The National Academies of SCIENCES ENGINEERING MEDICINE

Forum on NEUROSCIENCE and NERVOUS SYSTEM DISORDERS

Novel Molecular Targets for Mood Disorders and Psychosis

A Workshop

March 8-9, 2021 | Via Zoom

Workshop Objectives:

This public workshop will bring together experts and key stakeholders from academia, government, industry, and non-profit organizations to explore novel molecular targets for mood disorders and psychosis, including ketamine, other NMDA receptor antagonists, neurosteroids, muscarinic antagonists, and serotonergic receptor modulators.

Invited presentations and discussions will be designed to:

- Review the current landscape of novel therapeutic targets and agents in development for mood disorders.
- Discuss commonalities among mechanisms of action and lessons learned in translation and clinical development that could be applied across programs to develop novel therapeutics for mood disorders.
- Examine key clinical and ethical questions—such as those related to dosing, safety, treatment aims, duration, diagnosis, place in the sequence of treatments, strategies to prolong efficacy and minimize risk, and the treatment setting—and regulatory challenges and opportunities.
- Explore the different types of bioethical frameworks that will be needed to guide the regulation and administration of novel therapeutics that mediate profound effects on consciousness.
- Consider emerging molecular targets for treating psychosis and cognitive impairment in schizophrenia and how therapeutic development could be informed by lessons learned in developing novel therapeutics for mood disorders.
- Discuss open research questions and opportunities to move the field forward.

DAY 1, March 8, 2021

Session 1: Introduction to Drugs and Drug Targets for Mood Disorders and Psychosis

Objectives:

- Provide a high-level overview of the current landscape of novel molecular targets for mood disorders and psychosis.
- Discuss the scientific and clinical limitations of current pharmacological interventions to address mental illness.
- Highlight the unmet needs of people living with schizophrenia and treatment-resistant depression via testimonials from individuals who can speak to the subjective experience of these disorders.

2:00pm EST **Welcome and Overview of Workshop,** 10 min

LINDA BRADY, National Institutes of Mental Health (NIMH), *Workshop Chair*

2:10pm **The lived experience and unmet needs of individuals with schizophrenia and depression,** 20 min

CARLOS LARRAURI, *The National Alliance for Mental Illness*

ASHLEY CLAYTON, *Yale University*

2:30pm **Introductory talk: Scientific perspective on the history of drug treatments for mood disorder and psychosis**, 20 min

STEVE PAUL, *Karuna Therapeutics*

2:50pm **Audience Q&A,** 10 min

3:00pm **BREAK**, 10 min

Session 2: Promising Developments with Glutamate Receptors

Objectives:

- Review clinical and pre-clinical data of ketamine as a case study of a novel rapidly-acting antidepressant that acts by blocking glutamate receptors.
- Examine possible explanations for the underlying mechanism of action.
- Explore the clinical and regulatory ramifications of rapidly-acting antidepressants.
- Identify lessons learned and how they can help advance drug development targeting novel pathways.

3:10pm **Session Overview,** 5 min

HUSSEINI MANJI, *Janssen Research & Development, LLC*

3:15pm **GluRs as a novel molecular target: clinical data on the use case of ketamine and esketamine,** 20 min

CARLA CANUSO, *Janssen Research & Development, LLC*

- Who are the best candidates for treatment and why?

- Which specific MDD symptoms and behaviors show the most improvement?
- Is there evidence demonstrating that ketamine can prevent relapses?
- After a single treatment, how long does the antidepressive effect persist?
- What are the implications of intermittent drug administration over the long-term?

3:35pm **GluRs: Investigating the mechanism of action for therapeutic ketamine,** 20 min

JOHN KRYSTAL, *Yale University*

- What are the relevant downstream cellular events?
- How does ketamine alter cellular and circuit activity?
- Are there biomarkers that could be predictive of clinical efficacy?
- Why is NMDA-R antagonism via ketamine effective for depression, while NMDA-R antagonism via other drug compounds is not?

3:55pm **Panel discussion**: **Identifying lessons learned and key open questions,** 40 min

The Session 2 speakers above will be joined by panelists:

MORGAN SHENG, *Broad Institute of MIT and Harvard*

CARLOS ZARATE, *NIMH*

4:35pm **Audience Q&A**, 15 min

4:50pm **Day 1 synthesis and closeout**, 10 min

LINDA BRADY, *NIMH*, Workshop Chair

5:00pm **ADJOURN**

DAY 2, March 9, 2021

Session 3: Promising Developments with GABA Receptors

Objectives:

- Review clinical and pre-clinical data demonstrating that novel drugs targeting gamma-aminobutyric acid receptors (GABARs) can alleviate depressive symptoms.
- Examine how drug development directed towards novel targets and pathways could be informed by a new understanding of GABA modulators in depression.
- Discuss how emerging drug targets for GluRs and GABARs advances our understanding of excitation/inhibition balance in mood circuits.

10:00am **Overview of session**, 5 min

CHARLES ZORUMSKI, *Washington University School of Medicine*

10:05am **GABARs as a novel molecular target: promising clinical data**, 15 min

SAMANTHA MELTZER-BRODY, *University of North Carolina at Chapel Hill*

- How long does it take for a treatment effect to be observed?

- What is the treatment effect size relative to the standard of care?
- What is the impact of route of administration (oral vs. intravenous)?
- How is information like patient age, symptom severity, and disease onset used to design effective treatment plans?
- Which molecular pathways are presumed to be involved?

10:20am **GABARs: Mechanisms of action for GABA-A modulators in depression**, 15 min

JAMIE MAGUIRE, *Tufts University*

- How have hormone withdrawal and neurosteroid signaling been implicated in the pathophysiology of postpartum depression?
- How and why are phasic and tonic GABAR signaling differentially effected?
- Why are some GABAergic modulators, but not others, effective antidepressants and what does that tell us about the etiological specificity of depressive disorders?

10:35am **Panel discussion: Tuning the balance of excitation and inhibition**, 40 min

The Session 3 speakers will be joined by:

GYORGY BUZSAKI, *New York University*

LISA MONTEGGIA, *Vanderbilt University*

JOHN MURRAY, *Yale University*

11:15am **Lessons learned from a regulatory perspective**, 30 min

TIFFANY FARCHIONE, *Food and Drug Administration*

- How do the regulatory approaches to esketamine and brexanalone inform considerations for similar incoming programs?
- What framework do regulators use when considering rapidly-acting antidepressants and drugs that are administered via an intermittent dosing?

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

12:00pm **LUNCH**, 1 hour

Session 4: The Road Ahead for Emerging Drug Targets

Objectives:

- Consider emerging drug development pathways for mood disorders and psychosis.
- Discuss lessons learned in translation and clinical development that could be applied across programs to develop novel therapeutics.
- Explore how these emerging targets inform new scientific strategies for drug development.

1:00pm **Overview of session**, 5 min

DAVID GRAY, *Cerevel Therapeutics*

1:05pm **mTOR signaling in depression treatment**, 10 min

EDDINE SAIAH, *Navitor Pharmaceuticals*

1:15pm **Serotonin 5-HT2 receptor agonists for mental disorders,** 10 min

GABRIELLA GOBBI, *McGill University*

1:25pm **TAAR1/5-HT1$_A$R agonists in schizophrenia treatment,** 10 min

KENNETH KOBLAN, *Sunovian Pharmaceuticals*

1:35pm **M1/M4 acetylcholine muscarinic receptor targets,** 10 min

ALAN BREIER, *Indiana University – Purdue University, Indianapolis*

1:45pm **Panel Q&A: Emerging developmental pathways in mood disorder and psychosis,** 45 min

The Session 4 speakers will be joined by:
ROBERT DAVIS, *Intracellular Therapies*
BRYAN ROTH, *University of North Carolina, Chapel Hill*

- What are the challenges and opportunities of developing drug compounds that acts on mechanisms downstream of the primary target?
- How should we think about convergent modulation of multiple signaling mechanisms in the context of intracellular pathways and microcircuit networks?
- What are useful frameworks for predicting clinical efficacy for drugs with multiple targets and multiple measures of target engagement?

2:30pm **Audience Q&A**, 15 min

2:45pm **Break**, 5 min

Session 5: Bioethical Considerations

Objectives:

- Explore the different types of bioethical and scientific frameworks that will be needed to guide drug development as additional emerging targets are identified.

2:50pm **Overview of session**, 5 min

SHARON MATES, *Intracellular Therapies*

2:55pm **The bioethical considerations of using psychoactive drugs to treat mental illness,** 20 min

PAUL APPELBAUM, *Columbia University*

- How are the bioethical considerations even more pointed for agents where the dissociative experiences are a main effect, rather than a side effect?
- How do we ensure informed consent when referring to ineffable subjective experiences that may be induced?

- How do we helping the patient adapt to significant changes in/improvements to mood state?
- How do we ensure appropriate use, monitoring, and oversight?
- How do we weight the therapeutic benefit against the risk of adverse effects and abuse potential?

3:15pm **Panel Discussion,** 35 min

Dr. Appelbaum will be joined in the discussion by:

MASON MARKS, *Gonzaga University*

ILINA SINGH, *Oxford University*

- Is a precautionary approach appropriate here? Do these frameworks need updating as we know more about the science and as the public becomes more aware and interested?
- What can be learned from the systems developed around ketamine clinics in the UK?
- How are health inequities and unequal access to care exacerbated when in-need/vulnerable populations are not reached by these novel therapies?

3:50pm **Audience Q&A**, 10 min

4:00pm **Break**, 5 min

Session 6: Synthesis and Next Steps

Objectives:

- Synthesize key themes.
- Discuss critical research gaps, next steps, and promising areas for future action.

4:05pm **Synthesis of workshop's key themes,** 5 min

LINDA BRADY, *NIMH*, Workshop Chair

4:10pm **Next steps and opportunities,** 45 min

TIFFANY FARCHIONE, *Food and Drug Administration*

MAGALI HAAS, *Cohen Veterans Bioscience*

STUART HOFFMAN, *US Department of Veterans Affairs*

RUPERT MCSHANE, *Oxford University*

VENKATESHA MURTHY, *Takeda*

GREG SIMON, *Kaiser Permanente*

BRANDON STAGLIN, *OneMind*

JOSHUA GORDON, *NIMH*

4:55pm **Acknowledgements and concluding remarks**, 5 min

LINDA BRADY, *NIMH*, Workshop Chair

5:00pm **END OF WORKSHOP**