UNITED STATES HOUSE OF REPRESENTATIVES COMMITTEE ON VETERANS' AFFAIRS, SUBCOMMITTEE ON HEALTH, OVERSIGHT HEARING "*PSYCHEDELIC-ASSISTED THERAPIES FOR VETERANS: THE PATH FORWARD*"

Date/Time: Wednesday, November 18, 2026, 2:15 P.M. ET

Location: Cannon House Office Building, 27 Independence Ave SE, Washington, DC 20003, Room 360

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Chairwoman Miller-Meeks, Ranking Member Brownley, and other Members of the Subcommittee: thank you for inviting me here today to discuss this important topic. I'd also like to extend a belated Happy Veteran's Day to all. Your service and sacrifice is greatly appreciated.

My name is Mark Niciu, and I serve as an Assistant Professor of Psychiatry at the University of Iowa. In this role, I have been working to help lead the Iowa Psychedelics Research Program along with Dr. Peg Nopoulos. I appreciate the invitation, an opportunity to discuss our research in psychedelic medicine, and look forward to the discussion.

INTRODUCTION

After decades on inactivity due to legal restrictions, there has been a resurgence of classical psychedelic (5-HT_{2A} receptor agonist) research for psychiatric/substance use disorders. Classical psychedelics include lysergic acid diethylamide (LSD), psilocybin, and D-methyltryptamine (DMT), in contrast to non-traditional psychedelics/hallucinogens. e.g. the N-methyl-D-aspartate receptor antagonists phencyclidine (PCP) and ketamine, and empathogens/entactogens, e.g. 3,4-methylenedioxymethamphetamine (MDMA). Although the mechanisms of action differ, all these drugs, at sufficient doses with bioavailable means of administration, produce acute, robust, and/or profound experiences that separate them from typical non-rapid acting psychiatric interventional drugs (RAPIDs).

In 2022, the Departmental Executive Officer (DEO)/Chair of the Psychiatry Department, Dr. Peg Nopoulos, formed a psychedelic research interest group to discuss bringing psychedelic medicine to the University of Iowa, and, from these initial embers, the Iowa Psychedelic Research Program conflagrated, with weekly meetings and other programming across diverse expertise in the Carver College of Medicine and the Iowa Neuroscience Institute. We assembled a team that included: (1.) physician-scientists with expertise in clinical trials and neuroimaging; (2.) research assistants skilled in recruitment and assessments of subjects in clinical trials; (3.) assistants with experience in regulatory administration such as local and federal application to our Investigational Review Board (IRB) and the United States Food and Drug Administration (FDA) for an Investigational New Drug (IND) application, respectively; (4.) psychotherapists trained and experienced with psychedelic medicine; (5.) colleagues to serve on a Data and Safety Monitoring Board (DSMB); (6.) internist and cardiologist to review medical histories and baseline biological assessments; (7.) a biostatistician and (8.) a research scientist with expertise in neuroimaging/analyses.

With the financial backing of a generous philanthropic gift, the Iowa Psychedelic Research Program first sought to tackle a major hurdle in psychedelic medicine trials – **functional unblinding, the unmasking of subjects and/or researchers to randomization status**. The accepted "gold standard" for new medication approval by the FDA, other regulatory agencies,

and the broader scientific community, is the randomized, double-blind, placebo-controlled trial. Most placebo-controlled trials in the United States use inert placebos, which is often unproblematic as the active medication does not have acute, subjective effects that permit subjects and/or investigators to accurately ascertain group assignment. Nevertheless, even with inert placebos, non-specific improvements in symptoms often arise from treatment non-specific effects – expectations, context, and the therapeutic encounter(s) – rather than from the medication's specific physiologic action. This is collectively called the placebo effect. Closely related to the placebo effect, expectancy bias reflects a distortion in symptom perception, reporting, or assessment driven by preconceived beliefs about an active intervention. Expectancy bias is particularly salient in psychedelic medicine trials, where the drug's effects are acute, intense, highly salient, and reinforced, for example, by the recent re-galvanization of classical psychedelics by the media, government, etc. **When such drugs are compared with an inert or insufficiently matched placebo, participants and researchers immediately and accurately know their randomization assignment.** In other words, there is "double" functional unblinding, potentially affecting the thoughts and/or behaviors of both parties for the remainder of the trial.

In contrast to expectancy bias, participants assigned to an inert or poorly matched placebo typically lack acute intoxicating effects, fostering malignant (efficacy-discordant) unblinding and a "negative" nocebo effect. In many classical psychedelic and intravenous ketamine trials, the nocebo effect is not seen as clinical worsening. Instead, response in subjects randomized to an inert placebo typically "flat lines," i.e. little-to-no-improvement in symptoms over time, grossly inconsistent with typical placebo responses in neuropsychiatric trials discussed above. In the ketamine depression literature, when the better-matched active comparator midazolam was used in place of inert placebo (0.9% saline), a more typical "placebo response," is observed, i.e. a numerical reduction in depression ratings continues over time in both arms. In a recent systematic review, although only 29.5% of psychedelic trials formally evaluated blinding integrity, 57.1% of those identified functional unblinding as a major, if not primary, limitation. Some psilocybin studies have included randomization to "active" placebos, i.e. methylphenidate, niacin, and even lower (1 mg) dose psilocybin. While such "active placebos" may mimic certain features of the acute, subjective experience, suffice it to say, they do not recapitulate the often-desired aspects of higher dosing.

The Iowa Psychedelic Research Program proposed an important methodological shift for randomized controlled trials in psychedelic medicine: the use of an active comparator design, hypothesized to mitigate expectancy bias and nocebo effects. In this design, participants are randomized to **one of two drugs that both produce similarly recognizable acute, subjective effects, the classical psychedelic psilocybin and the non-traditional hallucinogen ketamine**. Although expectancy effects may be present in both groups (subjects know they are getting an active intervention), if designed appropriately to mirror the subjective experiences as much as possible, participants (and ideally investigators) should not be able to ascertain treatment assignment better than chance. By minimizing differential expectancy and nocebo effects between study arms, active comparator designs provide a more rigorous test of therapeutic efficacy and strengthen confidence that observed differences reflect specific pharmacologic mechanisms, rather than treatment non-specific "artifacts."

Understanding the neurobiological effects of such drugs is also essential for advancing mechanistic and therapeutic research. Although clinical studies have demonstrated promising efficacy across a range of psychiatric and substance use disorders, the neural mechanisms that mediate these therapeutic effects remain incompletely understood. Characterizing psychedelic-induced changes in brain activity, connectivity, and network organization can identify the circuits

and processes most closely linked to clinical improvement, distinguish therapeutic mechanisms from nonspecific treatment effects, and guide the development of surrogate, scalable markers of treatment response. Such mechanistic insights may also facilitate optimization of dosing strategies, patient selection, and combination treatments while informing the development of next-generation drugs designed to maximize therapeutic benefit while minimizing adverse effects. To this end, we perform structural and functional neuroimaging and neurophysiology before (baseline), during, and/or after the receipt of ketamine or psilocybin.

METHODS

A phase II pilot/feasibility study was approved by the University of Iowa IRB (HawkIRB #202205036), the FDA (IND #165296), and relevant state and federal regulatory agencies, and followed Consolidated Standards of Reporting Trials (CONSORT) guidelines for a parallel-group randomized controlled design.

Our pilot 8-week protocol randomized 10 men (ages 25–65) with moderate-to-severe alcohol use disorder (AUD) to receive either oral psilocybin (25 mg) or ketamine (200 mg) in a double-dummy design. Screening included psychiatric evaluation, structured diagnostic interview, laboratory testing, and cardiovascular assessment. Exclusion criteria included other (non-alcohol) substance use disorders in the prior year; prescribed neuropsychiatric medications in the past 3 months; psychedelic/hallucinogen use in the past year; a history of complicated alcohol withdrawal, cerebrovascular accident (stroke); severe coronary artery disease; heart failure; insulin-dependent diabetes mellitus; seizure disorder; uncontrolled hypertension (BP>140/90); significant brain injury, including loss of consciousness > 5 minutes, in the past year; and a personal or family history of psychosis. Eligible participants completed two preparatory psychotherapy sessions focused on rapport-building and readiness for the dosing experience. The drug administration session occurred in a controlled, supportive setting with trained therapists, standardized music, and optional eye mask. All subjects received either oral psilocybin (25 mg) or ketamine (200 mg) in a double-dummy design. In other words, if subjects were randomized to psilocybin, they received oral psilocybin and 0.9% saline diluted in 16 oz. of fruit juice (to mask salinity/bitterness). If randomized to ketamine, subjects received oral placebo and 200 mg liquid ketamine diluted in 16 oz. of fruit juice.

Integration therapy began the following day and continued with in-person and remote follow-up visits through Week 8. Participants and investigators were unblinded at study completion. Our primary outcome was a within-group reduction in the number of drinks/week from baseline (Week 1) to study end (Week 8) as assessed using the Timeline Follow Back methodology, a calendar-based method, with high reliability and validity for alcohol consumption over weeks-to-months in normal and problematic drinkers. Percent change for the primary outcome was calculated, as well as abstinence. We also assessed the acute, subjective response to study medication using the 30-item Mystical Experiences Questionnaire (MEQ30), revised from the original 43-item scale within the States of Consciousness Scale, and the 6-item Clinician Administered Dissociative States Scale, revised from the original 27-item scale. The MEQ30 has been validated and used extensively to measure altered states of consciousness in psychedelic/hallucinogenic administration paradigms. Although initially developed to measure dissociation in post-traumatic stress disorder (PTSD), the CADSS has been used extensively to measure ketamine-induced dissociative side effects. We also assessed blinding integrity, safety, and adverse effects. Finally, we performed high magnetic field strength (7-Tesla) structural and functional neuroimaging prior to (baseline), one day after drug administration, and at the end of the study. As our neuroimaging analyses are ongoing, and, hence, have not been submitted for peer-reviewed publication, we will not present these results herein.

After completion of our pilot protocol, we have commenced a larger (n=80), longer (16-week) randomized controlled trial of subjects with World Health Organization (WHO) moderate-or-greater drinking risk level; in this larger study, an AUD diagnosis is not required for inclusion. We have also modified our drug administration paradigm; opting for greater bioavailability and intensity of the psychedelic experience, we now randomize to psilocybin 30 mg or ketamine 0.75 mg/kg intramuscular, with continued double-dummy design. Our primary outcome remains the number of drinks per week. However, as this trial is ongoing, we will also not present preliminary results herein.

RESULTS

For blinding integrity, in our active comparator paradigm, our pilot sample could not discern better than chance (5/10, 50%) if they received psilocybin or ketamine. Our psychedelic therapists, who have advanced training and clinical experience in assisted psychotherapies with both drugs, correctly ascertained randomization assignment for 8/10 (80%) subjects.

The side effect profile was consistent with both drugs – hypertension, tachycardia, nausea, and dissociation – without significant differences between groups. No serious adverse effects or other safety concerns were encountered.

For drinking-related outcomes, in the interval from baseline-to-dosing, both groups numerically, but not statistically, decreased their drinks/week [total (n=10): 34.8±8.2 days; ketamine (n=5): 36.8±14.3 days; psilocybin (n=5): 33.0±9.7 days]. The effect sizes were large in both groups (ketamine: t(4)=1.58, p=0.19, *d*=0.71; psilocybin: t(4)=1.36, p=0.25, *d*=0.61) . Similar but numerically smaller effects were observed in the ~5-week period from dosing-to-final visit (ketamine: t(4)=0.61, p=0.56, *d*=0.27; psilocybin: t(4)=0.74, p=0.50, *d*=0.33). **Overall, from baseline-to-final visit, the ketamine group demonstrated an average decrease from 21.8-to-7.0 drinks/week, a 50.6% decrement [t(4)=3.98, p=0.02, *d*=1.78], while the psilocybin group displayed a reduction from 29.2-to-11.8 drinks/week, a 43.7% reduction.** Even though abstinence was not stressed, 3 subjects randomized to psilocybin and 1 subject randomized to ketamine endorsed no alcohol consumption for the duration of the study.

The average MEQ score for the psilocybin group was 79.2, and the average for the ketamine group was 90.6. Although these results suggest most subjects had a significant experience, the score on the MEQ scale did not correlate with percent change in drinking days (Pearson's r(8) = -0.24, p = 0.49). Additionally, there was no correlation between in-session dissociation, as measured by the CADSS-6, and percent change in drinking days (Pearson's r(8)= -0.31, p =0.38).

DISCUSSION

In this pilot sample, subjects could not discern above chance if they were randomized to psilocybin or ketamine. Our trained psychotherapists displayed greater discernment but, we hypothesize, this had little-if-any impact on outcome. This is a major methodologic improvement for psychedelic clinical trials, for at least the following two reasons: (1.) a less conflated, more accurate assessment of effect size of psychedelic-assisted psychotherapy in the treatment of neuropsychiatric disorders; and (2.) human-based mechanistic and/or biomarker studies of psychedelic-assisted psychotherapies not hampered by expectancy biases and/or nocebo response, for both the psychotherapeutic experience itself and its therapeutic benefits.

Consistent with other previous studies, including a meta-analysis of trials from the 1960s of LSD for alcohol use disorder, both ketamine and psilocybin groups displayed large-to-very large effect size reductions on drinking outcomes. A statistically significant percent change reduction

in the number of drinks/week was only observed for the ketamine group from baseline-to-final. We also attempted to correlate the intensity of the psychedelic experience with drinking outcomes, using the MEQ and CADSS. Both measures revealed that subjects with moderate-to-severe AUD had intense mystical and/or dissociative experiences in the current paradigm, but the intensity of the experience did not correlate with drinking-related outcomes.

Our pilot study has selected strengths and weaknesses. For strengths, we employed what is currently considered to be the standard of care manualized psychotherapy for both ketamine-assisted and psilocybin-assisted psychotherapies. Additionally, we performed rigorous clinical and medical assessments of all consented subjects, with a high retention rate. For weaknesses, to limit sex effects, we restricted the study to males, and race/ethnic diversity was limited, with all subjects identifying as Caucasian/non-Hispanic. Next, our active comparator design does not facilitate the study of psychotherapy alone or a control therapy condition, e.g. wait list or alcohol education, as has occurred in prior protocols. Finally, albeit we did not observe this in our small sample, prior drug experience may skew expectancies in either positive or negative directions.

In conclusion, our active comparator paradigm may represent a Kuhnian paradigm shift in psychedelic medicine, presently haunted by the specter of inadequate blinding and its attendant consequences, expectancy bias and/or nocebo response. This will be borne out by our group and potentially others, in replication with larger samples in AUD and/or other neuropsychiatric disorders.

FUTURE DIRECTIONS

In response to the Notice of Funding Opportunity (NOFO) RFA-MH-135 “Addressing Methodological Challenges with Clinical Trials of Rapid-Acting Psychotropic Interventional Drugs (RAPIDs)” (R01 Clinical Trial Required), in October 2026, Dr. Nopoulos and I both submitted applications. Both grants propose to use our active comparator design in diverse patient populations, treatment-resistant major depressive disorder (me) and methamphetamine use disorder (Dr. Nopoulos). There grants will be evaluated in February 2027, without opportunity for resubmission.