Risk Reduction and Safety Monitoring in Psilocybin and other Psychedelic Therapies

Presentation to NM RACI Meeting

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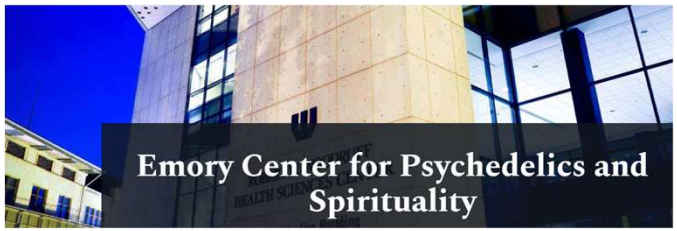

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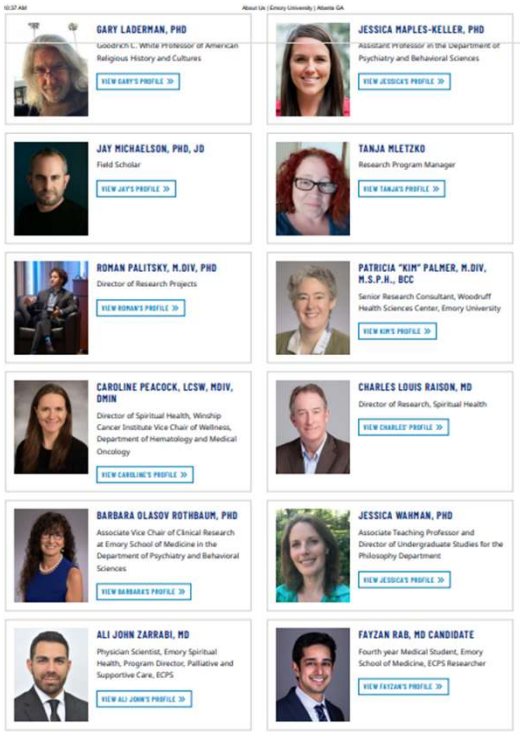

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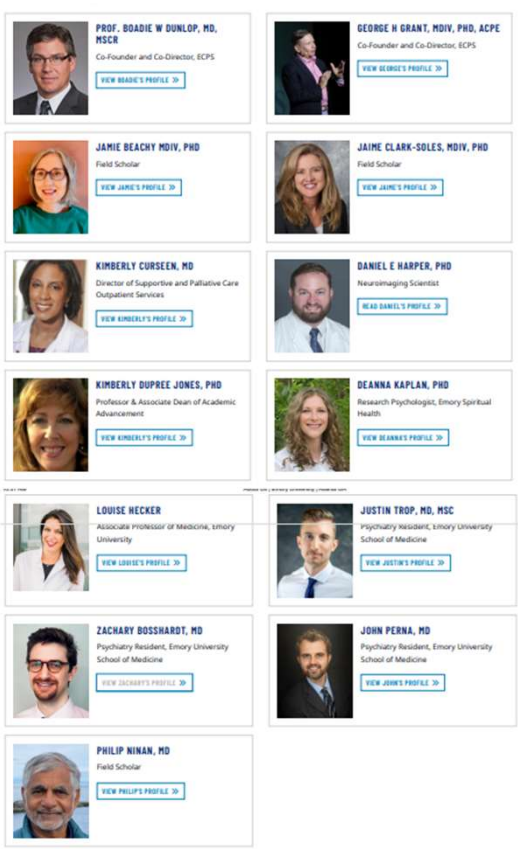

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PHILIP NINAN, MD
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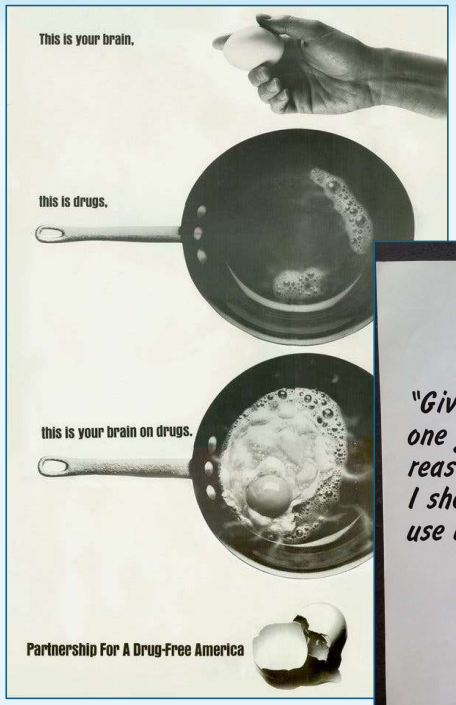
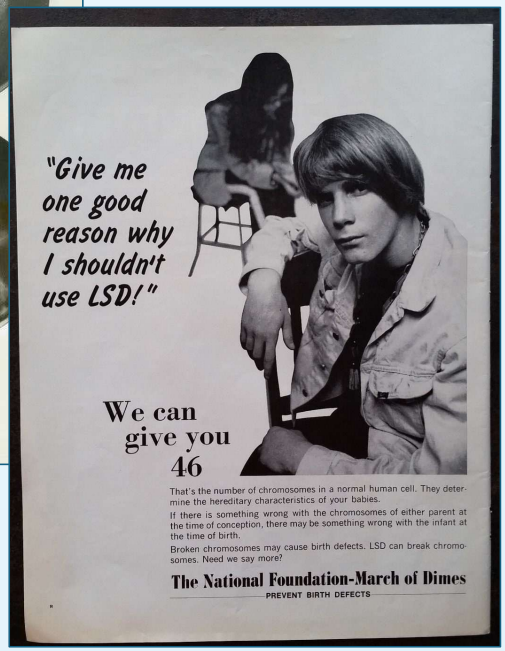
Spiritual, Existential, Religious, and Theological dimensions of psychedelic care

Optimizing psychotherapeutic components in PAT

Harm Reduction and Safety: Understanding, Measuring, and Addressing Adverse Effects


This is your brain.
this is drugs.
this is your brain on drugs.
Partnership For A Drug-Free America


"Give me one good reason why I shouldn't use LSD!"
We can give you 46
That's the number of chromosomes in a normal human cell. They determine the hereditary characteristics of your babies.
If there is something wrong with the chromosomes of either parent at the time of conception, there may be something wrong with the infant at the time of birth.
Broken chromosomes may cause birth defects. LSD can break chromosomes. Need we say more?
The National Foundation-March of Dimes
PREVENT BIRTH DEFECTS

State of the science on psychedelic*-related AEs: the good news

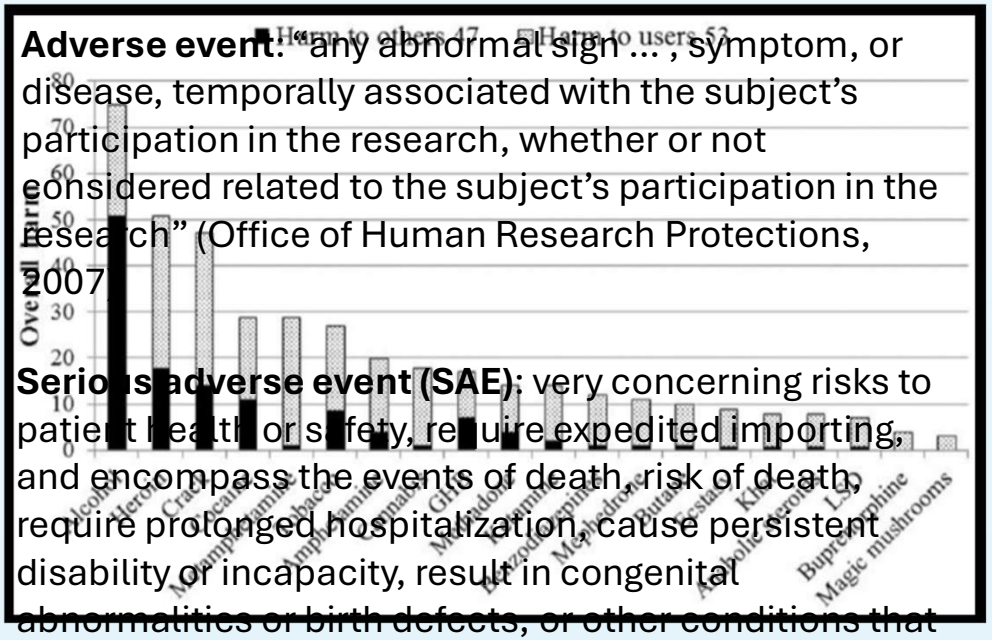
- Psychedelics are generally considered safe (Romeo et al. 2024)
- Low abuse potential (Johnson et al. 2018)

MedDRA — Medical Dictionary for Regulatory Activities

27 System Organ Classes
76,364 Lower-level terms

Clinical Trial AE Monitoring

Adverse event: "any abnormal sign …, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research" (Office of Human Research Protections, 2007)



Serious adverse event (SAE): very concerning risks to patient health or safety, require expedited importing, and encompass the events of death, risk of death, require prolonged hospitalization, cause persistent disability or incapacity, result in congenital abnormalities or birth defects, or other conditions that similarly present significant hazards. Johnson et al. 2018

* classical psychedelics such as 5HT2A receptor agonists lysergic acid diethylamide (LSD) and psilocybin, current schedule I drugs such as 3,4-Methylenedioxymethamphetamine (MDMA) and Ibogaine, and ketamine

State of the science on psychedelic*-related AEs: the good news

- Psychedelics are generally considered safe (Romeo et al. 202
- Low abus
- SAEs repo
  - Phase II trials of psilocybin:
    - Raison et al. 2023: AEs: 76%, SAEs: 8%
    - Goodwin et al. 2022: AEs: 84%, SAEs: 10%
      - Increased suicidality
  - Phase III trial of MDMA
    - Mitchell et al. 2023: Equivalent rates of psychiatric AEs in MDMA & placebo groups


Medical News in Brief

ONLINE FIRST FREE

May 3, 2024

Therapeutic Psilocybin's Adverse Effects Mostly Resolved Within 2 Days

Emily Harris

Article Information

JAMA. Published online May 3, 2024. doi:10.1001/jama.2024.6733

Clinical Trial AE Monitoring

Adverse event: "any abnormal sign … , symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research" (Office of Human Research Protections, 2007)

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* classical psychedelics such as 5HT2A receptor agonists lysergic acid diethylamide (LSD) and psilocybin, current schedule I drugs such as 3,4-Methylenedioxymethamphetamine (MDMA) and Ibogaine, and ketamine

State of the science on psychedelic-related AEs: the rest of the news

- Psychedelics are generally considered safe (Romeo et al. 2024; Hinkle et al., 2024)
- Low abuse potential (Johnson et al. 2018)
- AEs reported at low rates – undercounted? (Breeksema et al. 2022; Hinkle et al. 2024)
  - Passive monitoring
  - Low frequency or follow-up
  - Focus on acute dosing
  - Non-systematic assessment
  - Restricted criteria


Original Investigation FREE

Adverse Events in Studies of Classic Psychedelics
A Systematic Review and Meta-Analysis

Jared T. Hinkle, MD, PhD[1]; Marianna Graziosi, MA[1,2]; Sandeep M. Nayak, MD[1] ; et al

Author Affiliations | Article Information

RELATED ARTICLES MEDIA FIGURES SUPPLEMENTAL CONTENT

Since 2005, less than ¼ (23.5%) of studies systematically monitored and reported AEs.

State of the science on psychedelic-related AEs: the rest of the news

- Psychedelics are generally considered safe (Romeo et al. 2024)
- Low abuse potential (Johnson et al. 2018)
- AEs reported at low rates – undercounted? (Breeksema et al. 2022; Hinkle et al. 2024)
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  - Restricted criteria

n = 613, 3168: 59-88% reported no challenging experience
6.4-9% functional impairment lasting > 1 day | 1.3% > 1 year
2.6% sought medical, psychiatric, psychological assistance after worst experience

12 million have used psychedelics in the past year (RMPDS)
12M* 2.6% => **312,000** (seeking further support)
12M*1.3% => **156,000** (difficulties >1 year)

Poison control center calls for psychedelics tripled, 2018-2022 (Farah et al., 2024)
ED visits and hospitalizations increased ~50% 2016-2022 (Garel et al., 2024)

Use of Psychedelic Substances in the United States, 2024: Results from the National Survey Investigating Hallucinogenic Trends (NSIHT)

Encouraging flourishing with therapeutic psilocybin

...while reducing harm

Underwood & Underwood, 1930

Challenging Experience

Acute Adverse *Event*

- Specific to the dosing period
- Can be very distressing at dosing
- Can involve major concerns, injuries, or harms
- May or may not have negative impacts
- Both benefits and harms are commonly attributed to challenging experiences

Psychedelic-related challenge

Adverse *Effect*

- Occur in the days, weeks, months after dosing
- May or may not be distressing at dosing
- Distress or impairment after psychedelic effects wear off
- Typically involves some negative impact
- Despite negative impacts, may contribute to growth. Despite growth, may involve negative impacts

Our tasks

1. Detecting AEs in Psilocybin Research and Implementation
2. Understanding AE phenotypes for primary and secondary prevention
3. Developing monitoring systems that work

Adverse Events Measurement for Trials

Palitsky et al. 2024;
Palitsky et al. 2024b

Pharmacological

A Framework for Assessment of Adverse Events Occurring in Psychedelic Assisted Therapies

Palitsky, Roman, MDiv, PhD., Kaplan, Deanna M. PhD., Perna, John, MD., Bosshardt, Zacchary, MD., Maples-Keller, Jessica L. PhD., Levin-Aspenson, Holly F., PhD., Zarrabi, Ali John, MD., Peacock, Caroline, MDiv, ThD, MSW., Mletzko, Tanja., MA., Rothbaum, Barbara O., PhD., Raison, Charles L., MD., Grant, George H., MDiv, PhD., Dunlop, Boadie W., MD.

Headache	19 (24)
Nausea	17 (22)
Euphoric mood	4 (5)
Fatigue	5 (6)
Insomnia	2 (3)
Anxiety	3 (4)
Mood altered	4 (5)
Dizziness	5 (6)
Paresthesia	2 (3)
Abnormal thinking	0
Any serious adverse event	0

Goodwin et al. 2022

MedDRA
Medical Dictionary for Regulatory Activities

27 System Organ Classes
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Palitsky et al. 2024;
Palitsky et al. 2024b

Pharmacological

Sociocultural

Behavioral

Affective, cognitive, metacognitive

Psychospiritual

Psychotherapy-related

Perceptual

Interpersonal

A Framework for Assessment of Adverse Events Occurring in Psychedelic Assisted Therapies

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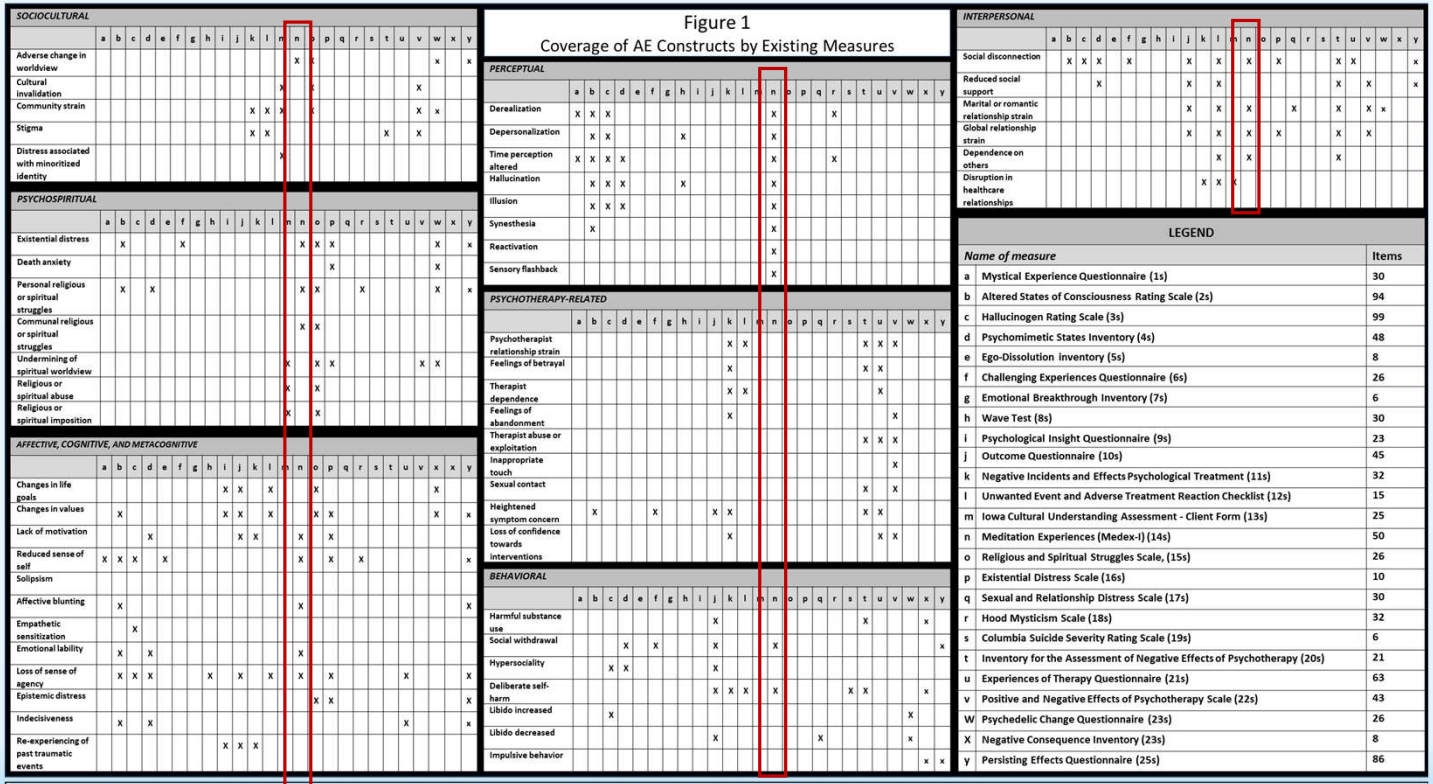
Figure 1
Coverage of AE Constructs by Existing Measures



LEGEND

	Name of measure	Items
a	Mystical Experience Questionnaire (1s)	30
b	Altered States of Consciousness Rating Scale (2s)	94
c	Hallucinogen Rating Scale (3s)	99
d	Psychomimetic States Inventory (4s)	48
e	Ego-Dissolution Inventory (5s)	8
f	Challenging Experiences Questionnaire (6s)	26
g	Emotional Breakthrough Inventory (7s)	6
h	Wave Test (8s)	30
i	Psychological Insight Questionnaire (9s)	23
j	Outcome Questionnaire (10s)	45
k	Negative Incidents and Effects Psychological Treatment (11s)	32
l	Unwanted Event and Adverse Treatment Reaction Checklist (12s)	15
m	Iowa Cultural Understanding Assessment - Client Form (13s)	25
n	Meditation Experiences (Medex-I) (14s)	50
o	Religious and Spiritual Struggles Scale, (15s)	26
p	Existential Distress Scale (16s)	10
q	Sexual and Relationship Distress Scale (17s)	30
r	Hood Mysticism Scale (18s)	32
s	Columbia Suicide Severity Rating Scale (19s)	6
t	Inventory for the Assessment of Negative Effects of Psychotherapy (20s)	21
u	Experiences of Therapy Questionnaire (21s)	63
v	Positive and Negative Effects of Psychotherapy Scale (22s)	43
W	Psychedelic Change Questionnaire (23s)	26
X	Negative Consequence Inventory (23s)	8
y	Persisting Effects Questionnaire (25s)	86

Note: This the tables in this figure represent domains for AE assessment, defined in Supplementary Document 1. Columns represent coverage of each relevant term by each of the measures described in the legend, as demarcated by lower-case letters (references are included parenthetically after measure names, followed by "s" to designate their location in Supplementary Document 2). "X" represents likely coverage of the relevant term and blanks represent lack of coverage. The legend includes the number of items within each of the included measures in the column labeled "Items."

Improving Safety & AE assessment in psychedelics

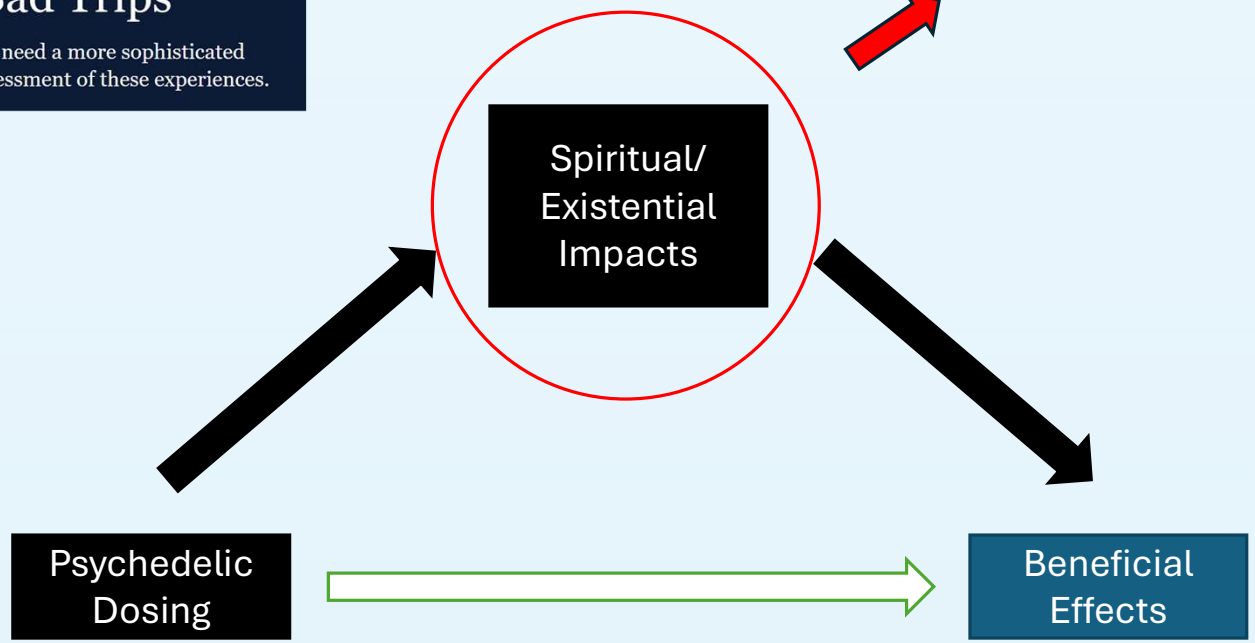
- Psychospiritual
- Psychotherapy-related
- Sociocultural

FEATURED

A Theological Reckoning with 'Bad Trips'

We need a more sophisticated assessment of these experiences.

Petersen, 2022
Harvard Divinity Bulletin



JAMA Psychiatry | Special Communication

Importance of Integrating Spiritual, Existential, Religious, and Theological Components in Psychedelic-Assisted Therapies

Roman Palitsky, MDiv, PhD; Deanna M. Kaplan, PhD; Caroline Peacock, DMin, LCSW, MDiv; Ali John Zarrabi, MD; Jessica L. Maples-Keller, PhD; George H. Grant, MDiv, PhD; Boadie W. Dunlop, MD; Charles L. Raison, MD

A framework for assessment of adverse events occurring in psychedelic-assisted therapies

Roman Palitsky[1,2,3], Deanna M Kaplan[1,3,4], John Perna[2], Zachary Bosshardt[2], Jessica L Maples-Keller[2], Holly F Levin-Aspenson[5], Ali John Zarrabi[1,3,6], Caroline Peacock[1,3,7], Tanja Mletzko[1,2], Barbara O Rothbaum[1,2], Charles L Raison[1,3], George H Grant[1,3] and Boadie W Dunlop[1,2]

Psychopharm

AKADÉMIAI KIADÓ

Journal of Psychedelic Studies

An investigation into the varieties of extended difficulties following psychedelic drug use: Duration, severity and helpful coping strategies

OLIVER C. ROBINSON[1*], JULES EVANS[2], ROSALIND G. MCALPINE[3], EIRINI K. ARGYRI[4] and DAVID LUKE[1]

Ko et al. 2022

A Framework for Assessment of Adverse Events Occurring in Psychedelic Assisted Therapies

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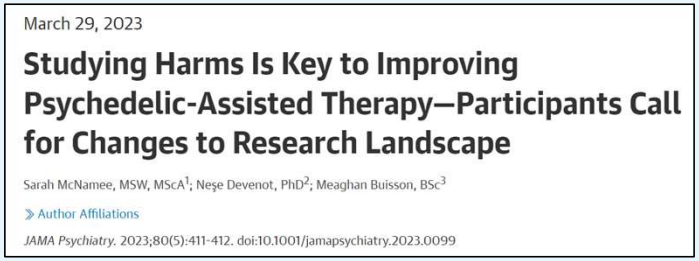
PSYCHOSPIRITUAL	
Existential Distress	Distress about loss of a sense of coherence, meaning or purpose, core aspects of one's existence, or mortality
Death anxiety	Anxiety or fear around mortality
Personal religious or spiritual struggles	Tension, strain, conflict, or alienation in relation to what people hold sacred
Communal religious or spiritual struggles	Experience of tension, strain, conflict, or relation in relation to one's religious or spiritual community
Undermining of spiritual worldview	Challenge or violation of religious or spiritual beliefs that is undesired and distressing
Religious or spiritual abuse	Perceived harm in the context of religious or spiritual activity, either psychologically or physically, including coercion, exploitation, ostracism, or manipulation (may include spiritual components of treatment, or activities in a religious setting).
Religious or spiritual imposition	Perceived proselytization or unwanted or distressing imposition of religious or spiritual frameworks

Palitsky et al. (2024) *Journal of Psychopharmacology*
Palitsky et al. (2024) *International Review of Psychiatry*

Improving Safety & AE assessment in psychedelics

Psychotherapy-related



March 29, 2023

Studying Harms Is Key to Improving Psychedelic-Assisted Therapy—Participants Call for Changes to Research Landscape

Sarah McNamee, MSW, MScA[1]; Neşe Devenot, PhD[2]; Meaghan Buisson, BSc[3]

» Author Affiliations

JAMA Psychiatry. 2023;80(5):411-412. doi:10.1001/jamapsychiatry.2023.0099

"...it would be unimaginable for clinical trials using a combination of 2 drugs to only examine or regulate one of the 2 components. However, this is the norm in psychedelic research, in which the psychological support is neither systematized nor evaluated as in traditional psychotherapy research."

- AE assessment reliant on pharmacology-derived criteria under-estimate AEs related to behavioral, lifestyle, and psychological therapies (Papaioannou et al. 2021)
- Standard therapy AEs: 3-7% of patients, 7-15% in substance use disorder treatment (Boisvert and Faust, 2003; Mohr, 1995; Moos et al. 2005; Strupp et al., 1977)

A Framework for Assessment of Adverse Events Occurring in Psychedelic Assisted Therapies

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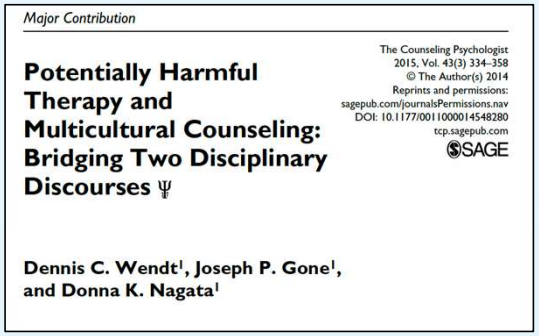
Figure 1
Coverage of AE Constructs by Existing Measures

PSYCHOTHERAPY-RELATED	
Psychotherapist relationship strain	Damage to therapeutic alliance between patient and clinician(s)
Feelings of betrayal	Experience of betrayed trust through the actions of clinicians or members of institution
Therapist dependence	Reliance on clinician for matters beyond the purview of therapy, or feels unable to function adequately without therapy relationship
Feelings of abandonment	Feelings of abandonment related to a member(s) of the PAT treatment team
Therapist abuse or exploitation	Coercion, manipulation, exploitation, abuse, or other inappropriate behavior by member(s) of treatment team
Inappropriate touch	Physical touch by team member(s) that is not consented to or is experienced as a boundary violation
Sexual contact	Sexual behavior of any kind between team member(s) and participant
Heightened symptom concern	Increased preoccupation with symptoms, which may either be the target of therapy or may be unrelated to the therapy target
Loss of confidence towards interventions	Belief that further benefit cannot result from any further treatment, or belief that one is beyond help

Palitsky et al. (2024) *Journal of Psychopharmacology*
Palitsky et al. (2024) *International Review of Psychiatry*

Improving Safety & AE assessment in psychedelics

Sociocultural



Major Contribution

Potentially Harmful Therapy and Multicultural Counseling: Bridging Two Disciplinary Discourses Ψ

Dennis C. Wendt[1], Joseph P. Gone[1], and Donna K. Nagata[1]

The Counseling Psychologist
2015, Vol. 43(3) 334–358

DOI: 10.1177/0011000014548280
tcp.sagepub.com
SAGE

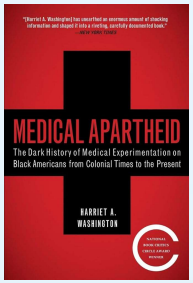
Absence of evidence:

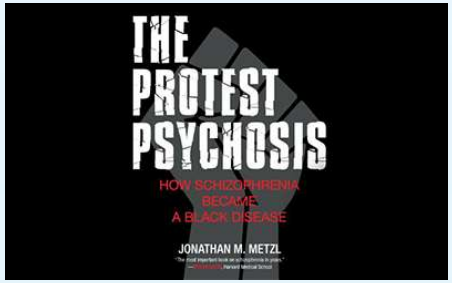
- Denial of care or early dropout
- Insensitive care
- Critical misdiagnoses

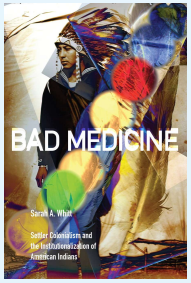
?

Evidence of absence?

- ~~Lack of assessment or research~~
- ~~Lack of framework in psychiatry~~
- Long-standing evidence







AKADÉMIAI KIADÓ

Journal of Psychedelic Studies

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

MONNICA T. WILLIAMS[1,2,3*], SARA REED[1,2] and JAMILAH GEORGE[1]

transcultural psychiatry

Article

Overcoming epistemic injustices in the biomedical study of ayahuasca: Towards ethical and sustainable regulation

Transcultural Psychiatry
2022, Vol. 59(5) 610–624

DOI: 10.1177/13634615211062962
journals.sagepub.com/home/tps
SAGE

Eduardo Ekman Schenberg[1] and Konstantin Gerber[2]

"Harm is a social construct…

…psychotherapy may be inherently ethnocentric…

strategies for collecting evidence of harm **should be integrated with a social justice agenda.**"

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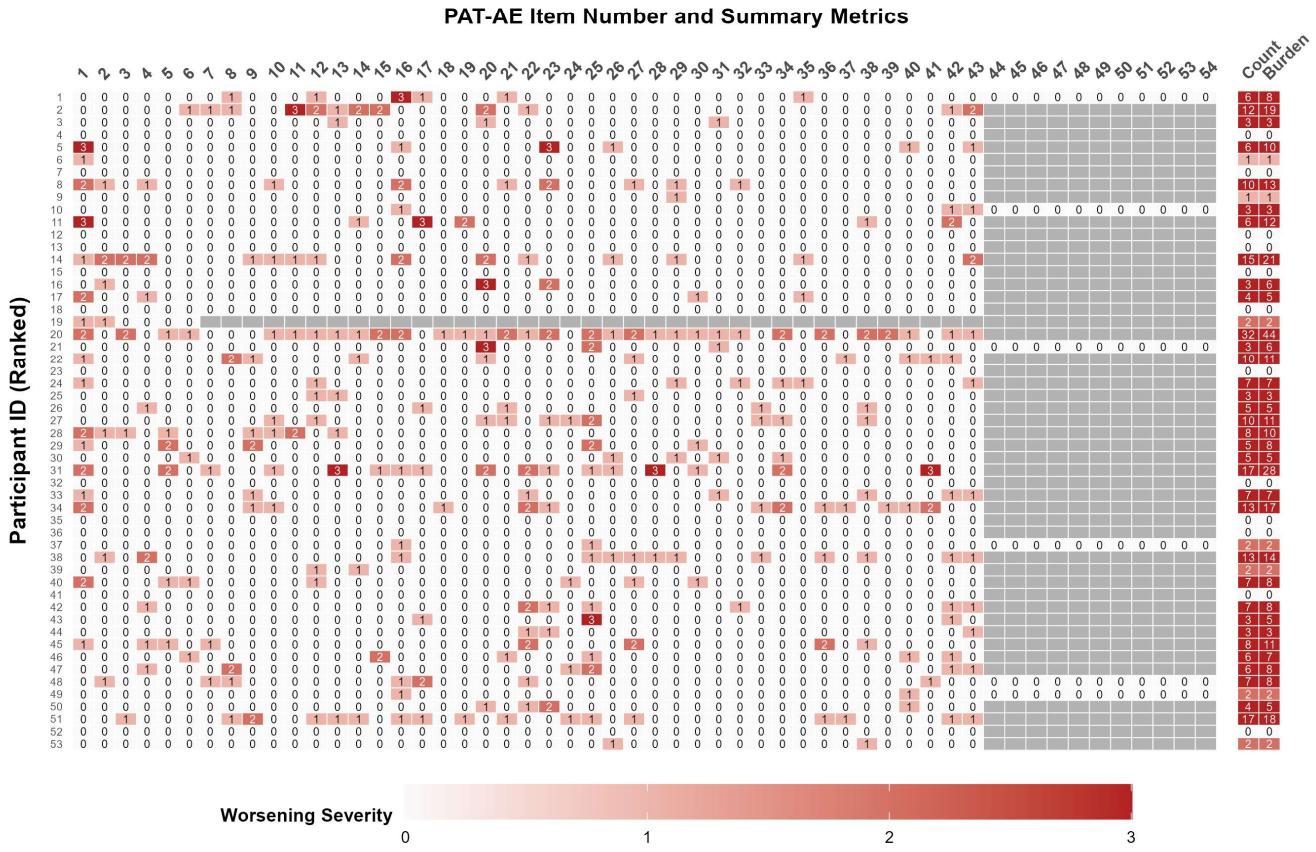
SOCIOCULTURAL	
Adverse change in worldview	A change in global beliefs about the world, one's place in it, or about others, which are distressing or impairing.
Cultural invalidation	Negation, devaluation, disregard for, or transgression against one's cultural norms, values, or commitments. (Substance Abuse and Mental Health Services Administration, 2014) (White et al., 2009)
Community strain	Difficult interactions with one's social network or community, as marked by experience of conflict or rejection, loss of social status or social capital, or experience of distress in integrating in one's community.
Stigma	Experience of degradation, stereotyping, or devaluation by others, or the internalization of such an experience into belief about oneself as unworthy or invalid, based on a personal characteristic (e.g., social identity) or behavior (e.g., help-seeking)
Distress associated with minoritized identity	Heightened salience, concern about, and distress associated with a minoritized identity (e.g., minority stress for sexual and gender minority patients)

Palitsky et al. (2024) *Journal of Psychopharmacology*
Palitsky et al. (2024) *International Review of Psychiatry*

Item-Level Trajectories of Adverse Events Following Psilocybin Administration

Heatmap of the Psychedelic Assisted Therapy-Adverse Events (PAT-AE) scale.
Values represent worsening severity (0 = no worsening/improvement; red continuum = worsening magnitude).
'Count' reflects the total number of endorsed adverse events; 'Burden' represents the cumulative severity score.
Gray cells denote missing data.

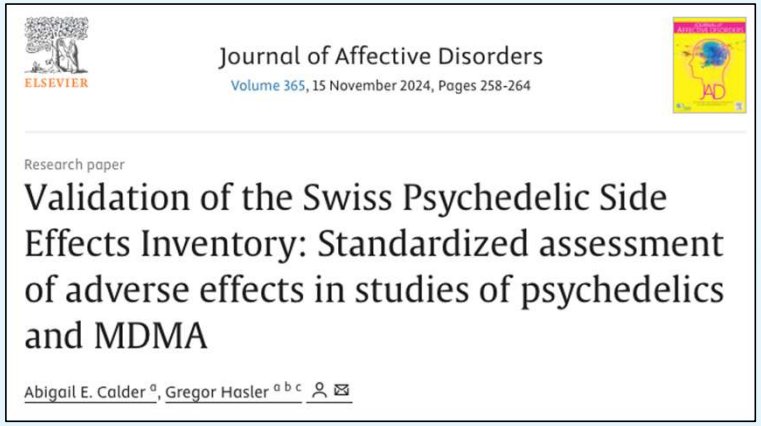


Most frequently endorsed

23%	Re-experiencing
23%	Isolation & Loneliness
23%	Distressing values change
21%	Symptom worry
19%	Relationship strain
19%	Decreased libido

Palitsky et al. (in prep)

Taking the measure of psychedelic AEs



Journal of Affective Disorders
Volume 365, 15 November 2024, Pages 258-264

Research paper

Validation of the Swiss Psychedelic Side Effects Inventory: Standardized assessment of adverse effects in studies of psychedelics and MDMA

Abigail E. Calder [a], Gregor Hasler [a b c]

32 side effects including an important subset of key criteria

Journal of Psychopharmacology

BAP British Association for Psychopharmacology

Impact Factor: 5.5 / 5-Year Impact Factor: 4.6

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A framework for assessment of adverse events occurring in psychedelic-assisted therapies

Roman Palitsky, Deanna M Kaplan, [...], and Boadie W Dunlop +10 View all authors and affiliations

Volume 38, Issue 8 | https://doi.org/10.1177/02698811241265756 | View related

54 harms criteria with recommendations for assessment, time points, and items for 3 groups:

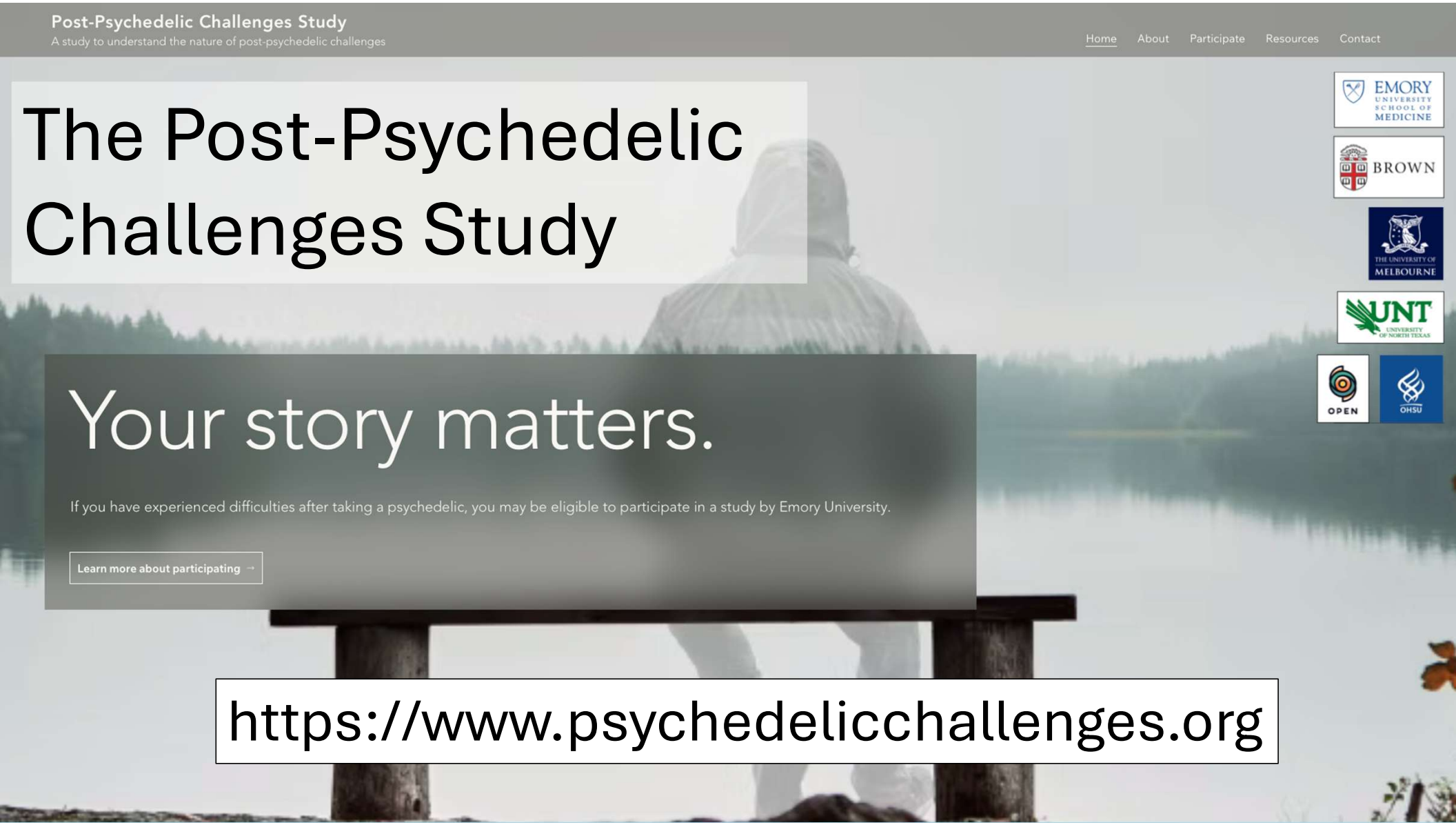
- Patients
- Facilitators
- Informants

2. Understanding AE phenotypes for primary and secondary prevention

What is the nature of post-psychedelic challenges?

What predicts them?

What helps?


Post-Psychedelic Challenges Study
A study to understand the nature of post-psychedelic challenges
Home
About
Participate
Resources
Contact
The Post-Psychedelic Challenges Study
Your story matters.
If you have experienced difficulties after taking a psychedelic, you may be eligible to participate in a study by Emory University.
Learn more about participating →
EMORY UNIVERSITY SCHOOL OF MEDICINE
BROWN
THE UNIVERSITY OF MELBOURNE
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OPEN
OHSU
https://www.psychedelicchallenges.org

N = 800 participants with post-psychedelic challenges

Cross-sectional study

N = 800
Stratified by compound
Detailed assessment
history, context, experience, impacts, remedies, supports
Self-report + 40 interviews

Longitudinal cohort

N = 400
1 year, every 2 months
Trajectories of symptoms, impairment, remedies
Longitudinal predictors of improvement vs worsening

Ambulatory

N = 40
Voicediary + EMA
3 months, weekly
In participants' own words

Cross-sectional study

N = 800
Stratified by compound
Detailed assessment
history, context, experience, impacts, remedies, supports
Self-report + 40 interviews

Longitudinal cohort

N = 400
1 year, every 2 months
Trajectories of symptoms, impairment, remedies
Longitudinal predictors of improvement vs worsening

Ambulatory

N = 40
Voicediary + EMA
3 months, weekly
In participants' own words

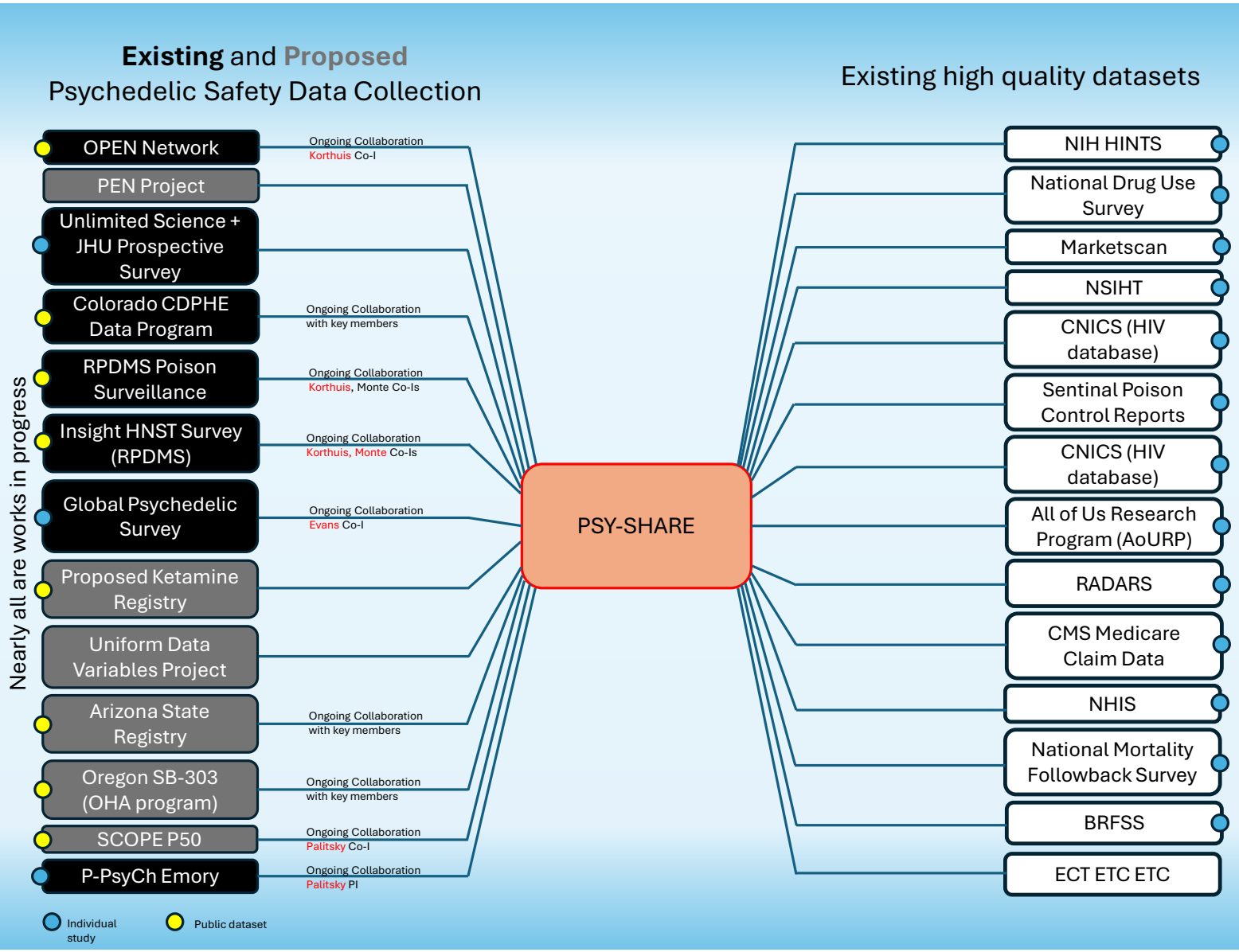
N = 800 participants with post-meditation challenges

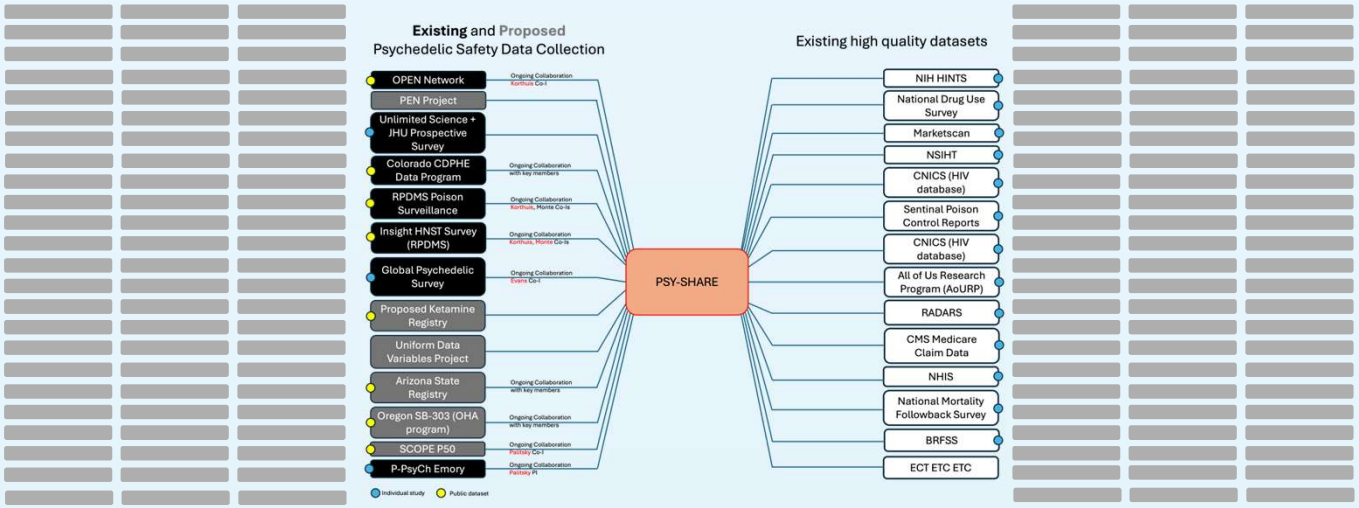
You may be eligible to participate if you have experienced any of the following after taking a psychedelic

- Difficulties or distress **or**
- Negative impacts on your life or daily functioning **or**
- You needed additional professional support or treatment
- **And** you are 18 years or older, can read and understand English, and currently resi

Now in Canada and Australia
Europe: coming soon

3. Developing monitoring systems that work


Existing and Proposed
Psychedelic Safety Data Collection
Existing high quality datasets
Nearly all are works in progress
OPEN Network
PEN Project
Unlimited Science + JHU Prospective Survey
Colorado CDPHE Data Program
RPDMS Poison Surveillance
Insight HNST Survey (RPDMS)
Global Psychedelic Survey
Proposed Ketamine Registry
Uniform Data Variables Project
Arizona State Registry
Oregon SB-303 (OHA program)
SCOPE P50
P-PsyCh Emory
Ongoing Collaboration
Korthuis Co-I
Ongoing Collaboration
with key members
Ongoing Collaboration
Korthuis, Monte Co-Is
Ongoing Collaboration
Korthuis, Monte Co-Is
Ongoing Collaboration
Evans Co-I
Ongoing Collaboration
with key members
Ongoing Collaboration
with key members
Ongoing Collaboration
Palitsky Co-I
Ongoing Collaboration
Palitsky PI
PSY-SHARE
NIH HINTS
National Drug Use Survey
Marketscan
NSIHT
CNICS (HIV database)
Sentinal Poison Control Reports
CNICS (HIV database)
All of Us Research Program (AoURP)
RADARS
CMS Medicare Claim Data
NHIS
National Mortality Followback Survey
BRFSS
ECT ETC ETC
Individual study
Public dataset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Ongoing Collaboration with key members
Ongoing Collaboration
Ongoing Collaboration
Individual study
Public dataset
PSY-SHARE
Existing high quality datasets
NIH HINTS
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Sentinal Poison Control Reports
CNICS (HIV database)
All of Us Research Program (AoURP)
RADARS
CMS Medicare Claim Data
NHIS
National Mortality Followback Survey
BRFSS
ECT ETC ETC

We could use your help!

https://www.psychedelicchallenges.org

Roman.paltsky@emory.edu

Thank you!

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Questions? Comments?

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