	<b>\$277.05</b>
<b>USA Total</b>	<b>\$3,254.27</b>	<b>\$1,747.05</b>

FDA, an agency within the U.S. Department of Health and Human Services, protects public health by regulating human and veterinary drugs, vaccines and other biological products, medical devices, our nation's food supply, cosmetics, dietary supplements, electronic radiation emitting products, and tobacco products.



# Some Things We *Don't* Regulate

- Psychotherapy
- The practice of medicine

# Role of Psychotherapy

- Many of the psychedelic development programs involve administering the investigational drug then engaging in psychotherapy either while the subject is experiencing the acute effects of the drug or in a subsequent session
- This additional variable both complicates the assessment of effectiveness and presents a challenge for any future product labeling

# Example Psychedelic Psychotherapy Components

## Preparatory 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

Goal: Prepare patient for drug treatment, build trust/rapport establish intentions/goals

## Drug Treatment Session

- 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

Goal: Reduce adverse psychological reactions, facilitate therapeutic session

## Integrative Psychotherapy

- 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: Ensure psychological stability, process and integrate experience

# 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 ... <b>should be part of a comprehensive management program that includes psychosocial support.</b> ”
Bupropion hydrochloride extended-release tablets for smoking cessation	Dosage and Administration	“It is important that patients continue to receive <b>counseling and support throughout treatment ... and for a period of time thereafter.</b> ”
Buprenorphine sublingual tablets for opioid dependence	Clinical Studies	“All trials used <b>buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program.</b> There were no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.”

# “Set and Setting”

- Set (Mindset)
  - Thoughts, mood, expectations, goals
- Setting
  - Physical and social environment
  - Deeply informed by the bond component of the therapeutic alliance
- What are the minimum requirements?
- How do we communicate this on a label?



# Monitor Credentials

- We can mandate certain credentials for clinical studies
- We do not have the authority to say that similar credentials will be needed for similar roles in the post-market setting

# Risk Evaluation Mitigation Strategies

- Drug **safety** programs FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks
- Focus on preventing, monitoring, and/or managing a specific serious risk by informing, educating, and/or reinforcing actions to reduce the frequency and/or severity of the event
- REMS are *not* intended to assure effectiveness



# If Not Us...Who?

- See Session 7...



# Session 7: Considerations for Potential Psychedelic Use in the Real World

## *Panelists:*

- **Richard C. Dart, MD, PhD**, Denver Health and Hospital Authority
- **Mason Marks, MD, JD**, Harvard Law School
- **Mark H. Rapaport, MD**, University of Utah School of Medicine
- **Lisa Robin, MLA**, Federation of State Medical Boards
- **Marta Sokolowska, PhD**, U.S. Food and Drug Administration
- **Ilse Wiechers, MD, MPP, MHS**, U.S. Department of Veterans Affairs



# Thank you!

Meeting materials will be posted on  
our website: [www.reaganudall.org](http://www.reaganudall.org)

