

IMPROVING PSYCHOSOCIAL TREATMENTS FOR MOOD AND PSYCHOTIC DISORDERS

Marc J. Weintraub, Ph.D.

Assistant Professor of Psychiatry

UCLA Semel Institute for Neuroscience and Human Behavior 8/12/2025

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- Pharmaceutical Support:
 - Psilo Scientific Ltd. (Filament Health)
- Conflicts of Interest:
 - None

ROADMAP

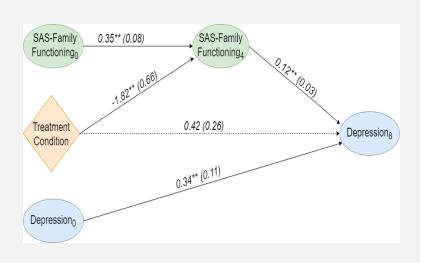
- I. Family-focused therapy for schizophrenia and mood disorders
- 2. Multi-family CBT for adolescents with serious mental illness (SMI) symptoms
- 3. Psychedelic-assisted therapy

RESEARCH BACKGROUND AND ORIENTATION

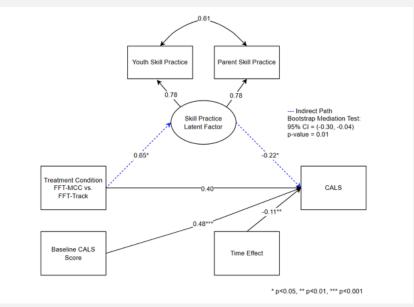
- Research lineage studying family therapies for psychotic and mood disorders:
 - Family-focused therapies (e.g., Miklowitz & Chung, 2016)
 - Culturally-informed family therapy for schizophrenia (Weisman de Mamani & Weintraub, 2014)
- Lens of psychological/psychiatric experiences:
 - Systems approach (micro- & mesosystems)
 - Focus on psychosocial causal/maintenance factors (e.g., family conflict)



MEDIATORS OF MOOD OUTCOMES IN FFT AMONG YOUTH WITH MOOD DISORDERS



*Lower values indicate better family functioning (i.e., less conflict) with SAS- Family Functioning variable.



Bootstrapped Mediational Model of App condition on Family Conflict via Therapist-Rated Family Skill Practice.

BACKGROUND FOR SMI

- Serious mental illness (SMI) refers to psychotic, bipolar disorder spectrum, and persistent or recurrent depressive conditions
- Affects 10-12% of the U.S. population (Kessler, Chiu, Demler, & Walters, 2005)
- Majority of individuals who develop an SMI exhibit their first symptoms in adolescence (Kessler, Demler, et al., 2005)
- Individuals with SMI symptoms are commonly excluded from general clinical programs AND clinicians report feeling unprepared/unwilling to treat these patients (Humphreys, 2017; Wong et al., 2018)



MULTI-FAMILY GROUP COGNITIVE BEHAVIORAL THERAPY



Available online at www.sciencedirect.com

ScienceDirect

Cognitive and Behavioral Practice 27 (2020) 202-214



Applying a Transdiagnostic Cognitive-Behavioral Treatment to Adolescents at High Risk for Serious Mental Illness: Rationale and Preliminary Findings

Marc J. Weintraub, Jamie Zinberg, Carrie E. Bearden, David J. Miklowitz, UCLA Semel Institute

- > 9 sessions of multi-family (teen + parent) group therapy
 - 90 minutes weekly
 - CBT curriculum based on Unified Protocol for Adolescents (UP; Ehrenreich-May et al., 2017)
 - Teen and parents separate for 75-80 minutes
 - Teens and parents come together for final 10-15 minutes
- ➤ High school-aged youth (13 17 years)
 - Depressive and bipolar spectrum disorders
 - Clinical high risk for psychosis
 - Exclude individuals with active suicidality or self-harm, full psychosis, or externalizing behaviors that would interfere with the group

TREATMENT OVERVIEW

- I. Building Motivation
- 2. Positive Activity Scheduling
- 3. Opposite Action for Unhelpful Behaviors
- 4. Emotion Identification & Communication
- 5. Awareness of Thoughts & "Thinking Traps"
 - 6. Modifying Unhelpful Thoughts

TESTING MULTIFAMILY GROUP

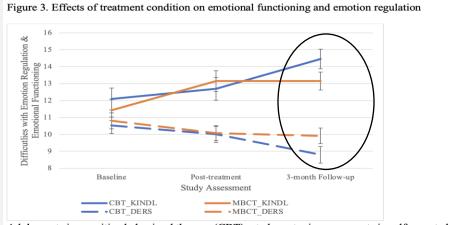
- Preliminary open trial (2018)
 - 10 families → 6 treatment completers
 - Mean age: 15.2 years
 - Improvements in youth psychiatric symptoms (SCL-90) and quality of life (KINDL) and high average satisfaction rating of 5 out of 7
- Randomized trial comparing treatment to group-based multifamily mindfulness-based cognitive therapy (Fall 2018-2020)
 - 66 youth (Mage = 15.1 years, SD = 1.4) initiated trial (32 in CBT and 34 in MBCT)
 - 44 females (66.7%); 25 identified as racial/ethnic minority (37.9%)
 - 54 retained at posttreatment and 53 at the 3-month follow-up

A Randomized Trial of Telehealth Mindfulness-Based Cognitive Therapy and Cognitive Behavioral Therapy Groups for Adolescents With Mood or Attenuated Psychosis Symptoms

https://doi.org/10.1037/ccp0000782

Marc J. Weintraub, Danielle Denenny, Megan C. Ichinose, Jamie Zinberg, Georga Morgan-Fleming, Monica Done, Robin D. Brown, Carrie E. Bearden, and David J. Miklowitz Department of Psychiatry, Semel Institute for Neuroscience and Human Behavior, David Geffen School of Medicine, University of California, Los Angeles

- Both treatments showed comparable improvements in symptoms and functioning
- CBT was rated as more satisfying by youth and parents
- Treatment moderator: emotional functioning and regulation

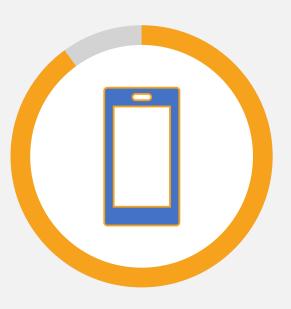


Adolescents in cognitive behavioral therapy (CBT) rated greater improvements in self-reported emotional functioning (KINDL) and emotion regulation (DERS) between the post-treatment assessment and 3-month follow-up compared to adolescents in mindfulness-based cognitive behavioral therapy (MBCT). Lower Difficulties with emotion regulation scale (DERS) indicate better emotional functioning while higher KINDL emotion functioning scores indicate better functioning. DERS scores were divided by 10 to allow for ease of graphing with the KINDL Emotion Functioning subscale.

THE PROBLEM (AND SOLUTION?) OF SKILL PRACTICE

- Skill practice compliance less than 50% (i.e., < 1 skill practice per session)
- Virtually all teens have a smartphone: >90% (Pew Research Institute, 2018)
- App has wide-ranging functionality
 - Can provide session content, practice of skills, symptom monitoring
 - Access for clinicians to track patients' progress
 - Reminder notifications built in
 - Gamifying options (e.g., reward contingencies for completed tasks)

*Testing at the time an app-enhanced family-focused therapy for youth with mood disorders (Miklowitz et al., 2023)



NIMH K23: CAREER DEVELOPMENT AWARD

- Phase I (2021-2022):
 - (A) Build mobile application as adjunct to group CBT, and
 - (B) Examine acceptability and feasibility of app-enhanced group CBT (AppUP) for adolescents with SMI symptoms
- Phase II: Conduct randomized controlled trial comparing AppUP to group treatment without app (2022-2024)
 - Hypotheses:
 - I. AppUP will lead to greater improvements in psychosocial functioning compared to treatment without app
 - 2. AppUP's benefits will be mediated by increased skill practice

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journal homepage: www.elsevier.com/locate/jad





App-enhanced transdiagnostic CBT for adolescents with mood or psychotic spectrum disorders

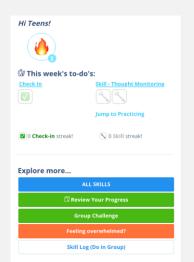


Marc J. Weintraub ^{a,*}, Megan C. Ichinose ^a, Jamie Zinberg ^a, Monica Done ^a, Georga M. Morgan-Fleming ^a, Catherine A. Wilkerson ^a, Robin D. Brown ^a, Carrie E. Bearden ^{a,b}, David J. Miklowitz ^{a,b}

- Held two focus groups (8 adolescent-parent dyads of past groups) to learn about:
 - Motivation for skill practice / Obstacles skill practice
 - Methods to improve skill practice
- Iteratively built mobile application (app)
 - Core components: session review, skill practice, and symptom tracking
 - System to remind participants (i.e., text reminders)
 - Gamification systems (e.g., challenges and prizes)
 - Clinician portal to view participant ratings and skill practice
- Four cohorts in open trial of AppUP (31 adolescent-parent dyads enrolled)
 - 24 treatment retained through post-treatment assessment [77.4%])
 - Mean teen age -15.1 years (SD = 1.5); Mean parent age -49.9 years (5.6)
 - 61.3% female teens; 89% female parents
 - 35.6% identified as racial or ethnic minority

^a Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles, USA
^b Department of Psychology, University of California, Los Angeles, CA, USA

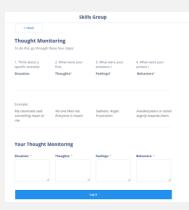
THE APP



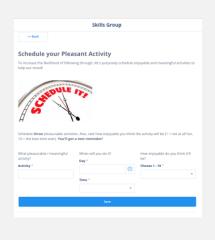
Homepage



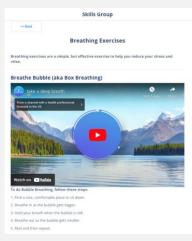
Identifying Emotions



Thought Monitoring



Scheduling Pleasant Activities

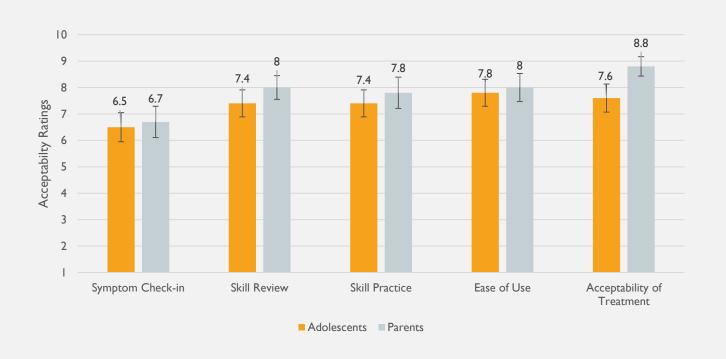


Breathing Exercises

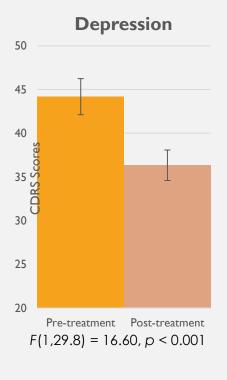


Review your Progress

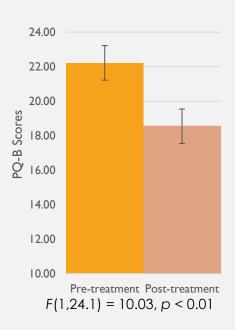
APP-UP TREATMENT ACCEPTABILITY



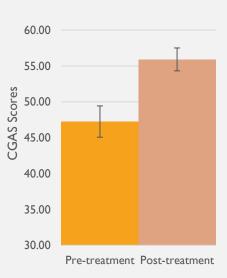
APP-UP OPEN TRIAL: CLINICAL OUTCOMES



Subclinical Psychosis



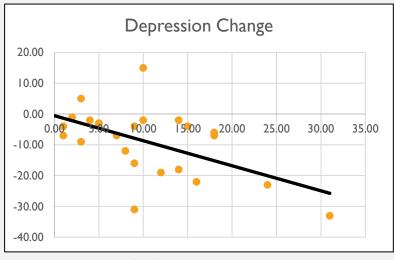
Global Functioning



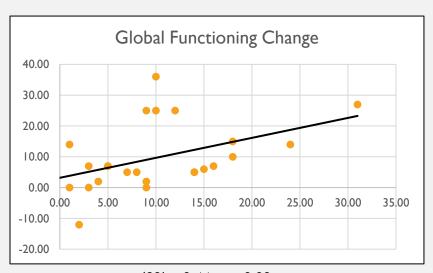
F(1,28.69) = 14.76, p < 0.001

APP SKILL PRACTICE & TREATMENT OUTCOMES

- App use average: I6.1 times (SD = 8.8)
- Skill practice average: 10.3 (SD = 7.5)







r(23) = 0.44, p = 0.03

PHASE II: RCT OF APPUP VS. GROUP WITHOUT APP



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A Randomized Trial of an App-Enhanced Group Cognitive Behavioral Therapy for Adolescents With Mood or Psychotic Spectrum Disorders

Marc J. Weintraub¹, Megan C. Ichinose¹, Jamie L. Zinberg¹, Anabel Salimian¹, Robin D. Brown¹, Georga Morgan-Fleming¹, Jennifer M. Gamarra², Tiffany Tran¹, and David J. Miklowitz¹

Department of Psychiatry, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles

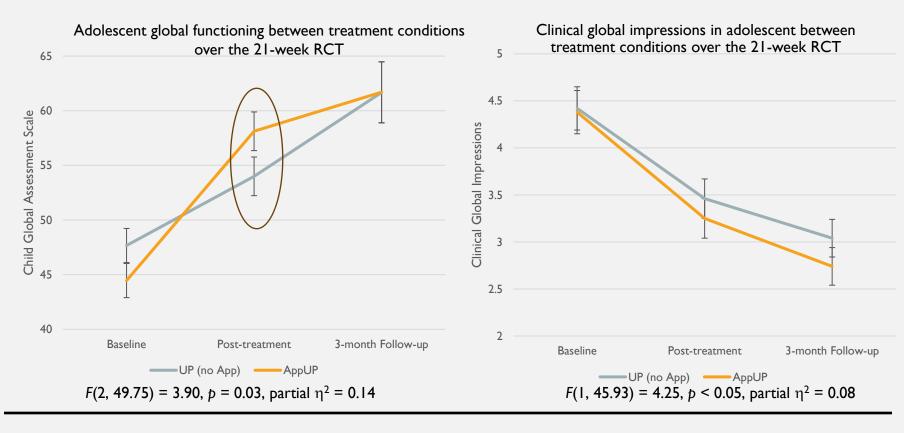
² Graduate School of Psychology, California Lutheran University

60 adolescent-parent dyads (30 in each condition) 48 retained (~80%) through 21-week (7 month) study

- Mean ages :
 - Adolescents: 15.0 years (SD = 1.3);
 Parents: 49.2 years (SD = 5.4)
- Biological sex:
 - Adolescents: 65.0% female; Parents:
 91.7% females
- Racial/Ethnic diversity
 - 33.4% racial minority
 - 36.7% Hispanic

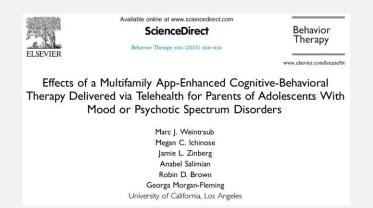
- Adolescent primary SMI diagnosis:
 - 25.0% Clinical high risk for psychosis diagnosis
 - 21.7% Bipolar spectrum diagnosis
 - 56.6% Depressive spectrum diagnosis

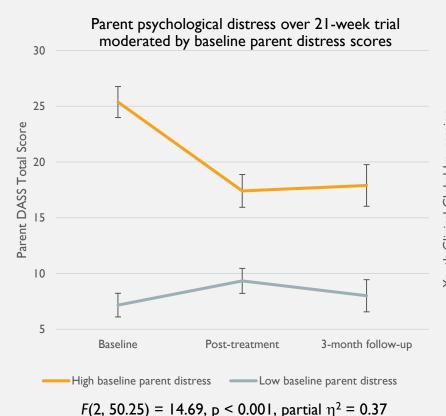
APPUP RCT: ADOLESCENT OUTCOMES OVER 21-WEEK TRIAL

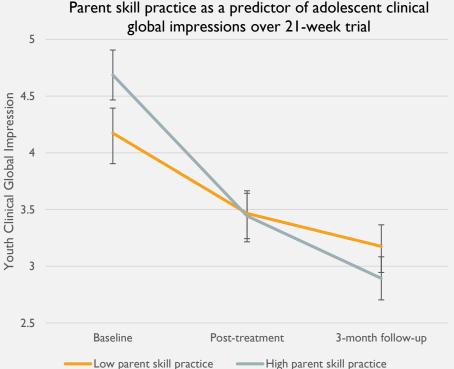


• No main effect of treatment condition on adolescent skill practice, although skill practice was associated with functional and depressive symptom improvement

APPUP RCT: PARENT OUTCOMES OVER 21-WEEK TRIAL







 $F(2, 52.80) = 3.84, p = 0.03, partial \eta^2 = 0.13$

- AppUP condition was associated with less parent skill practice compared to comparator treatment
- Both treatments associated with improvements in family functioning at post-treatment and 3-months (F(2,57.9) = 5.15, p = 0.009)

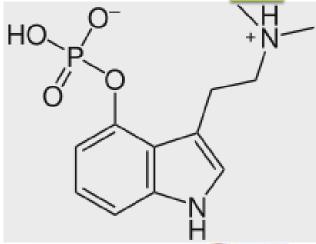
NEXT STEPS

- More closely examine effects of parent involvement in group (e.g., compare groups with and without parent component)
- Examine clinician portal/updates as moderator of adolescent treatment outcomes
- Begin dissemination efforts to examine acceptability and effectiveness of treatment in community settings



What is Psilocybin

- Fungus commonly known as "magic mushrooms"
- "Classic" psychedelic drug (currently DEA Schedule I)
 - Primarily 5-HT2A (serotonin) receptor agonist
- Breakthrough designation from FDA for depression
- From genus, Psilocybe
 - Many species. Cubensis most common
- Used by indigenous cultures for thousands of years for various healing practices and life milestones





How does psilocybin lead to psychiatric benefit?

- Psychodynamic perspective: Thought to amplify the "psyche"
 - Helps to lower defenses
 - "Non-specific amplification of unconscious mental processes" (Stanislav Grof, MD)
 - Experience provides thematic content (like a waking dream)
- Cognitive behavioral perspective
 - ▶ Increases cognitive flexibility and ability to modify thoughts (Doss et al., 2021)
 - Allows for easier approach of avoided thoughts and emotions
 - Greater openness to new experiences (MacLean et al. 2011)
- Brain-based perspective
 - Acting all over the brain
 - Decrease in functional connectivity between hippocampus and default mode network (Siegel et al., 2024)
 - Reduces connectivity between prefrontal cortex and amygdala (Roseman et al., 2018)
 - Increases neuronal entropy (Carhart-Harris et al., 2014)
- "Existential medicine" (Charles Grob, MD)

Classic Psychedelic-Assisted Therapy (PAT)

Preparation Session(s)

Medicine Session(s)

Integration Session(s)

- ▶ Developed in the 1950s
- Current iterations typically involve:
 - ▶ 1-3 sessions of preparation
 - ▶ 1-2 drug sessions
 - 2-3 integration sessions

Medicine/Drug Administration Session





- ▶ 6-8 hours in length
- Participant lays down with eyeshades
- Listens to pre-determined classical music
- Monitored by 2 therapists/clinicians
- ▶ Check in hourly to assess blood pressure and heart rate and verbally check on patient

Classic Integration

- ▶ Typically about 2-3 hours (Goodwin et al., 2023)
- Nondirective, unstructured psychological support
- Review psychedelic experience
- Identify what was learned and what is needed to heal
- Cull from various traditions/theoretical orientations:
 - Classic psychoanalysis
 - Rogerian person-centered therapy
 - Maslow's theory of self-actualization
 - Inner healing intelligence
 - Internal family systems



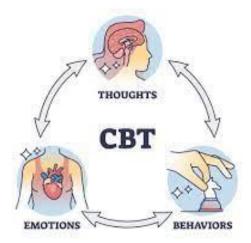
Limitations of Classic Integration

- Has not been empirically tested
- Not manualized or easily disseminable
- Nondirective and unstructured don't know what is happening
- Wide-ranging practices (particularly with integration)
- Notable advances in the psychosocial treatment of psychiatric illnesses



Why Cognitive Behavioral Therapies (CBTs)?

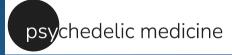
- Robust evidence base for enduring effects on symptom improvement and relapse prevention (Hollon et al., 2006)
- Manualized
 - Reducing the variability in treatment delivery
 - Allows for testing fidelity
 - More easily disseminable
- Proposed mechanisms of change (e.g., changes in cognition and behavior) can be tested as mediators
- "Default" therapeutic model for psychedelic medicine (Yaden et al. 2022)
 - Avoids issues of cultural insensitivity
 - Makes minimal speculative assumptions about the nature of the mind and reality



Aims of Study

Psilocybin-Assisted Cognitive Behavioral Therapy for Adults with Major Depressive Disorder: Rationale and Treatment Development

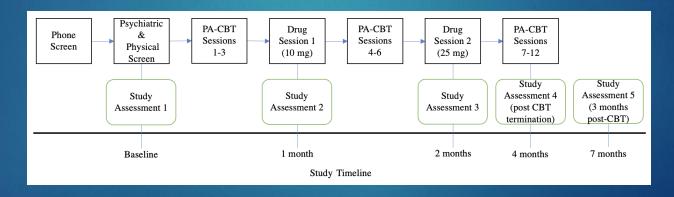
Marc J. Weintraub,^{1,*} Jessica K. Jeffrey,¹ Charles S. Grob,^{1,2} Megan C. Ichinose,¹ R. Lindsey Bergman,^{1,3} Ziva D. Cooper,^{1,4} and David J. Miklowitz¹



- Determine feasibility, safety, and acceptability of adjoining CBT with PAT and psilocybin
- 2. Refine and optimize PA-CBT protocol content, design, and procedures
- Examine the preliminary effects of the PA-CBT treatment on mood and psychosocial functioning over 7 months
- 4. Explore the preliminary effects of PA-CBT on modifying the following treatment targets: cognitive schemas, emotional regulation, strong responses during the drug experience, and the alliance between the patient and therapist

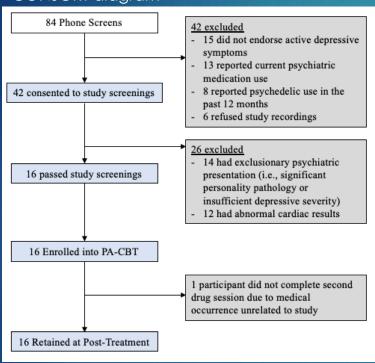
PA-CBT Session Outline

- Therapy sessions 1-3: Preparation
- Medication session 1 (10mg)
- ▶ Therapy sessions 4-6: CBT theoretical rationale and behavioral skills
- Medication session 2 (25mg)
- ▶ Therapy sessions 7-10: CBT continuation of behavioral skills + cognitive skills
- Therapy sessions 11-12: CBT -treatment review & relapse prevention planning



Open Trial Participants

CONSORT diagram



Enrolled: N = 16

- Age: M = 43.4 (SD = 9.5)
- Sex: 7 females (43.8%); 9 males (56.3%)
- Race:
 - 12 Caucasian (75%)
 - 2 Mixed (12.5%)
 - ▶ 1 Black (8.3%)
 - ▶ 1 Native American (8.3%)
- Ethnicity: 4 Hispanic (33.3%)

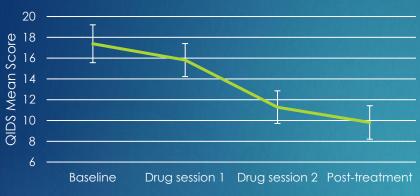
Feasibility and Acceptability

- Retention:
 - ▶ 93.8% (n = 15) completed full PA-CBT protocol
 - ▶ 1 participant had medical recurrence (unrelated to study) requiring withdrawal from drug protocol; CBT psychotherapy was completed
 - ▶ 100% (n = 16) completed CBT protocol
- Acceptability of PA-CBT
 - \triangleright Overall satisfaction (Client Satisfaction Questionnaire) M = 3.9 / 4 (SD = 0.3)
 - Was number of therapy sessions adequate to participants?
 - ► 58.8% (n=10) adequate number of CBT sessions | 29.4% (n = 5) too few CBT sessions | 5.9% (n = 1) too many CBT sessions
 - ▶ Satisfaction with CBT portion M = 4.6 / 5 (SD = 0.8)
 - ▶ Satisfaction of combining CBT with psilocybin M = 4.8 / 5 (SD = 0.5)

Clinical Effects

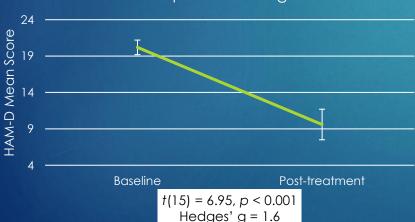
Depressive Severity

Quick Inventory of Depressive Symptoms



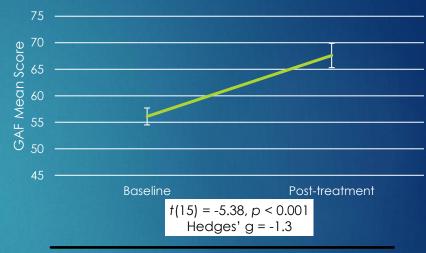
F(3,19.1) = 12.83, p < 0.001Partial eta squared = 0.53 | Cohen's f = 1.2

Hamilton Depressive Rating Scale

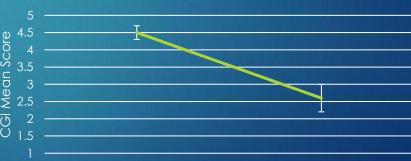


<u>Psychosocial Functioning</u>

Global Assessment of Functioning



Clinical Global Impressions



Baseline

Post-treatment

t(15) = 4.61, p < 0.001 Hedges' g = 1.1

Participant Quotes

- "I think the pair [CBT + psilocybin] helped me get back out there to live life."
- "The psilocybin is great...However, for long-term change the CBT is critical."
- "I think this is a good pairing with the drug therapy. I continually refer back to the tools I learned in CBT to see my thought patterns and know how to change them."
- "The CBT was essential in helping me understand how to incorporate information into my life, and especially how to proceed when I begin applying it in my daily life through constructive actions."
- "The CBT was every bit as important as the drug sessions. Either treatment on their own would not have had the same successful result."
- "CBT may work for some without psilocybin, but it didn't work for me until after this trial."

PA-CBT Refinement Suggestions

- Incorporate CBT into preparation sessions
 - Psychoeducation of depression
 - Principles of CBT
- 2. Goal-setting to primarily take place following first drug session
- 3. Increase acceptance-based principles and practices
 - Mindfulness-based practices
 - ACT practices (e.g., values)

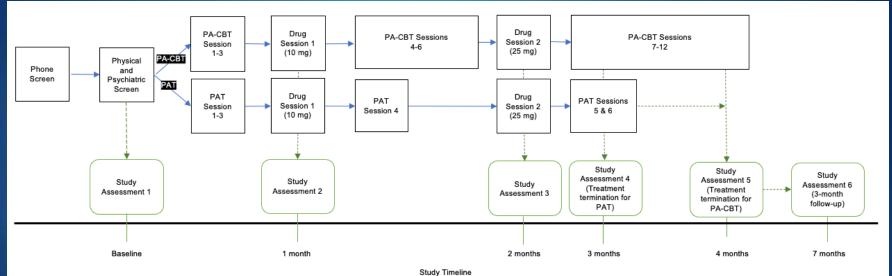
Conclusions

▶ PA-CBT was well-liked by participants and clinicians

- PA-CBT is related to beneficial psychiatric and functional outcomes
 - Large effect sizes for depressive symptom improvement and psychosocial functioning
- What participants and clinicians said:
 - ▶ The psilocybin provided direction and clarity for the psychotherapy
 - ▶ The psychotherapy facilitated cognitive and behavioral changes that were elicited from the psilocybin

RCT of PA-CBT (Currently Enrolling):

PA-CBT vs. Psilocybin with standard psychological support



*Solid blue lines represent treatment flow; Dashed green lines represent study assessment timepoints PA-CBT sessions 4 and 7 for the PA-CBT condition and Integration sessions 1 and 2 for the PAT condition occur within a couple business days following the drug session that immediately precedes them.

Future Directions

Awaiting NIH review to examine group-based PA-CBT administration compared to individual PA-CBT and PAT

Imaging comparing neural changes resulting from psilocybin alone
 vs. drug + psychotherapy

- Awaiting regulatory approvals for MDMA-Assisted Trauma-Focused Cognitive Behavioral Therapy for young adults with treatment-resistant PTSD
 - ► MDMA 3,4-Methylenedioxymethamphetamine ("Ecstasy" or "Molly")

Acknowledgements



Co-Investigators

- David Miklowitz, PhD
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- Ziva Cooper, PhD
- Jamie Zinberg, MA

Coordinators

- Anabel Salimian
- Georga Morgan-Fleming
- Robin Brown
- Shelby Grody

Research Assistants

- Rahul Ramesh
- Ava Diedrich
- Cordelia Kuiper Rauch
- Lorenzo Miller
- Guillermo Nunez Hernandez
- Many psychology trainees



LET'S DISCUSS!

CONTACT:

MJWEINTRAUB@MEDNET.UCLA.EDU