The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

Exploring Psychedelics and Entactogens as Treatments for Psychiatric Disorders: A Workshop

March 29-30, 2022

Statement of Task

A planning committee of the National Academies of Sciences, Engineering, and Medicine will organize and conduct a 1.5-day virtual public workshop that brings together experts and key stakeholders from academia, government, industry, and non-profit organizations to explore the use of psychedelics and entactogens - including LSD, psilocybin, and MDMA - as treatments for psychiatric disorders, such as major depressive disorder, anxiety disorder, post-traumatic stress disorder, and substance use disorders.

Invited presentations and discussions will be designed to:

1. Review the current state of knowledge regarding the mechanisms of action and pharmacokinetic/pharmacodynamic properties of these compounds, including considering the impact of polypharmacy;
2. Discuss the current evidence on the clinical efficacy of psychedelics and entactogens to treat psychiatric conditions, including:
    a) exploring the role of adjunctive psychotherapy,
    b) whether hallucinogenic and dissociative side effects are essential to treatment efficacy, and
    c) clarifying the importance of psychosocial contexts;
3. Consider the role of biomarkers to target treatments, stratify patients, and predict safety profiles;
4. Explore appropriate clinical trial design, the need for standardization of treatment regimens, the challenge of blinding and accounting for placebo effects, and regulatory considerations;
5. Discuss the impacts of these compounds' legal status and scheduling classifications on research;
6. Explore questions of biomedical ethics such as those regarding patient protections and consent, standards of clinical training and quality assurance, off-label use, equitable access to treatment options, and engagement with public interest and experimentation;
7. Discuss open research questions, policy needs, and opportunities to move the field forward.

The planning committee will develop the agenda for the workshop, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

DAY 1, March 29, 2022

9:30am EST **Welcome and workshop overview,** *10 min*
Sarah H. Lisanby, National Institute of Mental Health (NIMH), *Workshop co-chair*
Gerard Sanacora, Yale School of Medicine, Yale School of Medicine, *Workshop co-chair*

Session 1: An Introduction to Psychedelics and Entactogens as Treatments for Mental Health Conditions

Objectives:

1. Preview the key focus areas to be covered in the workshop.
2. Provide a high-level overview on the history of psychedelic medicine as treatments for mood and substance use disorders.
3. Highlight testimonials from individuals who can speak to the subjective experience of clinical treatment with these agents.

9:40am **Session overview,** *5 min*
Moderator: Sarah H. Lisanby, NIMH, *Workshop Co-char*

9:45am **Overview on the history of psychedelics and MDMA as treatments for psychiatric disorders,** *15 mi* n
Speaker: Charles Grob, University of California, Los Angeles (UCLA)

10:00am **Personal perspectives on clinical treatment with psychedelics and MDMA,** *20 min*
Speakers:
Nora Osowski, MPH
Lori Tipton, Psychedelic Society of New Orleans, LA

10:20am **Audience Q&A***, 5 min*

10:25am **Break**, *10 min*

Session 2a: State of the Evidence on Mechanisms of Action and Key Research Gaps for Classic Psychedelics and MDMA

Objectives:

1. Review the state of knowledge regarding the acute and enduring molecular and circuit mechanisms of action, and the state of knowledge by which psychosocial contexts modulate those mechanisms.
2. Provide a summary from the January 2022 NIMH psychedelics workshop: What key research gaps were identified?

10:35am **Session overview,** *5 min*
Moderator: Rita Valentino, National Institute on Drug Abuse (NIDA)

10:40am **Overview of state of knowledge on molecular mechanisms of action,** *20 min*
Speaker: Gabriella Gobbi, McGill University

11:00am **Overview of state of knowledge on circuit mechanisms of action,** *20 min*
Speaker: Katrin Preller, Yale School of Medicine/University of Zurich

11:20am **Overview of state of knowledge on the neuroplastic effects,** *20 min*
Invited Speaker: David E. Olson, University of California at Davis

11:40am **Overview of state of knowledge on the role of psychosocial contexts,** *20 min*
Speaker: Rosalind Watts, The Synthesis Institute

12:00pm **Summary of research gaps identified in the Jan 2022 NIH Psychedelics Workshop**, *10 min*
Speaker: Nora Volkow, NIDA

12:10pm **Audience Q&A,** *20 min*

12:30pm **Lunch**, *1 hr*

Session 2b: Exploring Critical Research Gaps and Opportunities

Objectives

1. Explore critical research gaps that need to be addressed to advance the field and discuss potential opportunities for action, including:
    1. What are the interactions between molecular/circuit mechanisms and the psychosocial context?
    2. During treatment, what other aspects of the patients psychoemotional state are being modified (e.g., changes in beliefs, social bonding, consciousness, and spirituality), and what are the implications?
    3. Is the hallucinogenic/dissociative experience part of therapeutic mechanism of action and what are the implications?

1:30pm **Session overview:** John Krystal, Yale School of Medicine, *5 min*

1:35pm **Panel discussion: Exploring three key research gaps**, *60 min*
Panelists:

1. Javier Gonzalez-Maéso, Virginia Commonwealth University
2. Roland Griffiths, Johns Hopkins University
3. Tristan McClure-Begley, Defense Advanced Research Program Agency
4. Robert Malenka, Stanford University
5. Gitte Moos Knudsen, University of Copenhagen

2:35pm **Audience Q&A,** *10 min*

2:45pm **Break**, *10 min*

Session 3: Key Opportunities to Advance Clinical Development

Objectives:

1. Provide an overview of the current evidence of clinical efficacy of psychedelics and entactogens to treat mood and substance use disorders.
2. Discuss key regulatory considerations.
3. Explore two challenges/questions that are critical for moving this field forward, and discuss potential opportunities for action.

2:55pm **Moderator introductions**, *5 min*
Moderator: Gerard Sanacora, Yale School of Medicine, *Workshop co-chair*

3:00pm **Landscape view of evidence of clinical efficacy**, *20 min*
Invited speaker: Collin Reiff, New York University, Langone

3:20pm **Key regulatory considerations***, 20 min*
Speaker: Javier Muniz, Food and Drug Administration (FDA)

3:40pm **Break**, *5 min*

3:45pm **Panel Discussion: Major challenges for clinical development,** *60 min*

1. How should clinical trial design evaluate the impact of the non-pharmacological factors, e.g., guided treatment sessions (in-person vs. digital administration; individual settings vs. group settings)
2. How can clinical trial design address challenges related to blinding, active comparators, expectancy effects, and placebo effects?

Panelists:

1. Collin Reiff, New York University, Langone
2. Javier Muniz, FDA
3. Luana Colloca, University of Maryland
4. Srinivas Rao, atai Life Sciences
5. Charles Raison, The Usona Institute/University of Wisconsin, Madison
6. Steven Levine, Compass Pathways
7. Corine de Boer, Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation

4:45pm **Audience Q&A,** *10 min*

4:55pm **Concluding Remarks**, *5 min*
Speakers: Gerard Sanacora, Yale School of Medicine, *Workshop Co-Chair*

5:00pm **Adjourn**

DAY 2, March 30, 2022

10:00am EST **Welcome, Recap of Day 1 Themes,** *10 min*
Gerard Sanacora, Yale School of Medicine, *Workshop Co-Chair*

Session 4: Anticipating implementation to guide clinical research and development

Objectives:

1. Identify anticipated implementation issues for psychedelic medicines and related treatments, should they be approved, and discuss how these considerations should be used now to guide clinical development by exploring these discussion questions:
    1. How does the legal status of these agents shape the path to clinical implementation?
    2. What are the implications of possible abuse, misuse, and off-label use? Lessons learned from esketamine as a case study to compare against MDMA.
    3. What special bioethical and patient protection risks may arise during implementation, e.g., need to prevent the sexual abuse and exploitation of a patient's psychoemotional vulnerability, and how can risk mitigation approaches be studied during the roll out?

10:10am **Session Overview,** *5 min*
Moderator: Paul Appelbaum, Columbia University

10:15am **Frameworks for accessible and equitable implementation,** *20 min*
Speaker: Melissa A. Simon, Northwestern University

10:35am **Panel discussions: Critical challenges for implementation,** *70 min*
Panelists:

1. Melissa A. Simon, Northwestern University

2. Anthony Coulson, Drug Enforcement Administration (retired)/NTH Consulting, Inc.
3. Dominic Sisti, University of Pennsylvania
4. Charma D. Dudley, National Alliance of Mental Illness (NAMI)
5. Caroline Dorsen (Rutgers, State University of New Jersey)
6. Steven Levine (Compass Pathways)

11:45pm **Audience Q&A,** *15 min*

12:00pm **Lunch***, 30 min*

Session 5: Synthesis and Next Steps

Objectives:

1. Synthesize key themes from the workshop.
2. Discuss critical research gaps, next steps, and promising opportunities for future action.

12:30pm **Session overview and synthesis of workshop's key themes***, 15 min*
Moderator: Sarah H. Lisanby, NIMH, *Workshop co-chair*

12:45pm **Panel discussion - Emerging themes and the road ahead,** *55 min*
Panelists:

1. Daniel Karlin, MindMed
2. Sean Belouin, Substance Abuse and Mental Health Services Administration
3. Walter Dunn, UCLA
4. Shirley Holloway, NAMI
5. Joshua Gordon, NIMH
6. Nora Volkow, NIDA

1:40pm **Audience Q&A,** *15 min*

1:55pm **Concluding remarks,** *5 min*
Sarah H. Lisanby, NIMH, *Workshop co-chair*
Gerard Sanacora, Yale School of Medicine, *Workshop co-chair*

2:00pm **Adjourn**