Advancing Psychedelic Clinical Study Design

The meeting will begin shortly

REAGAN-UDALL FOUNDATION FOR THE FDA

Funding Disclosure: This activity is one part of a multi-part Foundation project related to substance use disorder.
The multi-part project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of an overall award of $1,720,109 of federal funds (100% of the project). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA, HHS, or the U.S. Government. For more information, please visit FDA.gov.

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Welcome

Susan C. Winckler, RPh, Esq.
Chief Executive Officer
Reagan-Udall Foundation for the FDA

Thank you for joining

REAGAN-UDALL FOUNDATION FOR THE FDA

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)

REAGAN-UDALL FOUNDATION FOR THE FDA

10 a.m.	Welcome & Introduction
10:05 a.m.	Opening Remarks
10:15 a.m.	Session 1: Overview of FDA's Psychedelics Clinical Investigation Guidance
10:40 a.m.	Session 2: Psychedelics Study Design, Control Conditions, and Blinding
11:40 a.m.	Break
11:50 a.m.	Session 3: Dosing
1 p.m.	Session 4: Durability of Treatment Response
2 p.m.	Adjourn

REAGAN-UDALL FOUNDATION FOR THE FDA

Opening Remarks

Patrizia Cavazzoni M.D.
Director
Center For Drug Evaluation And Research
U.S. Food and Drug Administration

Session 1: Overview of FDA's Psychedelics Clinical Investigation Guidance

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

Psychedelic Drugs: Considerations for Clinical Investigations

An Overview of FDA's Draft Guidance for Industry

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

January 31, 2024

*No financial interests to disclose.

MARIJUANA MOMENT

FDA

TRAVEL

Are Psychede

BY MICHAELA TRIMBLE
January 22, 2024

Photographed by Arthur Elgort, *Vogue*, June

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HEALTH | PHARMA | HEARD ON THE STREET

Psychedelics Are Going Mainstream. Investing in
Hasn't.

Drugs like LSD have shown potential for treating psychiatric disorders. Wall Street and b
aren't convinced.

HIGH TIMES News Business Culture Events Grow Products IR

Researchers Using AI To Develop New Psychedelics

Researchers are using artificial intelligence to develop new drugs, including new psychedelics to use as antidepressants.

BY A.J. HERRINGTON · JANUARY 22, 2024

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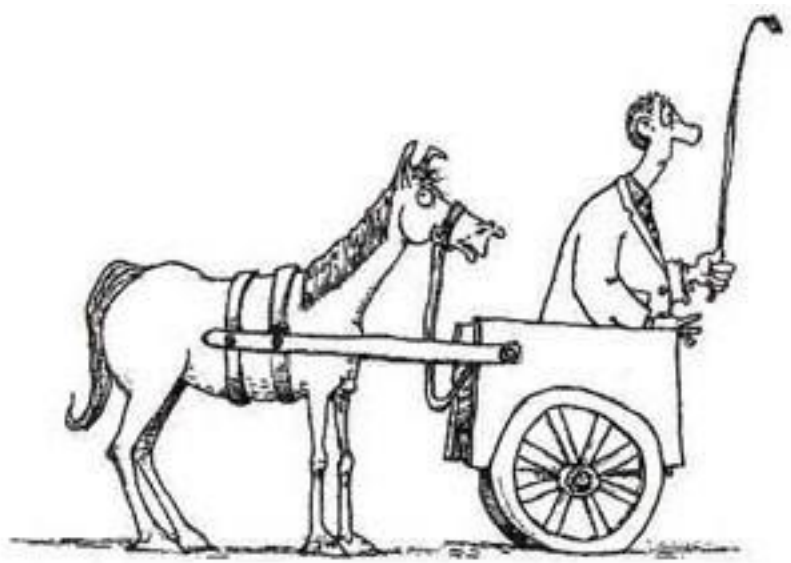


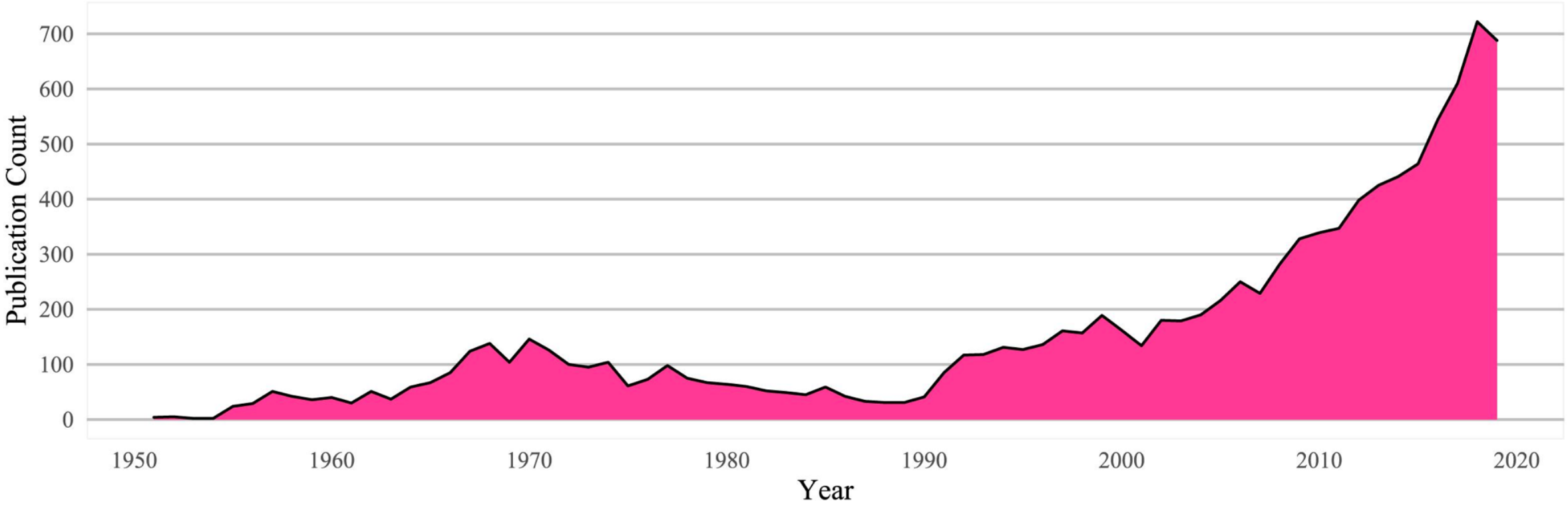
BLUF

- Psychedelic drug development programs are subject to the same regulations and same evidence standards as every other drug development program.

Overview

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

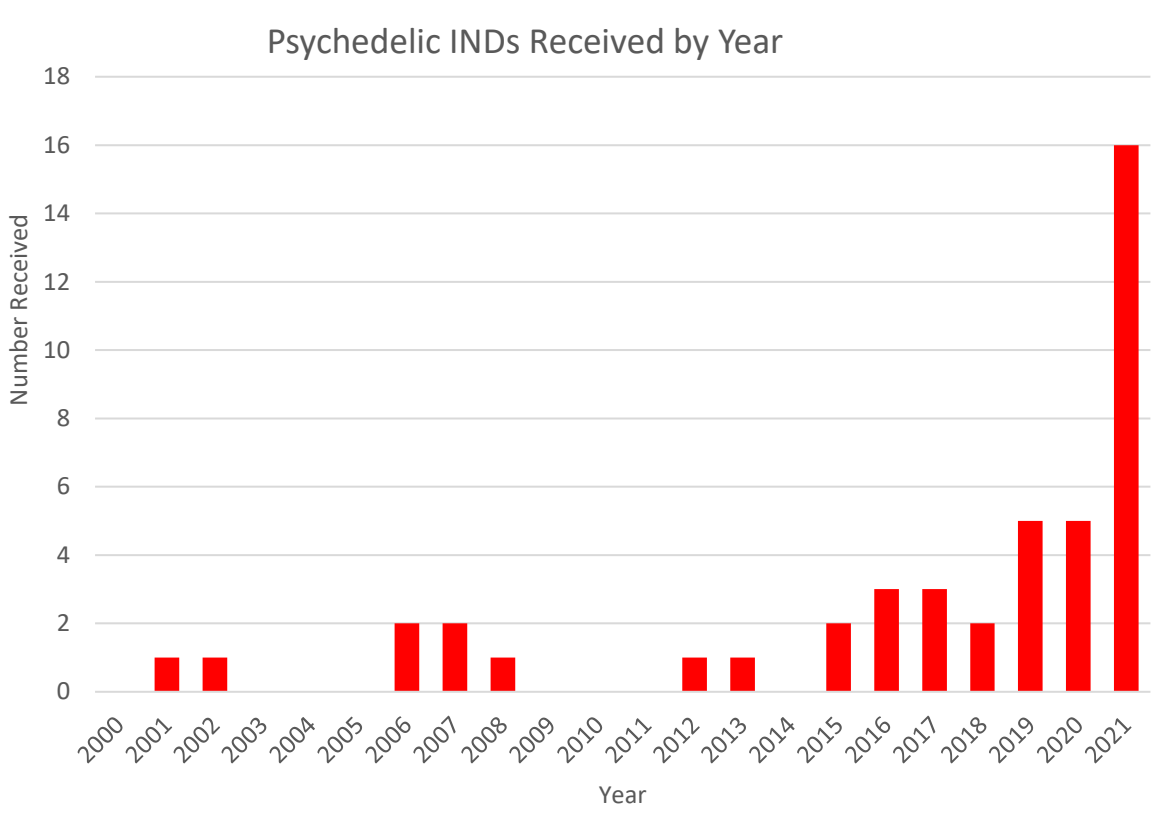
Psychedelic Publications by Year

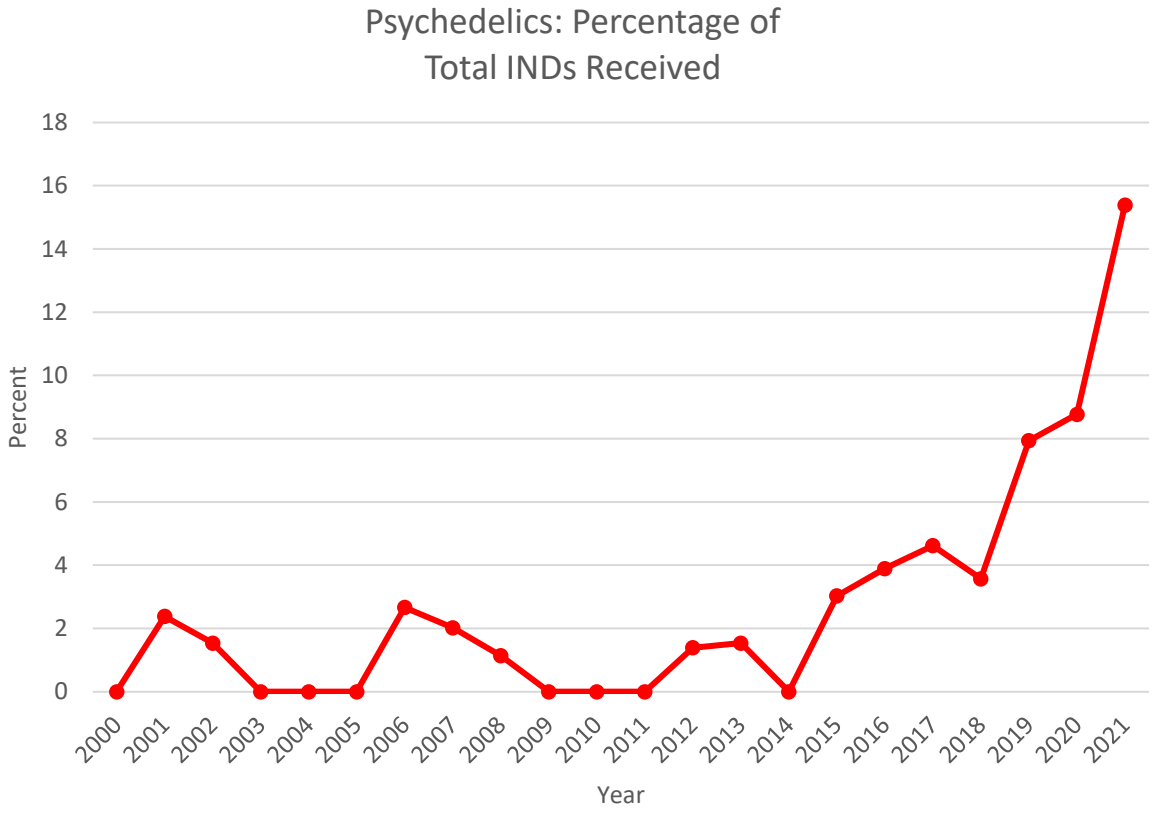


Petranker, R., et al. (2020). Psychedelic research and the need for transparency: Polishing Alice's Looking Glass. *Frontiers in psychology*, *11*, 1681.

Current FDA Landscape

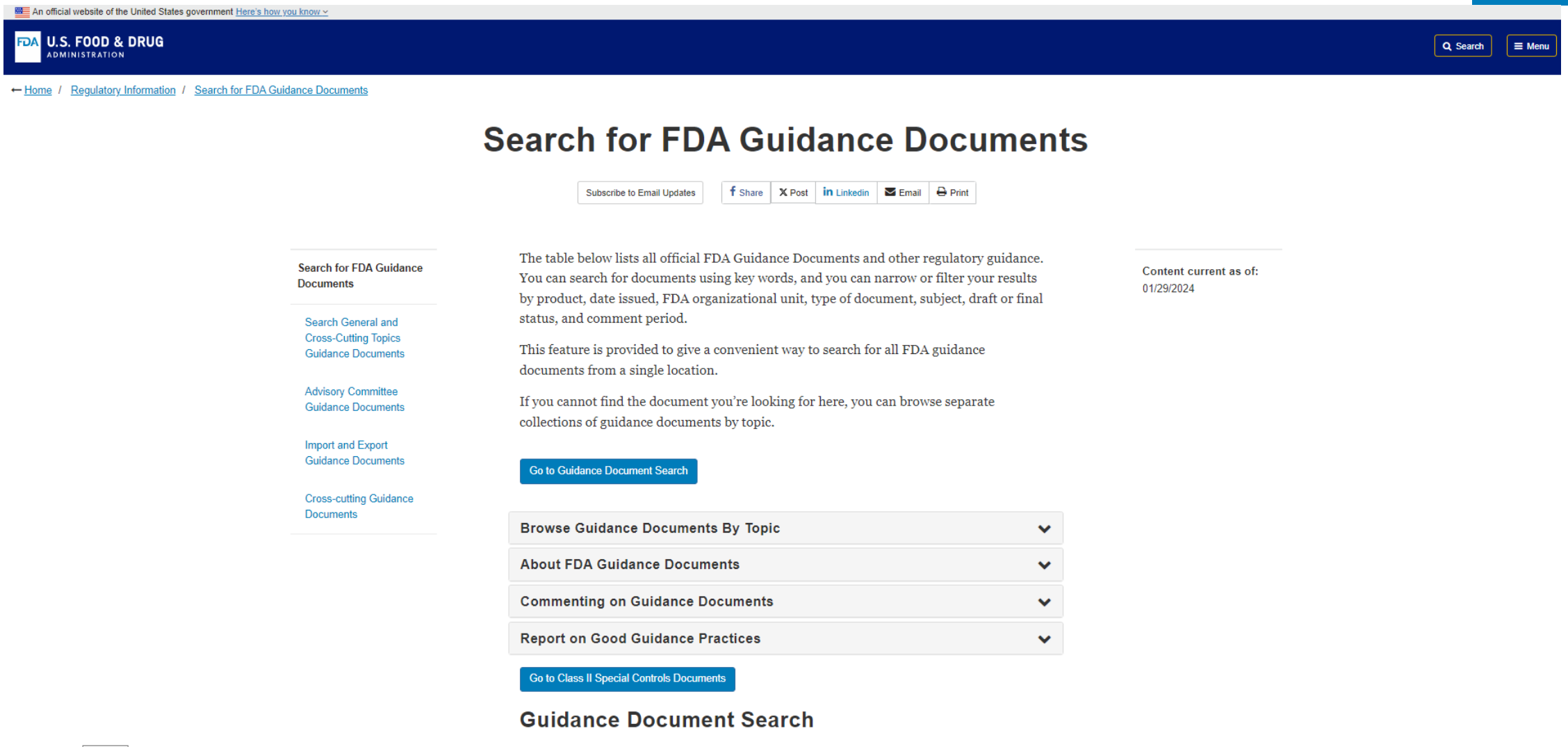
New IND Applications to DP: 2000 to 2021





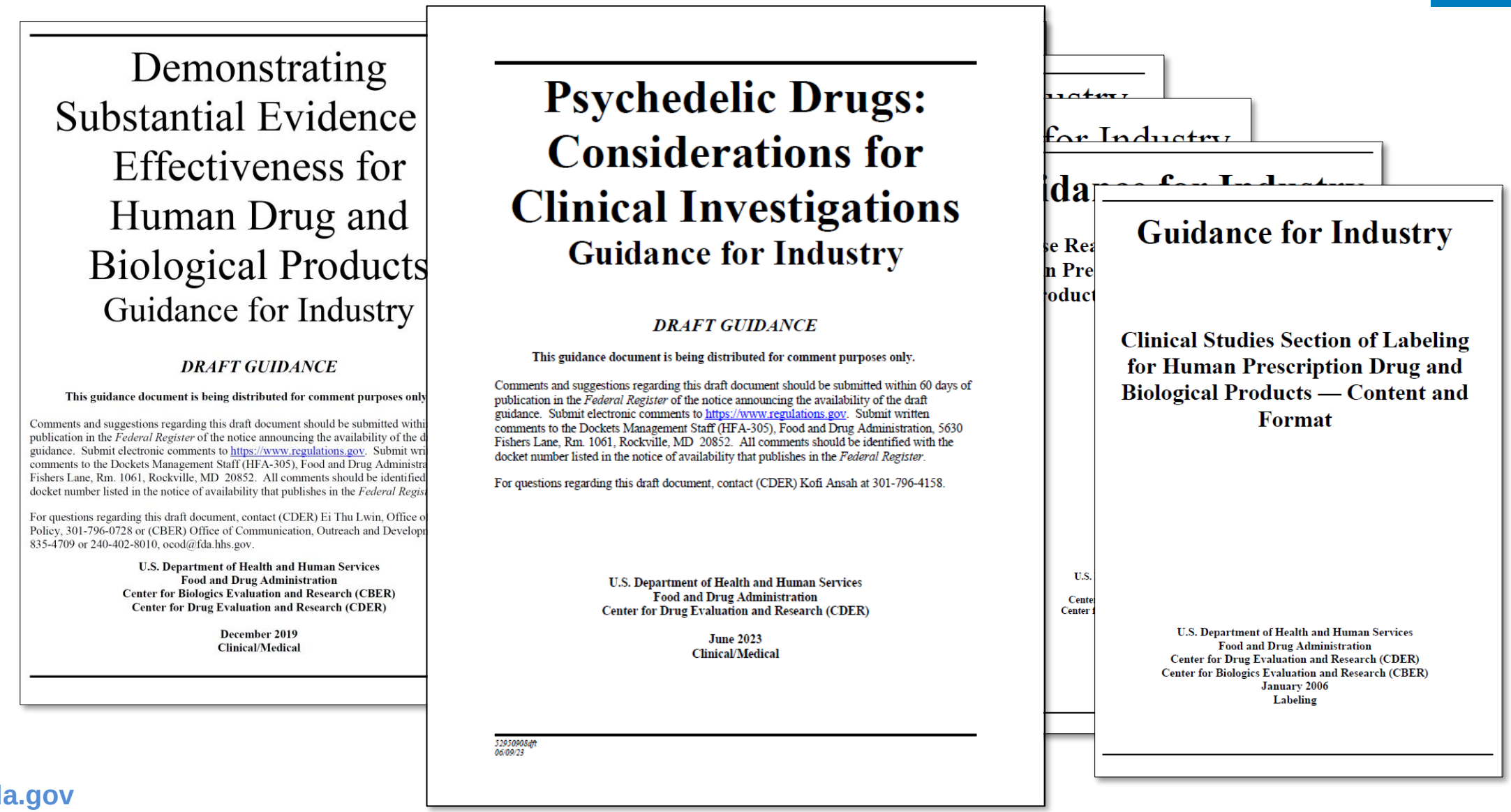
Unpublished internal analysis; includes research and commercial INDs
Psychedelics included: ayahuasca, DMT, LSD, MDMA, psilocybin

FDA Guidance



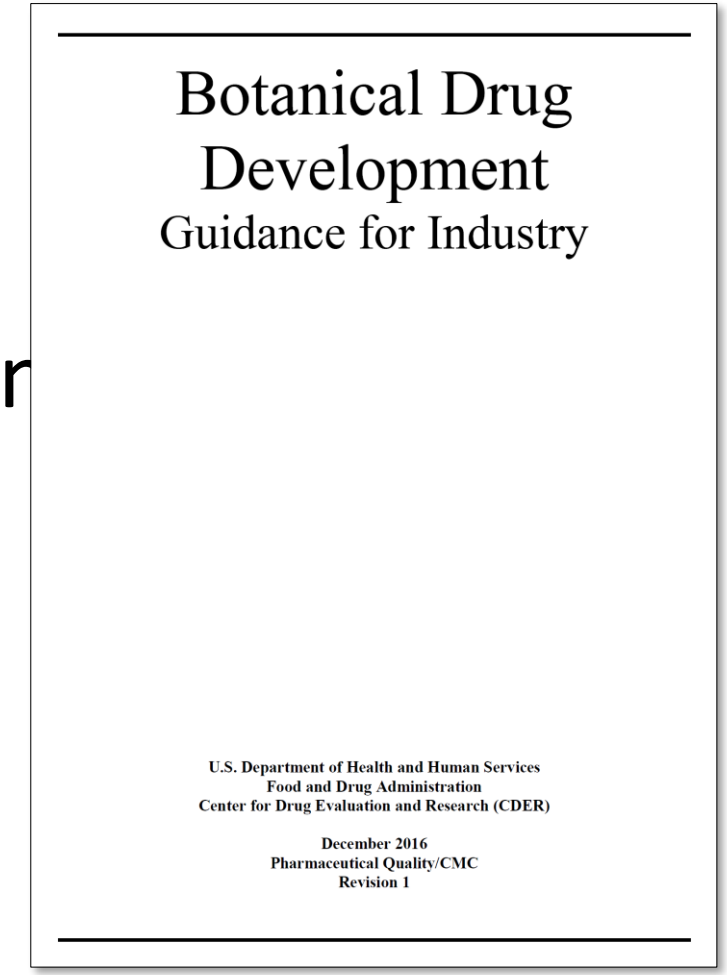
https://www.fda.gov/regulatory-information/search-fda-guidance-documents

Clinical Framework



Chemistry, Manufacturing, and Controls

- Standardized experimental compound with known chemistry and synthesis
- Own data or by right of reference
- For a botanical substance, conformation with the chemistry section of the 2016 FDA guidance for industry: *Botanical Drug Development*


Botanical Drug Development
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2016
Pharmaceutical Quality/CMC
Revision 1

Chemistry, Manufacturing, and Controls

- Current Good Manufacturing Practice (CGMP)
  - 21 CFR 210.2(c)- Phase 1 exempt from CGMP
  - 21 CFR 211- Phase 2 and 3 product in CGMP facility
- Guidance for Industry:
  - CGMP for Phase 1 Investigational Drugs- July 2008
  - INDs for Phase 2 and 3 Studies; Chemistry, Manufacturing, and Controls Information

Nonclinical Studies

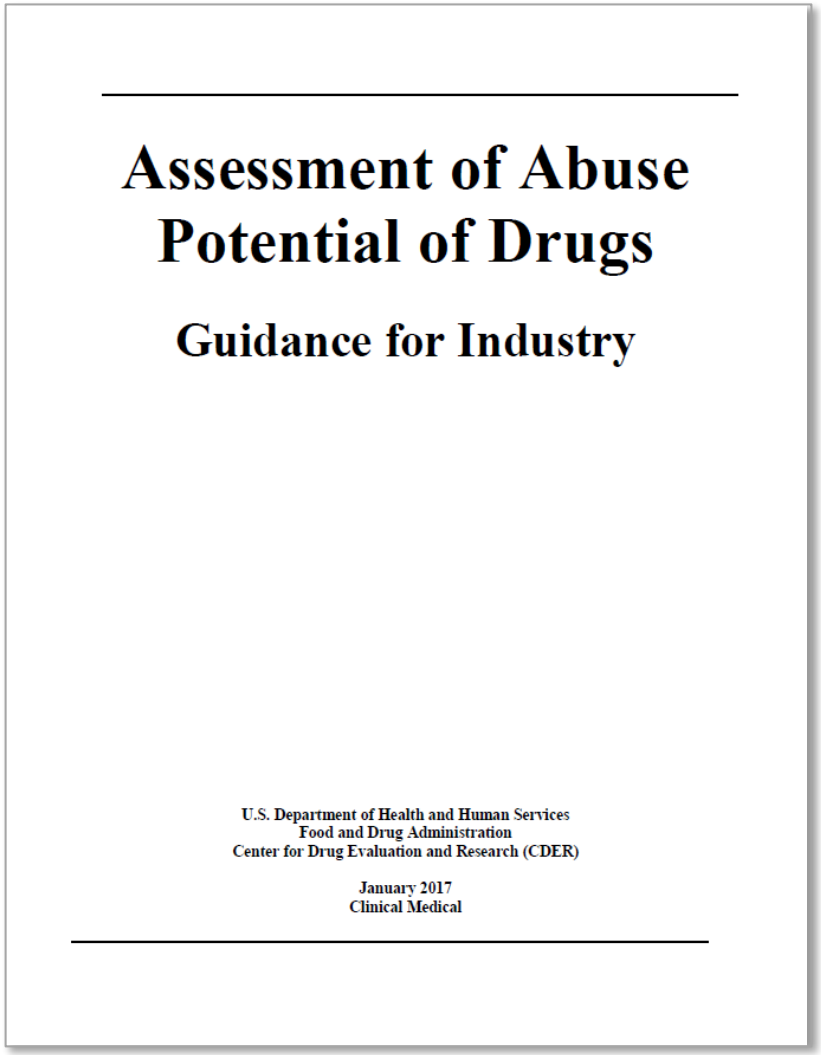
- Appropriate studies described in FDA and International Council for Harmonization (ICH) guidances (e.g., ICH M3(R2))
- If extensive human exposure, may be able to initiate studies
- Evaluate 5-HT receptor binding
- Number and type of nonclinical studies will largely depend on treatment paradigm

Clinical Pharmacology

- Food effect, drug-drug interactions, drug-disease interactions (e.g., organ impairment)
- Exclude valvulopathy and pulmonary hypertension
- Pharmacodynamic interactions
  - Acute vs chronic SSRIs, MAOIs
  - Chronic TCAs, lithium
- Characterize dose response relationship

Abuse Potential Assessment

- Currently Schedule I
- Abuse potential assessment would assist in determining appropriate rescheduling if approved
- Investigators need DEA registration to conduct research with Schedule I drugs



Assessment of Abuse Potential of Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Clinical Medical

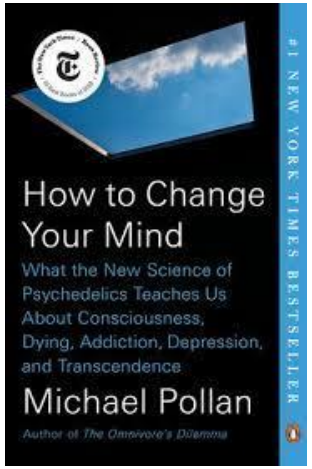
Clinical Considerations

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

Adequate & Well-Controlled Studies

- Select 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**.

Making Valid Comparisons

- "Inactive" placebo
  - Nocebo?
- "Active" placebo
  - Other psychoactive drugs
  - Subperceptual doses of psychedelic drugs

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

Monitoring Requirements

- Observation by two monitors for the duration of the treatment session
  - Lead Monitor: A healthcare provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently. Examples of acceptable professional credentials include:
    - Clinical or counseling psychologist (PhD or PsyD)
    - Psychiatrist or other physician (MD or DO)
    - Master of Social Work (MSW)
    - Licensed Clinical Professional Counselor (LCPC)
    - Licensed Marriage and Family Therapist (LMFT)
    - Psychiatric Nurse Practitioner (Psychiatric NP)
  - Assistant monitor: Bachelor's degree with at least one year of clinical experience in a licensed mental health care setting.
- If lead monitor not a physician, a licensed physician must be on call and able to reach the clinical site within 15 minutes in the event of a medical emergency

Additional Challenges

- Poorly understood dose-response relationship
- Need to understand durability of response to inform timeframe for repeat dosing
- How might risk mitigation strategies used in clinical trials translate into clinical practice?
- Consider public health effects as part of overall benefit-risk assessment


FUTURE AHEAD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Session 2: Psychedelics Study Design, Control Conditions, and Blinding

Presenters:

- **Suresh Muthukumaraswamy, PhD,** University of Auckland
- **Franz Vollenweider, MD,** University of Zürich

Panelists:

- **Matt Butler, MD,** King's College London
- **Michael Davis, MD, PhD,** Usona Institute
- **Bernard Fischer, MD,** U.S. Food and Drug Administration

Advancing Psychedelic Clinical Study Design
31st January 2024

Challenges for Psychedelic Clinical Trial Design

Associate Professor Suresh Muthukumaraswamy

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Intellectual credit to:

Dr Rachael Sumner
Dr Anna Forsyth
Dr Tehseen Noorani

Intellectual blame rests with me

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Disclosures

Research Funding from:
MindBio Therapeutics Ltd
atai Life Sciences
Health Research Council of New Zealand

Source Material

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2021.1933434

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REVIEW

http://www.tandfonline.com

Blinding and expectancy confounds in psychedelic randomized controlled trials

Suresh D. Muthukumaraswamy[a], Anna Forsyth[a] and Thomas Lumley[b]

[a]School of Pharmacy, The University of Auckland, Auckland, New Zealand; [b]Department of Statistics, The University of Auckland, Auckland, New Zealand

ABSTRACT

Introduction: There is increasing interest in the potential for psychedelic drugs such as psilocybin, LSD and ketamine to treat several mental health disorders, with a growing number of randomized controlled trials (RCTs) being conducted to investigate the therapeutic effectiveness of psychedelics.

Areas covered: We review previous literature on expectancy effects and blinding in the context of psychedelic RCTs – literature which strongly suggest that psychedelic RCTs might be confounded by de-blinding and expectancy. We conduct systematic reviews of psychedelic RCTs using Medline, PsychInfo and EMBASE (Jan 1990 – Nov 2020) and show that currently reported psychedelic RCTs have generally not reported pre-trial expectancy, nor the success of blinding procedures.

Expert opinion: While psychedelic RCTs have generally shown promising results, with large effect sizes reported, we argue that treatment effect sizes in psychedelic RCTs are likely over-estimated due to de-blinding of participants and high levels of response expectancy. We suggest that psychedelic RCTs should routinely measure de-blinding and expectancy. Careful attention should be paid to clinical trial design and the instructions given to participants to allow these confounds to be reduced, estimated and removed from effect size estimates. We urge caution in interpreting effect size estimates from extant psychedelic RCTs.

ARTICLE HISTORY
Received 10 March 2021
Accepted 19 May 2021

KEYWORDS
Psychedelics; randomized controlled trials; LSD; ketamine; psilocybin; causation; blinding; masking; placebo effect

Psychological Medicine

cambridge.org/psm

Review Article

Cite this article: Noorani T, Bedi G, Muthukumaraswamy S (2023). Dark loops: contagion effects, consistency and chemosocial matrices in psychedelic-assisted therapy trials. *Psychological Medicine* 1–10. https://doi.org/10.1017/S0033291723001289

Received: 19 December 2022
Revised: 5 April 2023
Accepted: 13 April 2023

Keywords:
Psychedelic; clinical trials; hype; chemosociality; dark loops; chemosocial minimisation; chemosocial description; chemosocial valorisation

Corresponding author:
Tehseen Noorani;
Email: tehseen.n.noorani@durham.ac.uk

Dark loops: contagion effects, consistency and chemosocial matrices in psychedelic-assisted therapy trials

Tehseen Noorani[1], Gillinder Bedi[2,3] and Suresh Muthukumaraswamy[4]

[1]Department of Anthropology, Durham University, Durham, UK; [2]Orygen, Parkville, VIC, Australia; [3]Center for Youth Mental Health, University of Melbourne, Parkville, VIC, Australia and [4]School of Pharmacy, University of Auckland, Auckland, New Zealand

Abstract

What happens when an emerging programme of medical research overlaps with a surging social movement? In this article we draw on the anthropological term 'chemosociality' to describe forms of sociality born of shared chemical exposure. Psychedelic administration in the context of recent clinical trials appears to have been particularly chemosocial in nature. We argue that one consequence is that psychedelic-assisted therapy (PAT) clinical research trials tend to breach key assumptions underlying the logic of causal inference used to establish efficacy. We propose the concept of *dark loops* to describe forms of sociality variously emerging from, and impacting participant experiences in, PAT trials. These dark loops are not recorded, let alone incorporated into the causal pathways in the interpretation of psychedelic trial data to date. We end with three positions which researchers might adopt in response to these issues: *chemosocial minimisation* where research is designed to attenuate or eliminate the effects of dark loops in trials; *chemosocial description* where dark loops (and their impacts) are openly and candidly documented and *chemosocial valorisation* where dark loops are hypothesised to contribute to trial outcomes and actively drawn upon for positive effect. Our goal is to fold in an appreciation of how the increasingly-discussed hype surrounding psychedelic research and therapeutics continues to shape the phenomena under study in complex ways, even as trials become larger and more rigorous in their design.

Viewpoint

ANZJP

Australian & New Zealand Journal of Psychiatry
1–6
DOI: 10.1177/00048674221081763

The challenges ahead for psychedelic 'medicine'

Suresh Muthukumaraswamy, Anna Forsyth and Rachael L Sumner

Abstract

With the extensive public, commercial and scientific interest from what has been widely termed the psychedelic renaissance, it is important that the scientific practices and results obtained from its implementation into medicine are put under a critical microscope. While there are numerous works on the potential benefits and applications of psychedelics as medicines, relatively little has been written about the challenges this field will face when incorporated into modern medical practice. Indeed, as a new or at least revived area of investigation, psychedelic medicine has a particular set of challenges which need to be addressed. In this viewpoint, we identify a number of these challenges. First, challenges related to the design of individual research studies are discussed, particularly focusing on current practices surrounding blinding, expectancy, the use of therapy and sources of bias. Second, the broader context of the research environment is considered, including how medical science typically establishes evidence, funding bodies and the impact of psychedelics being scheduled at odds with their risk profile. Finally, we describe challenges relating to the implementation of psychedelic therapies into modern medicine, considering the social and economic context. Alongside, we provide suggestions for what could be included into current research protocols to mitigate these challenges.

Keywords
Psychedelic medicine, mental health, research design

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2023.2279736

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Taylor & Francis Group

PERSPECTIVE

Overcoming blinding confounds in psychedelic randomized controlled trials using biomarker driven causal mediation analysis

Suresh D Muthukumaraswamy

School of Pharmacy, The University of Auckland, Auckland, New Zealand

ABSTRACT

Introduction: There is great interest in the use of psychedelic-assisted therapies to treat a range of mental health conditions and initial randomized controlled trials (RCTs) have generated positive results. However, the effect sizes reported in psychedelic RCTs are likely inflated due to expectancy effects due to the de-blinding of both participants and study personnel to treatment allocation caused by the distinctive psychoactive effects of psychedelic drugs.

Areas covered: An introduction to causal inference for RCTs, the underlying assumptions, and potential confounders along with graphical illustrations is provided. It is proposed that causal mediation analysis using objectively measured mediating biomarkers could be used to identify causal pathways between treatment and outcome in psychedelic RCTs, even with de-blinding of participants and give greater confidence as to the mechanistic basis and efficacy of psychedelic therapies.

Expert Opinion: It is argued that psychedelic therapies should not be approved as licensed medicines until causal pathways are clearly established between treatment and outcome. Potential downsides of doing so include, future indication expansion based on low quality clinical trial evidence, the approval of other therapies based on similarly low-quality evidence, and the potential for efficacy to change over time after approvals has been granted.

ARTICLE HISTORY
Received 7 June 2023
Accepted 1 November 2023

KEYWORDS
Psychedelics; randomized controlled trials; causal mediation analysis; blinding; masking; placebo effect

Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products

Guidance for Industry

Additional copies are available from:
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December 2019
Clinical/Medical

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148 **B. Scientific basis for the statutory standard**
149
150 To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other
151 influences, such as spontaneous change in the course of the disease, placebo effect, or biased
152 observation." [8] This is the basis for the statutory requirement that approval be based on adequate
153 and well-controlled investigations, as well as the basis for FDA's regulations describing the
154 characteristics of such investigations (i.e., design elements that are generally intended to
155 minimize bias and permit a valid comparison with a control to provide a quantitative assessment
156 of drug effect).
157

256
257 Poor execution can render a trial of any design to be not adequate or not well-controlled and,
258 therefore, unable to provide substantial evidence of effectiveness. Examples of this include (1) a
259 randomized, double-blind, placebo-controlled trial where there is extensive drop-out of trial
260 patients (with the potential for informative censoring), and (2) a randomized, double-blind,
261 placebo-controlled trial in which unblinding is common due to an effect of the test drug, and
262 where a modest treatment effect is found on a primary endpoint that is subject to bias when drug
263 assignment is known (e.g., a physician global impression). In these cases, the trials might not be
264 considered adequate and well-controlled.
265

An Exemplar Study

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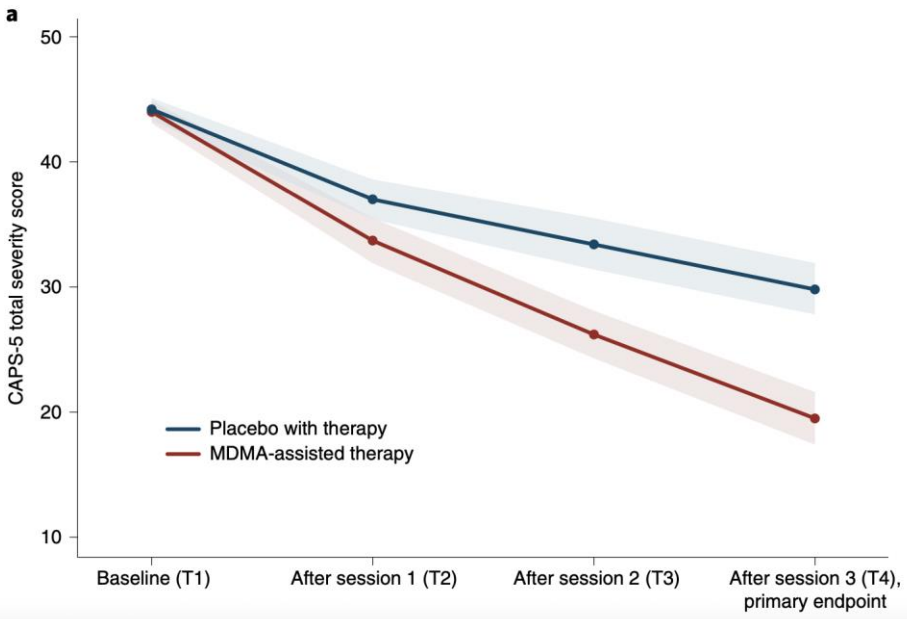
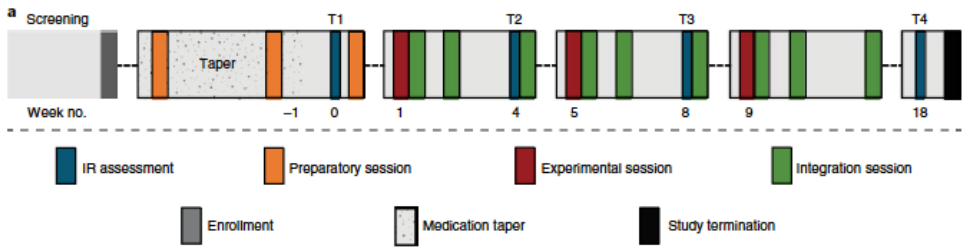
nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01336-3
Check for updates

OPEN

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study





effects[14]. However, although blinding was not formally assessed during the study, when participants were contacted to be informed of their treatment assignment at the time of study unblinding it became apparent that at least 10% had inaccurately guessed their treatment arm. Although anecdotal, at least 7 of 44 participants in the placebo group (15.9%) inaccurately believed that they had received MDMA, and at least 2 of 46 participants in the MDMA group (4.3%) inaccurately believed that they had received placebo.

We may soon be confronted with the potentially enormous

Is this study really “double-blind”?

Check for updates

OPEN

The difference between ‘placebo group’ and ‘placebo control’: a case study in psychedelic microdosing

Balázs Szigeti[1✉], David Nutt[1], Robin Carhart-Harris[2] & David Erritzoe[1]

In medical trials, ‘blinding’ ensures the equal distribution of expectancy effects between treatment arms in theory; however, blinding often fails in practice. We use computational modelling to show how weak blinding, combined with positive treatment expectancy, can lead to an uneven distribution of expectancy effects. We call this ‘activated expectancy bias’ (AEB) and show that AEB can inflate estimates of treatment effects and create false positive findings. To counteract AEB, we introduce the *Correct Guess Rate Curve (CGRC)*, a statistical tool that can estimate the outcome of a perfectly blinded trial based on data from an imperfectly blinded trial. To demonstrate the impact of AEB and the utility of the CGRC on empirical data, we re-analyzed the ‘self-blinding psychedelic microdose trial’ dataset. Results suggest that observed placebo-microdose differences are susceptible to AEB and are at risk of being false positive findings, hence, we argue that microdosing can be understood as active placebo. These results highlight the important difference between ‘*trials with a placebo-control group*’, i.e., when a placebo control group is formally present, and ‘*placebo-controlled trials*’, where patients are genuinely blind. We also present a new blinding integrity assessment tool that is compatible with CGRC and recommend its adoption.

The Problem of Blinding and Expectancy

"Given the obvious psychoactive effects of psychedelic drugs, those in an active intervention group likely know they have received the treatment and may show greater treatment response due to expectancy effects."

"Those participants that receive a placebo intervention may know they have received the placebo and disappointment may decrease their placebo response."

Note: A "disappointment" response is different to a nocebo response. A nocebo response is when a patient's expectation of a negative effect from a treatment cause the treatment to have a more negative effect than otherwise.

Muthukumaraswamy, Forsyth & Lumley. Blinding and expectancy confounds in psychedelic randomised controlled trials. Expert Rev Clin Pharmacol (2021).

BBC’s “The Drug Trial”

The Randomised Control Trial

- The goal is to demonstrate safety and efficacy (causation)
- Fundamental Problem of Causal Inference (Rubin Causal Model)

$$ITE = Y_t(i) - Y_c(i)$$

$$E(Y_t) = E(Y_A \mid A = \mathrm{t})$$
$$E(Y_c) = E(Y_A \mid A = \mathrm{c})$$

ITE = Individual Treatment Effect
ATE = Average Treatment Effect
i = individual participants
t|c = treatment|control
Y = outcome
A = Intervention

$$ATE = E(ITE) = E(Y_t - Y_c) = E(Y_t) - E(Y_c)$$

Muthukumaraswamy, Forsyth & Lumley. Blinding and expectancy confounds in psychedelic randomised controlled trials. Expert Rev Clin Pharmacol (2021).

Causal Inference Assumptions

$$ATE = E(ITE) = E(Y_t) - E(Y_c)$$

Causal inference has formal statistical assumptions:

- No interference between participants $Y_i(\mathbf{a}_i) = Y_i(\boldsymbol{a}'_i)$ for any $\boldsymbol{a}$ *and* $\boldsymbol{a}'$
- No hidden variation of treatments $Y_i(a) = Y_i$ when $A_i = a$
- No hidden confounders $Y_i(a) \perp\!\!\!\perp A_i | C_i$
- Positivity $P(A_i) > 0$ for all a in A

See for example the book by Hernan and Robins (2020). Causal Inference: What If.

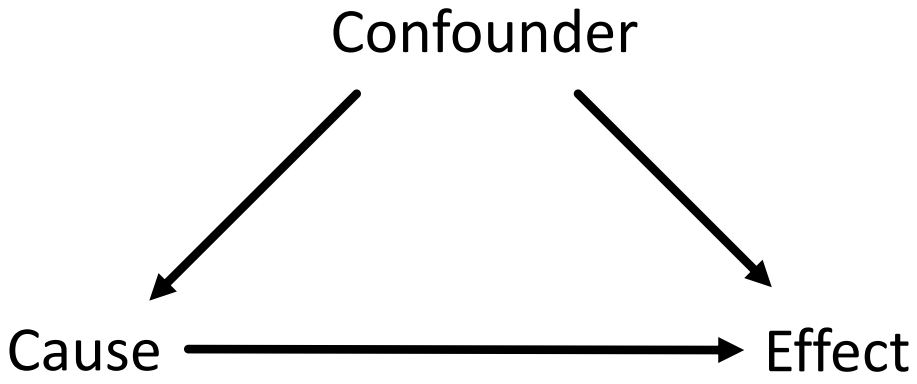
RCTs meet Causal Inference Assumptions by:

- Randomisation
- Sufficient sample size
- Allocation concealment
- Double-blinding

Blinding or masking is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on. The essential aim is to prevent identification of the treatments until all such opportunities for bias have passed."

Quote from the ICH Guidelines

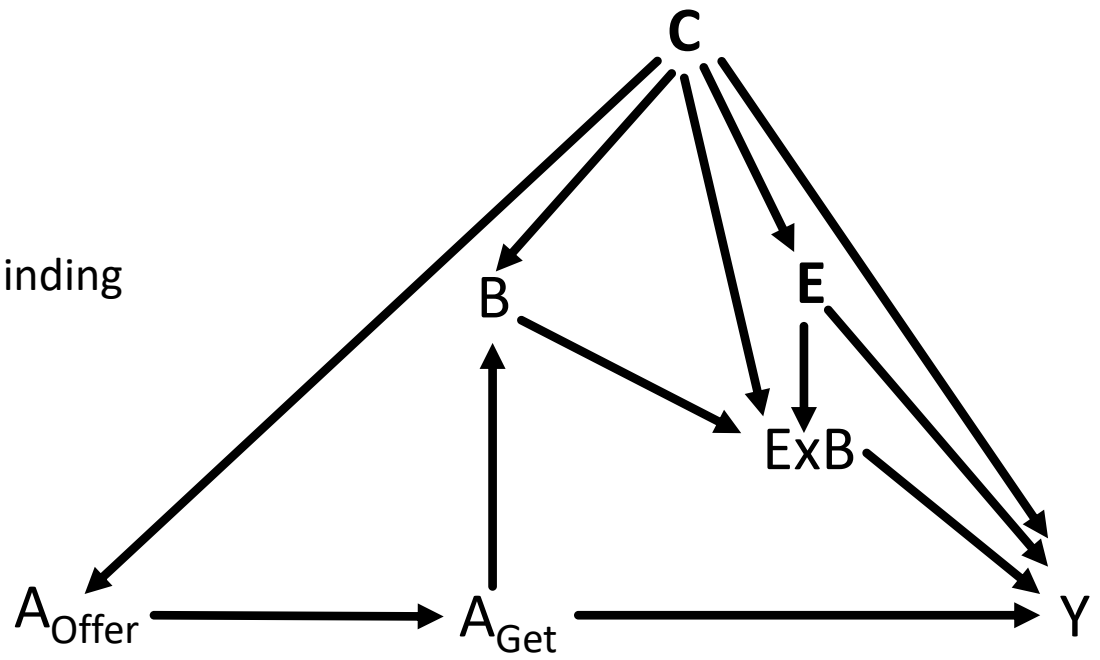
Causal Models in Diagram Format



Muthukumaraswamy. Overcoming blinding confounds in psychedelic randomized controlled trials using biomarker driven causal mediation analysis. Expert Rev Clin Pharmacol (2023).

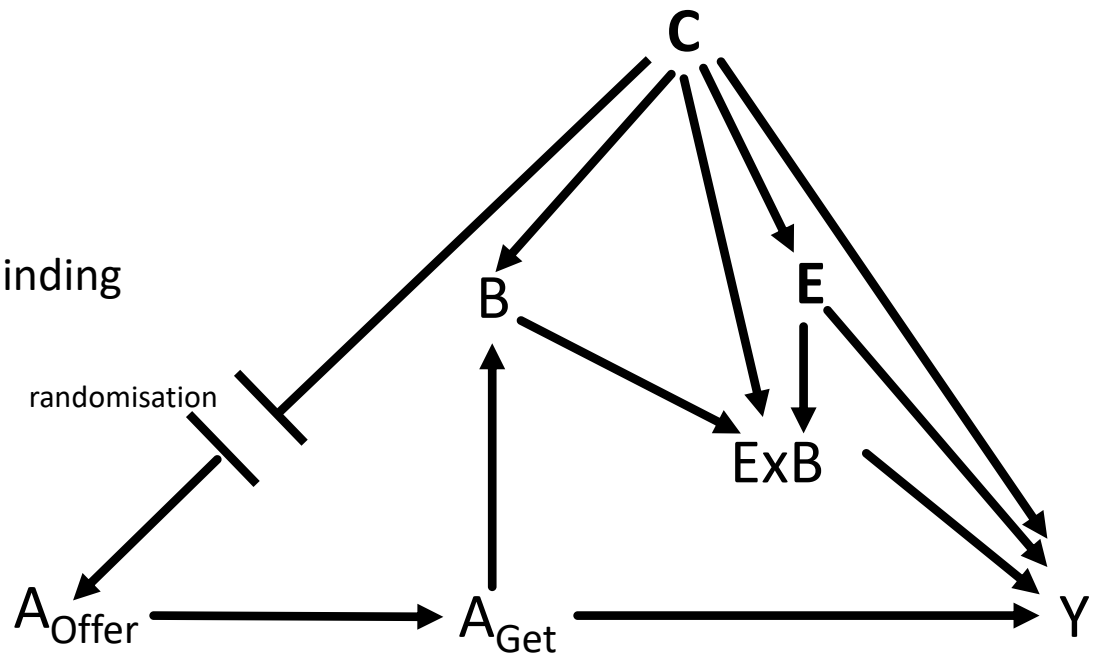
Casual Model for Treatment

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



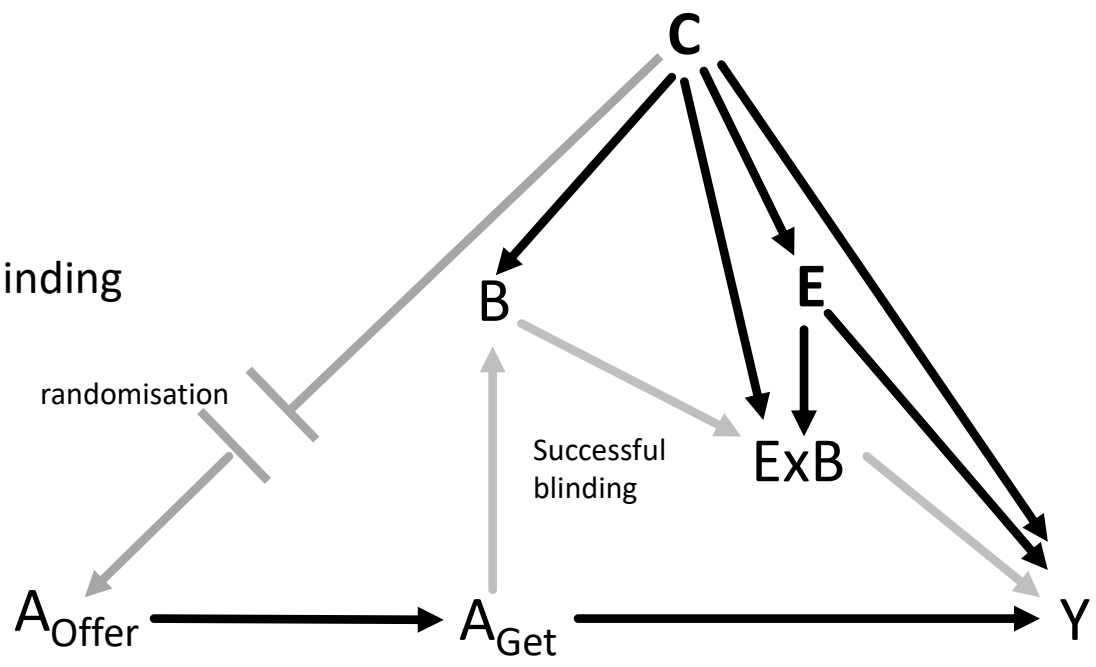
Casual Model with Randomisation

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



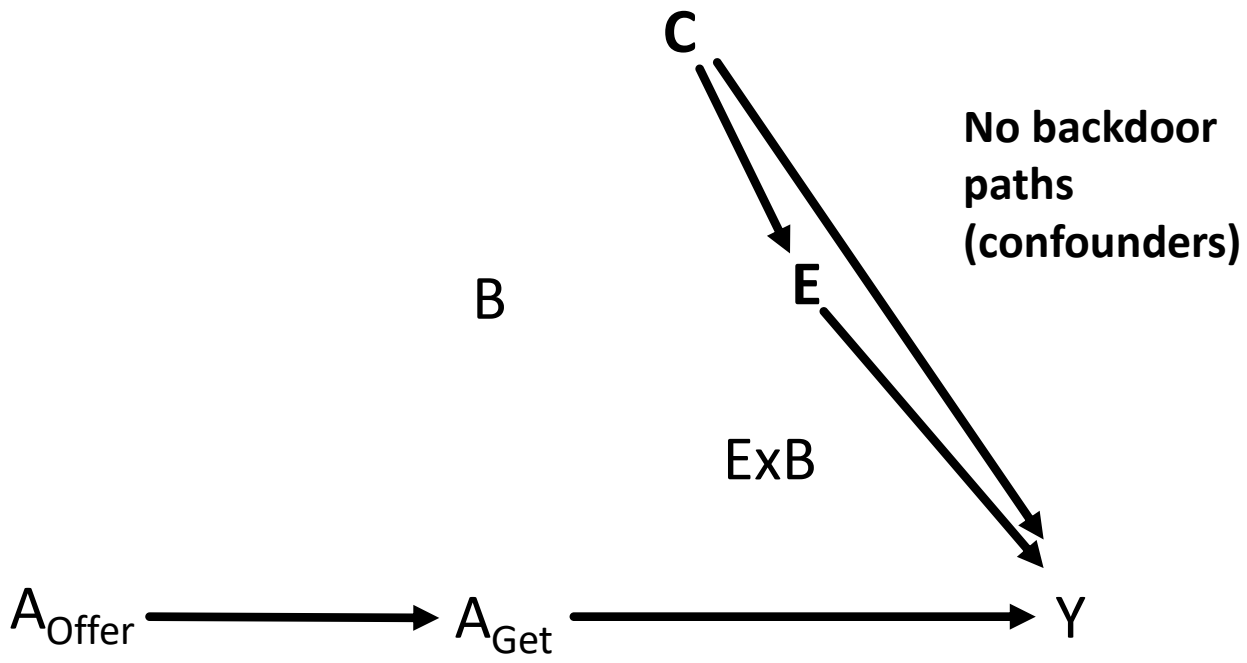
Casual Model with Randomisation + Blinding

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



Casual Model in a Blind RCT

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



Intention-to-treat effect is:

$A_{Offer} \rightarrow A_{Get} \rightarrow Y$

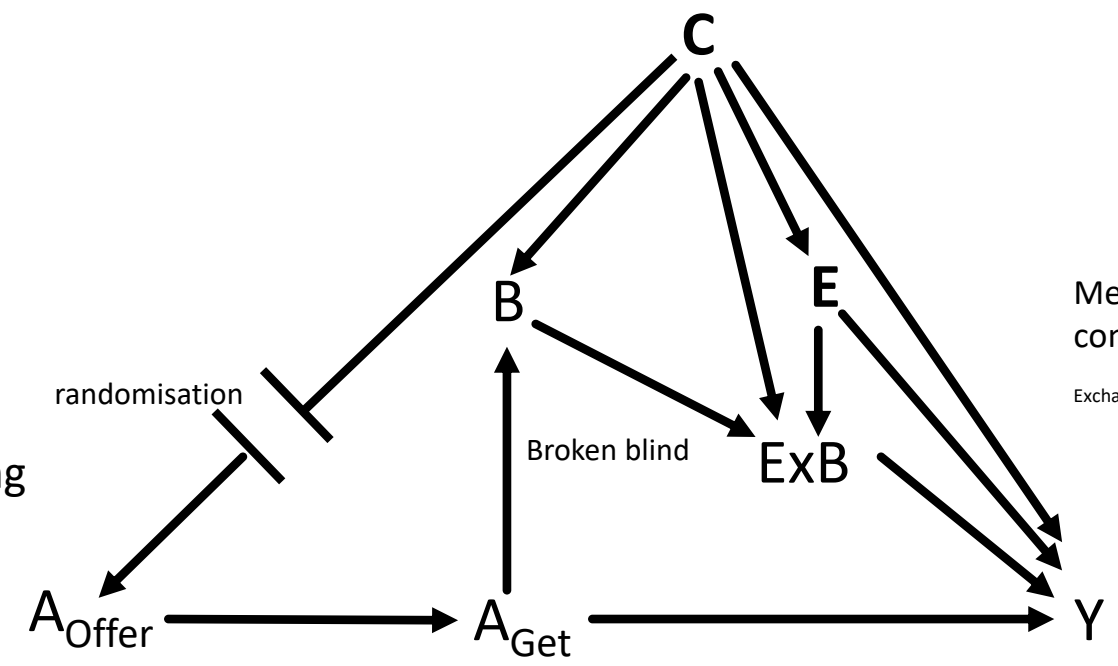
Placebo Treatment with Blind: $Y_{(a=0,b=0)} = \boldsymbol{C} + \boldsymbol{E}$

Active Treatment with Blind: $Y_{(a=1,b=0)} = \boldsymbol{C} + \boldsymbol{E} + A$

Treatment effect (A) is identified

RCT – with Blind Broken

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



Mediation effect is confounded

Exchangeability violation $Y_i(a) \perp\!\!\!\perp E_i|C_i$

Placebo Treatment with Blind: $Y_{(a=0,b=0)} = C + E$

Active Treatment with Blind: $Y_{(a=1,b=0)} = C + E + A$

Active Treatment no blind: $Y_{(a=1,b=1)} = C + E + A + ExB$

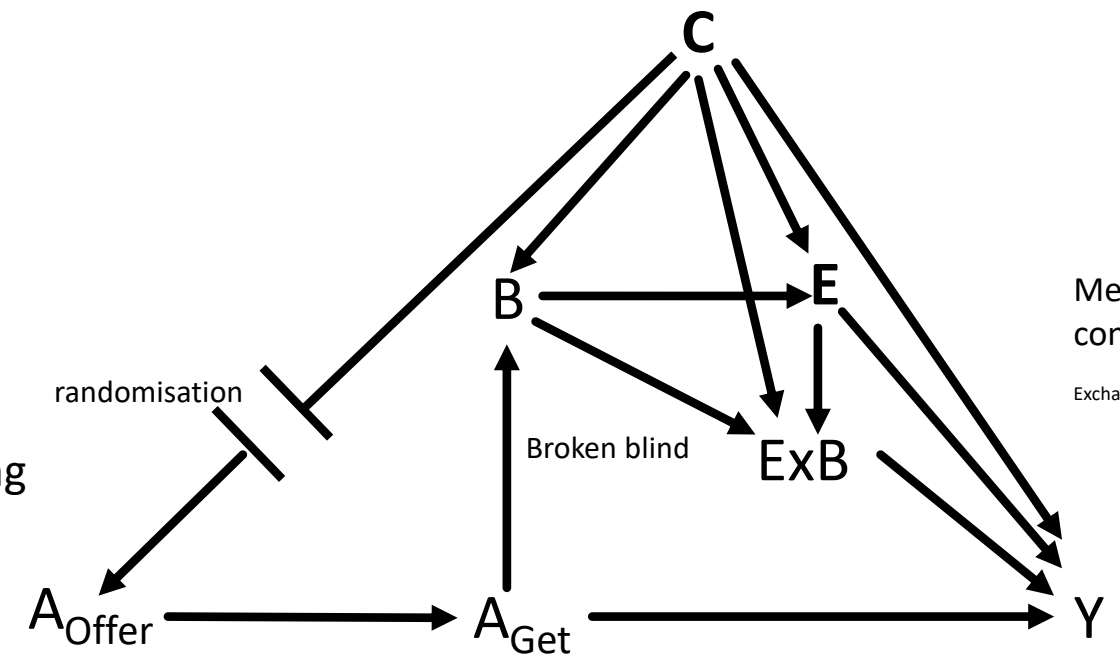
Treatment effect is not identified (in a two-arm trial with broken blind)

We cannot distinguish treatment effect (A) from placebo effect (ExB)

148 **B. Scientific basis for the statutory standard**
149
150 To establish a drug's effectiveness, it is essential to distinguish the effect of the drug "from other
151 influences, such as spontaneous change in the course of the disease, placebo effect, or biased
152 observation." [8] This is the basis for the statutory requirement that approval be based on adequate
153 and well-controlled investigations, as well as the basis for FDA's regulations describing the

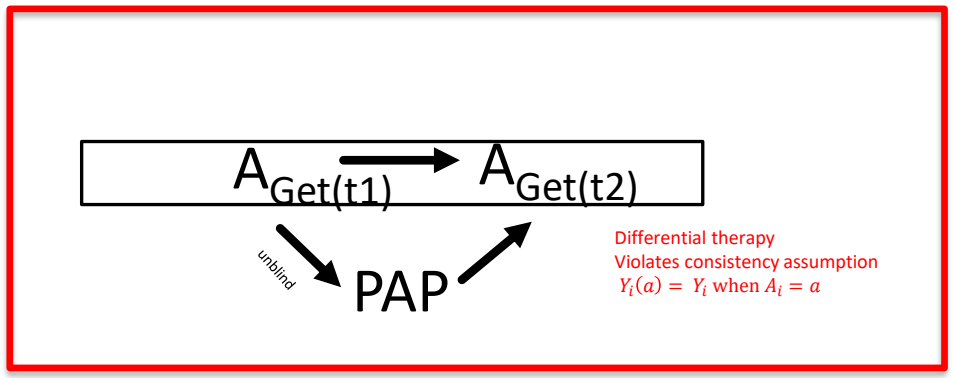
Therapist De-blinding

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



Mediation effect is confounded

Exchangeability violation $Y_i(a) \perp\!\!\!\perp E_i | C_i$



The Problem of Therapist De-Blinding and Expectancy

- The participant is unblinded. (exchangeability)
- The therapist is unblinded. (consistency)
- Differential therapy and “therapeutic alliance”.
- The content of psychedelic therapies are a little strange if you are on placebo! (Often invoke reflection on mystical experiences etc)

Violations of Non-Interference

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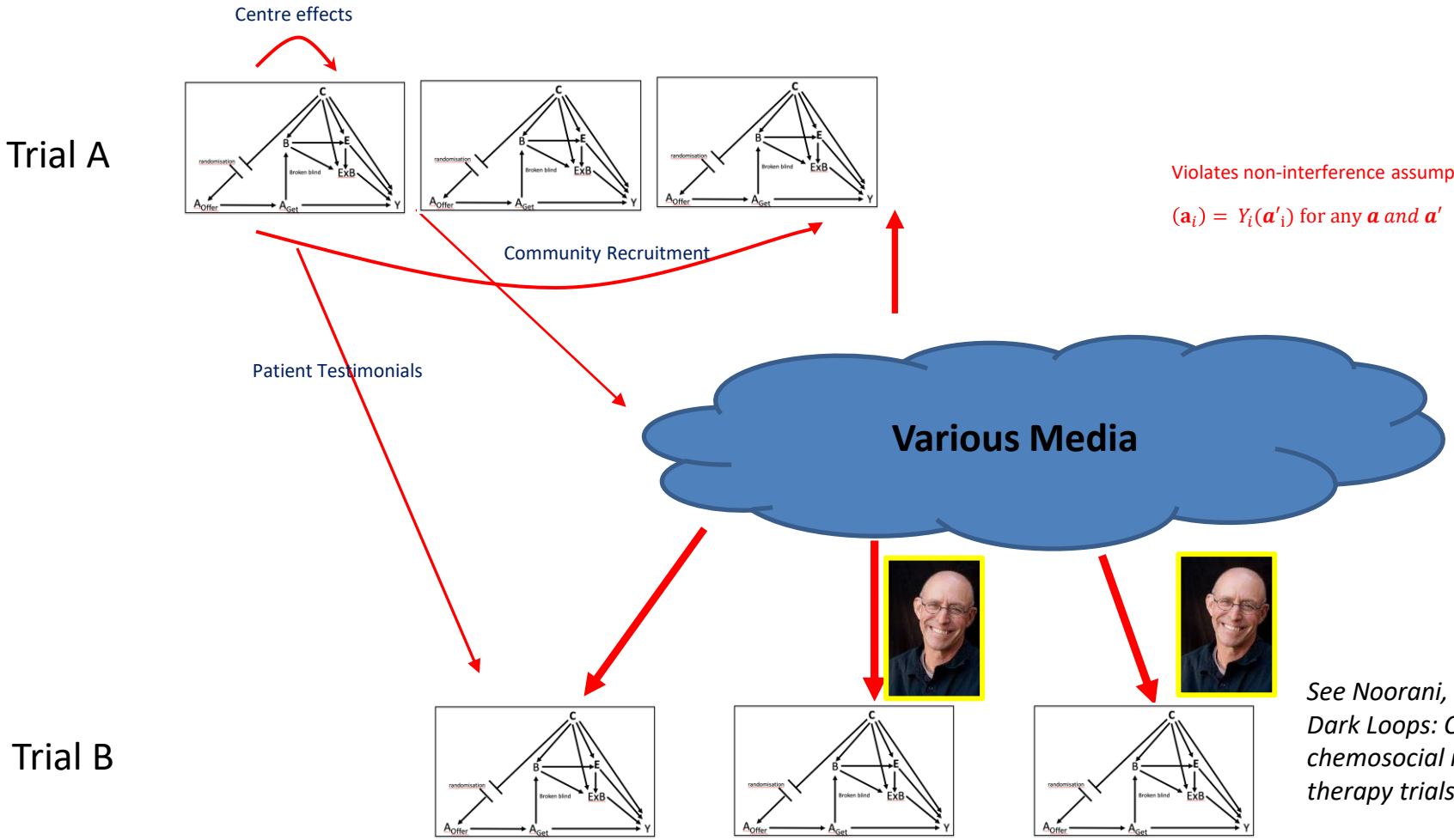
Contagion effects can be amplified by expectancy
Intra and inter-trial contamination!



Violates non-interference assumption

$(\mathbf{a}_i) = Y_i(\boldsymbol{a}'_i)$ for any $\boldsymbol{a}$ *and* $\boldsymbol{a}'$

See Noorani, Bedi & Muthukumaraswamy. Dark Loops: Contagion effects, consistency and chemosocial matrices in psychedelic-assisted therapy trials. Psychological Medicine, 2003

Violations of Non-Interference

- Group therapy
- Participants forming “integration groups”
- Sampling techniques – snowball and self-selection
- Media hype and concurrent trials

See Noorani, Bedi & Muthukumaraswamy. Dark Loops: Contagion effects, consistency and chemosocial matrices in psychedelic-assisted therapy trials. Psychological Medicine, 2023

Should Treatment Effects be Stable to Contagion?

- The authors argue that we will reach a plateau
- But this ignores contagion effects
- It is entirely possible that placebo/treatment effects will bounce around to the "whims" of the media and political landscape

New Online | Views 7,487 | Citations 0 | Altmetric 193 | Comments 1

Viewpoint

ONLINE FIRST

August 31, 2022

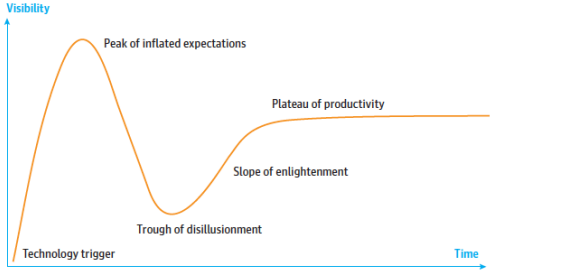
Preparing for the Bursting of the Psychedelic Hype Bubble

David B. Yaden, PhD[1,2]; James B. Potash, MD[1]; Roland R. Griffiths, PhD[1,2]

» Author Affiliations

JAMA Psychiatry. Published online August 31, 2022. doi:10.1001/jamapsychiatry.2022.2546

Figure. The Hype Cycle



Therapeutic applications of psychedelics appear to follow the general trajectory of other highly visible technologies. Concept from Gartner, Inc. Image is licensed under Creative Commons. Courtesy of Jeremy Kemp.

How do we know that psychedelics will "work" when the media landscape turns sour …. (?).
We may end up in a situation where harms gets amplified

"It has been argued that there is no pragmatic or epistemic need to separate expectancy effects from true treatment effects in psychedelic medicine (e.g. Schenberg, 2021). However, such an approach creates the unusual situation where the "efficacy" of a medical intervention is unstable over time and potentially at the whim of social zeitgeist."
Noorani, Bedi and Muthukumaraswamy., 2023

Summary of the Issues

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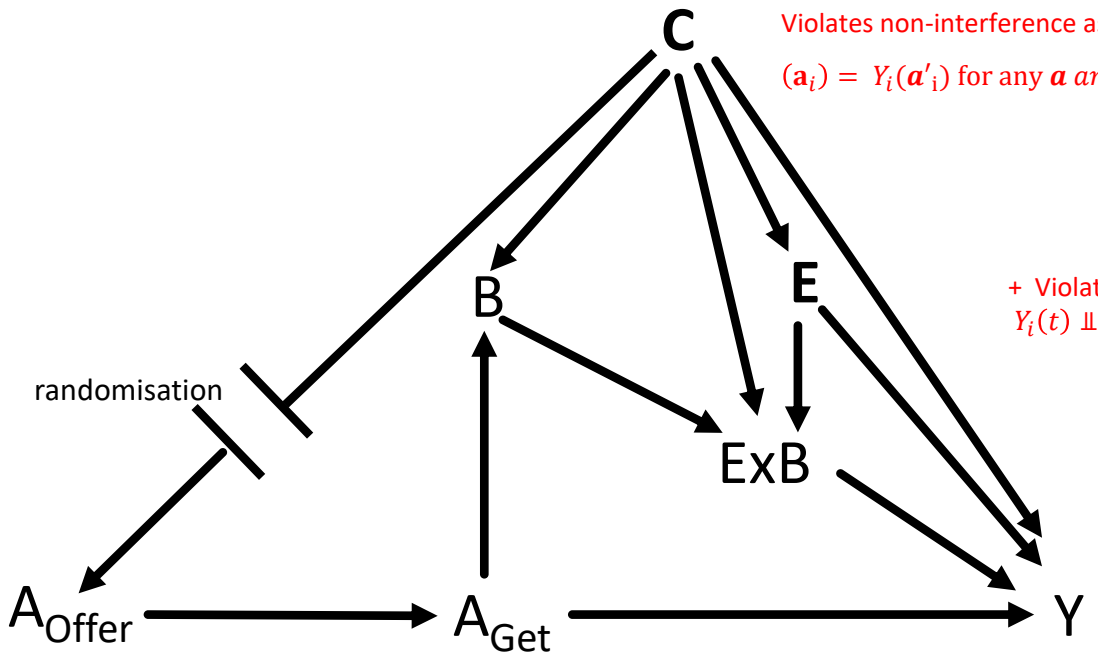


Violates non-interference assumption

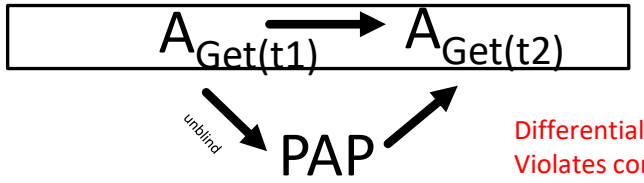
$(\mathbf{a}_i) = Y_i(\boldsymbol{a}'_i)$ for any $\boldsymbol{a}$ *and* $\boldsymbol{a}'$

\+ Violates exchangeability assumption

$Y_i(t) \perp\!\!\!\perp T_i | C_i$

Treatment effects are not identified

C = confounders (vector)
E = Expectancies (vector)
Y = Outcome
A_{Offer} = Treatment offered
A_{Get} = Treatment received
B = Blinding
ExB = Expectancy/Blinding Interaction



Differential therapy
Violates consistency assumption
$Y_i(a) = Y_i$ when $A_i = a$

Interpreting data: Examples

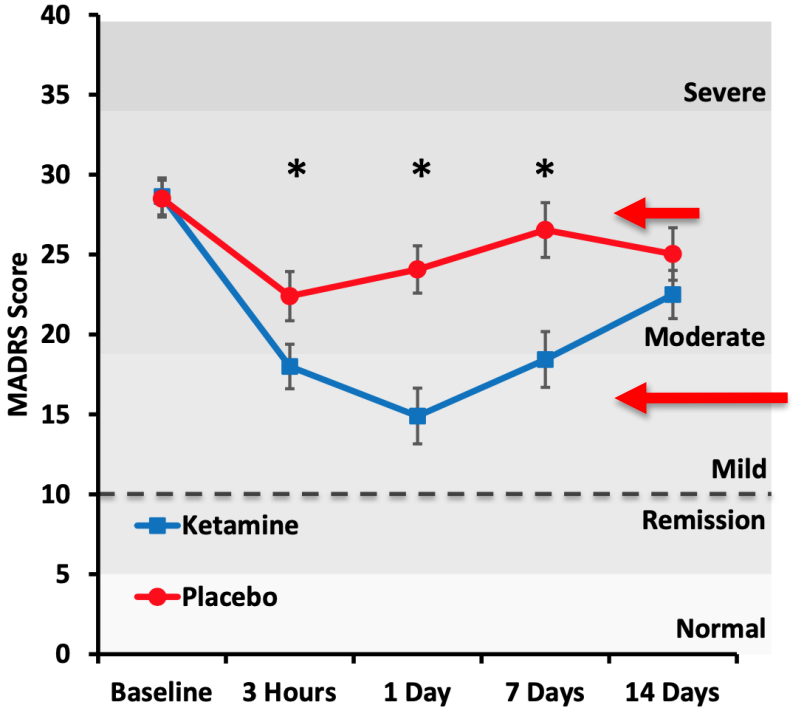


Figure 2. Mean change in Montgomery–Åsberg Depression Rating Scale (MADRS) over time following ketamine and placebo. *Significant differences were found at 3 hours, 1 day, and 7 days.

Disappointment

+

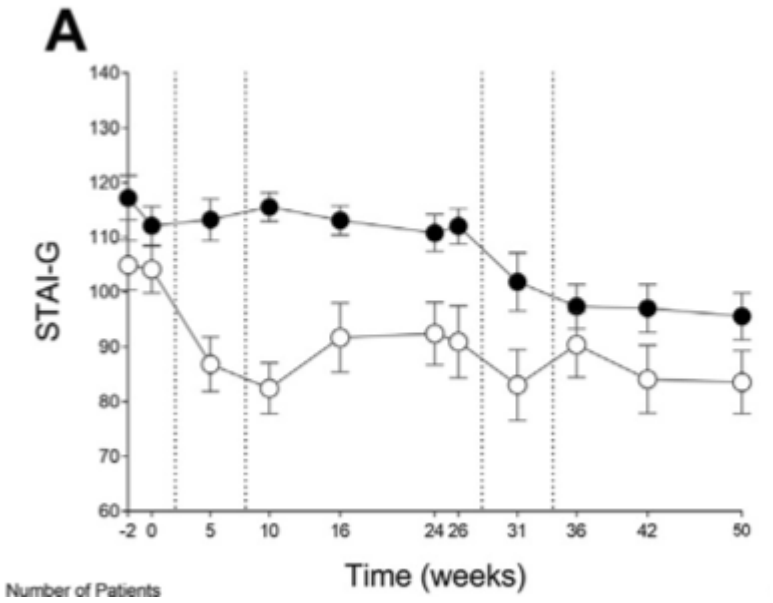
Expectancy

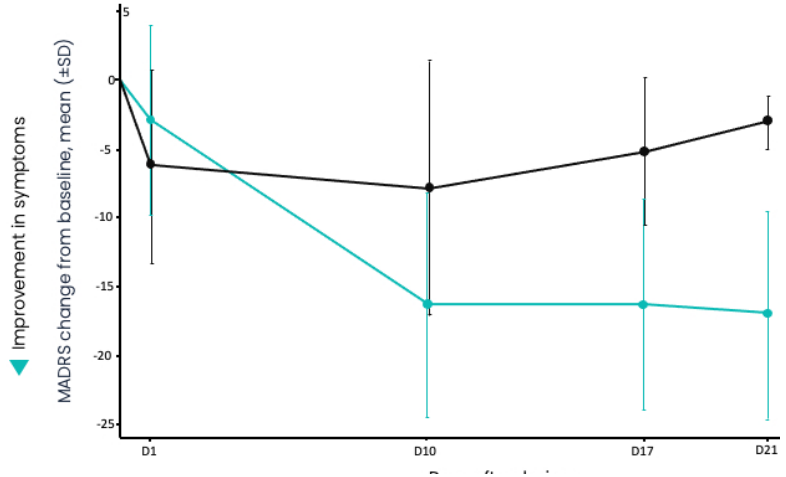
=

Effect-size overestimation !

Sumner, McMillan, Spriggs, . . . Muthukumaraswamy. Ketamine Enhances Visual Sensory Evoked Potential Long-term Potentiation in Patients With Major Depressive Disorder. *Biol Psychiatry Cogn Neurosci Neuroimaging* **5**, 45-55 (2020).

Interpreting data: Examples





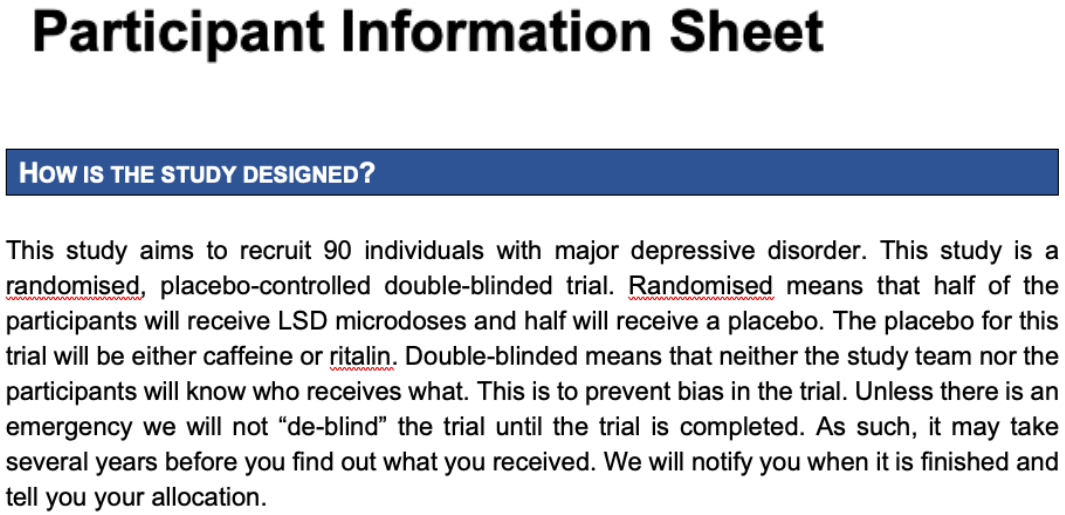
- A muted or non-existent response in the placebo group is a pretty clear indicator of an unblinding/disappointment response.
- Note to readers: compare with the placebo response in better-blinded trials

Open-label vs De-blinded RCTs

- To some extent a de-blinded RCT is an open-label trial……or is it?
- In an open-label trial participants fully expect to get the intervention (mental set A)
- In a double-blind RCT participants are not sure if they will be getting the intervention. Hence, they have different expectations (mental set B).
- Given the proposed (but never verified!) importance of set and setting it is not given that:

De-blinded RCT (mental set A) = open-label trial (mental set B) = real-world treatment

Expectancy is shaped by information given to participants



Participant Information Sheet

HOW IS THE STUDY DESIGNED?

This study aims to recruit 90 individuals with major depressive disorder. This study is a randomised, placebo-controlled double-blinded trial. Randomised means that half of the participants will receive LSD microdoses and half will receive a placebo. The placebo for this trial will be either caffeine or ritalin. Double-blinded means that neither the study team nor the participants will know who receives what. This is to prevent bias in the trial. Unless there is an emergency we will not "de-blind" the trial until the trial is completed. As such, it may take several years before you find out what you received. We will notify you when it is finished and tell you your allocation.

Participants ask questions about trials! What answers are they given?

Importance of Information/Expectancy

- Once the trial has established to have been de-blinded the information provided to participants becomes critical in interpreting data.
- What expectancies were they given by the research team about the treatment?
- **Unfortunately, these information sheets are almost never provided with data. IMHO this renders the data next to uninterpretable.**
- **Recommendation: Information sheets, advertising materials etc should always be provided/published to readers.**
- We know stunningly little about what participants think about having expectations met or not about participating in psychedelic RCTs and the psychological processes at play. This definitely needs deeper qualitative/quantitative investigation

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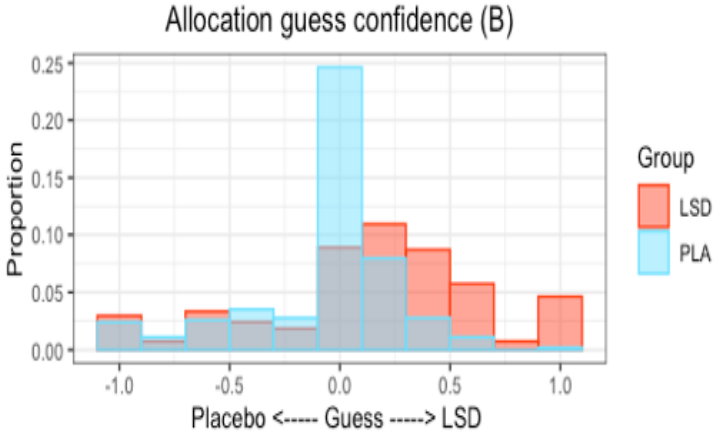
Measurement of De-blinding

- **IMHO this should be mandatory else there is no clue as to the extent of the problem**.
- Several approaches have been suggested:

Do you think you had placebo or study drug? ◯ Placebo ◯ Don't know ◯ LSD

How confident are you in your guess? Definitely placebo — No idea — Definitely LSD



Murphy, Sumner, Evans, . . . Muthukumaraswamy. MDLSD: study protocol for a randomised, double-masked, placebo-controlled trial of repeated microdoses of LSD in healthy volunteers. Trials 22, 302 (2021).

Questions:

1. Please indicate your best guess about the treatment you received:
   - Psilocybin
   - Placebo
2. Please rate your confident in your guess:
   No confidence, guess is random — Moderately confident — Completly confident
3a. Please rate the following statement: my guess is based on the side effects and/or perceptual drug effects (e.g. muscle tension, visual distortions etc.) that I attribute to receiving an active drug.
   Not true at all — Moderately true — Completly true
4a. Please rate the following statement: my guess is based on health improvements that I attribute to receiving an active drug.
   Not true at all — Moderately true — Completly true
3b. Please rate the following statement: my guess is based on the lack of side effects and/or perceptual drug effects (e.g. muscle tension, visual distortions etc.) that I attribute to receiving placebo.
   Not true at all — Moderately true — Completly true
4b. Please rate the following statement: my guess is based on the lack of health improvements that I attribute to receiving placebo.
   Not true at all — Moderately true — Completly true
5. If factors other than side effects and/or health improvements helped you to formulate your guess, please explain below.
   - [Optional text box response]

Szigeti, B., Nutt, D., Carhart-Harris, R. et al. The difference between 'placebo group' and 'placebo control': a case study in psychedelic microdosing. Sci Rep 13, 12107 (2023)

Phillips Paradox

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- BUT the purpose of a clinical trial is to become unblinded !
- An efficacious intervention heals the patient.
- Need to distinguish between malicious and therapeutic de-blinding
- When should we ask for de-blinding guesses?

Option 1: After the intervention but before outcome measurement?
(Might interfere with efficacy)

Option 2: End of trial for participant
(Might not distinguish therapeutic vs malicious de-blinding)

No perfect solution – but that hardly seems like an argument for doing nothing !

Muthukumaraswamy, Forsyth & Lumley. Blinding and expectancy confounds in psychedelic randomised controlled trials. *Expert Rev Clin Pharmacol* (2021).

Trial Design Options

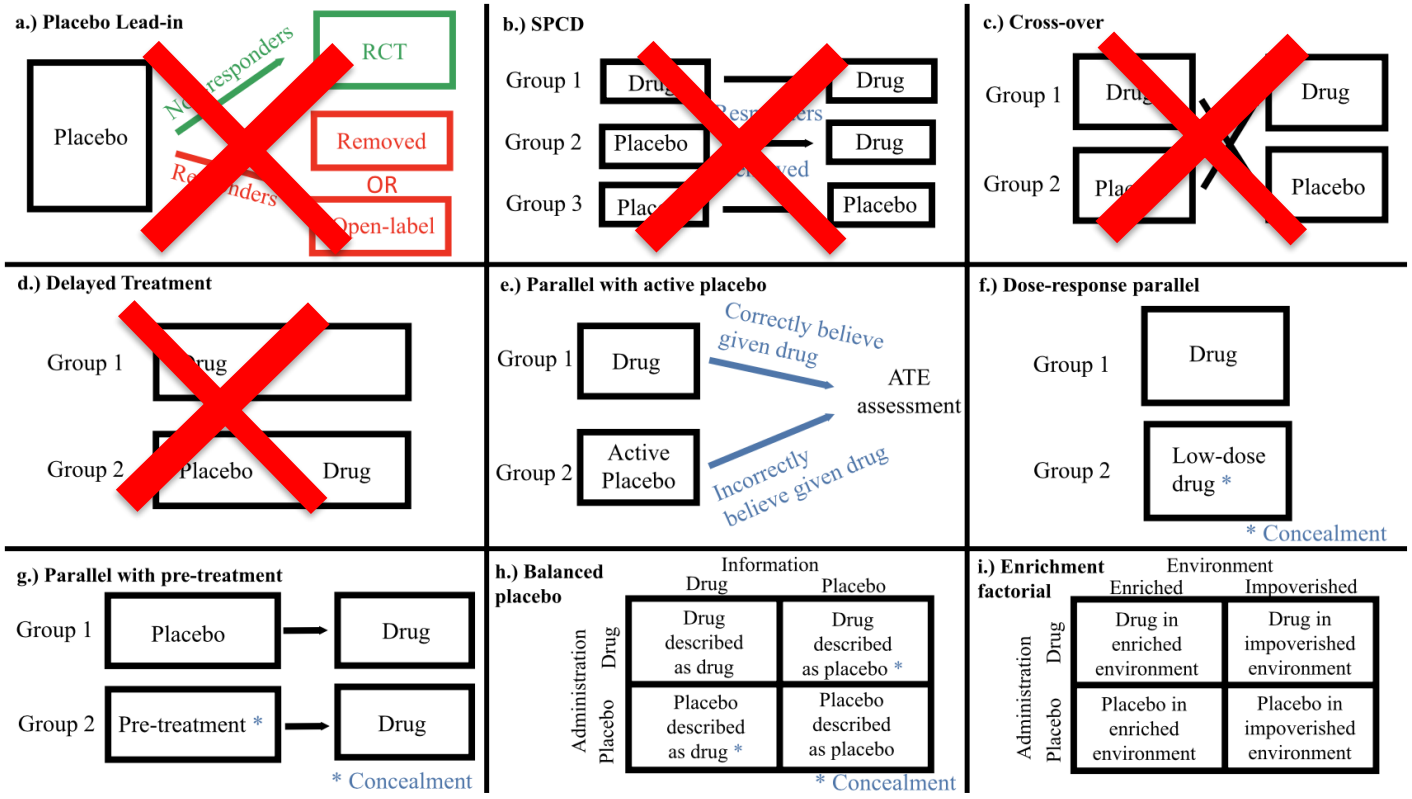


Figure 2. Potential trial designs for psychedelic RCTs as described in text. Designs a-d are not recommended.

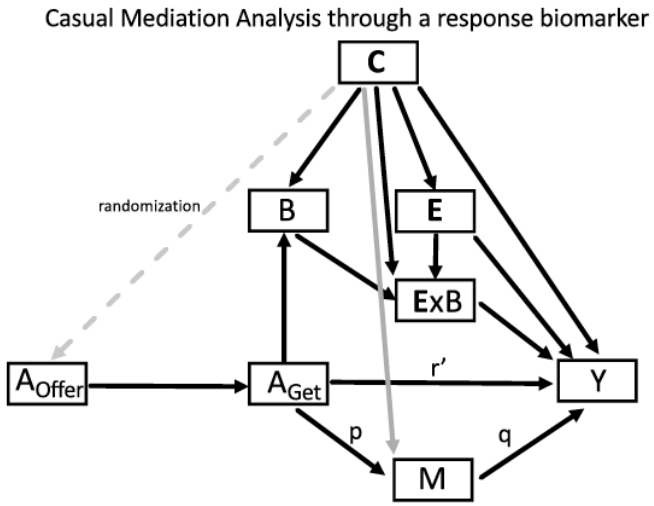
Muthukumaraswamy, Forsyth & Lumley. Blinding and expectancy confounds in psychedelic randomised controlled trials. *Expert Rev Clin Pharmacol* (2021).

But

We shouldn’t get so caught up in the intracicies of study design options when (arguably) the design of information sheets/ patient materials could have a such a large effect on clinical responses.

Need to carefully consider concealment options, information and trial design in tandem with de-blinding measurement

Could mediating variables provide a solution?



Muthukumaraswamy. Overcoming blinding confounds in psychedelic randomized controlled trials using biomarker driven causal mediation analysis. Expert Rev Clin Pharmacol (2023).

Does poor placebo control cause indication "bleed"?

Chronic pain and psychedelics: a review and proposed mechanism of action

Joel P Castellanos [1], Chris Woolley,[1] Kelly Amanda Bruno [1], Fadel Zeidan,[1] Adam Halberstadt,[2] Timothy Furnish[1]

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths[1,2], Matthew W Johnson[1], Michael A Carducci[3], Annie Umbricht[1], William A Richards[1], Brian D Richards[1], Mary P Cosimano[1] and Margaret A Klinedinst[1]

Response of cluster headache to psilocybin and LSD

Abstract—The authors interviewed 53 cluster headache patients who had used psilocybin or lysergic acid diethylamide (LSD) to treat their condition. Twenty-two of 26 psilocybin users reported that psilocybin aborted attacks; 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination; 18 of 19 psilocybin users and 4 of 5 LSD users reported remission period extension. Research on the effects of psilocybin and LSD on cluster headache may be warranted.

NEUROLOGY 2006;66:1920–1922

Psychedelic treatment of functional neurological disorder: a systematic review

Matthew Butler, Mathieu Seynaeve, Timothy R. Nicholson, Susannah Pick, Richard A. Kanaan, Andrew Lees, Allan H. Young and James Rucker

Study Protocol for "Psilocybin as a Treatment for Anorexia Nervosa: A Pilot Study"

Meg J. Spriggs[1], Hannah M. Douglass[1], Rebecca J. Park[2], Tim Read[1], Jennifer L. Danby[1], Frederico J. C. de Magalhães[1], Kirsty L. Alderton[1], Tim M. Williams[1], Allan Blemings[1], Adele Lafrance[3], Dasha E. Nicholls[4], David Erritzoe[1], David J. Nutt[1] and Robin L. Carhart-Harris[1]*

Original Paper

Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction

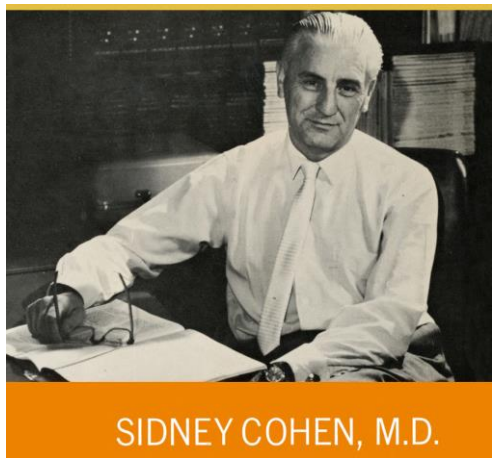
Matthew W Johnson[1], Albert Garcia-Romeu[1], Mary P Cosimano[1] and Roland R Griffiths[1,2]

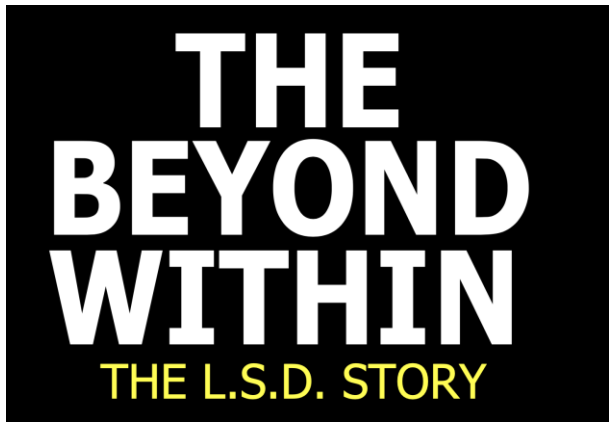
In Conclusion

- De-blinded trials cannot distinguish between placebo and treatment responses
- Interference, consistency and contagion effects contaminate probably all existing data

- IMHO measurement of de-blinding should be mandatory
- IMHO provision of information sheets should be mandatory
- Concealment/deception might need to be considered
- Thinking of trial design options is nice (e.g. active placebo/dose response but incomplete without careful consideration of the former. These are largely neglected at present

An historical perspective …





"The difficulties of doing a clear-cut study would be far from solved even with these precautions. A control group of patients matched as well as possible with the LSD patients must be given the identical treatment except that LSD is not used. A placebo or drug with some minor activity identical in appearance would have to be substituted. It is quite impossible to keep the therapist in the dark about who is getting the LSD because of its pronounced action. Will he invest as much energy and dedication to his non-LSD patients? The patients themselves will quickly know whether they have received LSD or not. Their expectations of its benefits will alter their therapeutic set. These difficulties and others are the reasons why a decisive test of the efficacy of LSD has not yet been performed. The problems are great but surmountable. Hopefully, this investigation will be done one day." 1964, p.199

Thank you for listening

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REAGAN-UDALL FOUNDATION FOR THE FDA

Session 2: Psychedelics Study Design, Control Conditions, and Blinding

Presenters:

- **Suresh Muthukumaraswamy, PhD,** University of Auckland
- **Franz Vollenweider, MD,** University of Zürich

Panelists:

- **Matt Butler, MD,** King's College London
- **Michael Davis, MD, PhD,** Usona Institute
- **Bernard Fischer, MD,** U.S. Food and Drug Administration

Universität Zürich[UZH]

Psychiatrische Universitätsklinik Zürich

Advancing Pychedelic Clinical Study Design

Session 2: Psychedelic Study Design, Control Conditions and Blinding

Prof. Dr. Franz X. Vollenweider, MD, FMH

Psychiatric University Hospital Zürich

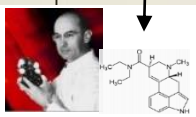
Dept.of Psychiatry, Psychotherapy and Psychosomatics
Center for Psychiatric Research

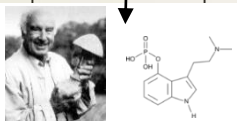
Neurophenomenology and Consciousness
Neuropsychopharmacology and Brain Imaging

Regan-Udall Foundation for the FDA, January 31, 2024

Brief History of Psychedelic Research (PUK, UZH)

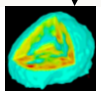
1926 1938 1943 1947 1952 1953 1958 1962 1963 1965 1966 1970 1983 1988 1990 1999 2000 2006 2010 2016 Revival of clinical studies





US:Schedule1

5-HTRs



1998: 2A

emotion regulation
self models
social interaction

CH: Psilocybin and LSD (and MDMA) in depression, anxietx disorders, and terminal cancer patients

1947: LSD **as model of psychosis** (Stoll, M. Bleuler)

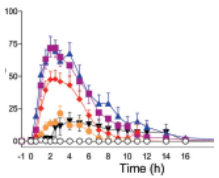
1948: LSD **as ajunct in depression** (Condrau)

Psilocybin
Ketamine
Amphetamine

«Psycholytic» Therapy (CH/EU)/»**Psychedelic» Therapy** (US)

1975-85: Phenomenology of ASC (e.g. 5D-ASC) (Dittrich)

1988-1993ff: SAPT (Clinical Studies, compassionate use)(Styk, Gasser, Oehen)



1992-ff: **Neuropsychopharmacology and Brain Imaging Unit** (Vollenweider)

- Phenomenology; emotion, cognition, social interaction, predictors of outcome
- Pharmacology/safety: metabolism (PO. IV, IM), dose-response, «blocker studies»
- Neurophysiology/neurocognitive-emotional models: perception, **emotion**, **cognition, self**

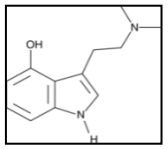
2018: **Psilocybin in MDD** (proof-of concept)

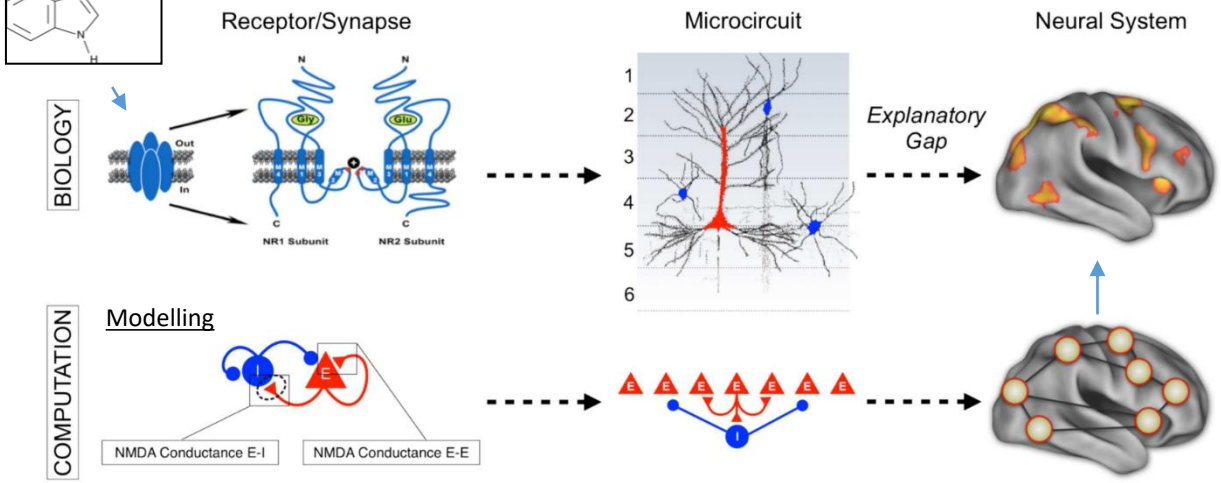
2020: **Psilocybin in Alcohol Dependence** (EU-ERA): translational animal models and human trials

2020: **Translational animal models, neuroplasticity, novel psychedelics**

Volllenweider and Kometer Nat.Rev. Neurosci. 2010

Mapping the brain-behavior space relationships along the psychedelic spectrum

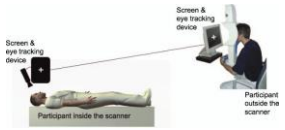




e.g. change in FC

correlational:

Psychometric Constructs:
(1.Person Perspective)
Correlates of Subjective Experience



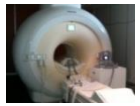
Neuroscience-based Concepts:
(3.Person Perspective)

Correlates of cognitive, emotional and perceptual processes affected by psychedlics

predictors of response and outcome
-e.g. emotion regulation, self-focus

PET, MRS (20-60 min)
Resting state:

- activation/deactivation
- receptor density/occupancy
- transmitter release



fMRI (2 sec):
Resting state:

- activation/deactivation (ASL)
- **functional and directed connectivity**
- complexity (e.g., entropy)

Task/Event related BOLD changes
(specific functions)

EEG (msec)
Resting state:

- **spectral power**
- **synchronisation, long-range oscillations**
- complexity (e.g. entropy)

Task/Event Related Potential (EEG-ERP):
(specific functions)

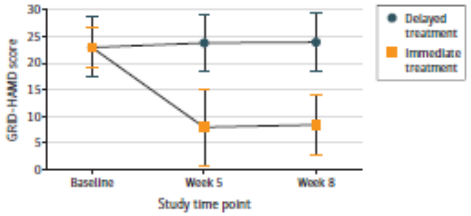
TMS-EEG (msec) («cause-effect»)
e.g. Pertubation complexity (PCI)

(adapted from Anticevic et al. 2013 Vollenweider and Smallridge 2022)

Challenges in psychedelic research for the treatment of psychiatric disorders

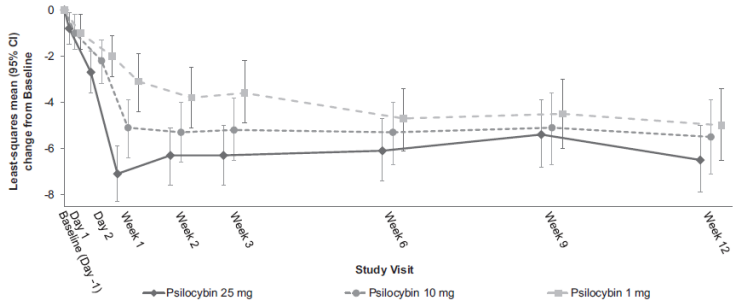
Recent studies with psilocybin have shown **promise**, demonstrating *rapid and sustained clinical benefits for the treatment* of psychiatric disorders, particularly depression.

MDD



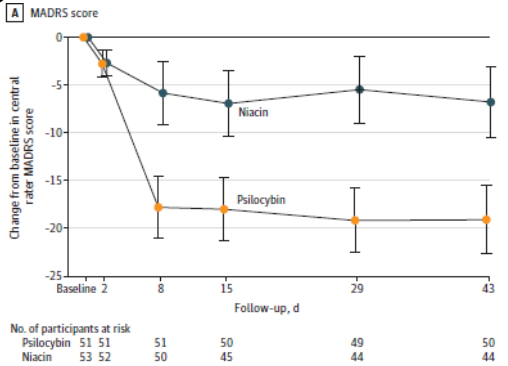
Davis et al. 2020

TRD



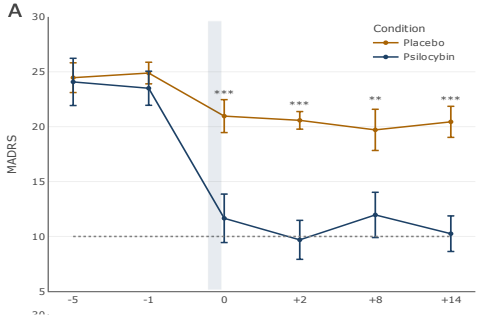
Goodwin et al. 2023

MDD



Raison et al. 2023

MDD



von Rotz et al. 2023

However, recent reviews into the methodological rigor of psychedelic clinical trials have highlighted a **number of methodological problems** that raise doubt on the inferences that have been drawn on the efficacy of psychedelic treatments.

According to van Elk and Fried (2023), these problems threaten in particular the internal, external and construct validity of a study:

1) Internal validity is the extent to which you can be *confident* that a *cause-and-effect relationship* established in a study *cannot be explained by other* factors.

> The internal validity of **r**andomized **placebo-controlled** trials strongly depends on the correct **assessment of the placebo response**

Muthukumaraswamy et al. 2021, Aday et al. 2023, van Elk and Fried 2023

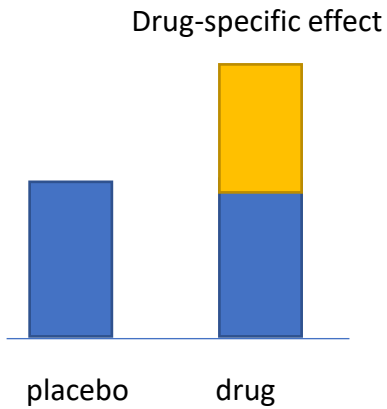
Notably, **the placebo response refers to the** average symptom response of a group of patients receiving a placebo in a CRT,

while the **placebo** (or nocebo) **effect** refers to the **individual** therapeutic effect of receiving a treatment.

Placebo response
- regression to the mean
- spontaneous remission
- response bias

- Placebo effect:
- expectancies (e.g. media hype)
- conditioning
- suggestions
- belief
- etc.

to uncover this would take an additional **no-treatment control condition** (ethical/unethical?) (masking?)



The **placebo effect is strongly influenced** by patient's **expectancies**
(trait/state-like and may change along the course of the trial)

and by the **efficacy of the condition blinding** (masking)

as well as by other non-pharmacological factors related to the „set" and „setting" including the effects from the concomitant therapy.

The **psychoactive** effects of psychedelics appear to be the main cause for **breaking the blind.**

- **Assessment of blinding and blinding efficacy** by «parametric» rating scales (e.g. visual analogue 1-100)
- **Assessment of expectancy** by validated rating scales (CEQ, SETS etc)

Multiple factors that may influence the Dynamics of Psychedelic Experience and Outcome

Patient´s expectations: pre-knowledge, mindset, myth, media hype etc. «state-like», may change with therapeutic experience

assessment of expectations (CEQ, SETS etc) x x x x x x

Study Advertisement | Patient Information | In-person screening

> self-selection, self-exclusion

Attrition

Sampling
Selection bias
(e.g. drug-naives, previous experience)

Non-pharm. Factors (set):
- personality traits
- previous experience
- age (gender ?)
- emotion regulation
  -Acceptance (+)
  -Suppression (-)
- absorption capacity
- mood state (past 7 days)

Setting: Environment, music

Dose of specific Drug
(Psilocybin, LSD, DMT)

Drug response (acute experience)

-low-dose of drug
or
-active (inactive) placebo

Placebo response (acute experience)

Outcomes:
-symptom reduction
-changes in behavior and social interaction
etc.

Potential Markers

baseline RS connectivity (fMRT)
baseline empathy (cogn./emot.)
baseline emotion regulation (fMRT)
(findings need to be confirmed)

Therapeutic model (manualized)
Rational/concept underlying the treatment
adjunct therapeutic interventions

Experimenter biases,
Therapist's expectations

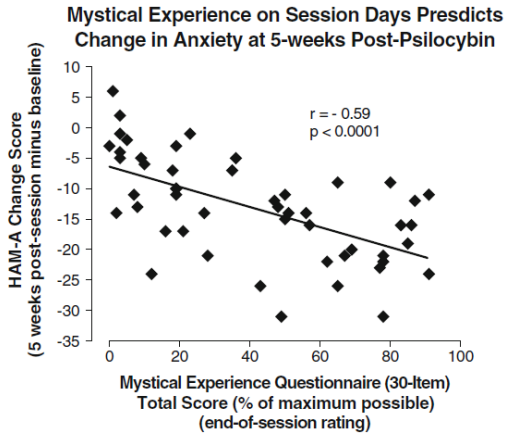
assessment of therapeutic alliance x x x x x x x

assessment of blinding x x x

study team (clinician, experimenter) Preparation sessions (number ?) drug session (1-2?) Integration sessions (number ?)

independent or central rater x x x x x

Mystical-type experience (MEQ) or Oceanic Self-Boundlessness (OB) mediate symptom reduction in depression and anxiety



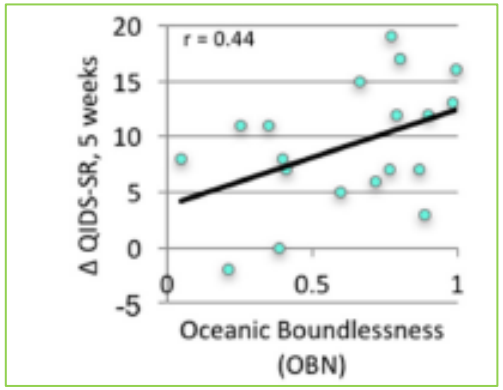
Griffiths et al. 2018

MEQ tot score

experience of unity
inner subjectivity
ego-loss

altered space-time sense
Ineffability

positive emotions
sacredness
noetic quality



Roseman et al. 2018

OBN of 5D-ASC

Second order Scales:

- **loosening of self-boundaries: unity, oneness, disembodiment**
- **positive emotions > bliss**

- **altered space-time sense**
- **insightfulness**
- **spiritual experience**

Other studies found <u>no relationship</u> between the intensity of MEQ/OBN and symptom reduction in MDD (Rotz et al. 2023, Raison et al. 2023, Sloshower et al. 2023)

Role of challenging experiences and its relation to „emotional breakthrough“ is not well understood

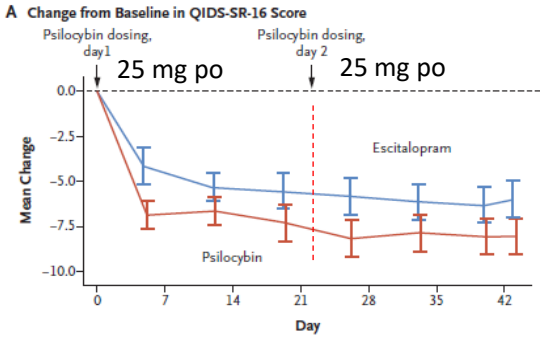
-More complex models needed
(e.g. multidimensional correlation models, path analysis, ANCOVA etc.)
> most available data sets are underpowered

Emotional and Cognitive models of MDD

- Negative cognitive bias (e.g. rumination)
- Negative emotional bias (e.g. increased response to neg. faces)
- increased self- and body-focus (e.g. self-referential processing)
- decreased social cognition/interaction (e.g. empathy)

The role of dose and of repeated dosing for the therapeutic outcome?

Double-blind, randomized, controlled trial:
Psilocybin versus Escitalopram for TRD



Open-label psilocybin trial for TRD

10 mg po — 7 day apart — 25 mg po

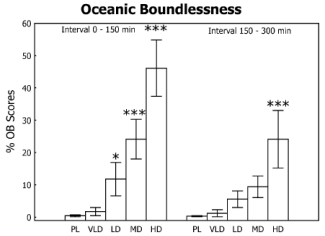
HAM-D:
21.4 to 10.7 (at 1w)
76% drop

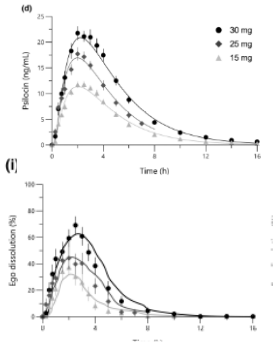
to 7.4 (at 5w)

Carhart-Haris et al. 2022, 2016

Psilocybin

0,3,8,15,25 mg





Hasler et al. 2006
Holze et al. 2021

Dose-response parallel group design with „low-dose“ placebo“

Groups 1-3

Drug: e.g. Psilocybin

Potential Biomarkers:
- Immuno Markers
- Stress Markers (e.g. ACTH, cortisol)

Emotional and cognitive Tasks:
- Emotion regulation
- Rumination
- Self-processing
- Social-interaction
- Empathy Task

Neuroimaging:
- RS connectivity
- Emotion regulation
- Social-interaction

-high dose :25 mg

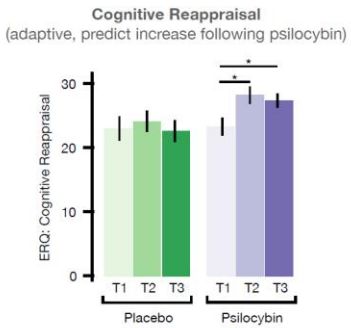
-medium dose: 12 mg

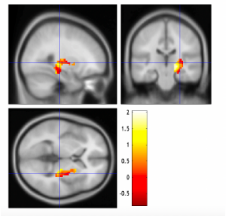
-low dose: 3 mg (5mg)

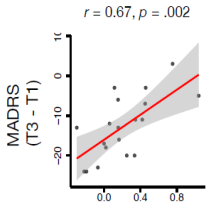
-1 0 -2 -14d

Follow-up
3-6 month

MDD

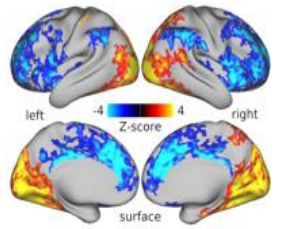


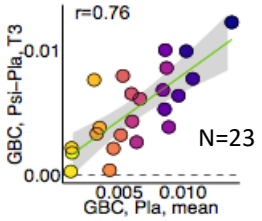




Moujaes et al., Work in progress

Psilocybin





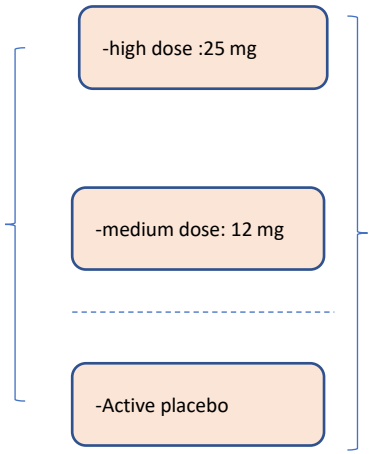
Preller et al. 2018, 2021

Parallel group design with active placebo

Single dose

Groups 1&3 or 1-3

Drug: e.g. Psilocybin



- Niacin (Ross et al. 2016, Raison et al. 2023
- Methylphenidate (Griffith et al. 2006)
- Amphetamine,
- MDMA
- LSD, DMT
- Dextromethorphan
- Ketamine
- Clonidin?

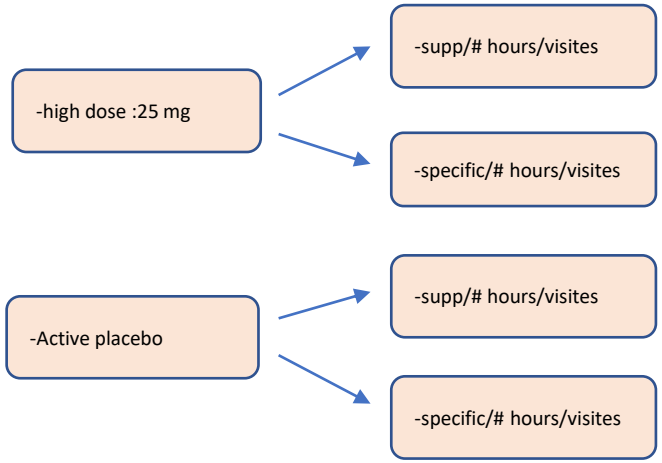
dose-dependent symptoms

Blinding is difficult

-Declare all possible symptoms or side effects:

-Selective or partial disclosure that the trial has 2 or more drug levels

Differential therapeutic interventions (factorial) or Enriched Environment

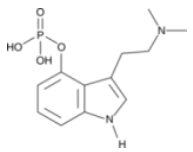


- Psychological support
- Emotion focused Therapy
- Acceptance and Commitment Therapy
- Cognitive Behavioural Therapy
- Needs large sample size

- or enriched environment

Classical Psychedelics: Primary and downstream mechanisms of action

Psilocybin



5-HT5, 5-HT-7

5-HT1A

5-HT2A

\- +

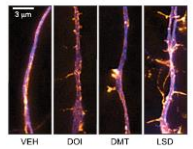
Glutamate

MRS: PFC GLU (-), Hipp Glu (+)
Mason et al. 2020

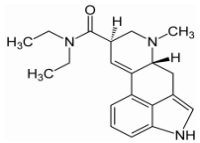
NMDA → Learning, memory

AMPA → *BDNF* > neuroplasticity

trkB
mTOR



Ly et al. 2018
De Gregorio et al. 2020
Shao et al.2021



LSD

D1
D2
$\alpha_{1,2}$

\+

Dopamine

PET: DA (+)ventr. Str.
Vollenweider et al 1999

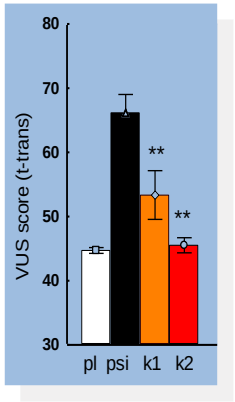
\+

GABA

MRS: mPFC GABA(+)
Mason et al. 2020

5-HT2A Antagonist
Ketanserin

Psilocybin
or LSD



Vollenweider et al. 1998, 2016

Possible candiates:

- Ketanserin (2A)
- Risperidone (2A/D2)
- Midazolam (GABA)
- Lamotrigine (Glu)
- Buspirone (1A)
- Clonidine (alpha-2)

Parallel with pre-treatment: Groups 1-3

Drug: e.g. Psilocybin

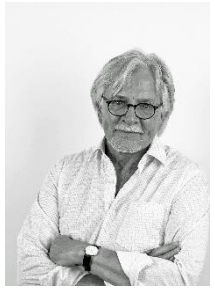
-pretreament high + -drug

-pretreament medium + -drug

-pretreatment low + -drug

Thanks to

Psychiatrische Universitätsklinik Zürich



Vollenweider Lab

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EEG/ERP

Andres Ort
TMS-EEG, fMRI

Eva Schindowski
Clinical Research
Depression

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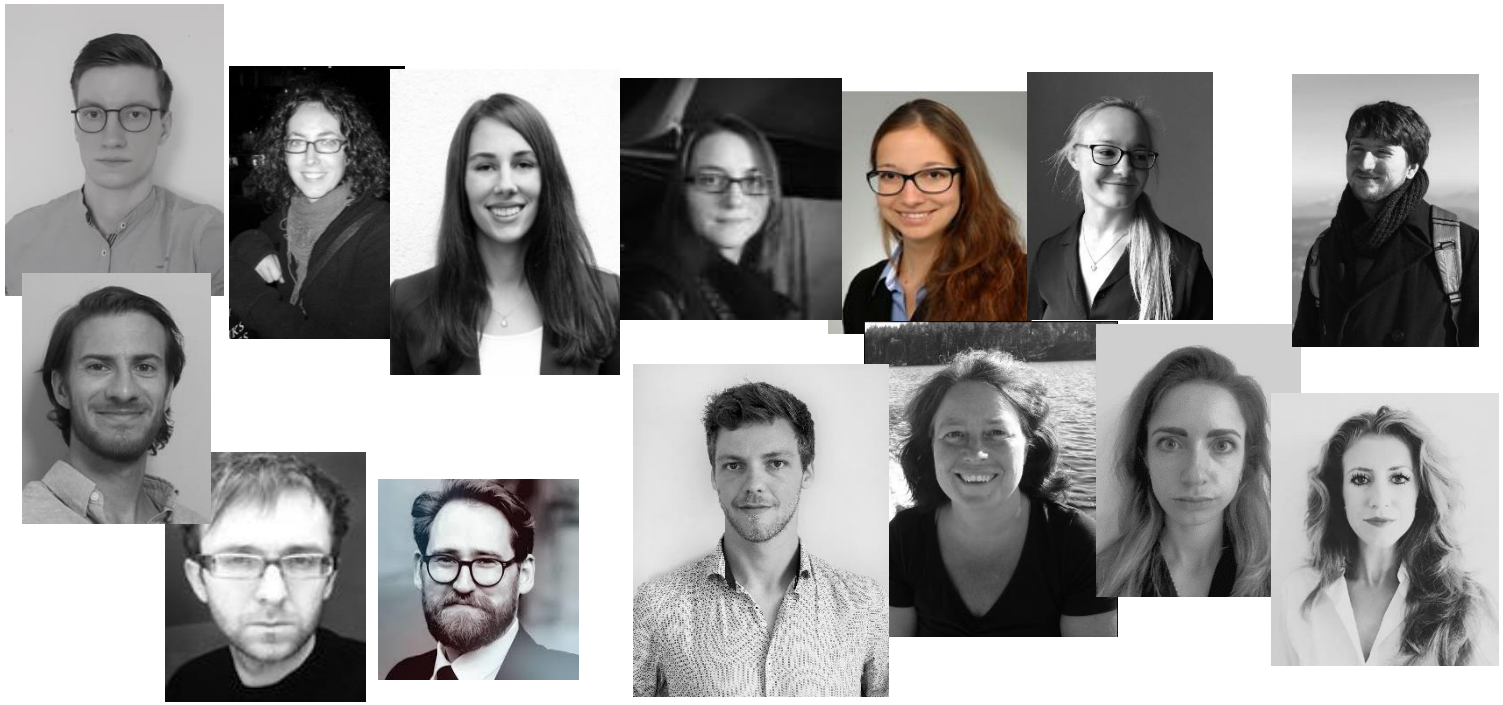
Translational Res.
Head Preclinical Lab.

Philipp Stämpli,
Head MTI Centre



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Katharina Zahoranszky
Anja Seidl
Sara Romer

Acknowledgments

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Wellcome Trust Centre for Neuroimaging
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FNSNF
Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra
Swiss Neuromatrix Foundation
HEFFTER RESEARCH INSTITUTE
RESEARCH AT THE FRONTIERS OF THE MIND
Usona Institute

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 2: Psychedelics Study Design, Control Conditions, and Blinding

Presenters:

- **Suresh Muthukumaraswamy, PhD,** University of Auckland
- **Franz Vollenweider, MD,** University of Zürich

Panelists:

- **Matt Butler, MD,** King's College London
- **Michael Davis, MD, PhD,** Usona Institute
- **Bernard Fischer, MD,** U.S. Food and Drug Administration

Break

The meeting will resume at 11:50 am ET

REAGAN-UDALL FOUNDATION FOR THE FDA

Session 3: Dosing

Presenters:

- **Robert Barrow, MSc,** MindMed
- **Guy Goodwin, DPhil,** Compass Pathways
- **Berra Yazar-Klosinski, PhD,** Lykos Therapeutics

Panelists:

- **Peter Hendricks, PhD**, University of Alabama at Birmingham
- **Jennifer Mitchell, PhD**, University of California, San Francisco
- **Martine Solages, MD**, U.S. Food and Drug Administration

MindMed

Reagan-Udall Foundation Public Meeting

Advancing Psychedelic Clinical Study Design

January 2024

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This Presentation contains, and our officers and representatives may from time to time make, "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995 and other applicable securities laws. Forward-looking statements can often, but not always, be identified by words such as "plans", "expects", "is expected", "budget", "scheduled", "estimates", "forecasts", "intends", "anticipates", will", "projects", or "believes" or variations (including negative variations) of such words and phrases, or statements that certain actions, events, results or conditions "may", "could", "would", "might" or "will" be taken, occur or be achieved, and similar references to future periods. Except for statements of historical fact, examples of forward-looking statements include, among others, statements pertaining to: the anticipated timing and results of the Company's 12-week data for their MM-120 Phase 2b study in Generalized Anxiety Disorder ("GAD"), the safety or efficacy of MM-120 in GAD or any other indications, the development and commercialization of any product candidate or treatment, or the safety or efficacy of either of the foregoing, the success and timing of our development activities; the success and timing of our planned clinical trials; our ability to meet the milestones set forth herein; the likelihood of success of any clinical trials or of obtaining FDA or other regulatory approvals; the likelihood of obtaining patents or the efficacy of such patents once granted and the potential for the markets that MindMed is anticipating to access.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions as of the date of this Presentation. While MindMed considers these assumptions to be reasonable, the assumptions are inherently subject to significant business, social, economic, political, regulatory, competitive and other risks and uncertainties that are difficult to predict and many of which are outside of MindMed's control, and actual results and financial condition may differ materially from those indicated in the forward-looking statements. Therefore, you should not rely on any of these forward-looking statements. Important factors that could cause actual results and financial condition to differ materially from those indicated in the forward-looking statements include, among others, the following: MindMed's ability to raise capital to complete its plans and fund its studies; the medical and commercial viability of the contemplated medicines and treatments being developed; MindMed's history of negative cash flows; MindMed's limited operating history; incurrence of future losses; lack of revenue; compliance with laws and regulations; difficulty associated with research and development; risks associated with clinical trials or studies; heightened regulatory scrutiny in connection with a controlled substance in approval processes; early stage product development; clinical trial risks; regulatory approval processes; novelty of the psychedelic inspired medicines industry; as well as those risk factors discussed or referred to throughout the "Risk Factors" sections of MindMed's most recently filed Annual Report on Form 10-K filed with the Securities and Exchange Commission (the "SEC"), Quarterly Reports on Form 10-Q for the periods ended March 31, 2023, June 30, 2023 and September 30, 2023 filed with the SEC and in other filings we make in the future with the SEC and the securities regulatory authorities in all provinces and territories of Canada, available under the Company's profile on SEDAR at www.sedar.com.

Any forward-looking statement made by MindMed in this Presentation is based only on information currently available to the Company and speaks only as of the date on which it is made. MindMed undertakes no obligation to publicly update any forward-looking statement, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise.

This presentation include preliminary clinical data from MindMed's Phase 2b clinical trial evaluating MM-120 in GAD. These preliminary data remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data included herein. As a result, data should be viewed with caution until the final data are available.

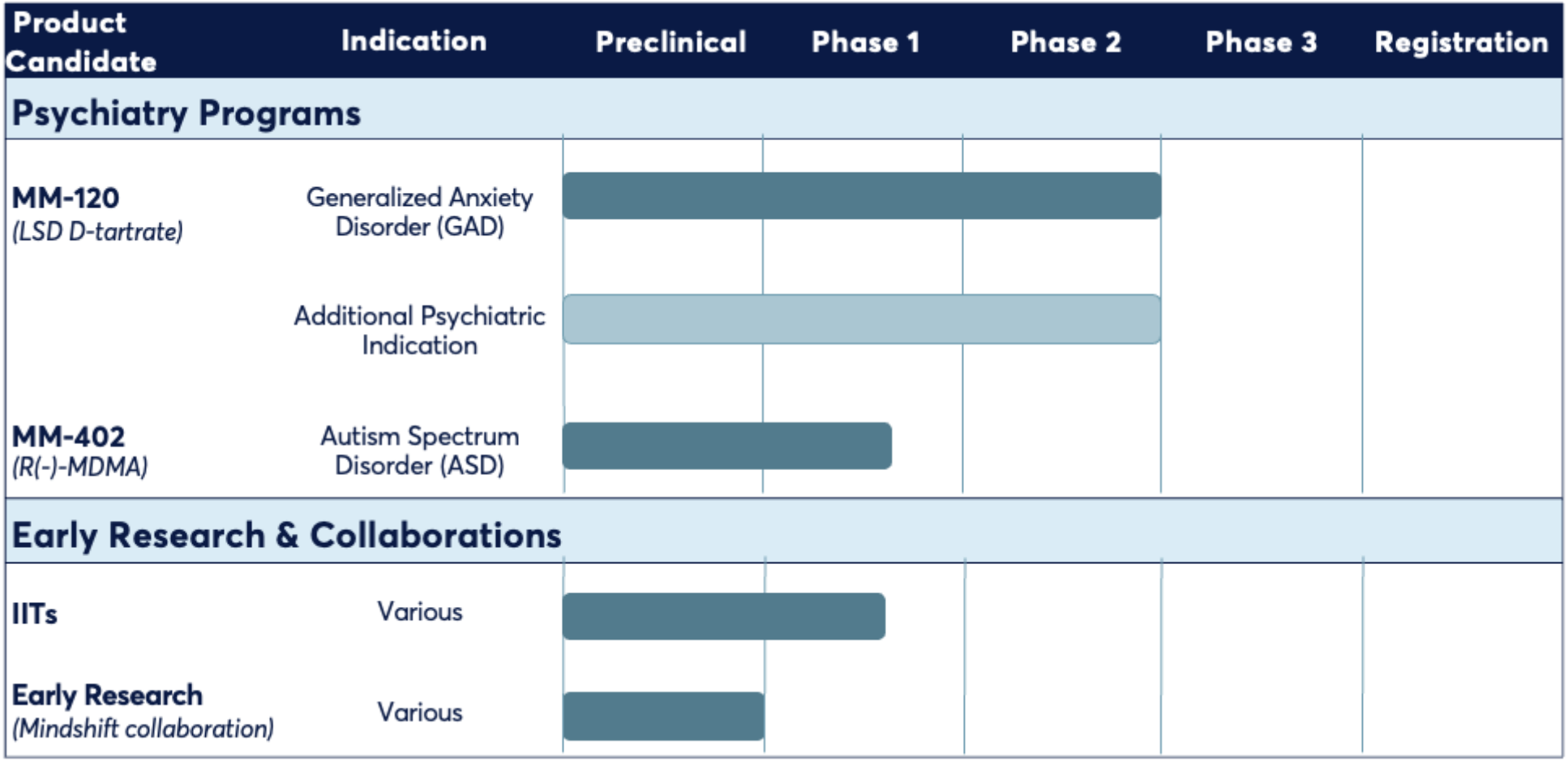
Cautionary Note Regarding Regulatory Matters

The United States federal government regulates drugs through the Controlled Substances Act. MM-120 is a proprietary, pharmaceutically optimized form of lysergide D-tartrate. Lysergide is a Schedule I substance under the Controlled Substances Act. While the Company is focused on programs using psychedelic or hallucinogenic compounds and non-hallucinogenic derivatives of these compounds, including in its MM-120 and MM-402 product candidates, the Company does not have any direct or indirect involvement with the illegal selling, production or distribution of any substances in the jurisdictions in which it operates. The Company is a neuro-pharmaceutical drug development company and does not deal with psychedelic or hallucinogenic substances except within laboratory and clinical trial settings conducted within approved regulatory frameworks. The Company's products will not be commercialized prior to applicable regulatory approval, which will only be granted if clinical evidence of safety and efficacy for the intended uses is successfully developed.

Market and Industry Data

This Presentation includes market and industry data that has been obtained from third-party sources, including industry publications. MindMed believes that the industry data is accurate and that the estimates and assumptions are reasonable, but there is no assurance as to the accuracy or completeness of this data. Third party sources generally state that the information contained therein has been obtained from sources believed to be reliable, but there is no assurance as to the accuracy or completeness of included information. Although the data is believed to be reliable, MindMed has not independently verified any of the data from third party sources referred to in this Presentation or ascertained the underlying economic assumptions relied upon by such sources. References in this Presentation to research reports or to articles and publications should be not construed as depicting the complete findings of the entire referenced report or article. MindMed does not make any representation as to the accuracy of such information.

MindMed's Pipeline

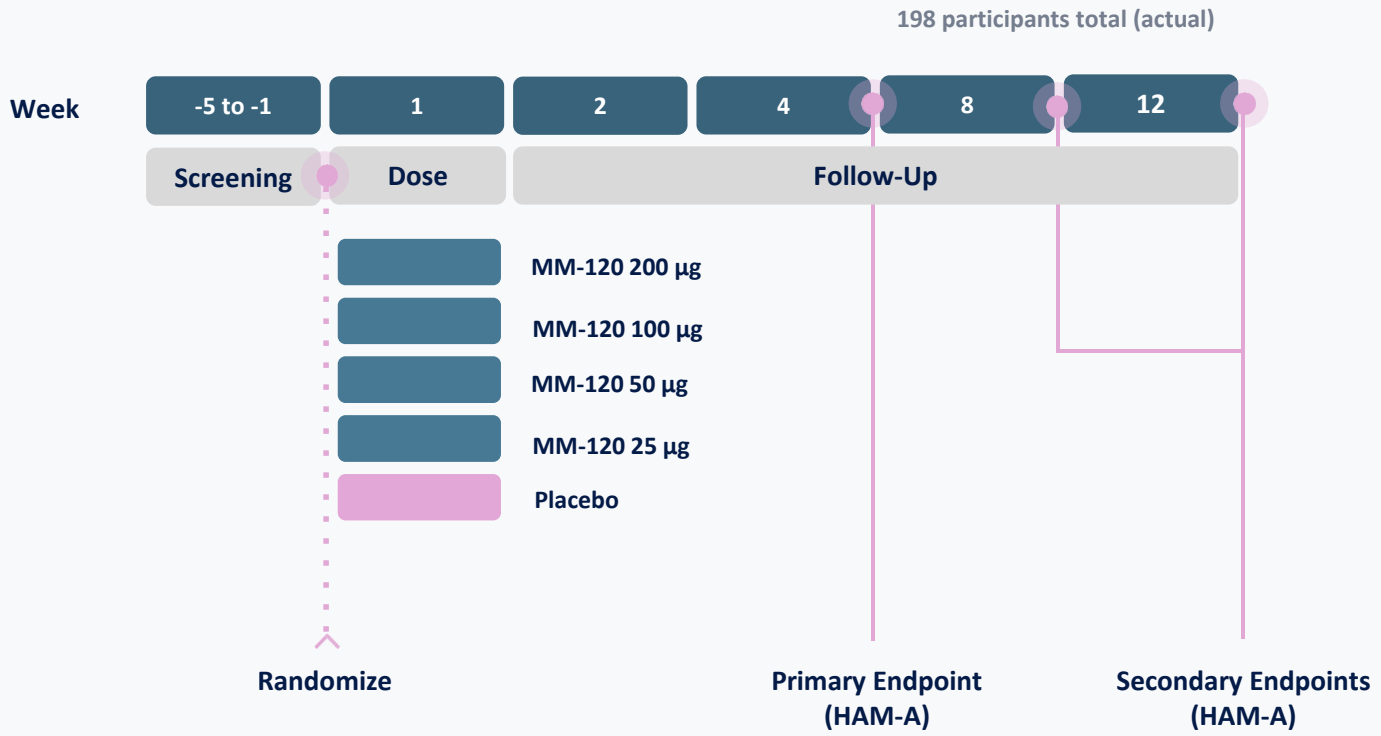


Full trial details and clinicaltrials.gov links available at mindmed.co/clinical-digital-trials/; LSD: lysergide; MDMA: 3,4-methylenedioxymethamphetamine. IIT: Investigator Initiated Trial; UHB: University Hospital Basel

Light colored line indicates study in exploration and/or planning stage.

Phase 2b Trial Design Overview[1]

PSYCHIATRY | **MM-120** (LSD D-tartrate) | Indication: GAD | PHASE 2b



Study MMED008 | MM-120 for GAD

A Phase 2b Dose Optimization Study of a Single Dose of MM-120 in Generalized Anxiety Disorder

KEY ENTRY CRITERIA

- Men and Women
- Ages 18-74
- Diagnosis of GAD
- HAM-A ≥ 20

ADDITIONAL ENDPOINTS

- MADRS
- CGI-S / I
- PGI-S / C
- SDS
- EQ-5D-5L
- PSQI
- ASEX

1. Source: Study MMED008 internal study documents.

µg: microgram; HAM-A: Hamilton Anxiety Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; CGI-S: Clinical Global Impressions - Severity; PGI-S: Patient Global Impression - Severity; SDS: Sheehan Disability Scale; EQ-5D-5L: EuroQol-5 Dimension; PSQI: Pittsburgh Sleep Quality Index; ASEX: Arizona Sexual Experiences Scale

Details of Phase 2b Treatment Delivery Protocol[1]

- Designed to demonstrate drug-only effect with no psychotherapeutic intervention

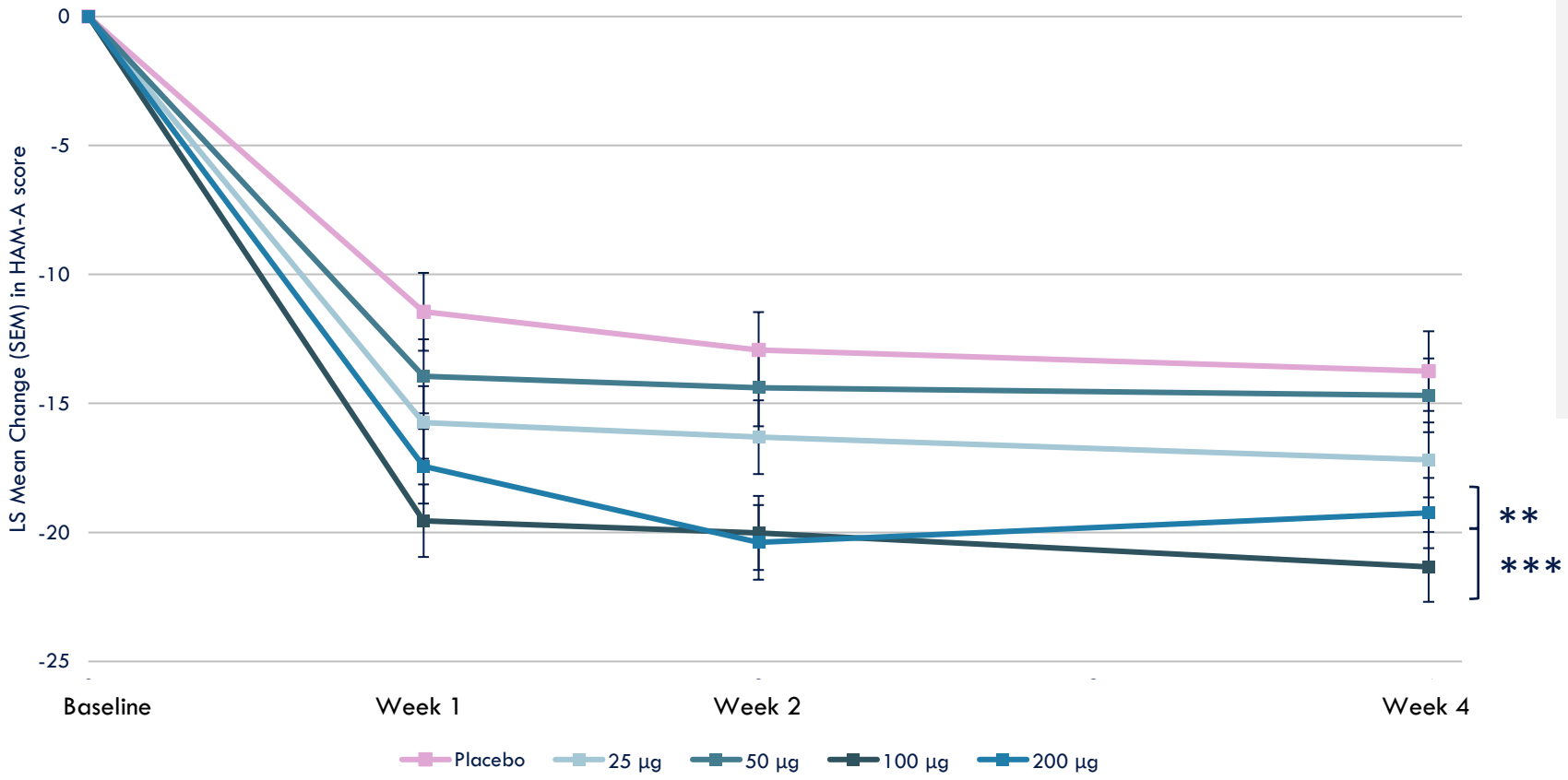
	Pre-treatment	During treatment	Post-treatment
Patient Journey in MMED008	✓ Comprehensive informed consent process ✓ Eligibility evaluation	✓ Continuous participant monitoring by dosing session monitors ✓ Participants provided with music, eye shades, reading and writing materials ✓ Participants released from observation when discharge criteria met	✓ Follow-up visits for safety and efficacy assessments
Not Part of Patient Journey in MMED008	x No “preparation” – pre-treatment activities consisted of only standard informed consent process	x No “assisted therapy” x No psychotherapy and no therapeutic intervention beyond study drug administration	x No “integration” x No ongoing therapeutic engagement as part of clinical trial activities

1. Source: Study MMED008 internal study documents.

Phase 2b in GAD | Primary Endpoint: Change in HAM-A Score through Week 4[1]

Statistically and clinically significant reductions in HAM-A score at all timepoints through week 4 in 100 and 200 µg dose groups

HAM-A Change from Baseline



Change to Week 4

- 100 µg: -21.3 points
- 200 µg: -19.3 points

Improvement over Placebo

- 100 µg: -7.6 pts, p=0.0004
- 200 µg: -5.5 pts, p=0.01

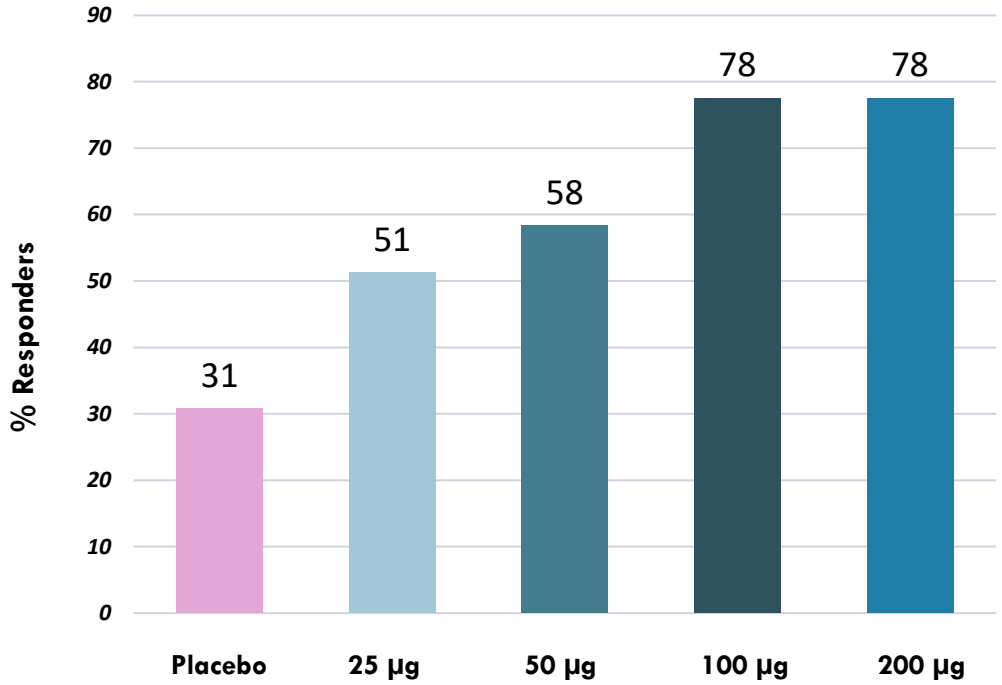
**p≤0.01
***p≤0.001

1. Source: Study MMED008 internal study documents and calculations. Full analysis set population.
µg: microgram; HAM-A: Hamilton Anxiety Rating Scale; NOTE: Significance achieved despite study not being powered for these pairwise comparisons.

Phase 2b in GAD | HAM-A Response and Remission at Week 4[1]

Dose-dependent increases in response with 78% responders in 100 and 200 µg dose groups; 50% of participants achieved remission in 100 µg dose group

HAM-A Response Rate at Week 4[2]



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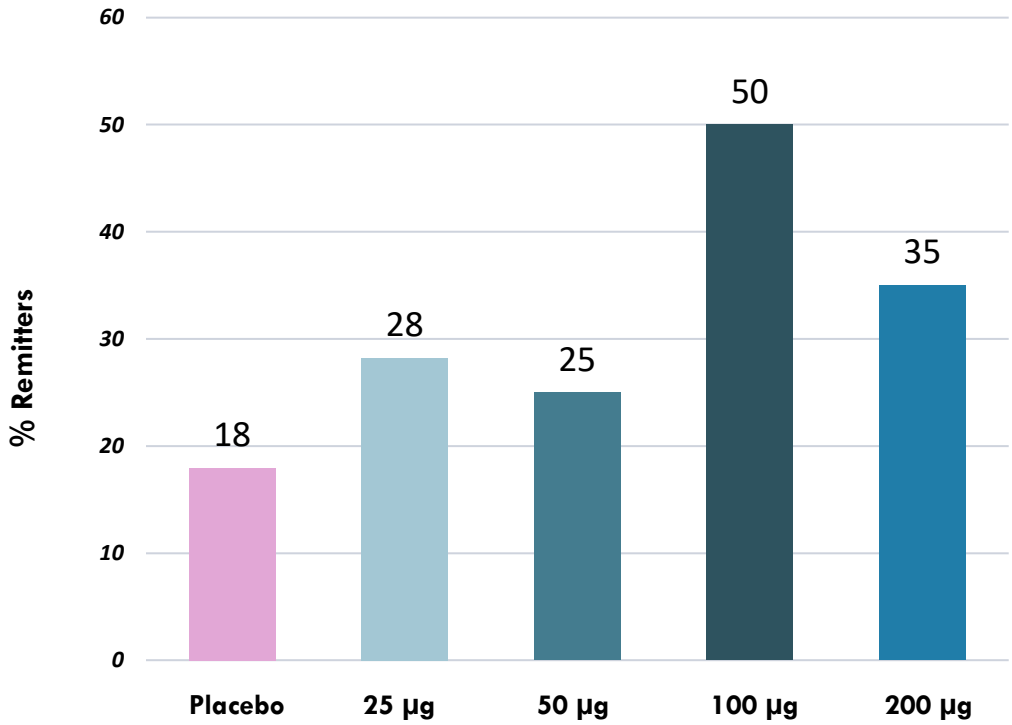
HAM-A Remission Rate at Week 4[2]



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1. Source: Study MMED008 internal study documents and calculations. Full analysis set population.
2. Response is defined as a 50% or greater improvement on HAM-A score; Remission is defined as a HAM-A score of ≤ 7.

µg: microgram; HAM-A: Hamilton Anxiety Rating Scale

Effects of Psychedelics Appear to be “Unique”…But Are They?

- How unusual are psychedelics, beyond qualitative perceptual effects?
- Does this demand differently designed trials?
- Does this require a change in fundamental principles of clinical trials?
- What specific purposes would these changes achieve?

Common to CNS Active Drugs	Unique to Psychedelics vs. CNS Active Drugs
• Altered mental state due to PD effects • Functional unblinding • Expectancy / placebo/nocebo effects • Need to demonstrate safety & effectiveness (acutely & chronically) • Specific safety monitoring procedures	• Specific nature of perceptual changes (and associated potential risks) • Potential for clinical activity that extends far beyond drug exposure

Considerations for Clinical Trials & Potential Implications for Post-Approval Patient Care[1]

Category	Specific Considerations[1]	Potential Drug / Clinical Precedents[2]
Participant Monitoring Ratio	• Are more monitors safer? • What specific risks are being mitigated?	• Psychotherapy • Spravato® / ketamine
Monitor Qualifications	• What is utility of advanced degree requirements in monitoring dosing sessions?	• Emergency medicine (e.g. EMTs) • Hospital delirium
Release from Dosing Session	• What specific clinical status / risks need to be mitigated before a patient can be released?	• Surgery / anesthesia
Placebo / Controls	• Do alternate controls benefit or harm blinding and study validity/interpretability?	• Approved CNS active drugs (Spravato®, psychostimulants, etc.)
Establishment of Safety & Effectiveness	• Is any deviation from established program/study designs warranted to establish acute and long-term effect?	• Clinical trial program for approved MDD and GAD drugs

1. If the product candidate should receive regulatory marketing authorization and be marketed.
2. Select precedents.

MindMed

Session 3: Dosing

Presenters:

- **Robert Barrow, MSc,** MindMed
- **Guy Goodwin, DPhil,** Compass Pathways
- **Berra Yazar-Klosinski, PhD,** Lykos Therapeutics

Panelists:

- **Peter Hendricks, PhD**, University of Alabama at Birmingham
- **Jennifer Mitchell, PhD**, University of California, San Francisco
- **Martine Solages, MD**, U.S. Food and Drug Administration

The dosing of COMP360 psilocybin

Guy Goodwin

Compass Pathways

January 2024

Compass

Disclosures

Employee of Compass Pathfinder Ltd., a subsidiary of Compass Pathways plc, and holds shares and share options in Compass Pathways plc

Disclosures

- This presentation has been prepared by Compass Pathways plc ("we," "us," "our," "Compass" or the "Company"). This presentation may contain "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, relating to our business, operations, and financial conditions, including but not limited to current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results and other future conditions. In some cases forward-looking statements can be identified by terminology such as, but not limited to, "may," "will", "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "potential," "would," "should" and "could," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Compass's control and which could cause actual results, levels of activity, performance or achievements to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others: clinical development is lengthy and outcomes are uncertain, and therefore our clinical trials may be delayed or terminated; our efforts to obtain marketing approval from the applicable regulatory authorities in any jurisdiction for COMP360 or any of future product candidates may be unsuccessful, and those risks and uncertainties described under the heading "Risk Factors" in Compass's most recent annual report on Form 10-K or quarterly report on Form 10-Q and in other reports we have filed with the U.S. Securities and Exchange Commission ("SEC") , which are available on the SEC's website at www.sec.gov. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.
- COMP360 is an investigational drug and has not been approved by any regulatory authority in any country. The safety and efficacy of investigational drugs have not been established. There is no guarantee that COMP360 will receive health authority approval or become commercially available in any country for the uses being investigated.

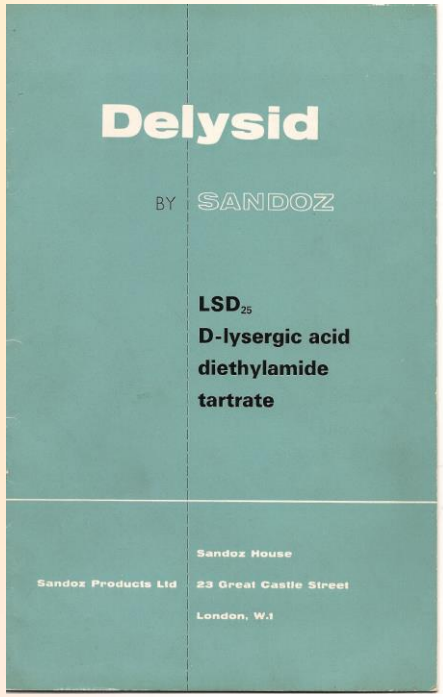
A history of dosing of classic psychedelic drugs in the first medical era

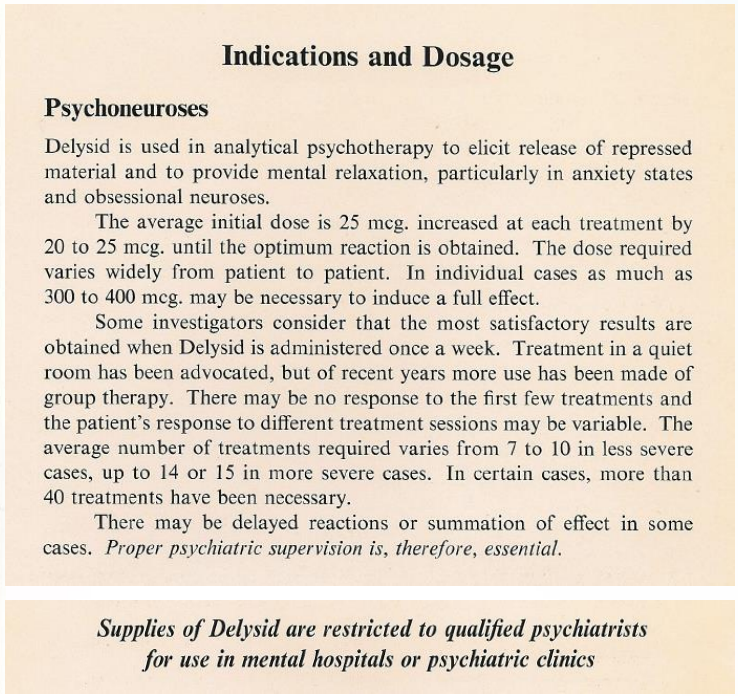
- Low dose as a psycholytic to “assist psychotherapy”
- High dose to achieve the characteristic psychedelic state with psychological preparation and support – found to be therapeutic

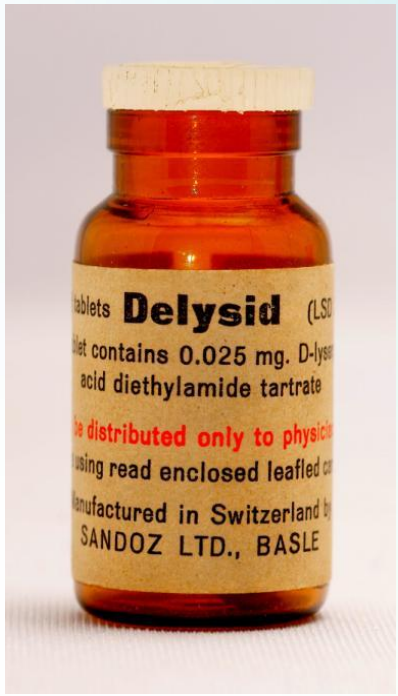
Pollen 1916 How to change your mind

A history of dosing of classic psychedelic drugs in the first medical era

- 1947: Sandoz introduced LSD as a psychedelic drug
- 1949: Brought to the US for testing and research
- Low dose as a psycholytic to “assist psychotherapy”
- High dose to achieve the characteristic psychedelic state with psychological preparation and support – found to be therapeutic







Psilocybin Dose finding experiments in modern era

- Roland Griffiths and colleagues in healthy volunteers
  - *Psychopharmacology (2011) 218:649–665*
- 20 and 30 mg oral doses of synthetic psilocybin produced similar dose related positive/wanted effects
- 30 mg oral dose produced more distressing/unwanted experiences

Psychedelic effects correlate with 5-HT_{2A} receptor occupancy and plasma psilocin

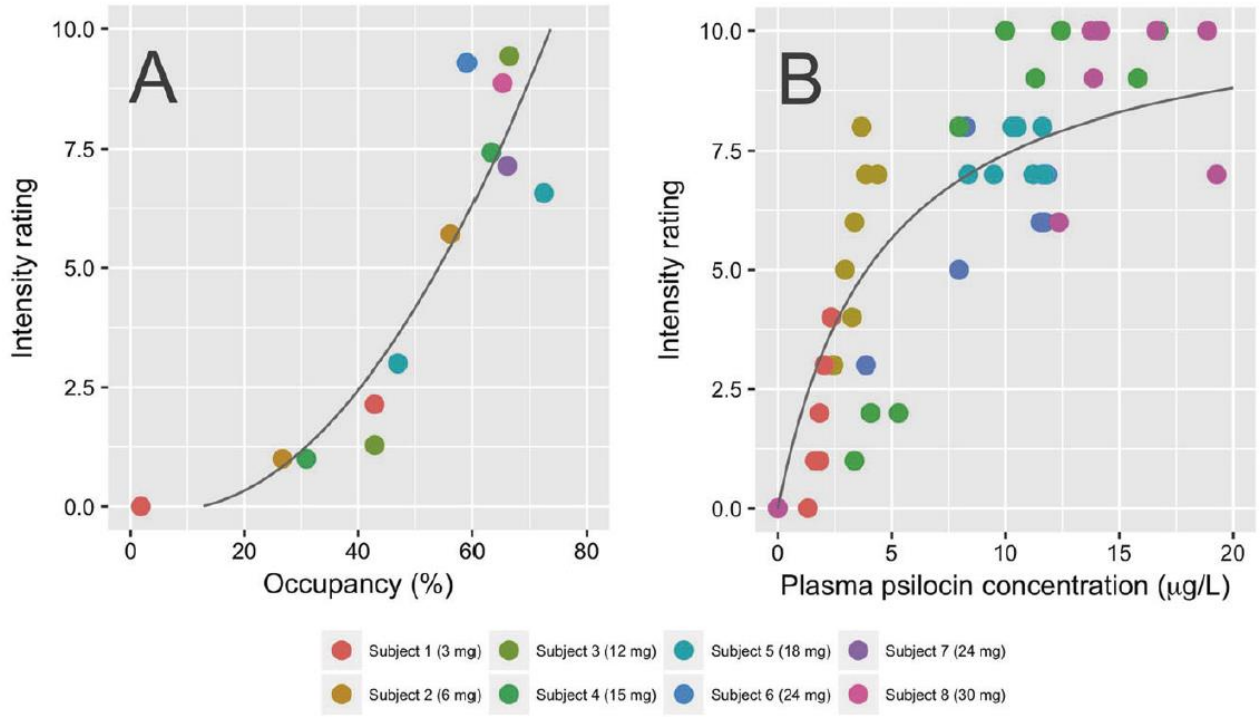


Fig. 4 Subjective intensity of the psychedelic experience at the time of the PET scan, neocortical 5-HT2AR occupancy and plasma psilocin concentration. **a** Relationship between intensity ratings and neocortical 5-HT2AR occupancy. The fitted line was obtained using a quadratic function. **b** Relationship between intensity and psilocin concentration, fitted to a single site receptor binding model

Source: Madsen et al., 2019 Neuropsychopharmacology. 2019 Jun;44(7):1328-1334. doi: 10.1038/s41386-019-0324-9. Epub 2019 Jan 26.

COMP360 psilocybin treatment

COMP360

Synthetic, high-purity, polymorphic crystalline formulation of psilocybine, a psychoactive proprietary compound developed to cGMP standards

Psychological support

With well trained qualified staff in a suitable setting

COMP360 psilocybin treatment:
Comprehensive standalone NCE package

- Nonclinical development programme
  - As per ICH M3 requirements
- Clinical pharmacology package underway
  - according to ICH standards
- Clinical efficacy and safety in TRD
  - Phase IIb trial in TRD: study completed (n=233)
  - Phase II exploratory, open-label trial: adjunct to an SSRI completed (n=19)
  - Long-term follow up of phase II participants completed (n=66)
  - Two phase III trials are ongoing

Note: TRD = treatment-resistant depression; SAD = single ascending dose; SSRI = selective serotonin reuptake inhibitor; NCE = new chemical entity

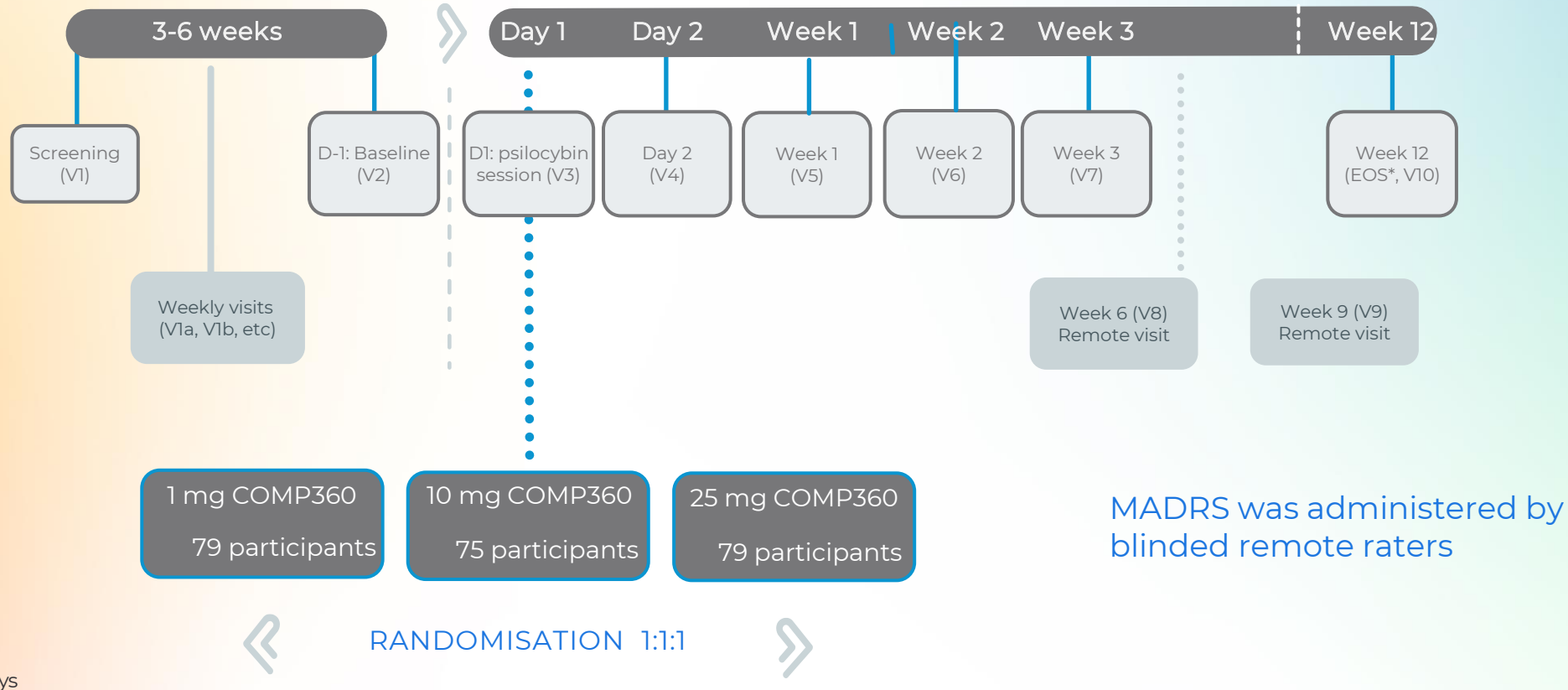
COMP 001 Phase IIb trial: COMP360 psilocybin treatment for TRD Target enrolment of 216 patients achieved (233 dosed)

Primary endpoint

- Reduction of symptoms of depression as measured by MADRS from baseline to 3 weeks

Secondary endpoints

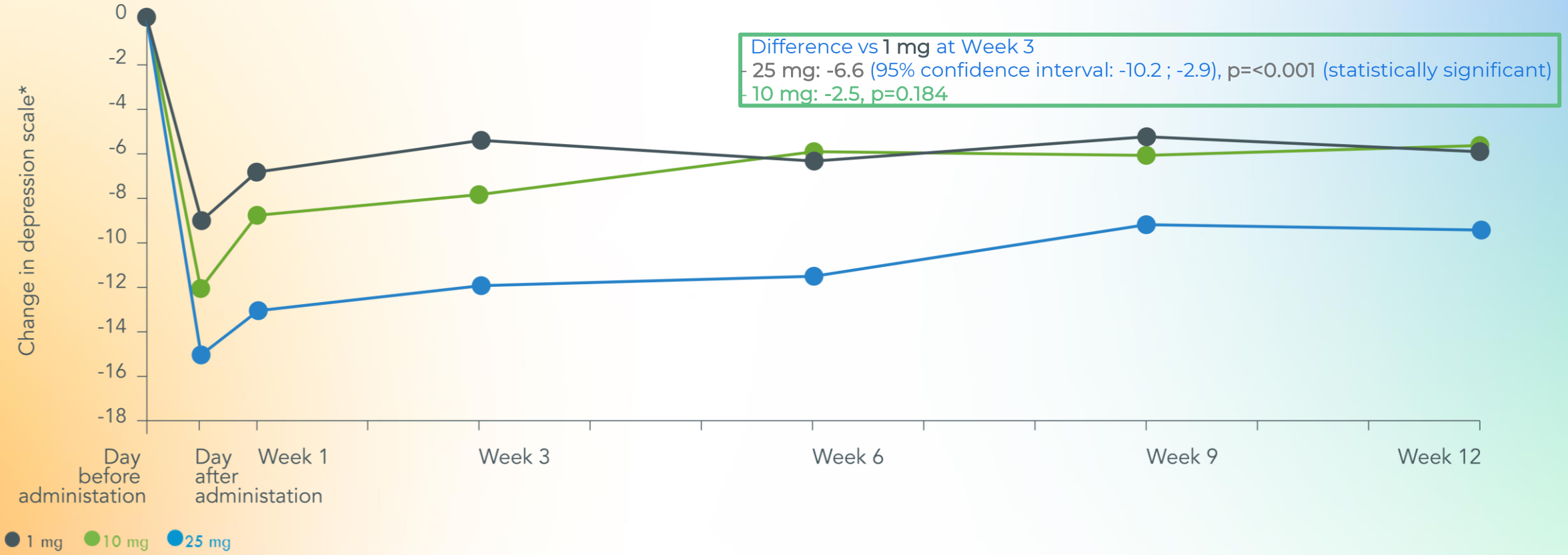
- Proportion of participants with response (≥50% decrease in MADRS from baseline) and remission (MADRS ≤10) at Week 3
- Proportion of responders who maintained ≥50% improvement in MADRS up to Week 12 (durability of effect)



MADRS was administered by blinded remote raters

Note: TRD = treatment-resistant depression, MADRS = Montgomery-Åsberg depression rating scale; EOS = end of study; V = visit. NEMJ - Goodwin et al. (2022)

Our Phase IIb trial results demonstrated the potential for a rapid, sustained response in TRD patients



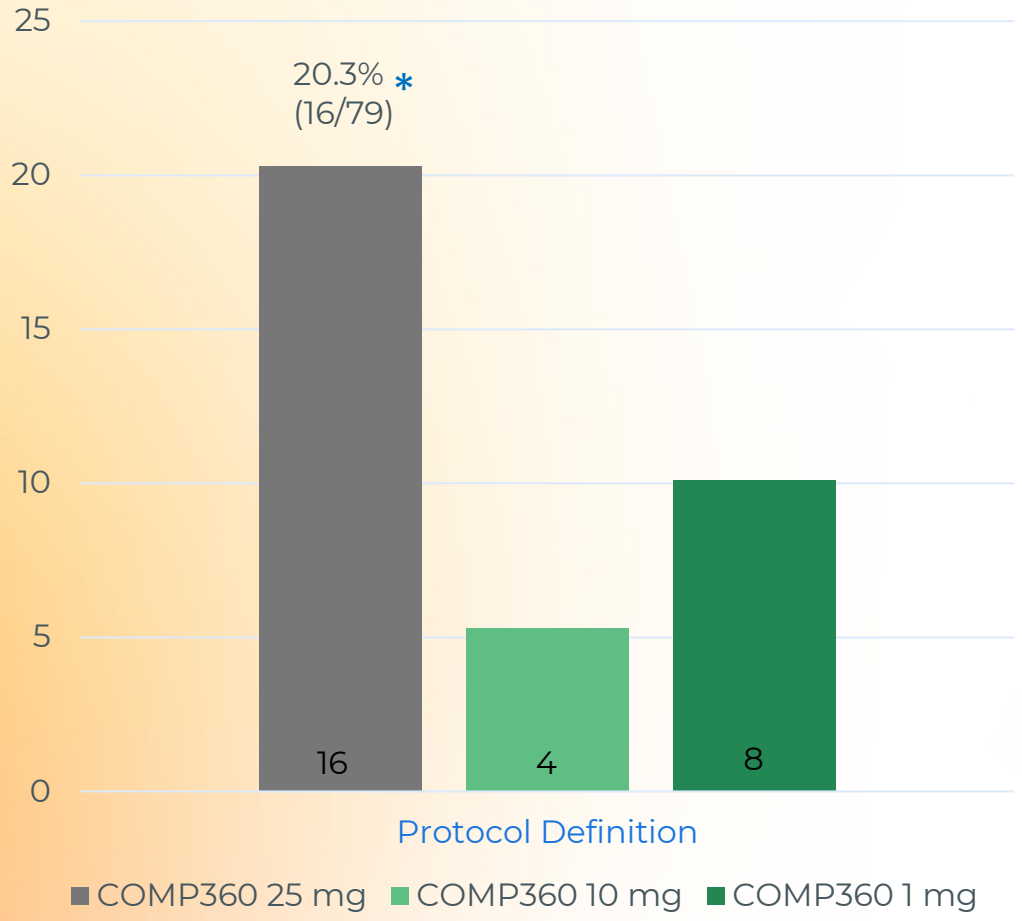
Efficacy: a statistically significant and clinically meaningful reduction in depression symptoms

Rapid onset action: the effect occurred the day after the administration

Durability: a sustained response at Week 12 – a positive indication for high potential as a monotherapy

Note: TRD = treatment-resistant depression. *Montgomery-Asberg Depression Rating Scale

Double the number of patients who received 25 mg dose had a sustained response at Week 12, compared to 1 mg (20.3% vs 10.1%)



25 mg vs 1 mg odds ratio = 2.2; p = 0.081
10 mg vs 1 mg odds ratio = 0.7; p = 0.460

Definition of sustained response: participants meeting the MADRS response criteria at any visit up to and including Week 3 and also at all visits after Week 3 until Week 12

  Note: * = nominal sig odds ratio vs 1 mg; p = p-value; number of sustained responders stated in bar, MADRS: Montgomery-Åsberg Depression Rating Scale

COMP360 was generally well-tolerated in the phase IIb study

Treatment-emergent adverse events (TEAEs)

>90% of TEAEs were of mild or moderate severity

5 most frequent TEAEs across the 10 mg and 25 mg doses were headaches, nausea, fatigue, insomnia and anxiety

>77% of TEAEs occurring on the day of administration resolved on the same or next day; most were mild or moderate

There were no concerns with vital signs, ECG or clinical laboratory data in any of the treatment groups

TEAEs involving hallucinations (which only occurred in the 25 mg and 10 mg groups) and illusions (all groups) started and resolved on the day of administration

TESAEs of suicidal ideation, suicidal behaviour and intentional self-injury were uncommon but occurred unevenly across groups in non-responders

Table 32: TESAEs by Primary MedDRA SOC and PT – Safety Analysis Set

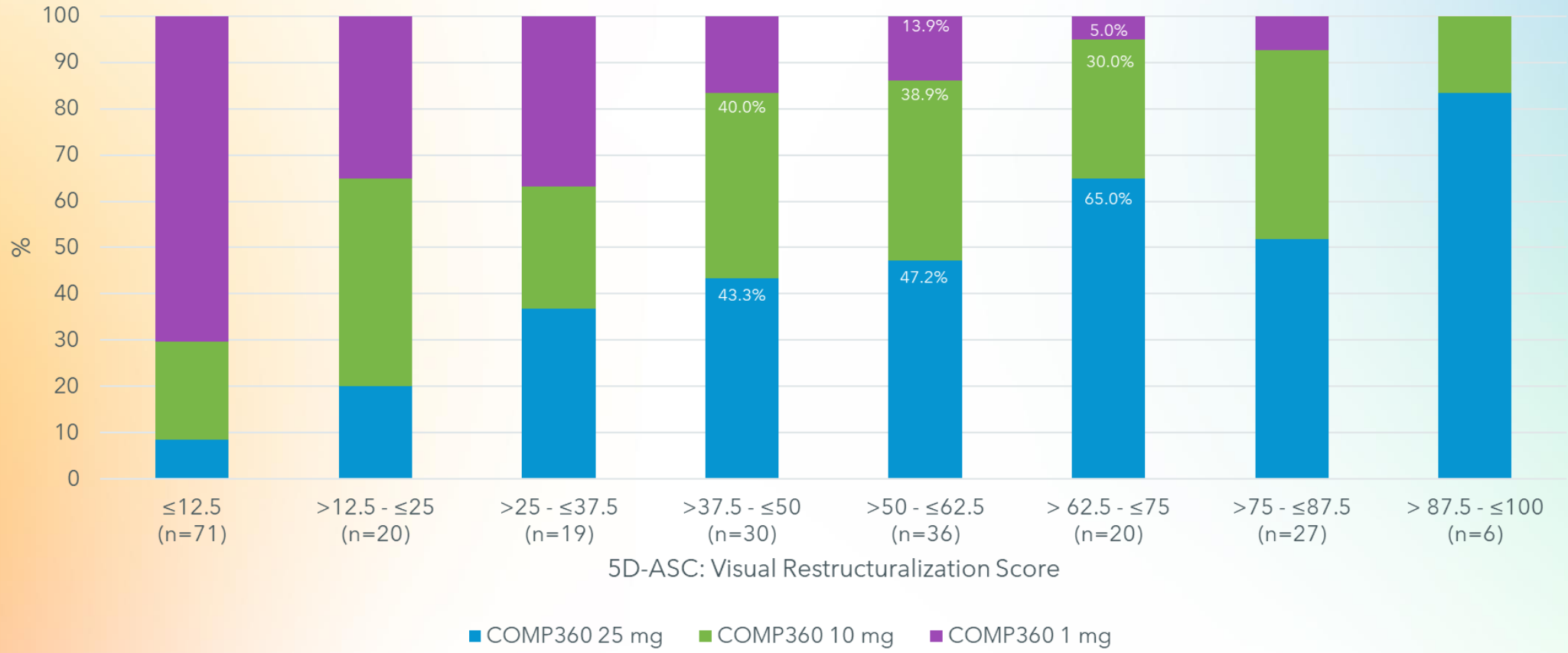
SOC PT	COMP360 25 mg (N=79)		COMP360 10 mg (N=75)		COMP360 1 mg (N=79)		Overall (N=233)	
	n (%)	events	n (%)	events	n (%)	events	n (%)	events
Any TESAEs	5 (6.3)	10	6 (8.0)	7	1 (1.3)	2	12 (5.2)	19
Psychiatric disorders	5 (6.3)	9	5 (6.7)	6	1 (1.3)	2	11 (4.7)	17
Intentional self-injury	2 (2.5)	2	2 (2.7)	2	1 (1.3)	2	5 (2.1)	6
Suicidal ideation	2 (2.5)	2	2 (2.7)	3	0	0	4 (1.7)	5
Suicidal behaviour	3 (3.8)	3	0	0	0	0	3 (1.3)	3

 Note: TEAEs = treatment-emergent adverse event, TESAEs = treatment-emergent serious adverse events, TRD = treatment resistant depression; ECG = electrocardiogram

Key lessons for end of phase II (1)

- Minimal effective single dose
    - Clear evidence for efficacy of a single 25 mg dose v 1 mg and apparent numerical separation from 10 mg
- Durability of response to 12 weeks
- Consider more than one administration of drug
    - E.g. especially of interest for 10 mg dose

Blinding or dose uncertainty



Key lessons for end of phase II (2)

- Three dose design appears largely to ensure blinding
- Nevertheless, placebo study required for safety baseline
- Further standardize psychological support to ensure we are clearly measuring the drug effects and not the impact of differential psychological support.

The Phase III studies are designed to address these key clinical objectives

- To investigate the **efficacy of COMP360 25mg** as a single dose (in Study COMP 005) or two fixed doses (in Study COMP 006), administered with psychological support in improving symptoms of depression at Week 6
- To characterise the **efficacy and durability of two fixed COMP360 10 mg doses** (in Study COMP 006)
- To establish the **safety profile** of COMP360 25 mg and COMP360 10 mg versus placebo and/or COMP360 1 mg

End

Session 3: Dosing

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Panelists:

- **Peter Hendricks, PhD**, University of Alabama at Birmingham
- **Jennifer Mitchell, PhD**, University of California, San Francisco
- **Martine Solages, MD**, U.S. Food and Drug Administration

COMMITTED TO TRANSFORMING MENTAL HEALTHCARE

Midomafetamine Capsules in Combination with Psychological Intervention for Treatment of PTSD

ADVANCING PSYCHEDELIC CLINICAL STUDY DESIGN

January 31, 2024

Berra Yazar-Klosinski, Ph.D.
Chief Scientific Officer

MDMA-assisted therapy has not been approved by any regulatory agency.
The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

lykos THERAPEUTICS

Our agenda

COMMITTED TO TRANSFORMING MENTAL HEALTHCARE

01.

Context

02.

Nonclinical & Early Phase Trials

03.

Clinical Dosing Regimen

From development stage to commercial ready

PENDING REGULATORY APPROVAL

- **1986**: MAPS created to support MDMA-assisted therapy research
- **2010:** Pilot study published in *Psychopharmacology*
- **2014**: MAPS Public Benefit Corporation (MAPS PBC) formed as drug development company
- **2016**: Successful End of Phase 2 meeting with FDA
- **2017**: FDA Breakthrough Therapy designation
- **2019:** First Phase 3 participant treated in MAPP1 PTSD clinical trial
- **2021**: MAPP1 published in *Nature Medicine*
- **2022**: Phase 3 completion with end of MAPP2 PTSD clinical trial
- **2023**: MAPP2 published in *Nature Medicine*
- **2023**: Submitted New Drug Application for MDMA-assisted therapy for PTSD
- **2024**: First equity financing and MAPS PBC rebranded to **Lykos Therapeutics**

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1. Greer GR & Tolbert, R. J Psychoactive Drugs. 1998;18(4):371-379. **2.** Stolaroff, MJ. (2004). The Secret Chief Revealed. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies. **3.** Doblin, RE. (2001) Regulation of the Medical Use of Psychedelics and Marijuana. [Doctoral dissertation, Harvard University]. Accessed Jan 25, 2024. https://maps.org/2014/11/18/dissertation-rick-doblin-ph-d.

MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

MDMA is an Entactogen

- MDMA-Assisted Therapy: midomafetamine capsules administered in combination with psychological intervention provided by Qualified Healthcare Provider (QHP) [1]


Image credit: Bryce Montgomery.

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Rationale and Use of Key Terms

- "Psychological intervention" and "entactogen" are terminology recognized in the industry and utilized by FDA[2]
- "Qualified Healthcare Provider" (QHP) was selected for prescribers and payors to be able to convey the qualifications of the provider of the psychological intervention.
- MDMA is the active pharmaceutical ingredient of midomafetamine capsules.[1]

1. Lykos Therapeutics Announces Submission of New Drug Application to the FDA for MDMA-Assisted Therapy for PTSD. Dec. 12, 2023. https://lykospbc.com/press-releases/maps-pbc-announces-submission-of-new-drug-application-to-the-fda-for-mdma-assisted-therapy-for-ptsd/ **2.** FDA Draft Guidance for Industry, Psychedelic Drugs: Considerations for Clinical Investigations (June 2023) MDMA, 3,4-methylenedioxymethamphetamine.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Dosing and administration

RECOMMENDED DOSING REGIMEN* PENDING REGULATORY APPROVAL

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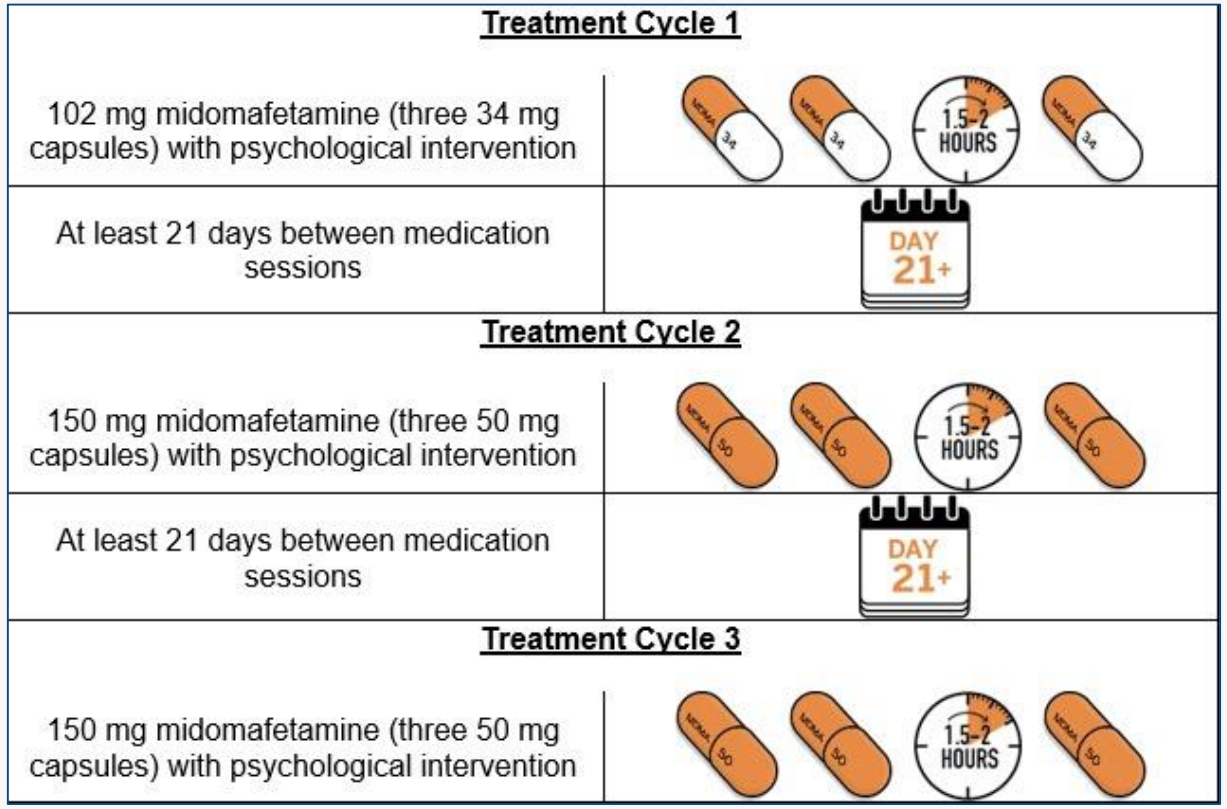

***free base dosage strength**

Rationale and Use of Terms

Midomafetamine capsules + "psychological intervention" = "**medication session**"

"Medication session" + follow-up integration psychotherapy sessions = one "**treatment cycle**"

Three "treatment cycles" = a "**complete treatment course**"

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Nonclinical & Early Phase Trials

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Complete nonclinical program highlights

CONDUCTED CONCURRENT WITH CLINICAL DEVELOPMENT

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- IND-enabling single and repeat-dose toxicology studies in dog, rat (did not translate to clinical doses)
- hERG Channel inhibition patch clamp assays
- In vitro & in vivo GLP genotoxicity standard battery
- Developmental & reproductive repeat-dose GLP toxicology studies in rabbit, rat
- Definitive (pivotal) GLP 28-day repeat-dose toxicology studies in dog, rat covering Maximum Tolerated Dose
- Included toxicokinetics, special neurohistopathology, and safety pharmacology assessments
- Evaluated central and autonomic nervous systems, as well as cardiovascular and respiratory effects

Key Results:

- No unusual findings in toxicology studies[1,2]
- No Observed Adverse Event Level (NOAEL) doses reported in developmental & reproductive toxicology studies were established based on repeat-dose toxicology studies[2]
- Toxicokinetic studies adequately demonstrated kinetics. No further pharmacokinetic characterization was required[2]
- No evidence of neurotoxicity with weekly dosing or single-dose[2]
- Carcinogenicity studies were not required as the genotoxicity battery was negative, and the product is intended for acute use[2]
- No findings suggestive of QT prolongation[2]

1. Cohen, IV et al. *J Psychopharmacol.* 2021;35(11):1431-1434. **2.** Data on File, Mod 2.4 Nonclinical Overview, Lykos.

hERG, human ether-à-go-go-related gene; IND, Investigational New Drug; GLP, Good Laboratory Practice.

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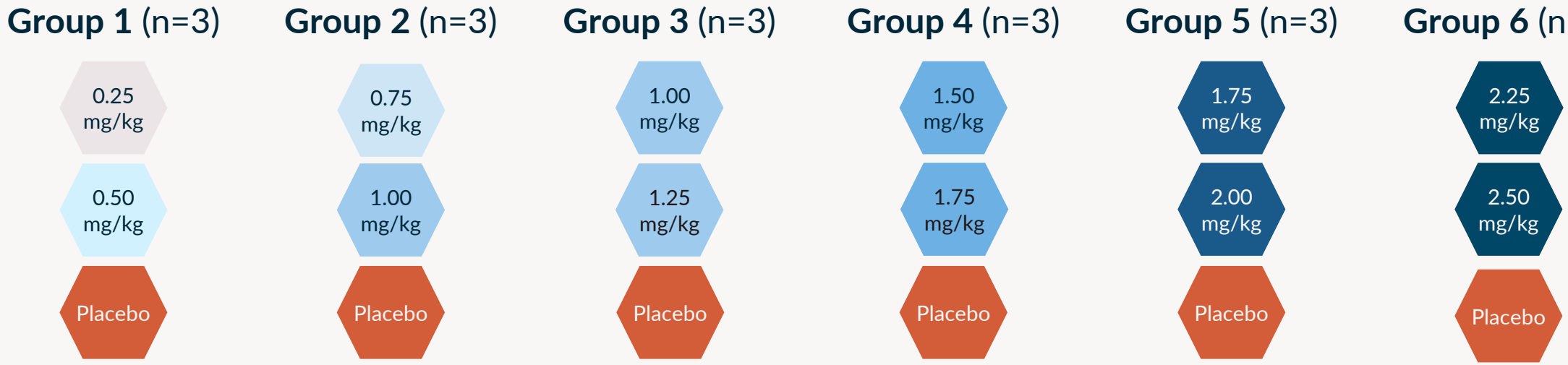
Designing an empiric dosing regimen

Phase 1 Research conducted by Charlie Grob, MD: May 1994 – November 1995 | Results published: 1996, 1998[1,2]

18 subjects each had 3 separate sessions 2 weeks apart. Ordering of sessions was randomized.

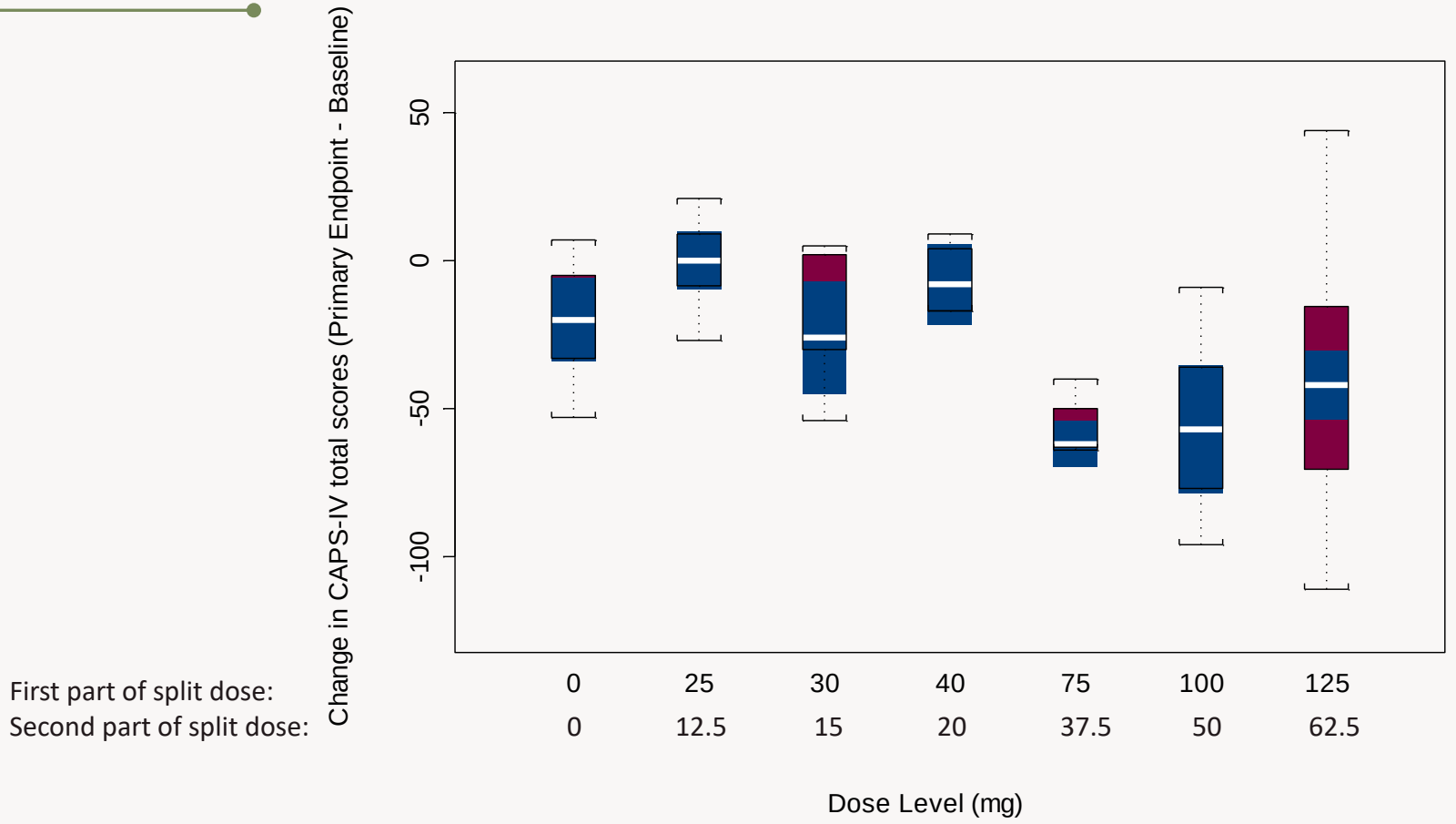


- Wider variability in subjective effects & pharmacodynamics (PD) than expected with mg/kg dosing, justifying fixed dosing
- Ability to adjust dosing necessary to assure maximum efficacy
- Acceptable safety results for further research

1. Grob CS. *Behav Brain Res.* 1996;73(1-2):103-107. **2.** Grob CS. *Int J Drug Policy*. 1998;9:119-124.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Phase 2 PTSD pilot studies explored a range of doses



- Estimated Therapeutic Bounds determined after two medication sessions with split dosing in 6 studies[1]
- Second part of split dose taken in (179/197) 90.9% of blinded Phase 2 medication sessions[1]

1. Mithoefer MC et al., *Psychopharmacology (Berl).* 2019;236(9): 2735-2745. This article is licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/. **2.** Doblin, RE. (2001) Regulation of the Medical Use of Psychedelics and Marijuana. [Doctoral dissertation, Harvard University]. Accessed Jan 25, 2024. https://maps.org/2014/11/18/dissertation-rick-doblin-ph-d.

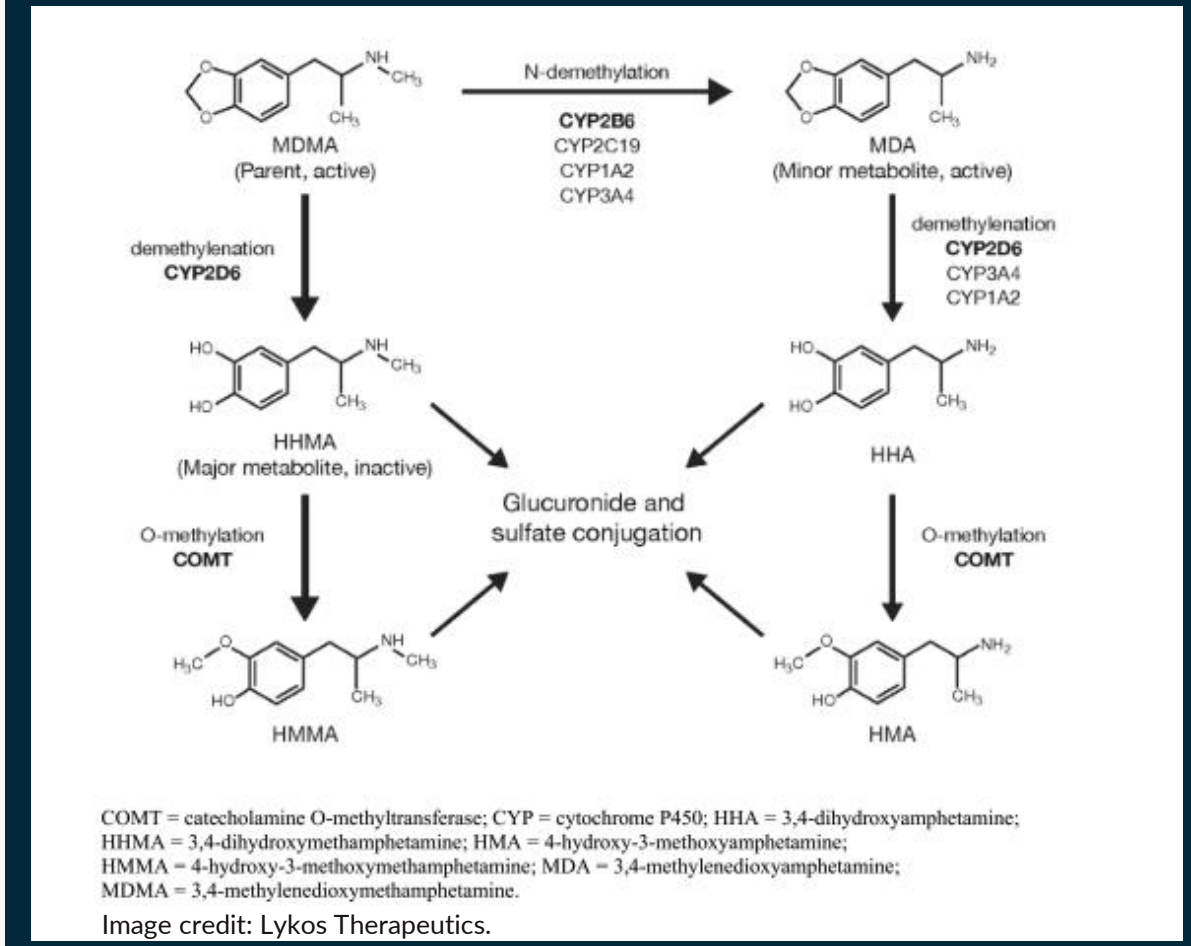
PTSD, post-traumatic stress disorder.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Metabolism of MDMA in humans

WELL-CHARACTERIZED

- Body weight was identified as a covariate affecting MDMA clearance and volume of distribution
  - Not clinically meaningful when considering therapeutic bounds [1]
- Age and sex were not identified as significant covariates on the pharmacokinetics of MDMA[1]
- No impact of a high fat meal on the maximum observed C_{max} and AUC[1]
- C_{max} and $AUC_{0\text{-}44h}$ were not meaningfully affected by split dosing over 2 hours relative to administering the total dose in a single dose[1]



COMT = catecholamine O-methyltransferase; CYP = cytochrome P450; HHA = 3,4-dihydroxyamphetamine; HHMA = 3,4-dihydroxymethamphetamine; HMA = 4-hydroxy-3-methoxyamphetamine; HMMA = 4-hydroxy-3-methoxymethamphetamine; MDA = 3,4-methylenedioxyamphetamine; MDMA = 3,4-methylenedioxymethamphetamine.

Image credit: Lykos Therapeutics.

1: Data on File, Mod 2.7.2, Lykos. **2:** MAPS-05; **3:** Kolbrich et al. *Ther Drug Monit.*. 2008;30(3): 320-332.
MDMA, 3,4-methylenedioxymethamphetamine. Cmax, highest concentration. Tmax, time to achieve highest concentration. AUC, area under the curve. H, hours.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Clinical Dosing Regimen

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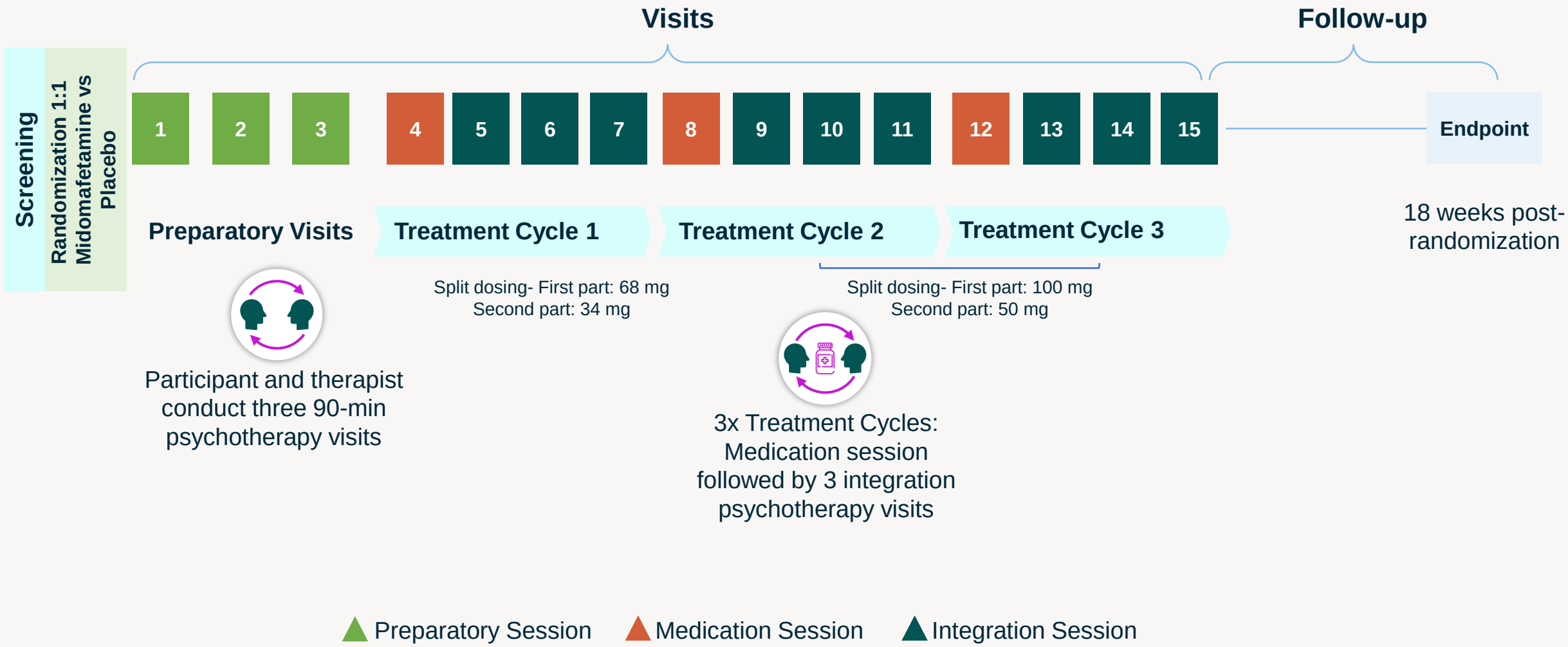
Randomized, double-blind, placebo-controlled Phase 3 trial design



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1. Mitchell JM et al. *Nat Med*. 2021;27(6):1025-1033. **2.** Mitchell JM et al. *Nat Med.* 2023;29(10):2473-2480.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Two Phase 3 trials met endpoints

AFTER THREE MEDICATION SESSIONS

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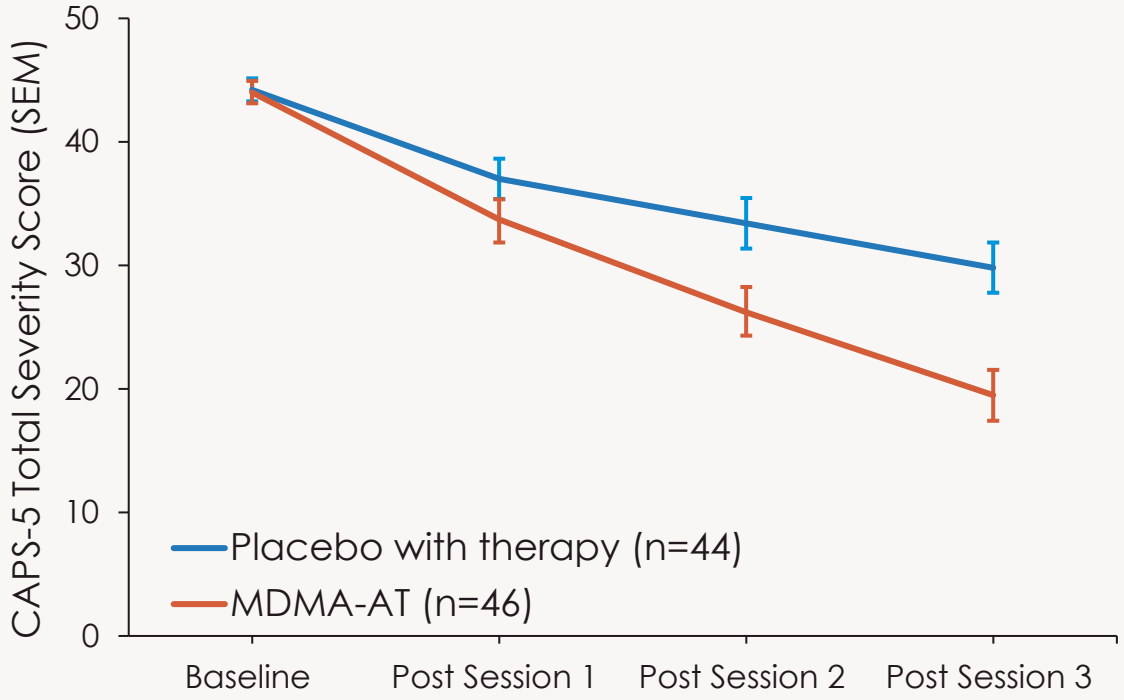
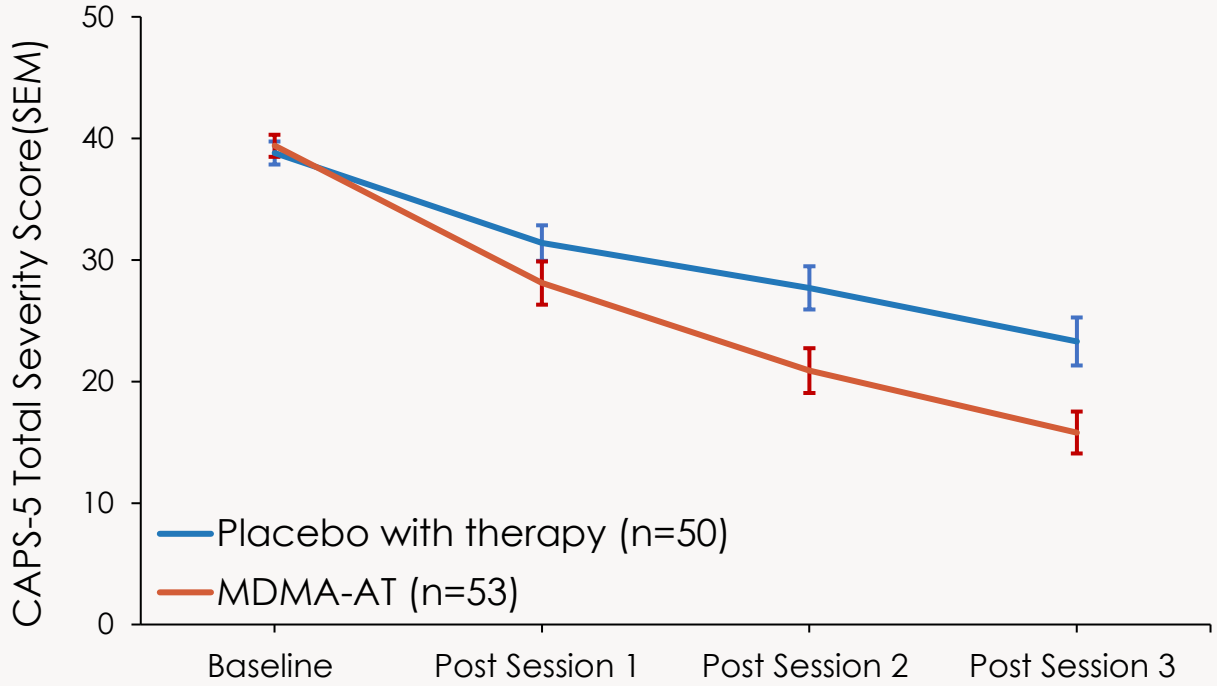
MAPP1: MDMA-Assisted Therapy Demonstrated Significant Reduction in PTSD Severity[1]



- LSMean changes in CAPS-5 scores after 3 medication sessions were −24.4 for MDMA-AT vs. -13.9 for placebo + therapy group (p<0.0001)[1]

MAPP2: MDMA-Assisted Therapy Demonstrated Significant Reduction in PTSD Severity[2]



- LSMean changes in CAPS-5 scores after 3 medication sessions were −23.7 for MDMA-AT vs. -14.8 for placebo + therapy group (p<0.001)[2]

1. Mitchell JM et al. *Nat Med*. 2021;27(6):1025-1033. **2.** Mitchell JM et al. *Nat Med.* 2023;29(10):2473-2480.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

Pooled Phase 3 adverse event reports

SAFETY SET

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Treatment Emergent Adverse Event Reports in 2x MDMA Group vs. Placebo Group in ≥10% of Participants Who Received MDMA, n (%)[1,2]

Reaction	MDMA (n=99)	Placebo (n=95)
Muscle tightness	59 (59.6%)	19 (20.0%)
Decreased appetite	43 (43.4%)	10 (10.5%)
Nausea	38 (38.4%)	16 (16.8%)
Hyperhidrosis (sweating)	28 (28.3%)	4 (4.2%)
Feeling cold	20 (20.2%)	6 (6.3%)
Paraesthesia	15 (15.2%)	4 (4.2%)
Restlessness	15 (15.2%)	2 (2.1%)
Dry mouth	14 (14.1%)	6 (6.3%)
Bruxism	13 (13.1%)	2 (2.1%)
Mydriasis (pupil dilation)	13 (13.1%)	0 (0%)
Feeling jittery	13 (13.1%)	0 (0%)
Nystagmus	13 (13.1%)	1 (1.1%)
Vision blurred	12 (12.1%)	1 (1.1%)
Chest discomfort	11 (11.1%)	4 (4.2%)
Chills	11 (11.1%)	1 (1.1%)
Tremor	11 (11.1%)	3 (3.2%)
Abdominal pain upper	10 (10.1%)	5 (5.3%)

Serious Adverse Event Reports[2,3]

- 2 participants in the placebo group reported 3 SAEs, consisting of suicide attempts or suicidal ideation, which resulted in self-hospitalization
- No SAEs in the MDMA group in Phase 3 trials

Treatment Emergent Adverse Event Reports of Special Interest

Suicidal Ideation or Behavior

- Suicidal Behavior: 0.0% (0/99) MDMA vs. 2.1%(2/95) Placebo[2,3]
- At least Moderate Ideation:
  - 13.1% (13/99) MDMA vs. 10.6%(10/95) Placebo[2,3]
- Intentional Self-Injury: 3.0% (3/99) MDMA vs. 5.3% (5/95) Placebo[2,3]

Cardiac Events

- Palpitations: 4.0%(4/99) MDMA vs. 2.1% (2/95) Placebo[2,3]

Abuse (dependence, misuse, and diversion)

- Overt Abuse: 0% in MDMA vs. 0% in placebo[2,3]

MDMA-AT has not been approved by any regulatory agency. The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

1. Data on File, Draft USPI, Lykos. **2.** Mitchell JM et al. Nat Med. 2021;27(6):1025-1033. **3.** Mitchell JM et al. Nat Med. 2023;29(10):2473-2480.

MDMA, 3,4-methylenedioxymethamphetamine; SAE, Serious Adverse Event.

Summary of MDMA dosing considerations

AFTER TWO DECADES OF RESEARCH

- Complete nonclinical program was conducted, however not informative for extrapolation of clinical doses
- Therapeutic bounds estimated based on Phase 1 and Phase 2 pilot studies
- Due to multiple metabolic pathways, with non-linearity better observed at higher end of dose range, variable subjective and pharmacodynamic effects
- Phase 2 dose response & placebo-controlled studies provided efficacy data in PTSD participants which supported a threshold dose response
- Phase 3 dosing regimen incorporates split dose and dose escalation with 3 medication sessions
- Generally, temporary dose-dependent increases in blood pressure and pulse were observed that resolved by the end of the medication session without treatment and no serious outcomes
- Empiric development of dosing regimen was beneficial in the context of improving efficiency in development program and prediction of effect size observed in Phase 3 trials.

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MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder.

MDMA-assisted therapy has not been approved by any regulatory agency. The safety and efficacy of MDMA-assisted therapy have not been established for the treatment of PTSD.

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We thank all the study participants and their support networks. We acknowledge and appreciate the oversight of the Clinical investigators and study therapists for their expert treatment of participants. We also thank the study coordinators, medical providers, night attendants, data monitoring committee members, Independent and Adherence Raters, and Lykos Therapeutics and MAPS staff for their efforts.

We also thank NIDA for providing primary PK data.

Session 3: Dosing

Presenters:

- **Robert Barrow, MSc,** MindMed
- **Guy Goodwin, DPhil,** Compass Pathways
- **Berra Yazar-Klosinski, PhD,** Lykos Therapeutics

Panelists:

- **Peter Hendricks, PhD**, University of Alabama at Birmingham
- **Jennifer Mitchell, PhD**, University of California, San Francisco
- **Martine Solages, MD**, U.S. Food and Drug Administration

Session 4: Durability of Treatment Response

Presenters:

- **Michael P. Bogenschutz, MD,** NYU Langone Center for Psychedelic Medicine
- **Carla Canuso, MD,** Janssen Pharmaceuticals

Panelists:

- **Valentina Mantua, MD, PhD,** U.S. Food and Drug Administration
- **Charles L. Raison, MD,** University of Wisconsin-Madison

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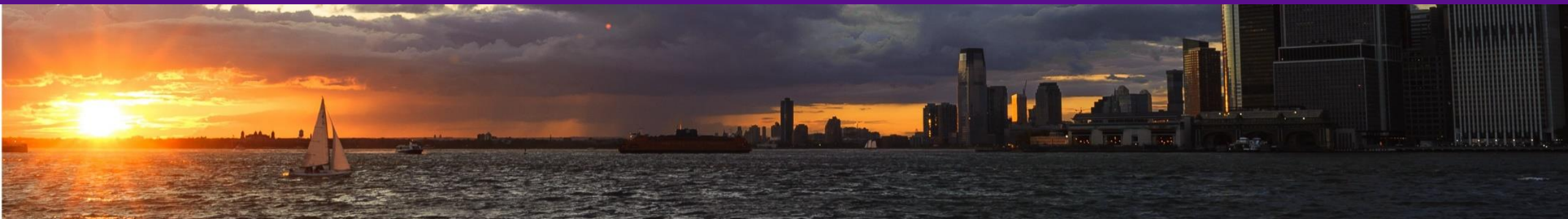
Some thoughts on durability of psychedelic treatment response

Michael Bogenschutz

Workshop on Advancing Psychedelic Study Design

January 31, 2024



Presentation Aims

- Define some of the questions surrounding durability of treatment response.
- Summarize existing knowledge concerning durability of response.
- Consider strategies to answer some of the most important questions.

Two big questions:

1. How can we maximize the durability of the effects of a treatment episode?
2. How should we decide if and when follow-up treatment should be administered?

Durability of effects of a treatment episode could depend on:

- Drug
- Dosage
- Number and schedule of doses
- Indication
- Patient characteristics
- Co-occurring treatment (psychotherapy, medications, etc.)
- Whether we are looking for within- or between-group effects

Whether and when to administer follow-up treatment could depend on:

- Duration of effects of the primary treatment episode
- Efficacy of follow-up treatment for
  - Maintenance of effect
  - Treatment of relapse
- Safety (risk profile could change with greater exposure)
- All three could depend on many factors (see previous slide)

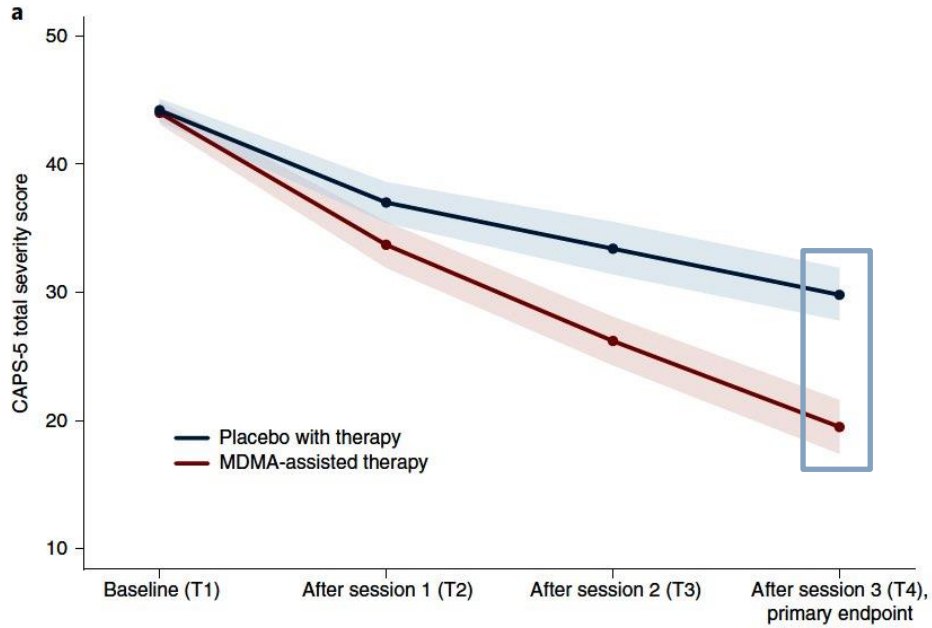
What do we know about the durability of treatment episode effects?

MDMA for PTSD

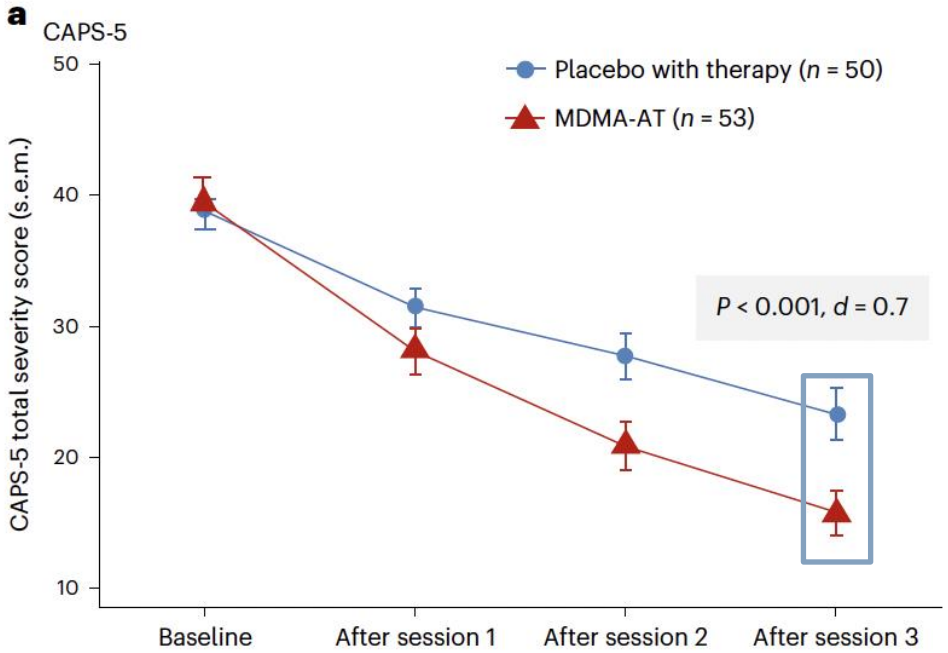
- Treatment model: 3 high-dose sessions, 4-6 weeks apart, combined with extensive somewhat idiosyncratic therapy before, during, and after sessions (duration of treatment episode = approx. 16 weeks)
- Effects increase over the course of the episode and persist for at least 4 weeks after final dose.

Questions

- Long-term outcomes? (6-month F/U study under way)
- Is dosage, timing, and number of doses ideal?
- Would non- or partial responders show improvement with further treatment, either immediately or in subsequent episode?
- Safety issues that emerge with greater exposure?



Mitchell, et al. *Nature Medicine*, 2021



Mitchell et al., *Nature Medicine*, 2023

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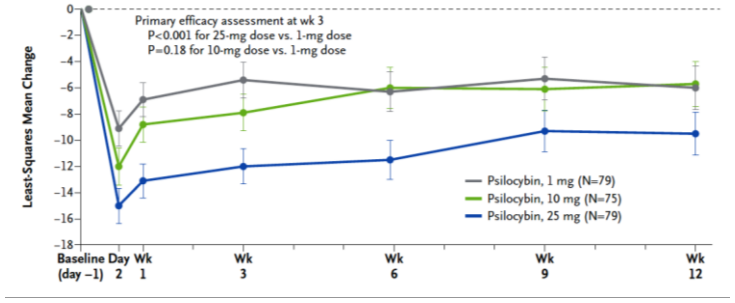
Psilocybin for MDD

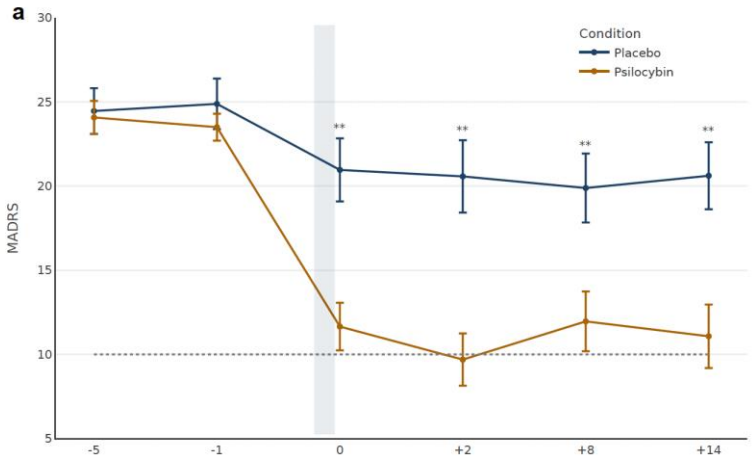
- Treatment model: 1-2 sessions (15-30 mg), combined with variable amounts of therapy, before and after sessions (minimal therapy during the session).
- Effects increase over the course of the episode and persist for at least 3-6 weeks after final dose.

Questions

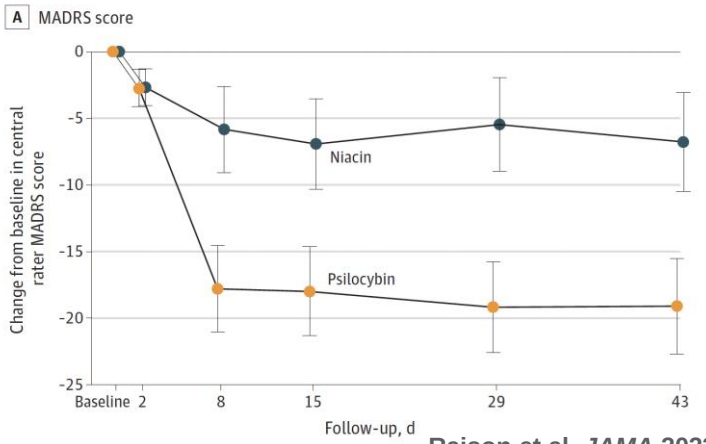
- Does duration of response depend on dose, number of sessions, concurrent psychotherapy?
- Would non- or partial responders show improvement with further treatment, either immediately or in subsequent treatment episode?
- Predictors of response (e.g., smaller effect with TRD)?



Goodwin et al. *NEJM* 2022



Von Rotz et al. *Lancet* 2023



Raison et al, *JAMA* 2023

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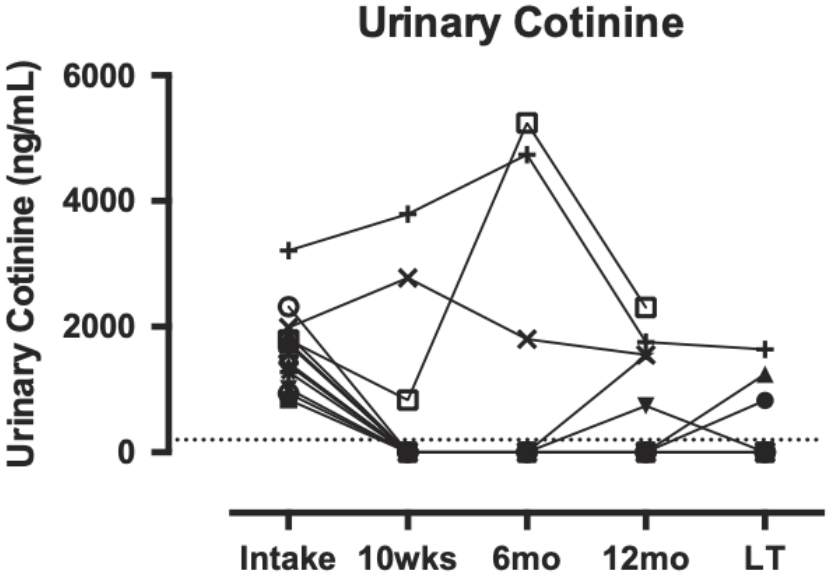
Psilocybin for Substance Use Disorders

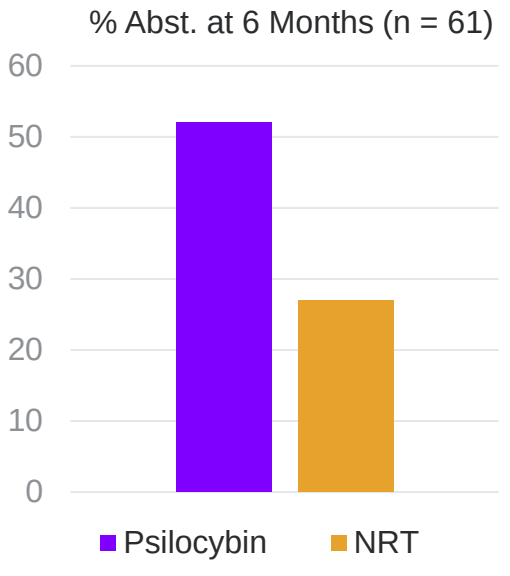
- Treatment model: 1-3 sessions (20-40+ mg), combined with variable amounts of therapy, before and after sessions (2-20 weeks)
- Effects persist for at least 6 months after final dose.

Questions

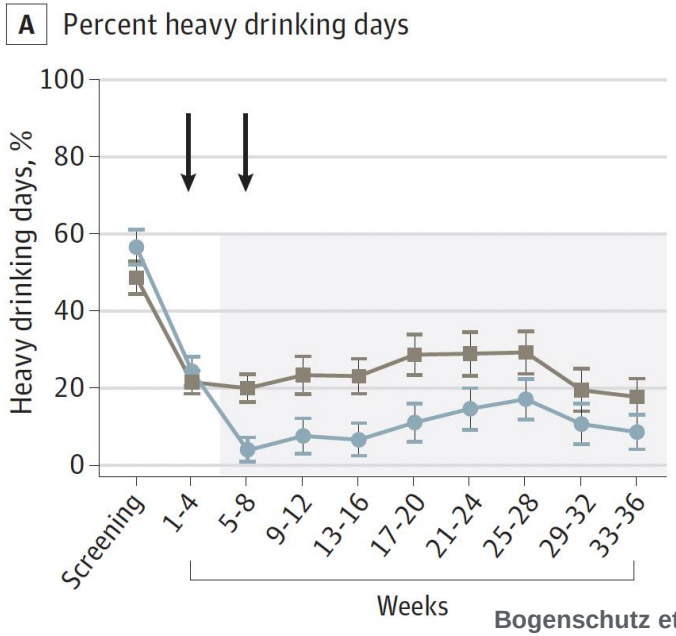
- Does magnitude and duration and of response depend on substance?
- Dose, number of sessions, concurrent psychotherapy (is one session enough)?
- Dose titration?
- Would non- or partial responders show improvement with further treatment?
- Predictors of response (e.g., larger effect with more severe AUD)?

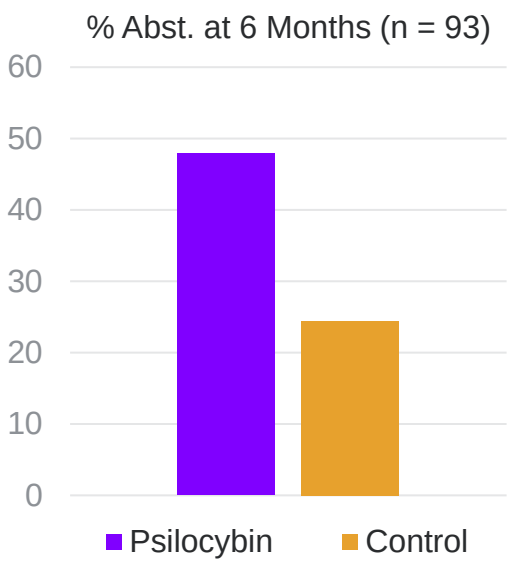


Johnson et al., *J Psychopharm* 2014



Johnson et al., *Neuropsychopharm* 2022





Bogenschutz et al., *JAMA Psychiatry* 2022

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Subjective Effects

- Correlated with treatment outcomes across several studies across multiple diagnoses.
- Correlation does not imply causality.
- However, these experiences present one of the more plausible explanations for long-term persistence of treatment effects.
- They may or may not be separable from whatever direct actions on the brain are also predictive of treatment outcome.

Questions

- Does magnitude and duration of response depend on aspects of self-reported experience?
- If so, which aspects are important?
- Can size and durability of treatment effects be improved by maximizing the relevant effects?

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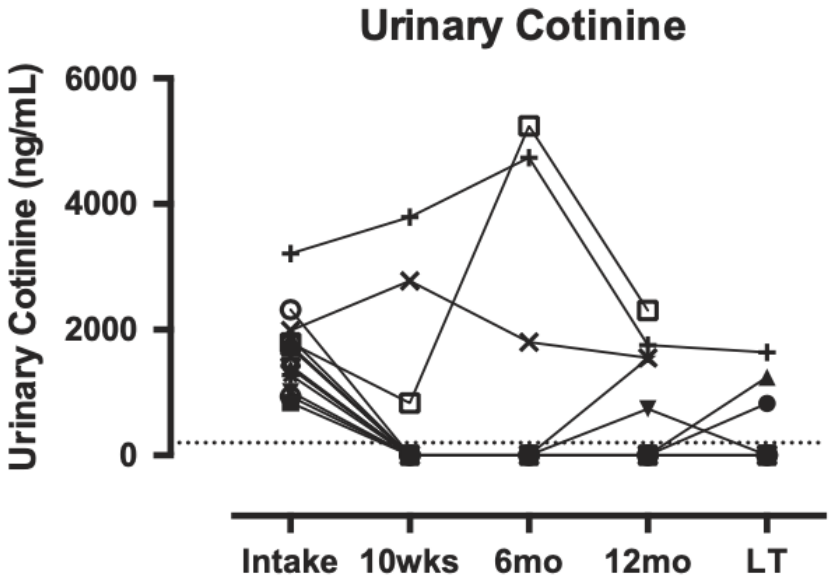
Study Designs to Address Durability

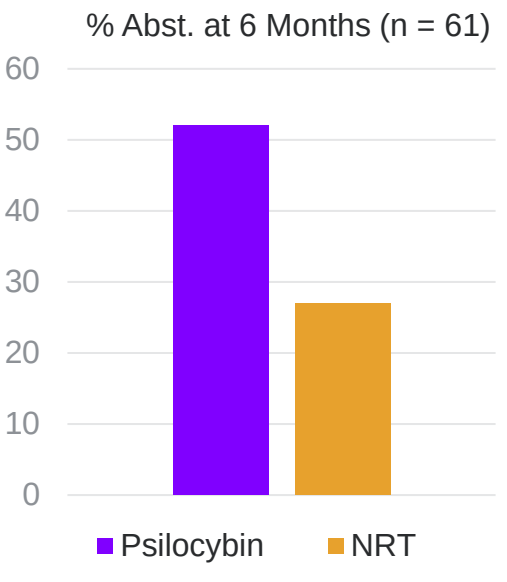
- Treatment model: 1-3 sessions (20-40+ mg), combined with variable amounts of therapy, before and after sessions (2-20 weeks)
- Effects persist for at least 6 months after final dose.

Questions

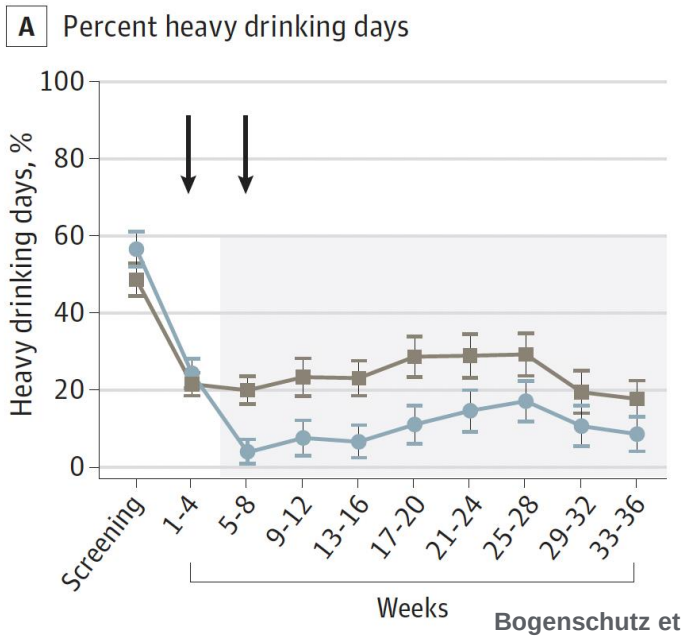
- Does magnitude and duration and of response depend on substance?
- Dose, number of sessions, concurrent psychotherapy (is one session enough)?
- Dose titration?
- Would non- or partial responders show improvement with further treatment?
- Predictors of response (e.g., larger effect with more severe AUD)?

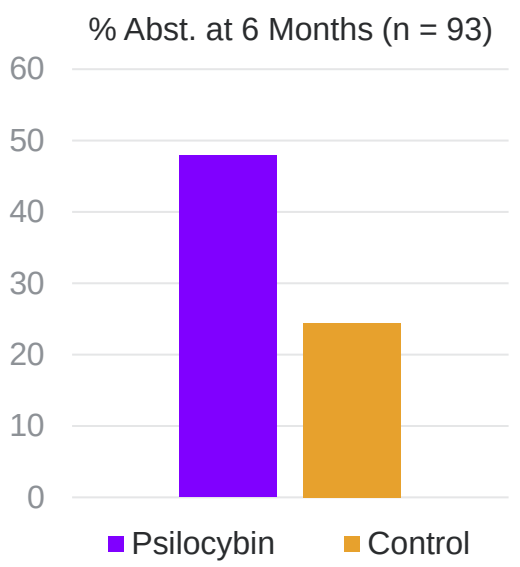


Johnson et al., *J Psychopharm* 2014



Johnson et al., *Neuropsychopharm* 2022





Bogenschutz et al., *JAMA Psychiatry* 2022

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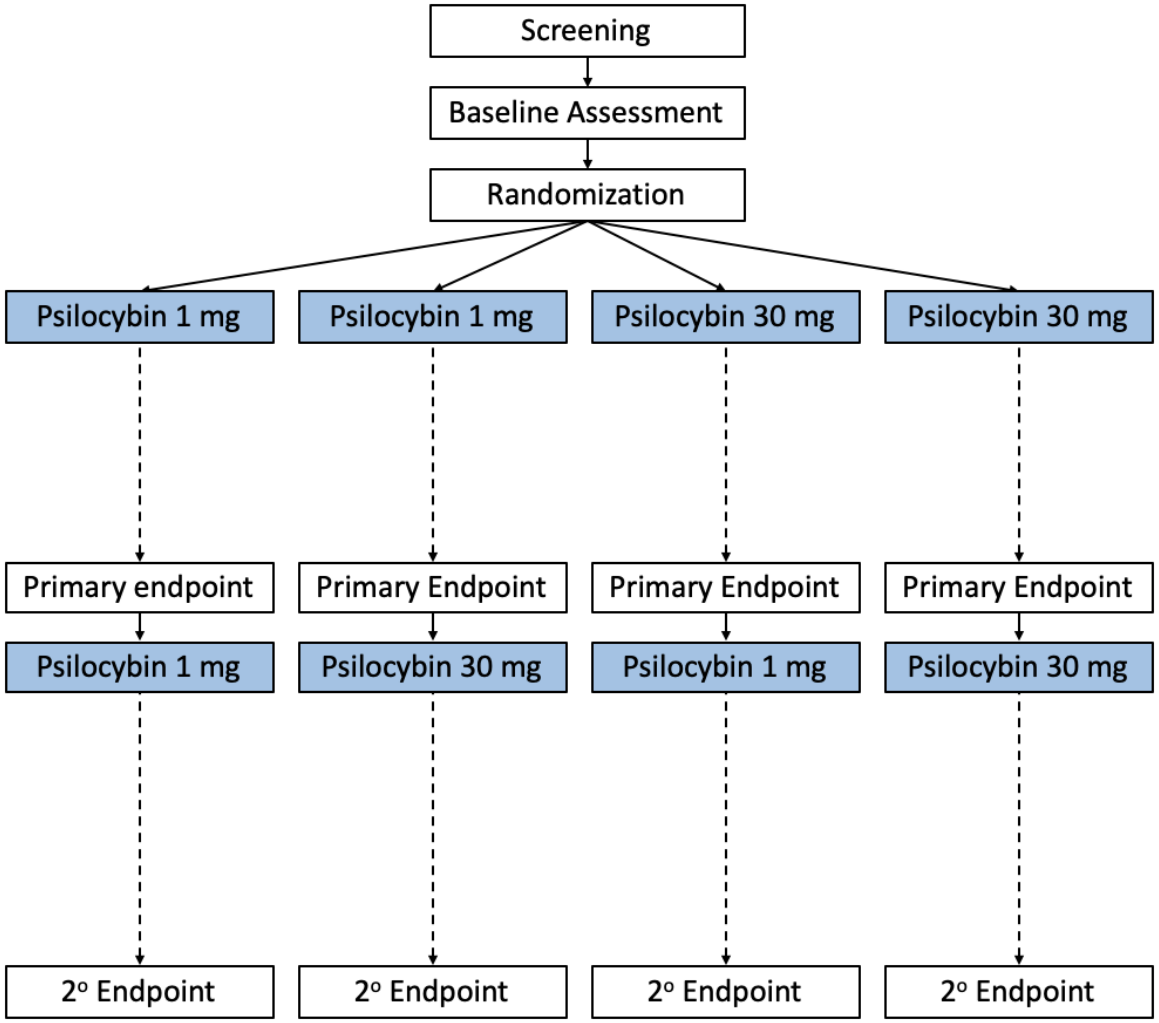
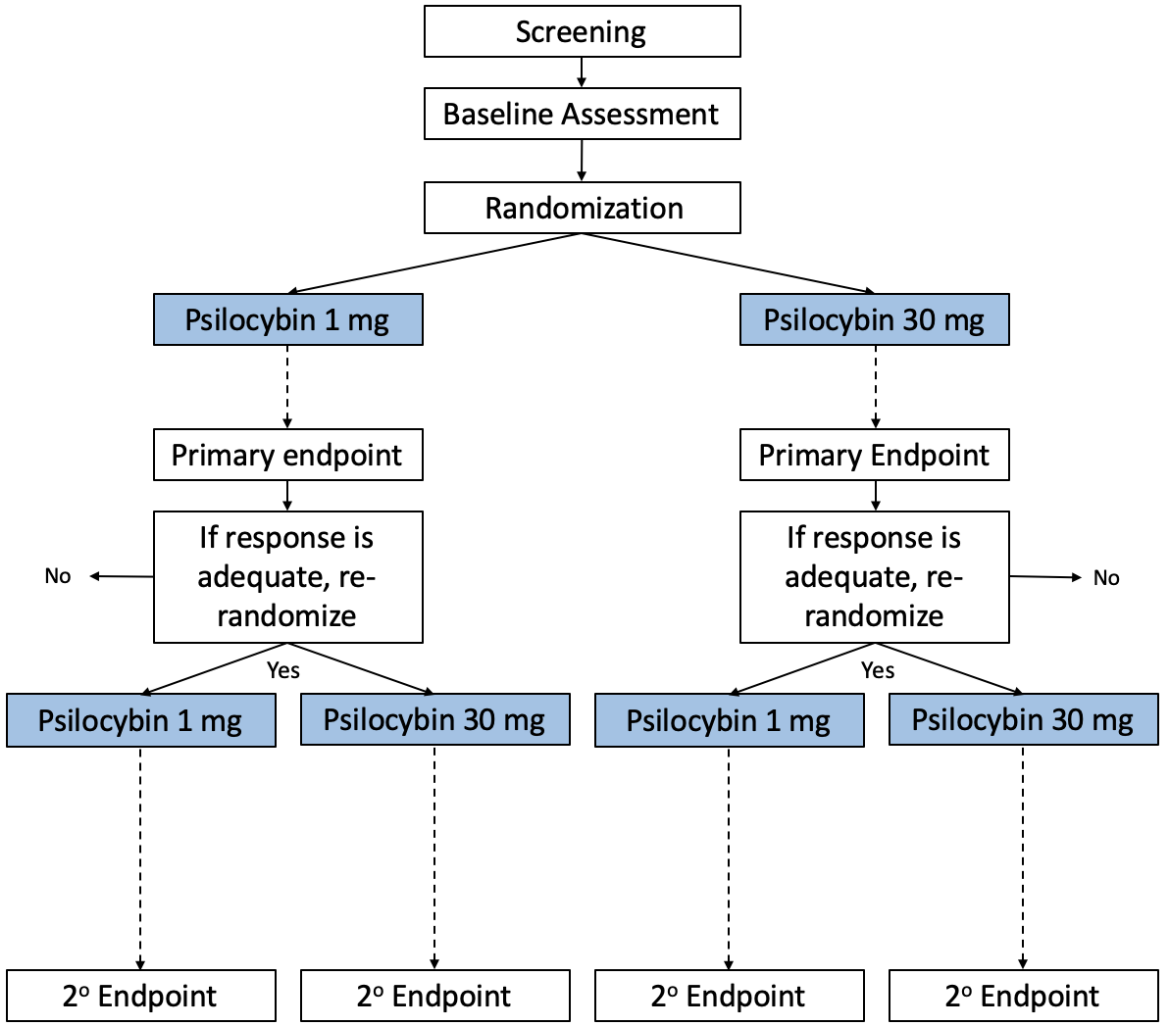
Study designs to address durability of effects

1 vs. 2 Sessions



Relapse Prevention



NYU Langone Health

Thank you

NYU Grossman School of Medicine

Session 4: Durability of Treatment Response

Presenters:

- **Michael P. Bogenschutz, MD,** NYU Langone Center for Psychedelic Medicine
- **Carla Canuso, MD,** Janssen Pharmaceuticals

Panelists:

- **Valentina Mantua, MD, PhD,** U.S. Food and Drug Administration
- **Charles L. Raison, MD,** University of Wisconsin-Madison

Durability of Treatment Effect: Insights from the Esketamine Nasal Spray Treatment-Resistant Depression Program

Carla M. Canuso, MD
V.P., Neuropsychiatry Clinical Development
Johnson & Johnson Innovative Medicine
January 31, 2024

Esketamine Nasal Spray TRD Clinical Development Program

Nineteen Phase 1, Four Phase 2, and Seven Phase 3 Studies

Evaluated for Safety in >1700 Esketamine-treated Patients

Five Completed Phase 3 Studies with Intranasal Esketamine

3 Short Term

- TRANSFORM-1 (3001)
- TRANSFORM-2 (3002)
- TRANSFORM-3 (3005) (patients ≥65 years)

1 Maintenance of Effect

- SUSTAIN-1 (3003)

1 Long Term Open Label Safety

- SUSTAIN-2 (3004)

Ongoing Studies at FDA Approval

- TRD3006 Short Term Study
- SUSTAIN-3 (3008) - Continuation Phase 3 Study

Establishing the Treatment Paradigm

How will esketamine nasal spray be used in clinical practice?

How frequently and for how long should a patient be dosed initially?

How long will a clinical response achieved with esketamine last, and can it be maintained with an oral antidepressant?

Will periodic “booster” doses of esketamine be required to maintain responsiveness to an oral antidepressant? If so, what is the minimal effective frequency of such doses?

Will withdrawal of treatment result in discontinuation syndrome?

1. aan het Rot M, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry. 2010;67(2):139-145. 2. Mathew SJ, Shah A, Lapidus K, et al. Ketamine for treatment-resistant unipolar depression: current evidence. CNS Drugs. 2012 Feb 3.

Clear and Consistent FDA Feedback

- “In order to approve such a product, we would need to be able to advise clinicians on how best to use the product after an initial response.”

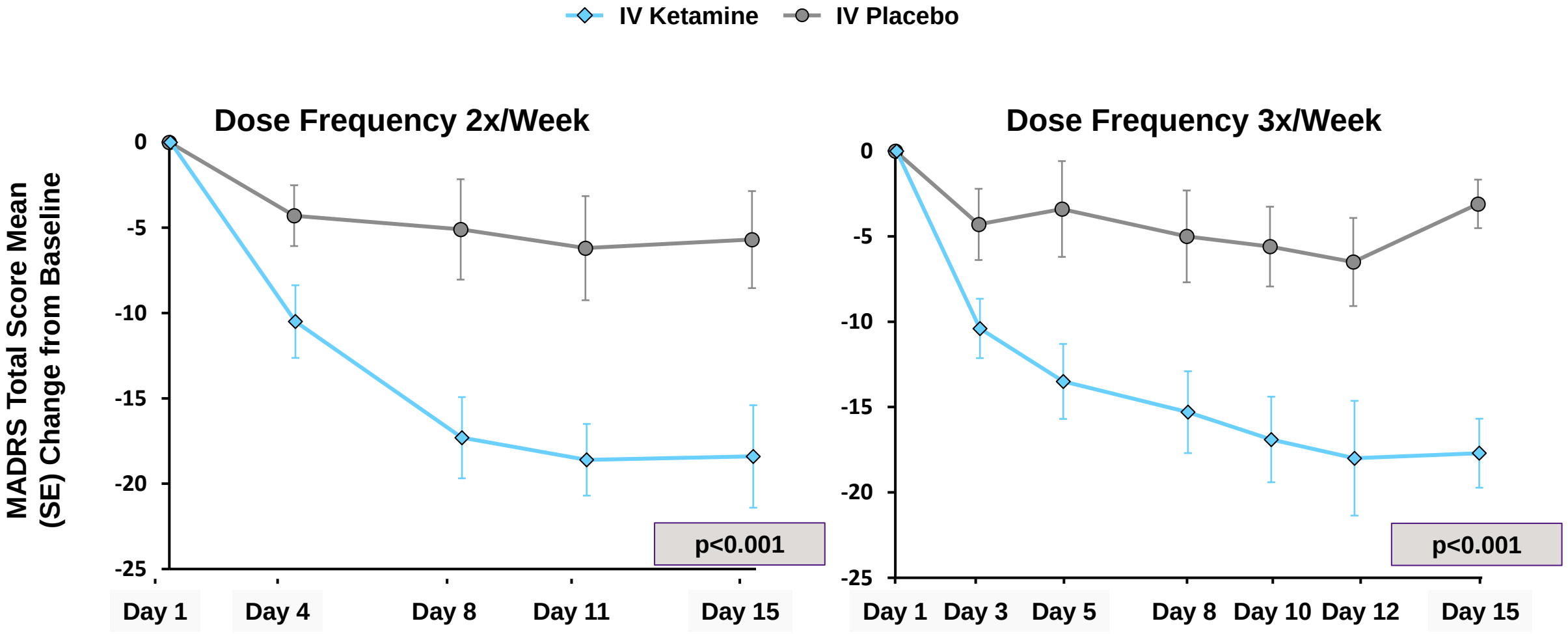
- “Due to its uniqueness (e.g. safety concerns, questions of how to maintain response), we view esketamine very differently than the previously approved oral antidepressants. We would therefore need to see maintenance data at the time of filing.”

- “Given the great importance of the maintenance-of-effect data with this drug, we would consider one positive short-term study along with a positive maintenance-of effect-study to be sufficient for NDA submission.”

- “If the duration of the randomized withdrawal phase is not sufficient, the study will not yield useful information as to how well patients can be maintained on oral antidepressant drug alone after induction and stabilization with esketamine.”

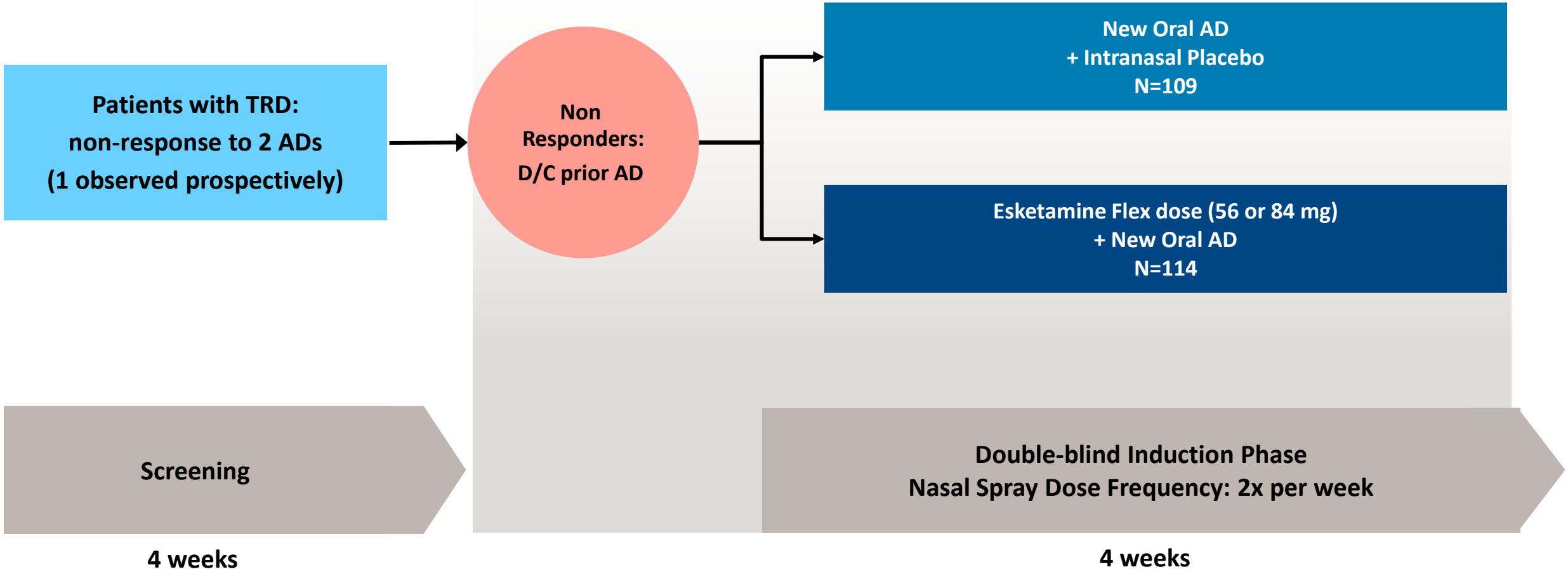
Phase 2 Study Dose Frequency

Study 2002



Singh JB, Fedgchin M, Daly EJ, et al. *Am J Psychiatry*. 2016 Aug 1;173(8):816-26.

Short-Term Study Design
TRANSFORM-2 (3002)



Acute studies designed to evaluate efficacy of 4-week induction treatment, allowing for meaningful comparison of Esk + New Oral AD vs New Oral AD + PBO

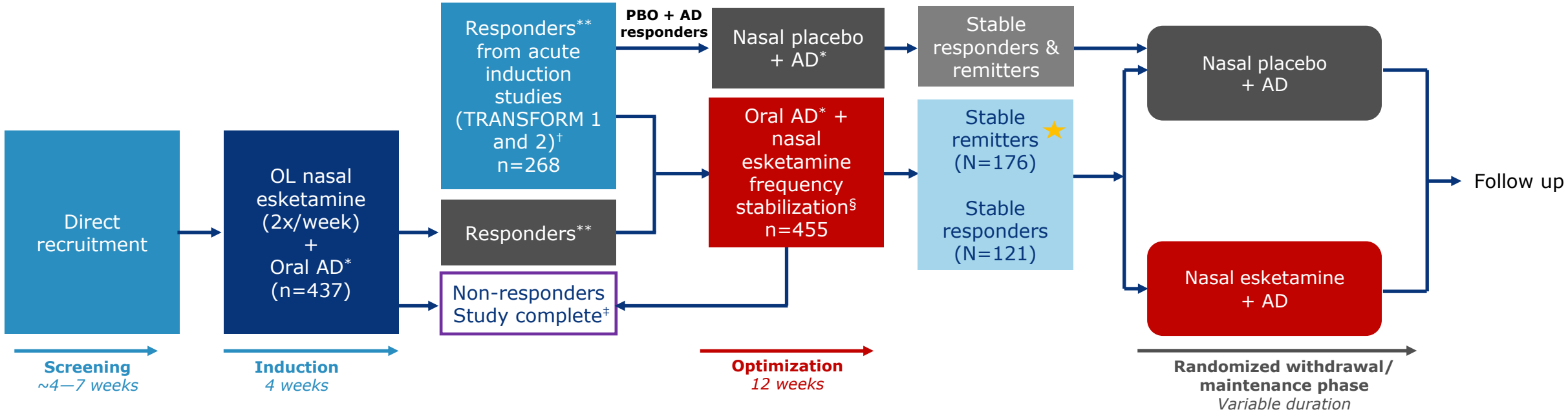
AD, antidepressant; D/C, discontinued; OL=Open Label

Popova V, et al. Am J Psychiatry 176:6, June 2019

Maintenance of Effect Study Design

SUSTaIN-1 (3003)

Integrated acute/maintenance trial designed to investigate the maintenance of remission of nasal esketamine + oral AD versus placebo + oral AD in adult patients with TRD[1]



Individualized Dosing Frequency

Weekly for 1st 4 weeks of Optimization

Weekly or every other week thereafter based on MADRS score

★ Primary analysis set

*Duloxetine, escitalopram, sertraline or venlafaxine extended-release; **Responders defined as ≥50% reduction in the MADRS total score from baseline [Day 1 pre-randomization] at the end of the 4-week double-blind induction phase of the acute 3001 and 3002 studies; †Responders who entered the optimization phase remained on the same intranasal study drug as taken in the induction phase; ‡Frequency of intranasal medication sessions was reduced to once weekly for 4 weeks, then individualized to weekly or every other week based on severity of depressive symptoms (lowest dosing frequency adequate to maintain remission [MADRS ≤12]).

AD, antidepressant; OL, open label; PBO, placebo; TRD, treatment-resistant depression.

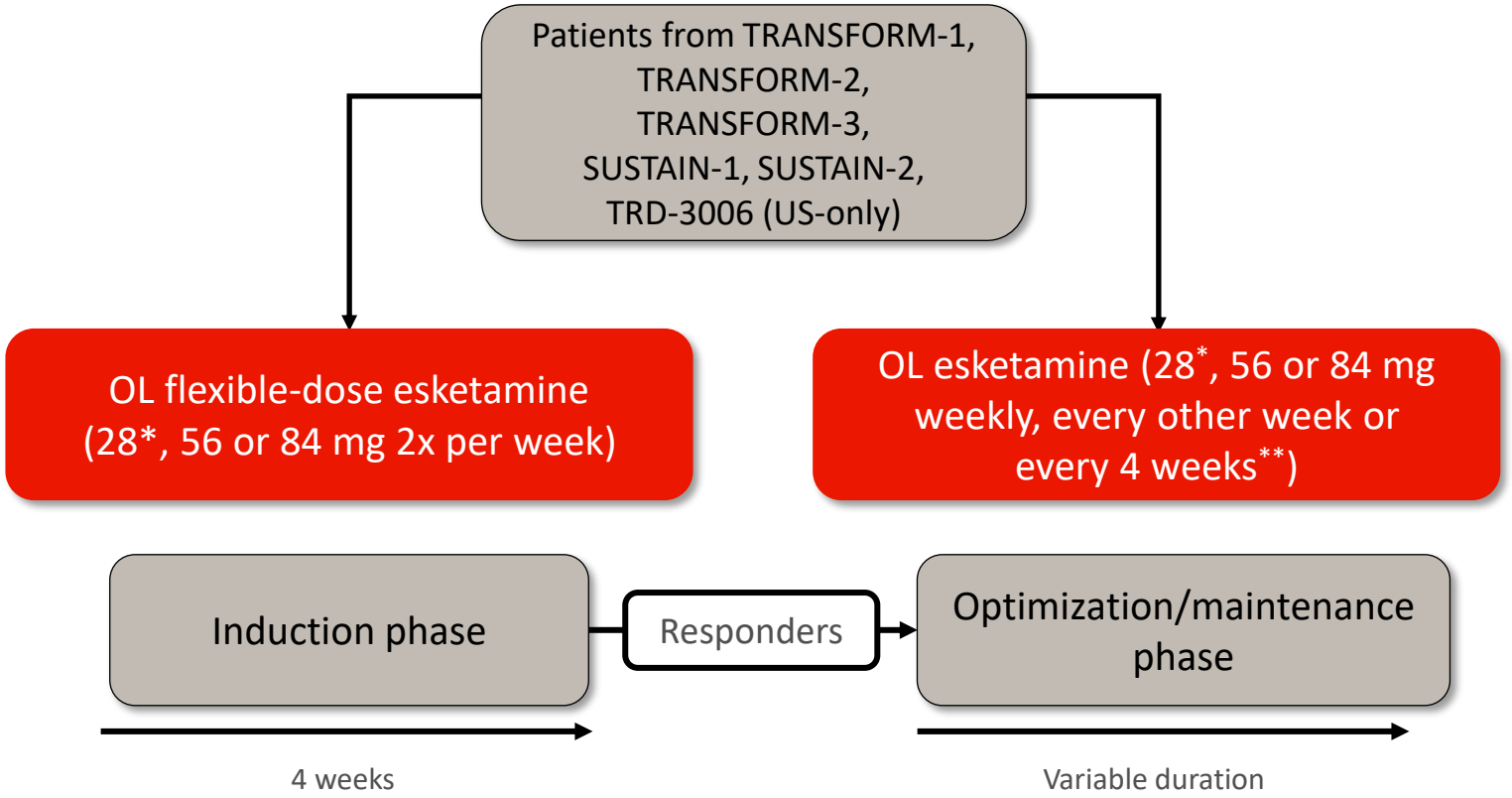
Daly E, et al. *JAMA Psychiatry* September 2019 76 (9)

Open-Label Continuation Study Design
SUSTaIN-1 (3008)

SUSTAIN-3 provided participants in prior studies access to esketamine nasal spray while assessing the long-term effects of individualized dosing

Primary Objective: long-term safety and tolerability. Secondary Objective: long-term efficacy

Post-Approval Commitment: characterize LT effects on cognition and urinary function



Assessments

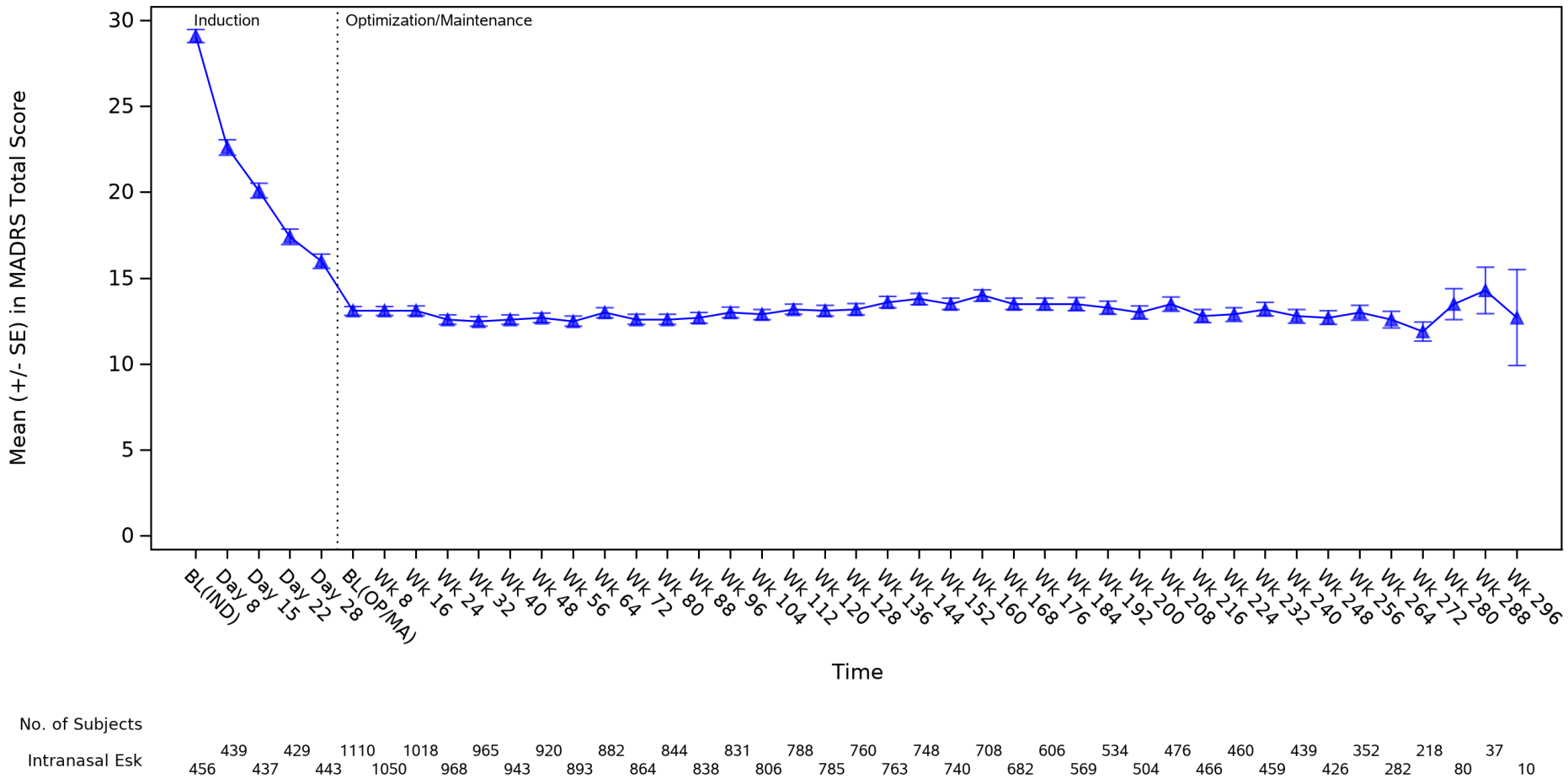
- AEs, including those of clinical interest (e.g. dissociation, sedation, increased blood pressure and interstitial cystitis)
- Discharge Readiness
- Cognition: Cogstate computerised test battery and HVLT-R
- Clinical Rating: MADRS, CGI-S
- Patient Rating: PHQ-9

*28 mg dose only an option for patients >65 years; **Based on CGI-S & tolerability.
AE, adverse event; CGI-S, Clinical Global Impression-Severity; HVLT-R, Hopkins Verbal Learning Test-Revised; OL, open label.

Fu DJ et al, Dec 4th, 2023, ACNP Annual Meeting

MADRS Total Score Over Time

SUSTaIN-3 (3008)



- Mean MADRS total score decreased during the induction phase
- The reduction persisted during optimization/maintenance phase

Fu DJ et al, Dec 4th, 2023, ACNP Annual Meeting

Key Take Aways

Consider how a treatment will be used in clinical practice and generate data to support this

What would you want to know ?

Treatments with novel mechanisms of action and new dosing paradigms will require unique clinical development plans to inform labelling and clinical use

Durability of effect becomes an even greater factor in the overall benefit-risk assessment of novel therapeutics with safety and abuse liabilities

Depending on how a treatment will be used, maintenance of effect studies may be required pre-approval

Post-approval data collection can further inform durability of effect

Collaborate early and often with regulators!

Thank you

Session 4: Durability of Treatment Response

Presenters:

- **Michael P. Bogenschutz, MD,** NYU Langone Center for Psychedelic Medicine
- **Carla Canuso, MD,** Janssen Pharmaceuticals

Panelists:

- **Valentina Mantua, MD, PhD,** U.S. Food and Drug Administration
- **Charles L. Raison, MD,** University of Wisconsin-Madison

Thank you!

Day 2 will resume tomorrow
Thursday, February 1 at 10 am ET

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