Concurrent Treatment of PTSD and SUD: Prolonged Exposure vs. MDMA-Assisted Therapy

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Disclosure Information

- Presenter 1: Jeoffrey Hill, MD
  - Presenter 1 Commercial Interests: No Disclosures
- Presenter 2: Jeffrey Foote, PhD
  - Presenter 2 Commercial Interests: No Disclosures
- Presenter 3: Carrie Wilkens, PhD
  - Presenter 3 Commercial Interests: No Disclosures

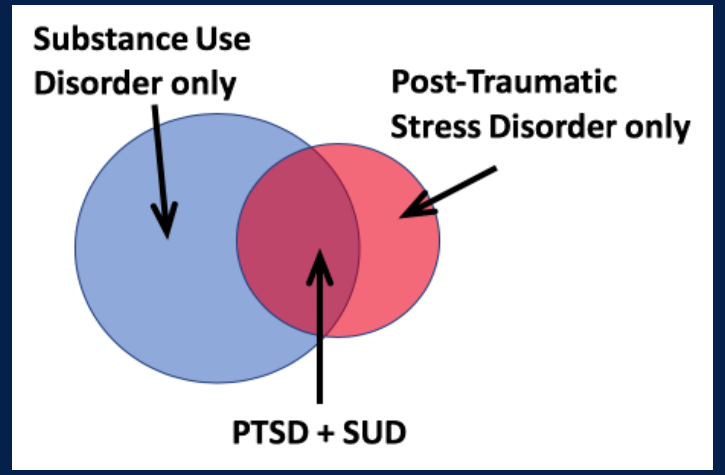
Learning Objectives

At the conclusion of this session, participants will be able to:

- Understand procedures and processes involved in two specific PTSD protocols: Prolonged Exposure Therapy and MDMA – Assisted Therapy
- Examine and consider contrasting putative mechanisms of change in Prolonged Exposure and MDMA-AT
- Be aware of potential adverse effects of the two treatment approaches to PTSD and SUD populations, and potential cautionary steps to take when conducting these treatments

SUD & PTSD: High Comorbidity

- Among individuals with PTSD, nearly half (46.6%) meet criteria for SUD (Pietrzak, et. Al. 2011)
- 30-60% of patients presenting for alcohol treatment meet criteria for PTSD (Brown, et. al., 1995: Kessler et. Al., 2005)
- People with PTSD are six times more likely to develop AUD than those without (Creamer, Burgess & McFarlane, 2001)



Bidirectional Relationship of Comorbidity

- **High-Risk Hypothesis** – SUD and associated high risk behaviors lead to traumatic events (e.g., assaults, rape, etc.) (Windle, 1994)
- **Susceptibility Hypothesis** – underlying vulnerabilities to both disorders (e.g., anxious temperament, unwillingness to experience difficult emotions, avoidant coping style) (Chilcoat & Breslau, 1998; Jacobsen, Southwick, & Kosten, 2001)
- ***Self-medication Hypothesis*** – PTSD may cause substance use (in most cases PTSD precedes SUD) (Chilcoat & Breslau, 1998; Reed et al., 2007)

Behaviors Make Sense

- A few drinks help me feel brave enough to make eye contact
- Heroin helps me numb the intensity of the flashback of being raped
- A couple of shots help me not tremble and shake when in public
- A joint helps me feel a little less disgusted with myself
- If I smoke, I can go to the grocery store without having a panic attack
- Oxy keeps me asleep instead of covered in sweat thinking I'm dying
- Being high all day helps me not want to kill myself
- Stimulants help me leave the house
- Being high helps me forget how much I hate myself

Impact of PTSD & SUD

Overall worse life functioning than either diagnosis alone with increased rates of:

- Mental and physical health problems
- Suicidal ideation and attempts
- Healthcare utilization (frequent and long-standing misdiagnosis)
- Functional impairments (unemployment, divorce, difficulty parenting)

Poorer SUD treatment response including:

- Higher drop out rates (30-70%)
- Faster return to use

Sample of SUD Treatment Seekers

Assessment Measures Used at CMC Residential and Outpatient Settings:

- PCL-5, BDI-II, GAD-7, SCL-10, PTCI, SIP-AD, PANAS, BARC-10, ISI

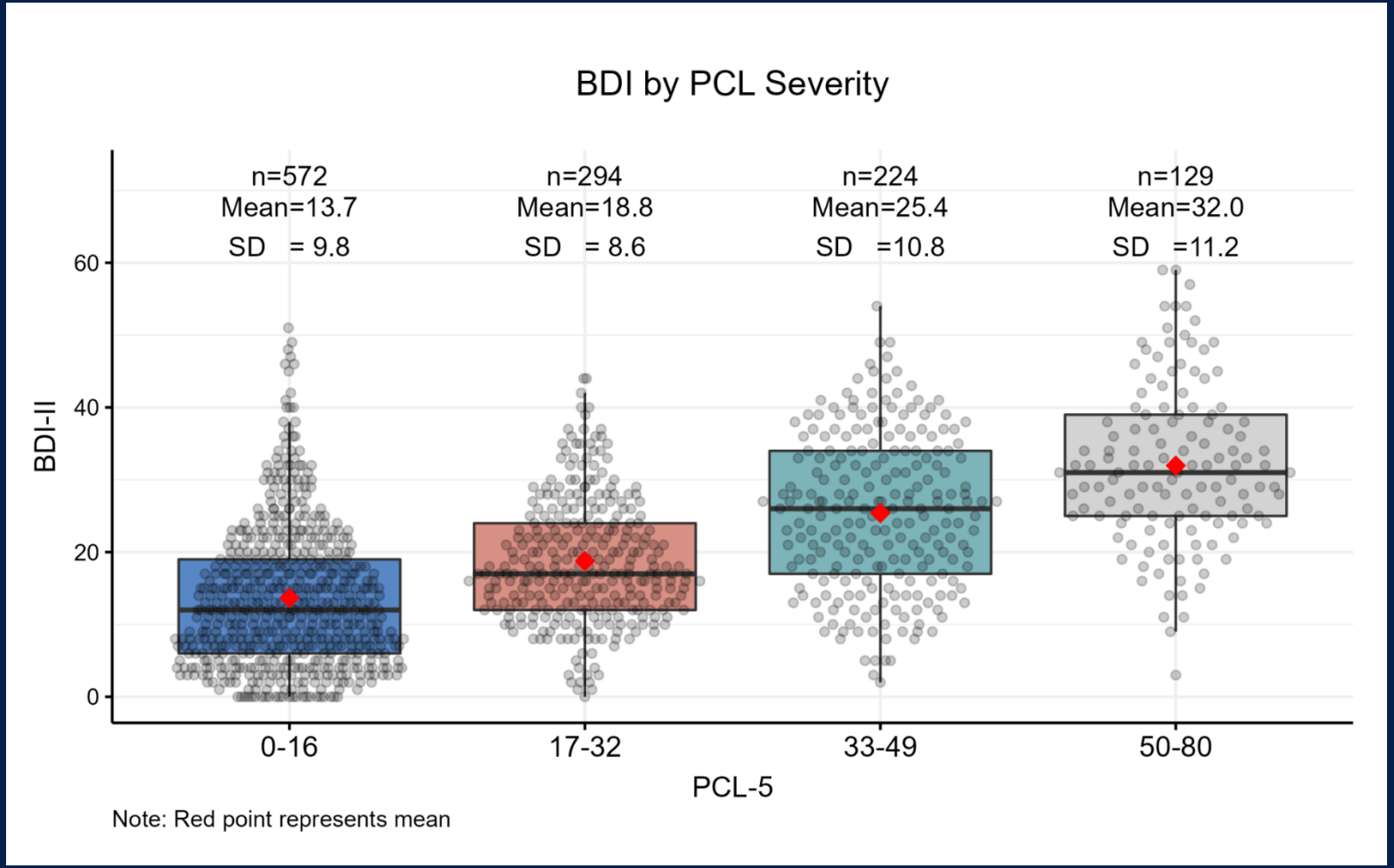
Outpatient setting:

- *N* = 1219 initial evaluations (03/2016 - 08/2022)
- **PCL-5 = 33 or above: 29%**

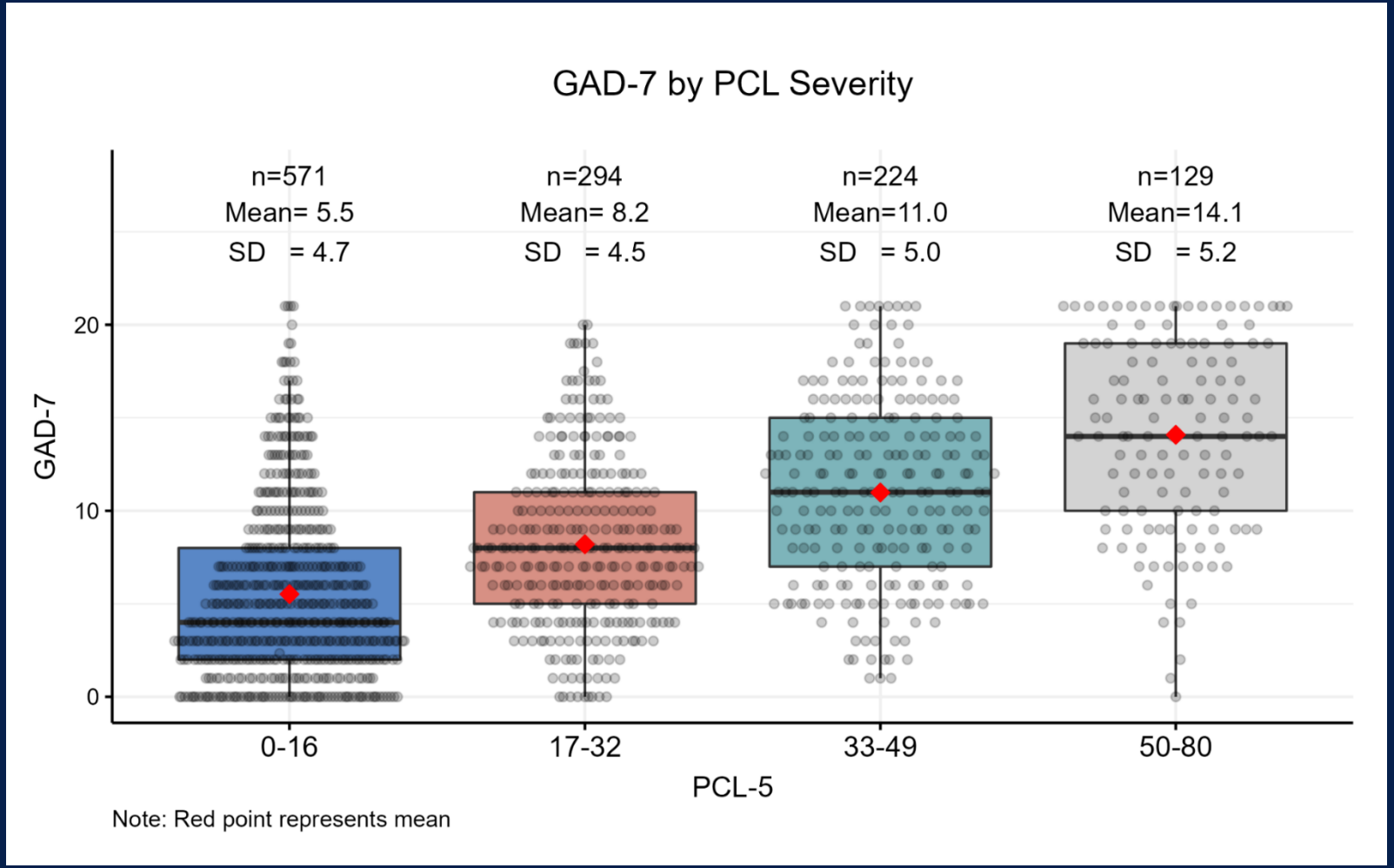
Residential setting:

- *N* = 663 initial evaluations (03/2016 - 08/2022)
- **PCL-5 = 33 or above: 40%**

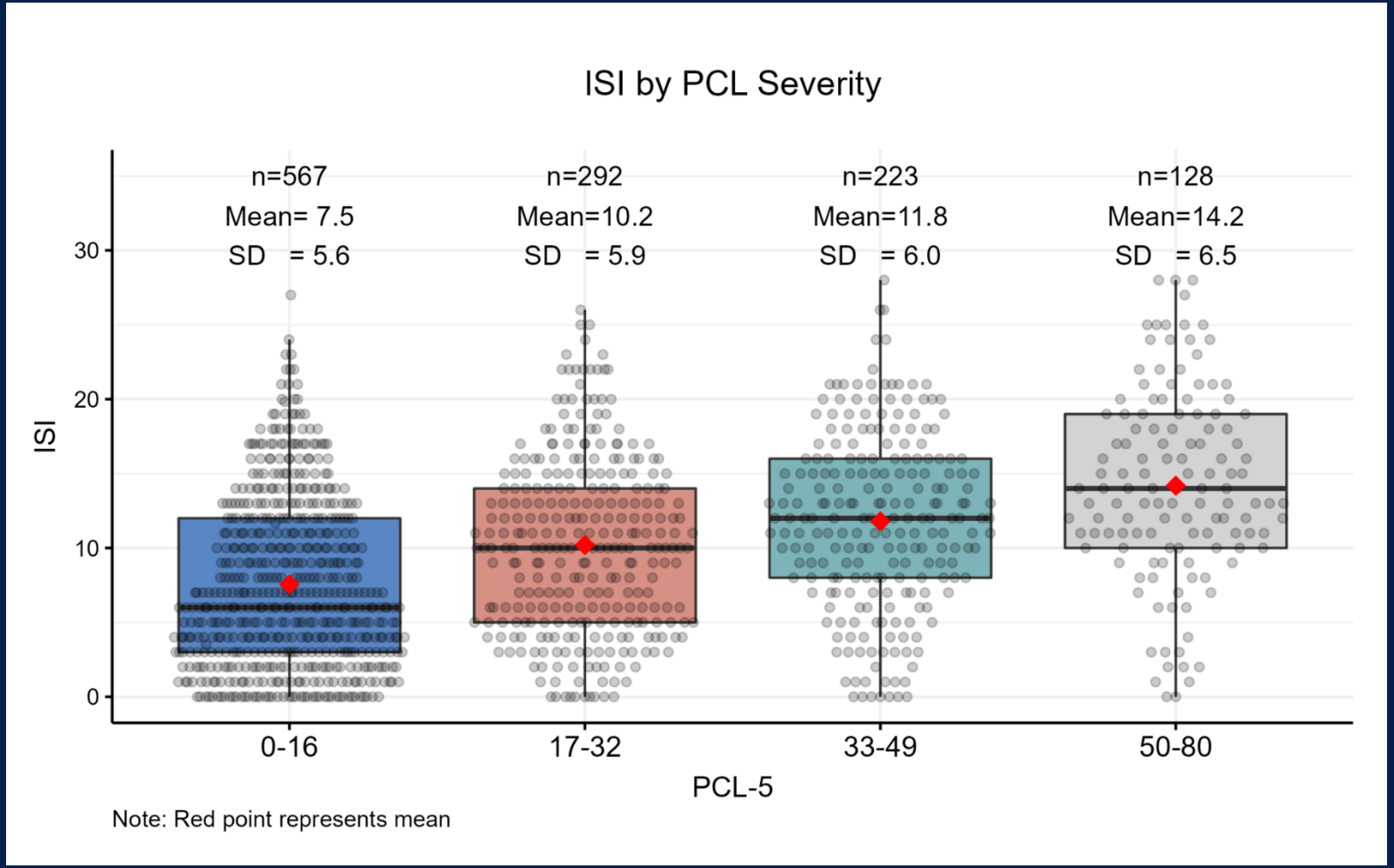
BDI-II by PCL Severity - Outpatient



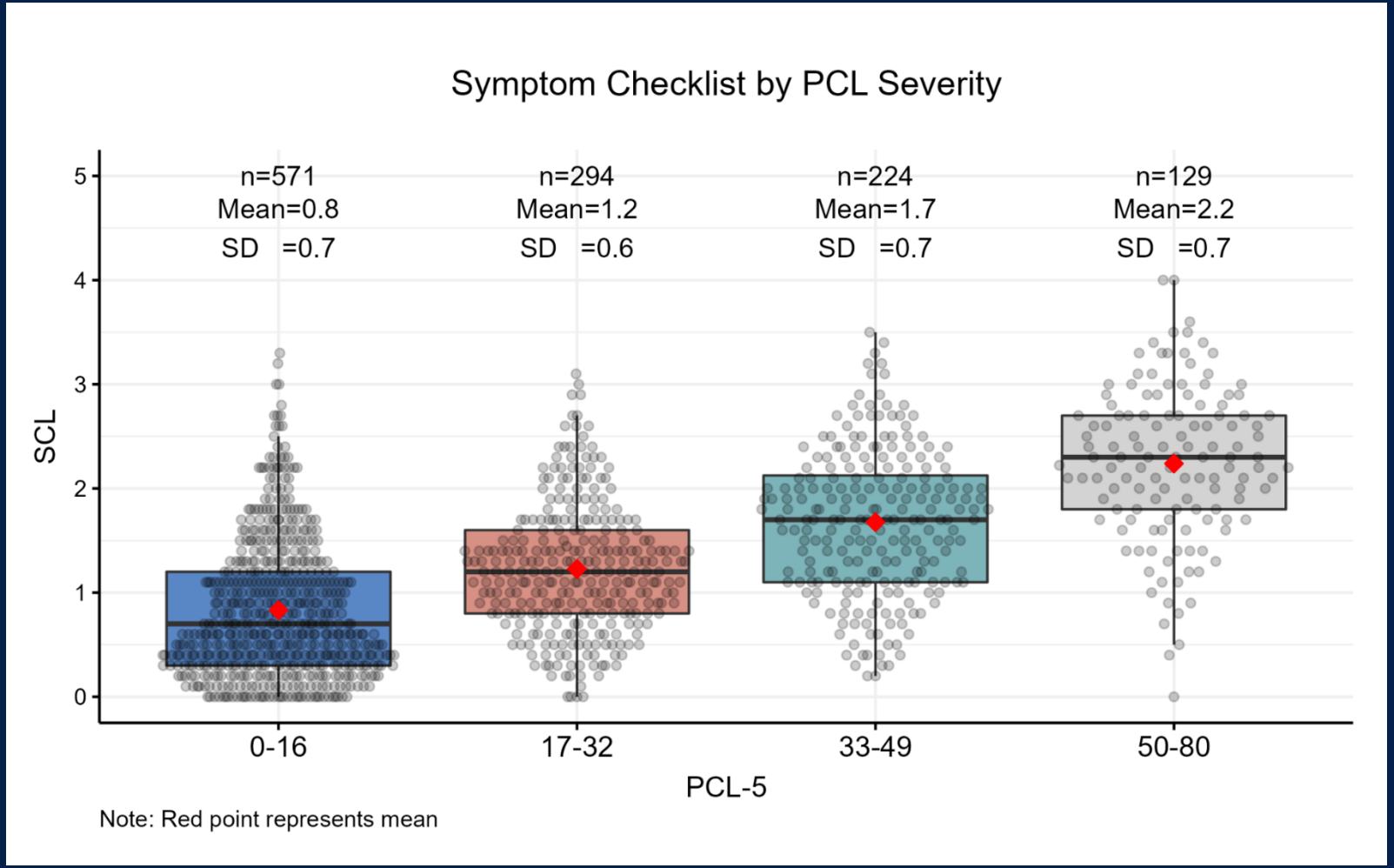
GAD-7 by PCL Severity - Outpatient



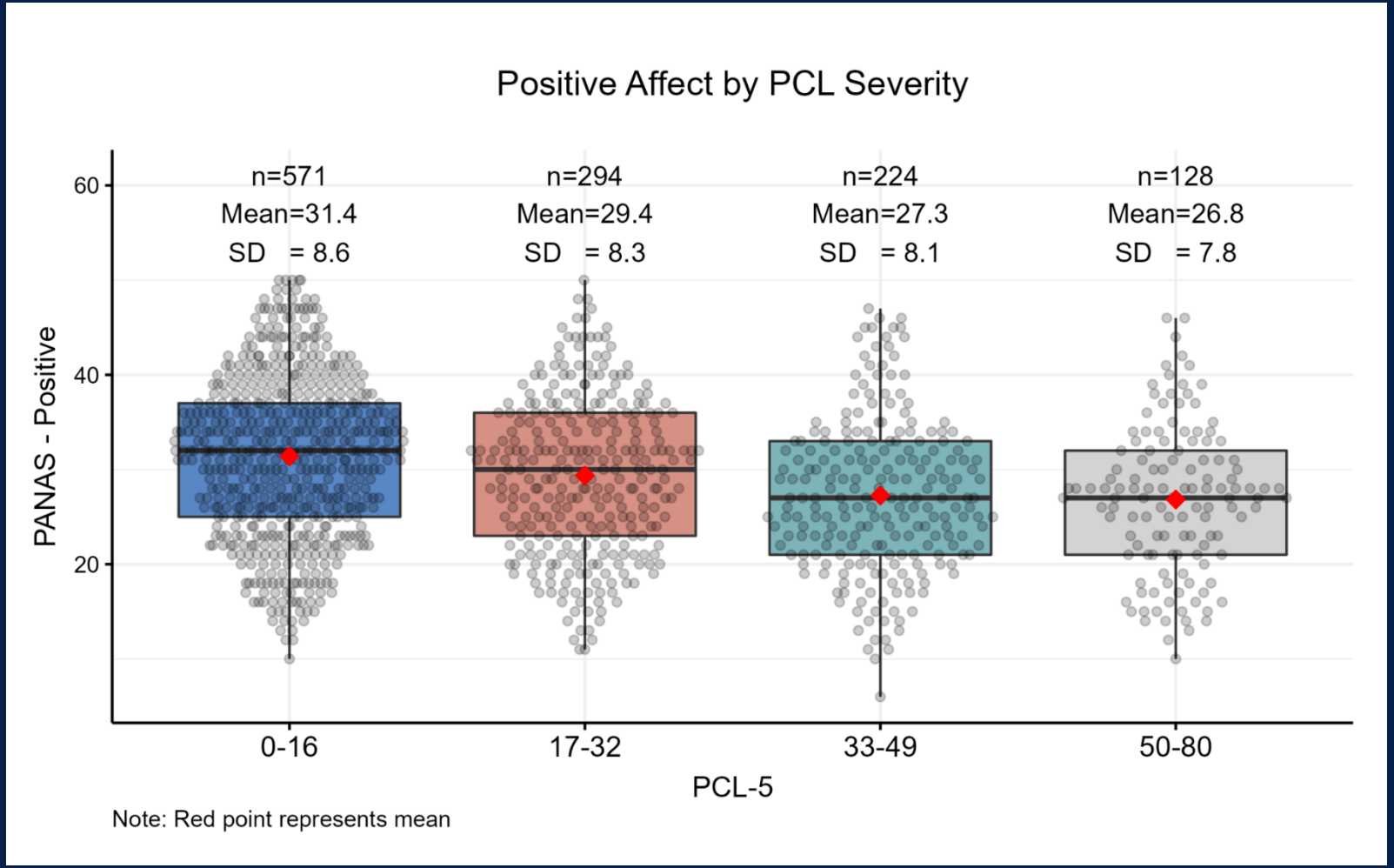
ISI by PCL Severity - Outpatient



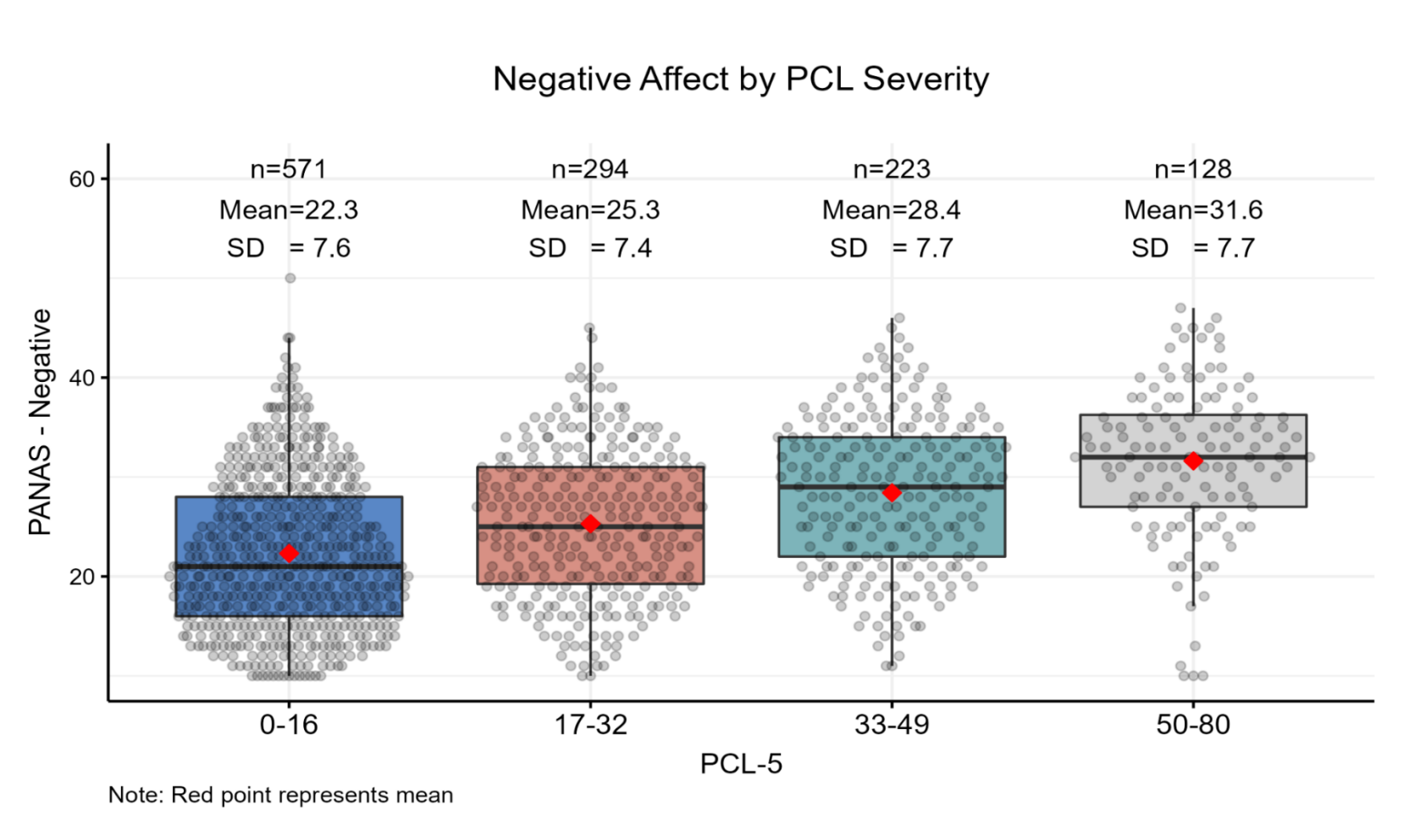
SCL by PCL Severity - Outpatient



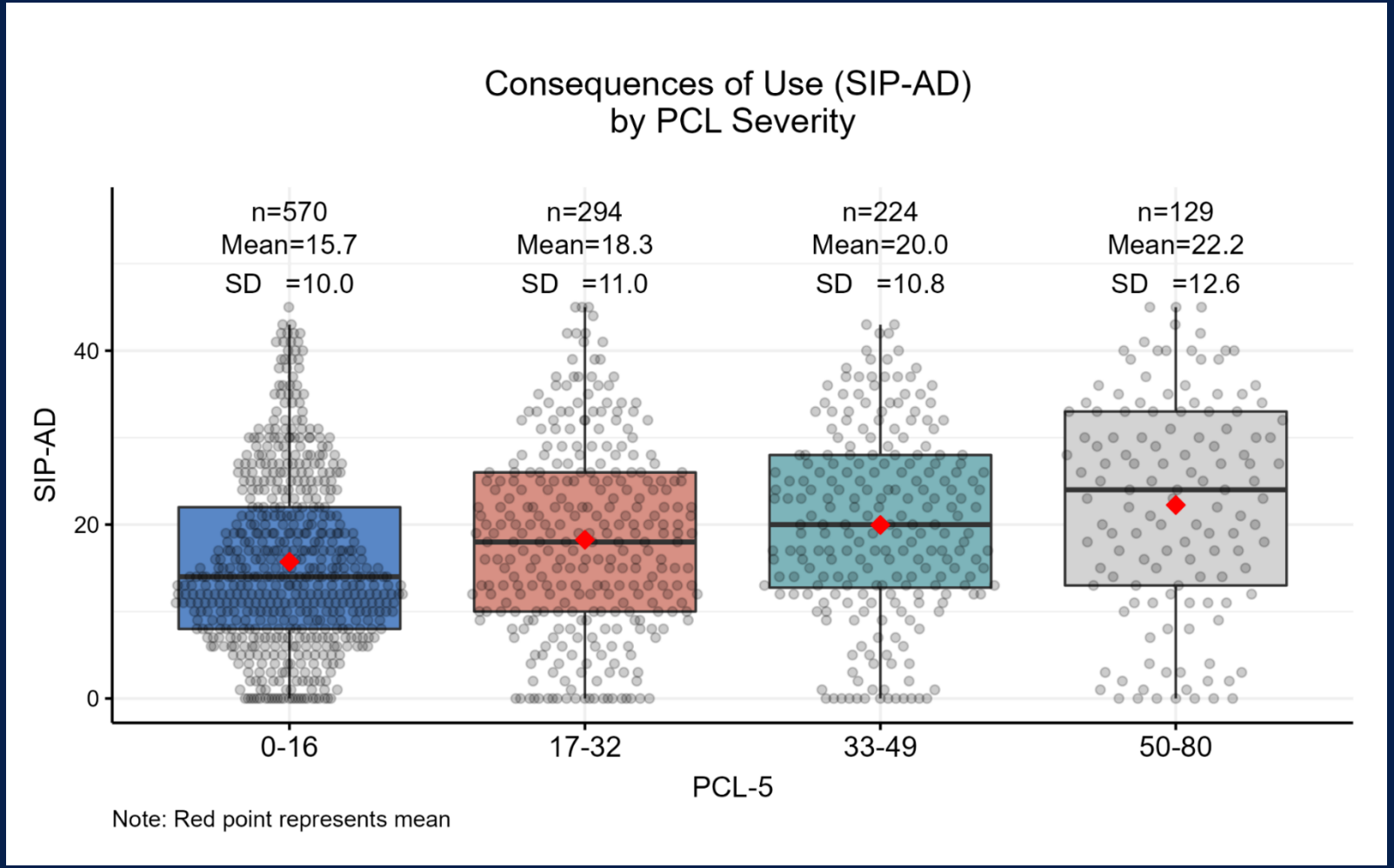
Positive Affect by PCL Severity - Outpatient



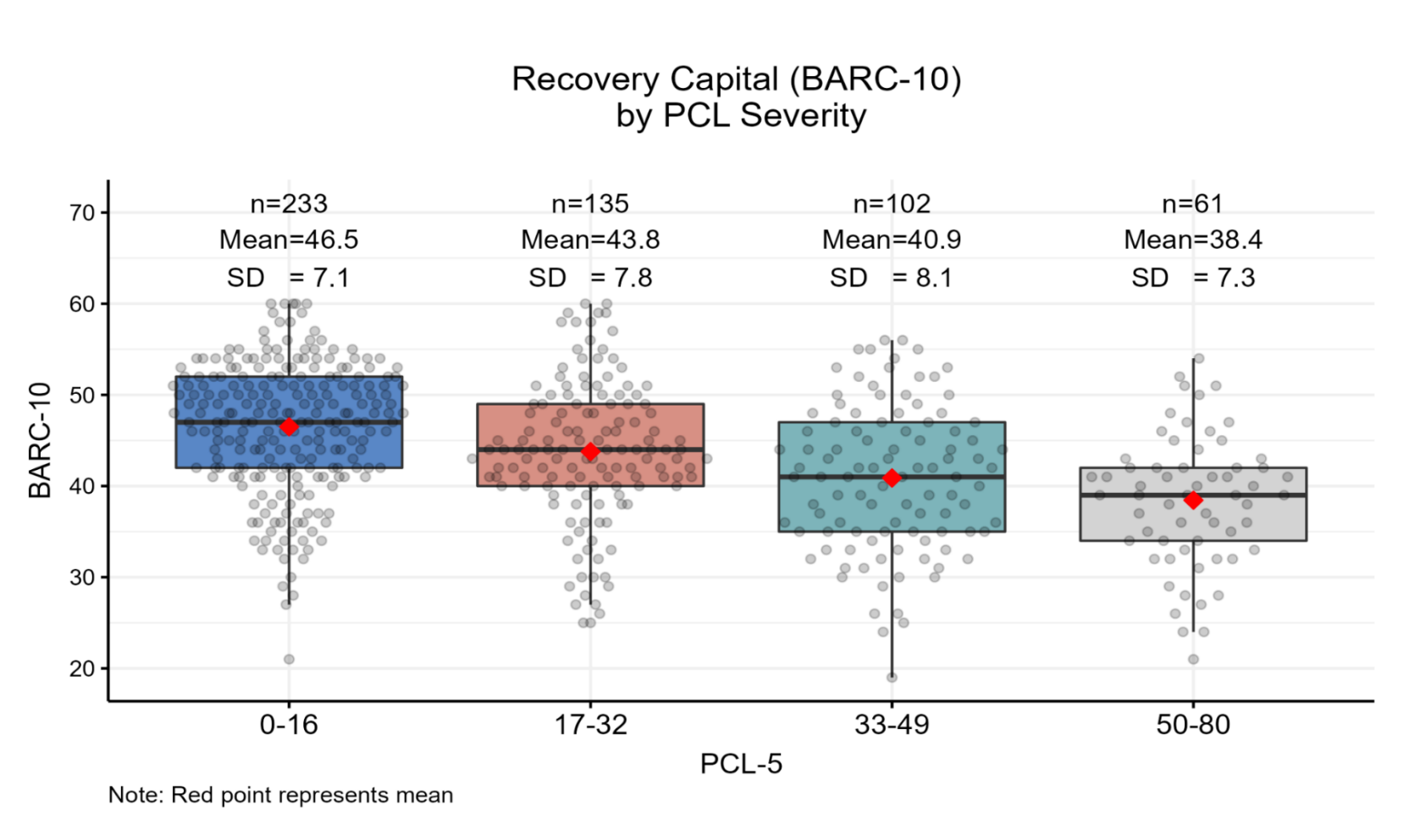
Negative Affect by PCL Severity - Outpatient



Consequences of Use by PCL Severity - Outpatient



Recovery Capital by PCL Severity - Outpatient



Impact of PTSD

INCREASED DISTRESS

AND DYSFUNCTION

AS A FUNCTION OF

TRAUMA SYMPTOM SEVERITY

Barriers to Concurrent Treatment

Mental health treatment programs:

- suggest ***period of sobriety*** before addressing trauma
- providers not trained to address SUD
- providers not trained in EBT's for PTSD

Substance Use programs:

- suggest ***period of sobriety*** before addressing trauma
- **negative affect** (Pandora's box) associated with trauma processing will cause return to use (often true in short term)
- lack of individualized care (group only)

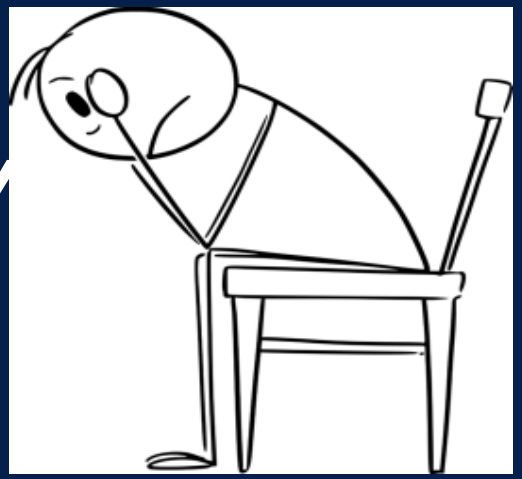
Even in Treatment Research ...

Research settings:

- RCT's for either disorder have ruled out participants with the other disorder as a typical exclusion criteria
- Psychedelic research trials: almost all MAPS sponsored trials of MDMA-AT for PTSD have excluded SUD subjects

Patients with SUD mostly do not receiv

effective treatment for PTSD



The Value of Treating Both

If you don't treat both:

- After standard SUD treatment, patients w/ PTSD are less likely to enter remission (Hien et al., 2000)
- Patients w/ PTSD may relapse more quickly on substances (Brown et al., 1996)

If you treat both:

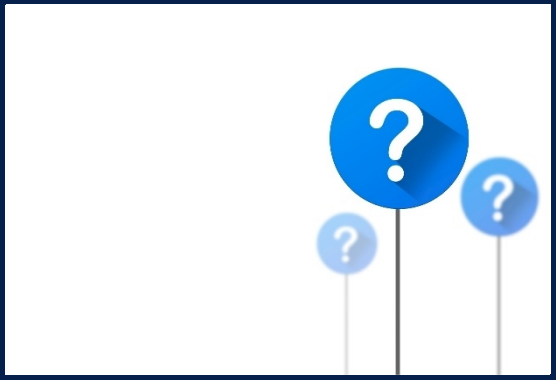
- Reduction in SU and risk of developing co-occurring disorders (Kessler, 2000)
- PTSD symptom change mediates change in ETOH use
- 5-10 year follow up, there was only a 6% PTSD relapse rate (Resnick et al, 2013).

Trauma/PTSD Protocols

Non-Trauma Focused (Stabilize/Coping Skills):
- Present – Centered Therapy (PCT)
- Dialectical-Behavioral Therapy

Trauma Focused (Exposure/Process):
- Prolonged Exposure (PE)
- Eye Movement Desensitization and Reprocessing (EMDR)
- Cognitive Processing Therapy (CPT)
- Written Exposure Therapy (WET)

Integrated Models (for PTSD/SUD):
- Seeking Safety (stabilize/coping skills)
- COPE (exposure/process)



Teaser: Where does MDMA-AT fit into this picture?

Trauma-Focused Integrated Treatment

Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE) – CBT treatment for PTSD and SUD

- Information about how PTSD symptoms and substance use interact
- Information about the most common reactions to trauma
- Techniques to help manage cravings/thoughts about using alcohol or drugs
- Breathing retraining relaxation exercise

- *Repeated in **vivo (real life) exposures** to safe situations, places and people the client is avoiding due to trauma-related distress*
- *Repeated **imaginal exposures** to the client's trauma memories*

Back, S. E., Foa, E. B., Killeen, T. K., Mills, K. L., Teesson, M., Dansky Cotton, B., Carroll, K. M., & Brady, K. T. (2015). *Concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE): Therapist guide.* Oxford University Press.

Prolonged Exposure

Highly effective, safe and robust treatment for PTSD

- One of the most studied psychotherapeutic interventions for PTSD using gold standard RCT methodologies – including non-inferiority trials compared to medications, CPT, EMDR, counseling

- Meta-analysis of 21 studies: 58.9% of participants were White, 31.1% were African American, 4.9% were Latinx, 0.6% were Asian American or Pacific Islander, and 4.7% reported race as “other.” (Benuto, Bennett, & Casas, 2020)

- RCT found clinically equivalent PTSD outcomes for African Americans and Caucasians in both treatments. Groups showed comparable improvements in depression and functioning, and similar treatment preferences and beliefs. (Kline, Feeny, Zoellner, 2020)

COPE - Outcomes

- Significantly lower PTSD symptoms
- Higher rates of PTSD remission compared with present focused PTSD or SUD only
- Comparable reductions in SUD
- Does not result in increased SUD (pandora's box)

- Drop out issues

Mills, K., Barrett, E., Merz, S., Rosenfeld, J., Ewer, P., Sannibale, C., Baker, A., Hopwood, S., Back, S., Brady, K., & Teesson, M. (2016). Integrated Exposure-Based Therapy for Co-Occurring Post Traumatic Stress Disorder (PTSD) and Substance Dependence: Predictors of Change in PTSD Symptom Severity. *Journal of Clinical Medicine*, 5.

Why Exposure: Addressing Fear Structures

Transdiagnostic Theory - specific pathological fear structures in memory underlie and maintain anxiety disorders. A fear structure is blueprint to avoid danger and includes:

- Details associated with the trauma (who, what, where)
- Behavioral & physiological responses (racing heart, numbing, sweating, running, freezing)
- Meaning & interpretation of experience ("I'm going to die," "I should have seen this coming")

Details encountered in life after the trauma that are similar enough to elements of the fear structure activate entire memory network which results in desire to avoid or escape

Not all Fear Structures are Bad

Normal/Helpful Fear Structures	Pathological/Unhelpful Fear Structures
• Includes helpful details about danger and safety • Associations accurately reflect reality • Can be changed to incorporate new information - flexible	• Includes **excessive and unhelpful** details and responses • Associations are emotionally charged, vague • Resistant to change or modification - rigid
Driving *very fast* is dangerous	*Driving* is dangerous *Driving over bridges* is dangerous

Natural Recovery: "Natural Exposure"

People who experience trauma but do not go on to develop PTSD:

- Able to think about the trauma
- Able to talk with supportive people about trauma
- Able to allow trauma related emotions to be felt
- Do not avoid or try to escape situations and stimuli that are reminders of the trauma

Recovery involves repeatedly activating the fear structures without any feared outcomes happening

Developing PTSD: Stuck in Fear Structure

Survivors who develop PTSD:

- Avoid thinking or talking about the trauma
- Dismiss or suppress trauma related emotions
- Do not return to regular, pre-trauma daily routines and functioning
- Change habits and behaviors to avoid trauma reminders
- Develop problematic cognitions to explain experiences (“I’m disgusting,” “I’m evil,” “All men are dangerous,” “Nothing works out”)

Emotional Processing to Modify Fear Structures

Imaginal exposure: repeated revisiting, recounting, and processing of the traumatic event (alone and with therapist)

- Enhances the emotional processing of the trauma memories
- Helps client attain a realistic perspective on the trauma
- Helps client overcome internal avoidance

In-vivo exposure: repeated exposure to safe conditions, activities, and places that are reminders of the trauma and therefore feared and avoided

- Reduce trauma-related distress by helping client to realize that the avoided situations are not dangerous in the present

Course of PE Treatment

Early phase (approx. sessions 1 - 2)

- psychoeducation on PTSD
- establishment of therapeutic alliance/connection
- create *in vivo* exposure hierarchy (hierarchy of feared/avoided stimuli)

Middle phase (approx. sessions 3 - 10)

- in session revisiting and processing target memory repeatedly
- daily homework: listening to recording of past session; practice with in vivo exposure situations
- movement from full memory processing to “hot spots” approach

Late phase (approx. sessions 11 - 14)

- SUDS scores significantly reduced in revisiting target memories
- emergence of subjective sense of perspective and compassion shift
- consolidation of gains/increased confidence in change

Impact of PTSD on Shelby

Trauma: Car accident while rushing children to day care. Occurred while driving into oncoming traffic over a bridge. Resulted in death of child in back seat of the car.

Post traumatic event:

- Avoids driving
- Avoids bridges
- Becomes numb to partner
- Avoids music reminding of accident (no more Bruce)
- Avoids smells reminding of accident
- Shuts down affection to remaining child ("I'm a terrible parent")

Activate one part of the web and the whole structure is triggered

Outcome for Shelby

Increased flexibility in assessing *what is dangerous*

- Danger is not Bruce Springsteen, all bridges, the smell of gasoline or Old Spice
- Allowing living child to play with friends is worth the risk

Addressed negative cognitions that maintained avoidance

- "I'm a parent who was in a terrible accident and lost my child, but I can love my other child because they still need me."
- "My husband knows it was an accident and still loves me."

Who is Appropriate PE Candidate

Requires Criterion A traumatic event - exposed to actual or threatened death, serious injury, sexual violence (direct or hearing about close person, or repeated exposure)

Client need access to memory of the traumatic event(s) that they can narrate.

- Fragmented memories with few details are OK if the patient can visualize and describe the emotional and physical experience of the trauma

Who should not do PE?

- Imminent risk of suicidal/homicidal behavior
- Serious, current self-injurious behavior
- Current psychosis or mania
- Acute safety issues, risk of assault
- No memory of trauma

Integrated Treatment in Residential Setting

A real-world example at a residential LOC for primary SUD's:

- Initial self-report screen (LEC/PCL), followed by clinical interview/evaluation (PSSI-5 or CAPS-5) to determine PTSD diagnosis
- PE sessions typically conducted 2X weekly (90 min sessions) with separate PE therapist
- PE treatment occurs concomitantly with individual (4 x week with primary therapist) and daily group sessions (CBT, DBT, ACT)
- Primary and PE therapists all versant in behavioral and motivational approaches (MI, CRA, DBT, ACT, etc.)

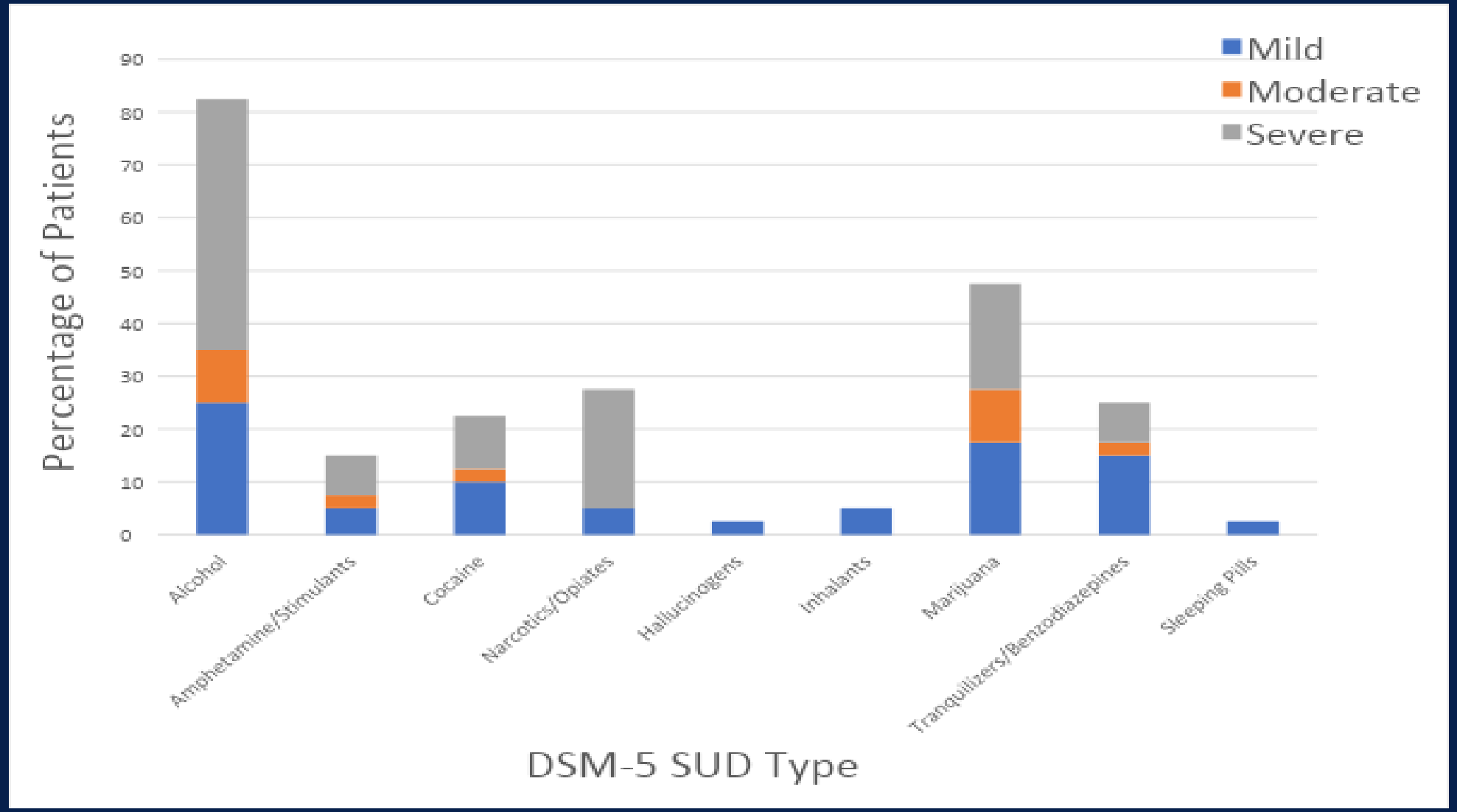
Prolonged Exposure – Residential

Client Demographics/Tx Descriptors

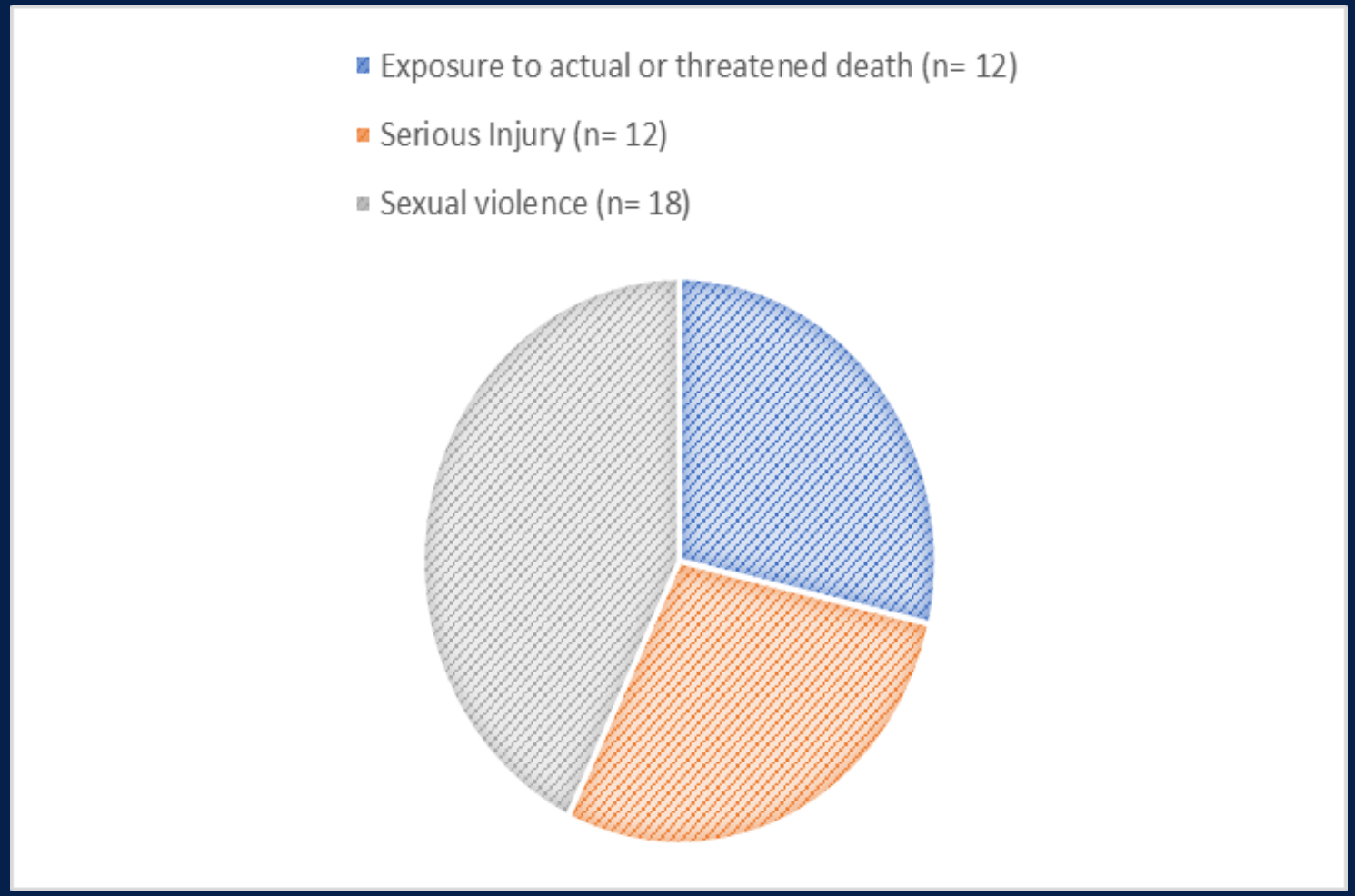
- **N = 42**
- **Age:** M = 34 years (SD=13)
- **Gender:** 67% female (N=29)
- **Race/Ethnicity**: 95% Not Hispanic, 88% White, n=2 missing
- **Relationship status**:

  43% single, 48% married/committed relationship, 5% separated/divorced, n=2 missing
- **# of PE sessions: M =** 14 sessions (SD=6)
- **Range:** 5 – 30 sessions

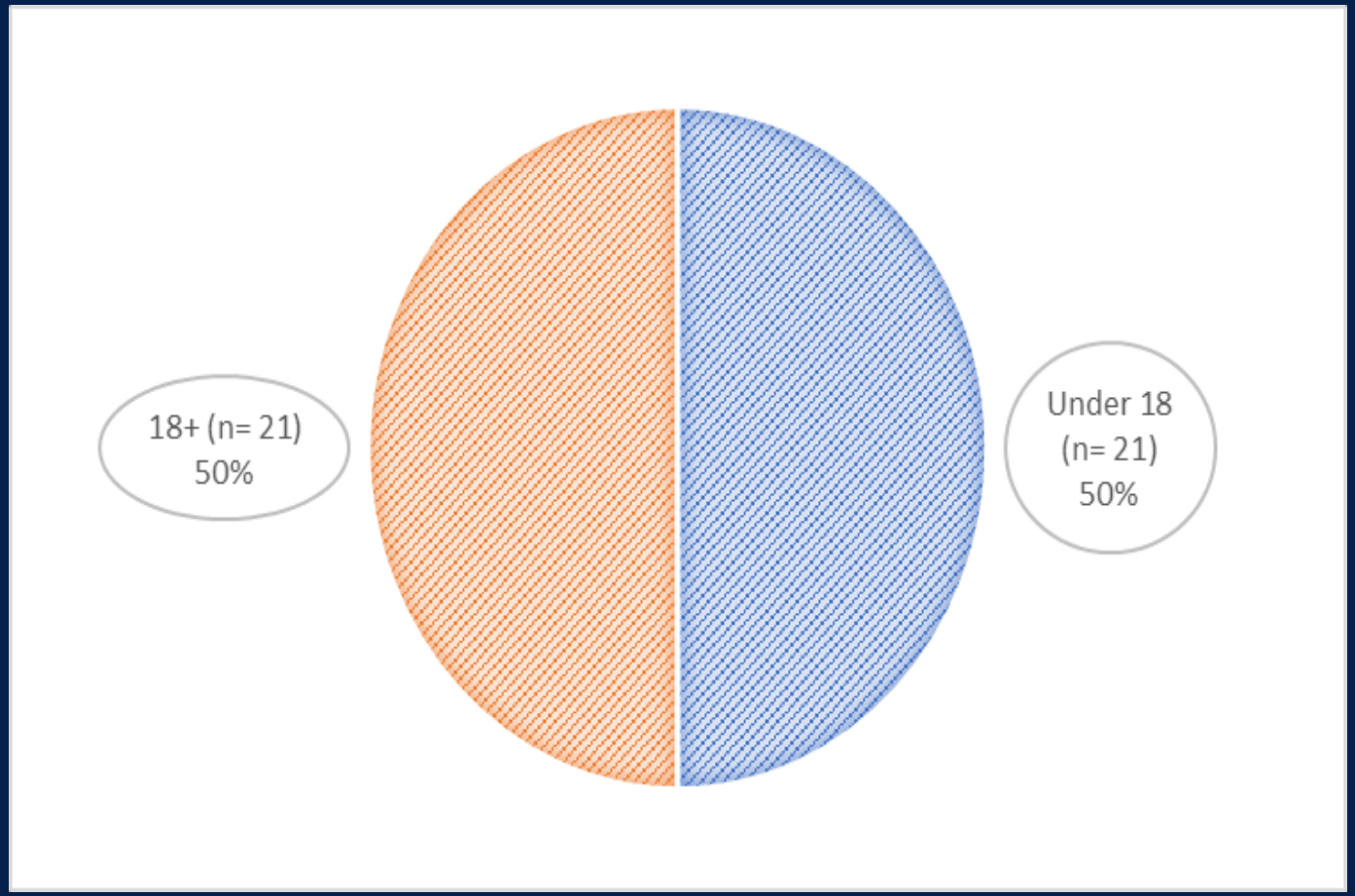
PE Patients Substance Use



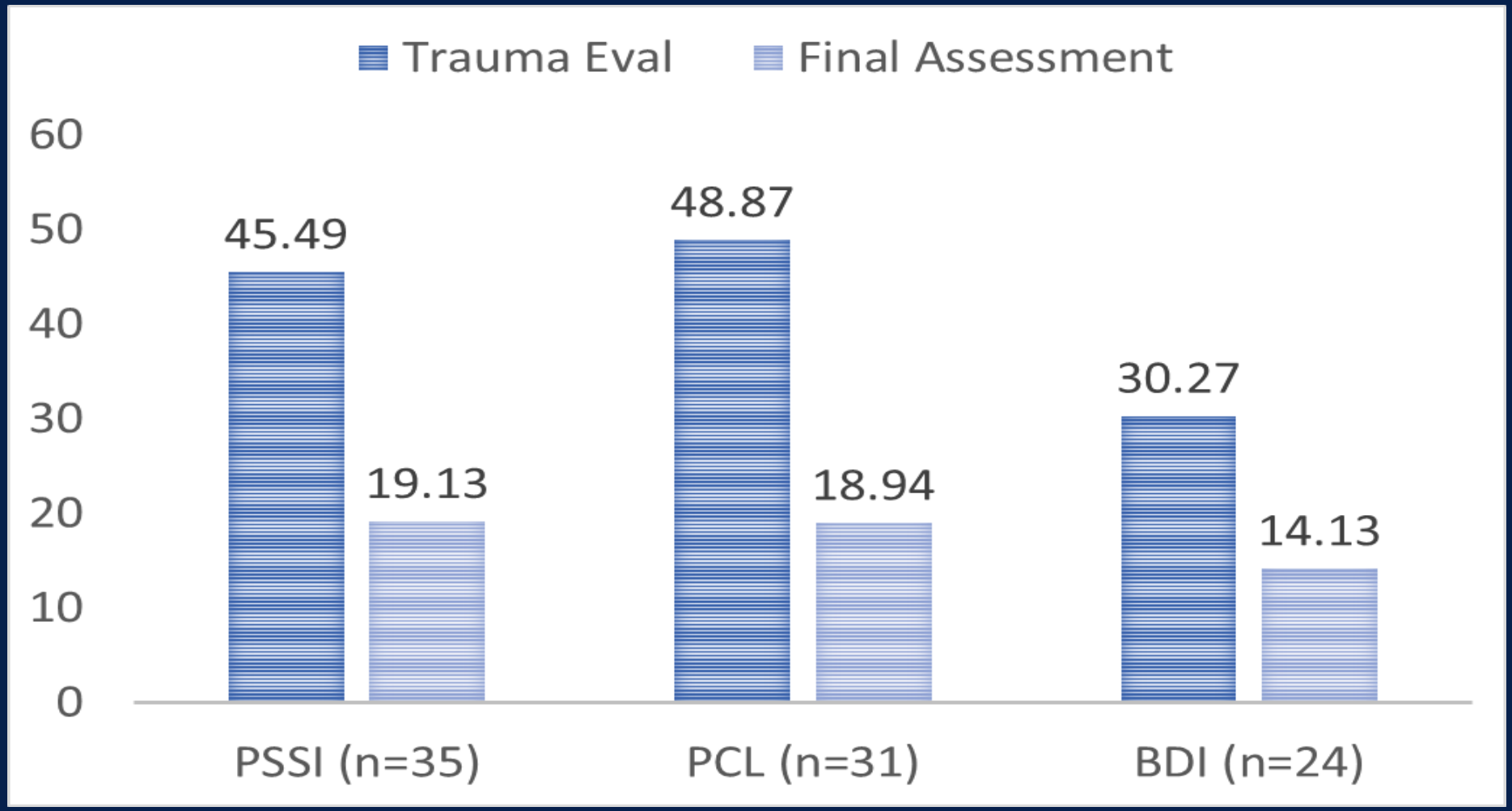
Reported Criterion A Traumatic Event



Target Trauma: Childhood vs. Adult Trauma

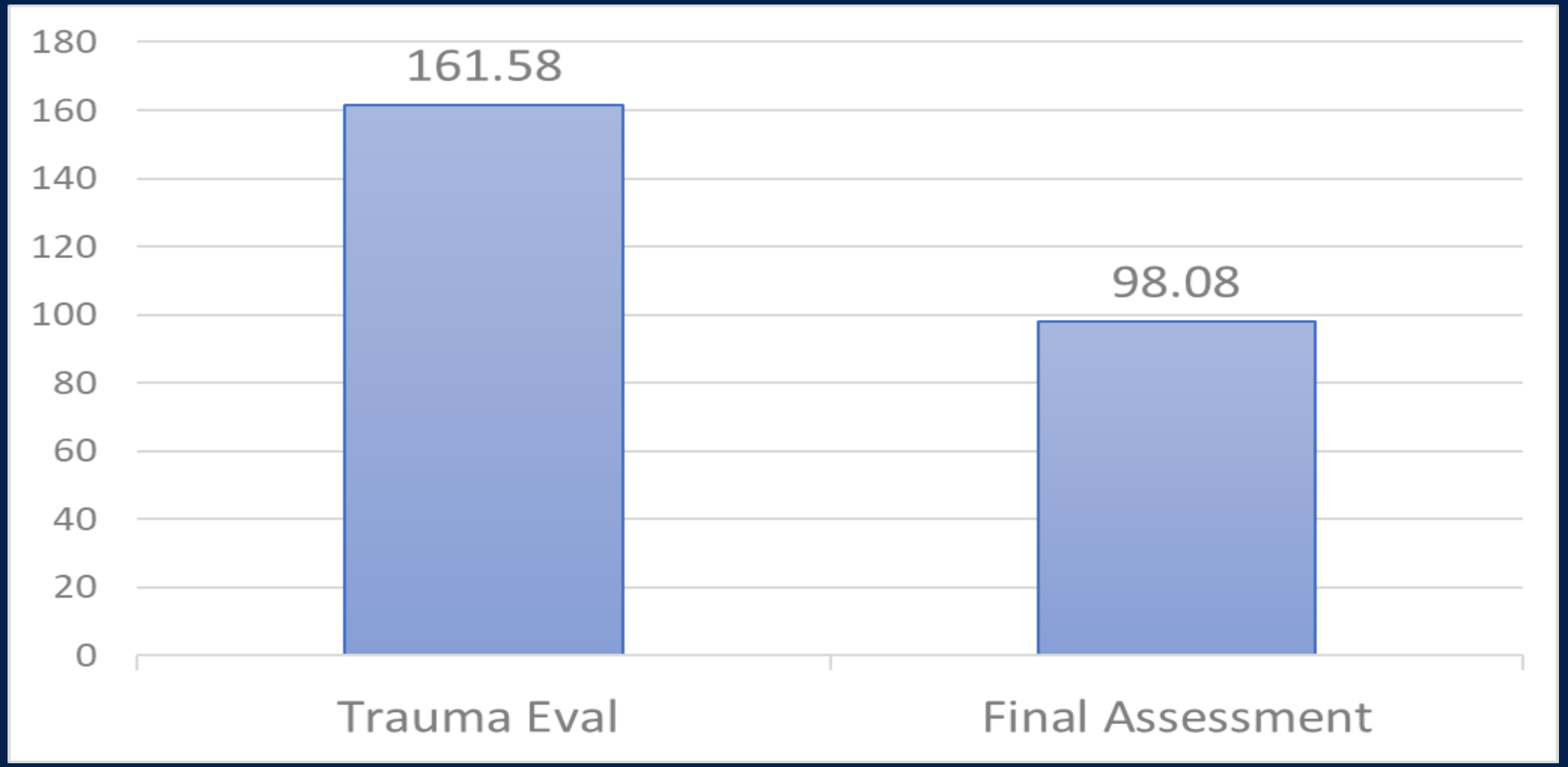


Change in PTSD & Depression Symptoms



p-values for pre-post treatment change all significant at p<.001
Cohen's d effect sizes large in magnitude, Range: 1.36-2.03

Change in PTSD Cognitions (PTCI total)



p-values for pre-post treatment change all significant at p<.001
Cohen's d effect sizes large in magnitude, d=1.55

Overall Outcomes

Measure	Initial Eval	Final Eval	*t* value	Cohen's D	% Change
PSSI (n=35)	45.49 (14.71)	19.13 (12.53)	10.04	1.70	58% reduction
PCL (n=31)	48.87 (13.50)	18.94 (13.89)	11.30	2.03	61% reduction
BDI (n=24)	30.27 (12.63)	14.13 (11.94)	6.65	1.36	53% reduction
PTCI total (n=31)	161.58 (40.76)	98.08 (40.13)	8.65	1.55	39% reduction
SCL (n=26)	2.35 (0.80)	0.93 (0.63)	9.66	1.89	60% reduction
PANAS Positive (n=30)	27.93 (8.20)	31.17 (7.88)	-2.91*	-0.53	11% increase
PANAS Negative (n=30)	33.77 (9.36)	21.77 (7.45)	6.30	1.15	36% reduction

Patient Experiences

During Treatment:

- “I know I need this, but it makes me sick to do my homework”
- “After every session, I feel hit by a truck”
- “I’m not sure I can get through this, it’s too overwhelming”
- ”That last session made me want to to drink pretty badly”

After Treatment Completion:

- “I can’t put words to all the ways I have changed. I feel my body. I feel present”
- “I don’t hate myself anymore”
- “Going through PE leaves me feeling I can go through almost anything and be OK”
- “I feel a shed a layer of darkness and fear that was always with me”

Integrated Treatment in Residential Setting

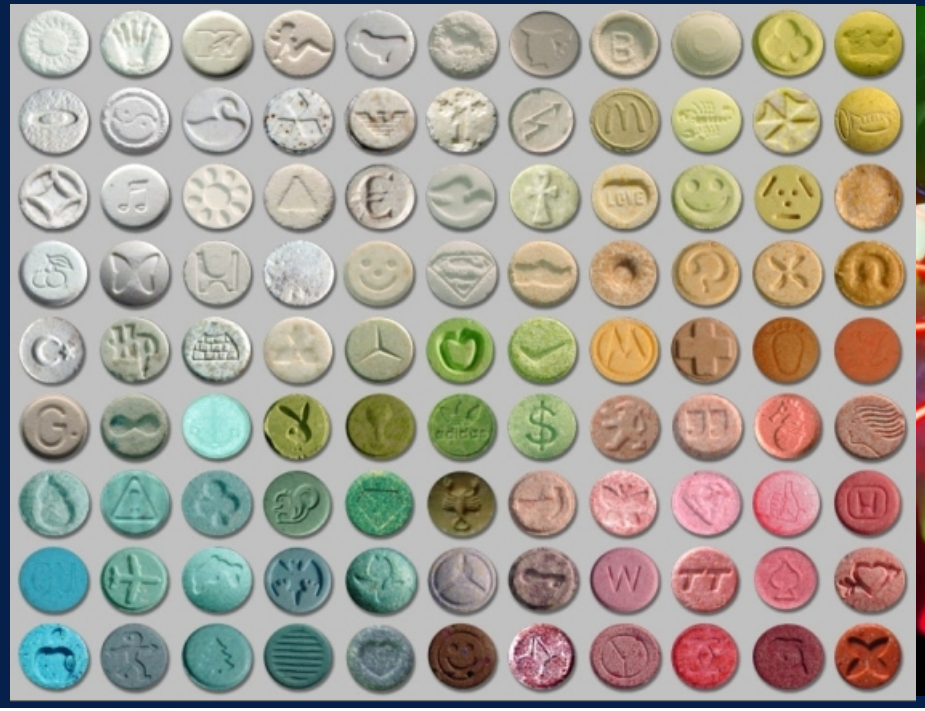
Benefits: It works!

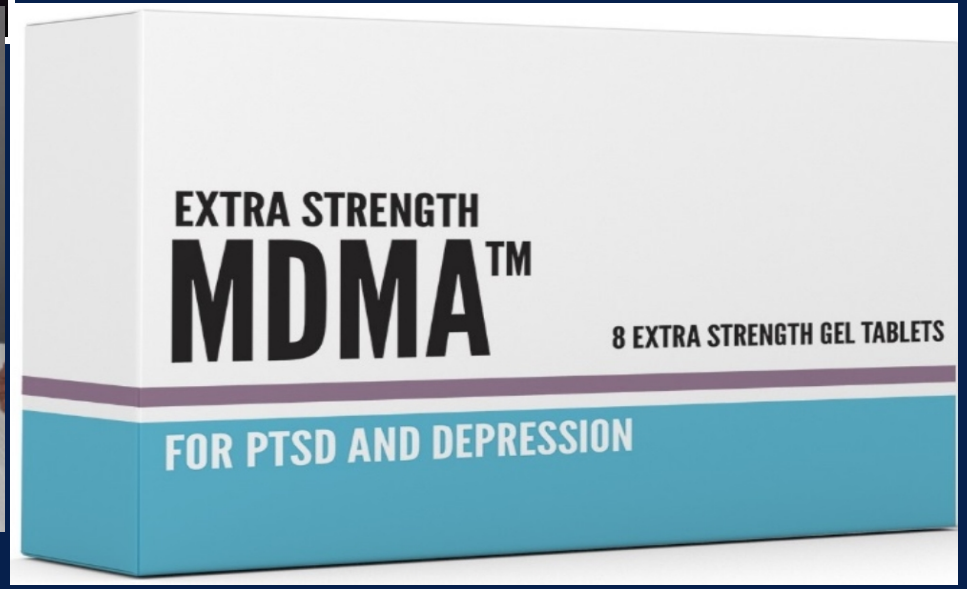
- extremely positive outcomes related to reduction of PTSD symptoms and other psychological sequelae
- extremely low dropout or non-completion rate in residential setting
- reduced/eliminated risk of substance relapse during treatment protocol

Integrated Treatment in Residential Setting

Challenges: It's hard!

- Relative length of protocol (cost, loss of life functioning, etc.)
- Therapist variability in targeting values, meaning, joy/expansion, somatic experiences
- Subjective discomfort/acceptability of protocol
  - avoidance is the reasonable "nature of the beast"
  - high dropout rates in outpatient settings



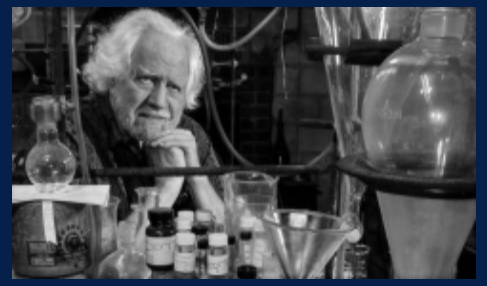

EXTRA STRENGTH
MDMA™
8 EXTRA STRENGTH GEL TABLETS
FOR PTSD AND DEPRESSION


Experimental Sessions
ClinicalTrials.gov Identifier: NCT01211405
Mithoefer - Psychedelic Science 2013 - Oakland

History of Research with MDMA

1912
Merck synthesizes & patents MDMA

First MDMA studies on animals at Merck
1927



Alexander Shulgin re-synthesizes MDMA
1965

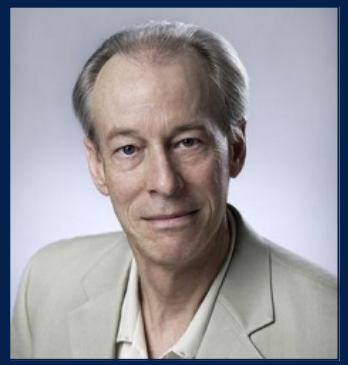
MDMA-assisted psychotherapy used by thousands, including for PTSD and couples therapy
1976-1985

1953-54
US Army conducts experiments on animals for use as truth pill

U.S.ARMY

1976
Shulgin introduces MDMA to psychologist Leo Zeff

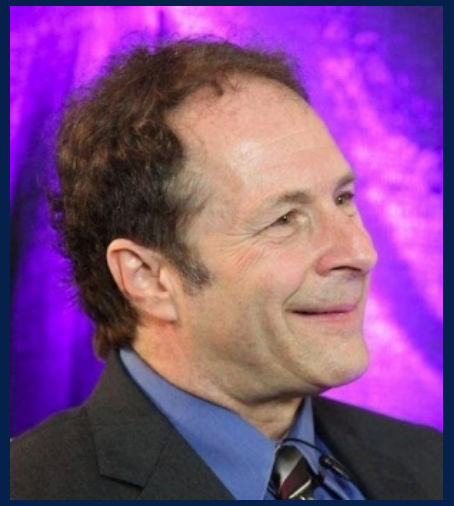
History of Research with MDMA



MAPS formed by Rick Doblin
to fund psychedelic research
1986-present

1985
DEA emergency
scheduling
MDMA as schedule I

1986
Greer & Tolbert
clinical experience & 2-
year follow-up 29
patients MDMA-
assisted psychotherapy



Psychedelics

Mind manifesting: term "psychedelic" is derived from the Greek words ψυχή (psyche, soul, mind) and δηλοῦν (to manifest)

Psychedelics are a **subclass** of hallucinogenic drugs

- Primary effect is to trigger non-ordinary mental states
- Produce changes in cognitive processing, perception, mood, and sense of time
- Affect all the senses

The "classic" hallucinogens or serotonergic hallucinogens include substances like **LSD, DMT, Mescaline, and Psilocybin** and are potent psychedelics

However, the term psychedelic is often used more broadly to include various types of hallucinogens, including those that are less potent, *atypical or adjacent to psychedelia e.g., MDMA*

Psychedelic Pharmacology

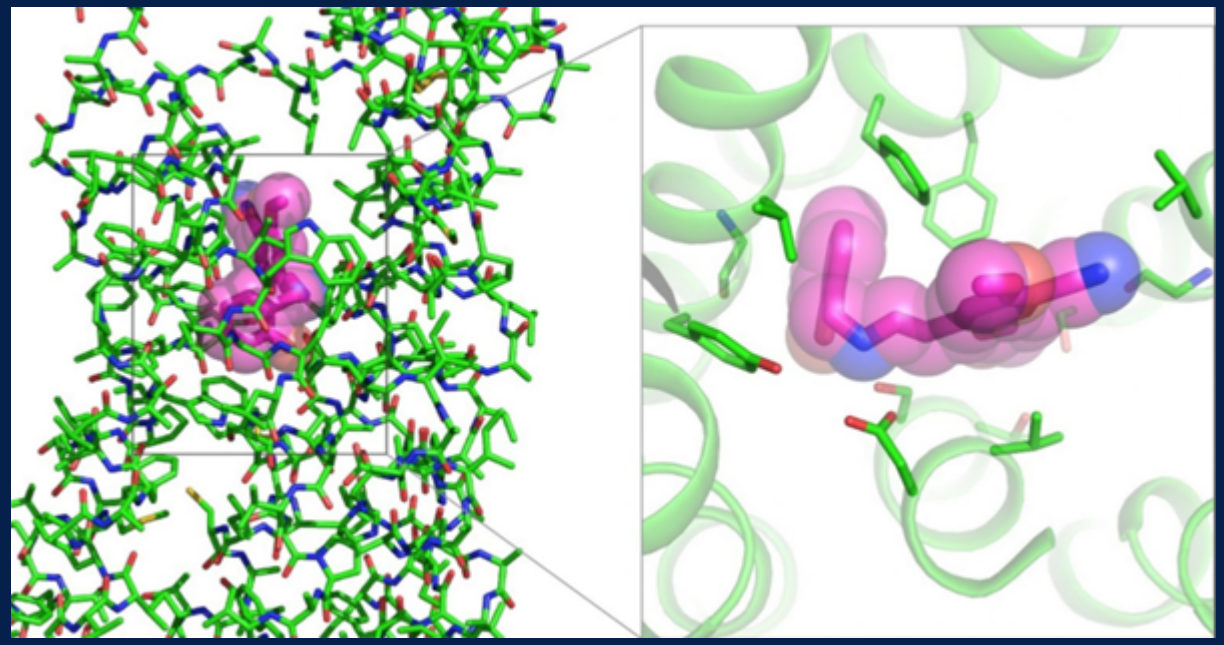
Most psychedelics fall into one of the three families of chemical compounds

1. tryptamines
2. phenethylamines
3. lysergamides

All act via serotonin 2A agonism

Binding at 5-HT2A receptors modulates the activity of key circuits regulating

1. sensory perception
2. cognition
3. arousal; physiological response to stress



Bryan Roth Lab (UNC School of Medicine)

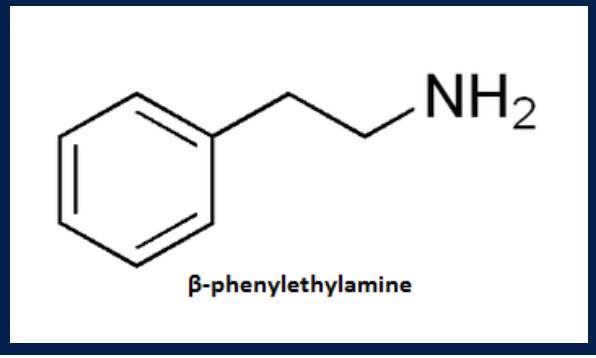
MDMA Pharmacology

- Substituted amphetamine structurally, and a monoamine-releasing agent mechanistically
- Onset of action: 30 – 45 minutes. Duration of action: 4 – 6 hours
- A potent empathogen–entactogen with stimulant and minor psychedelic properties

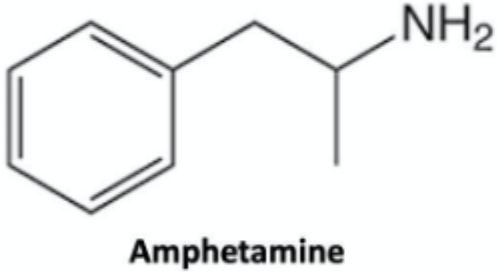
*Induces feelings of emotional openness, trust, oneness, relatedness, extroversion, empathy, compassion toward others (and self)

*But also produces an energizing effect, distortions in perception and time, and enhanced enjoyment of tactile experiences

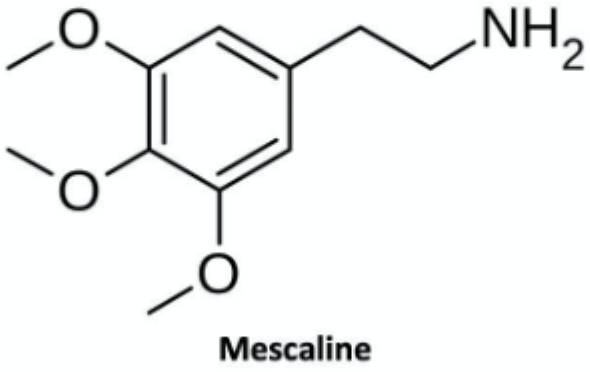
MDMA Pharmacology



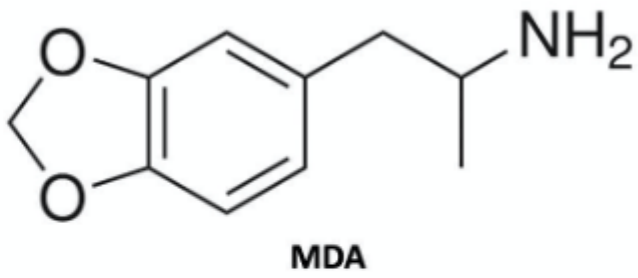
Amphetamines

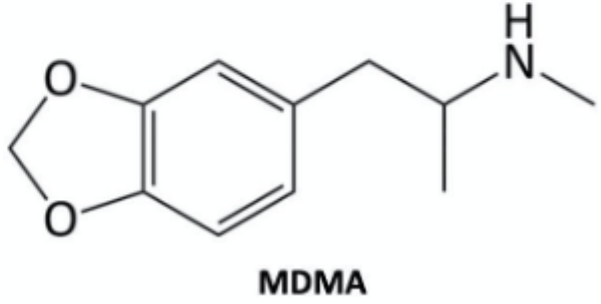


Psychedelics



Entactogens





MDMA Pharmacology

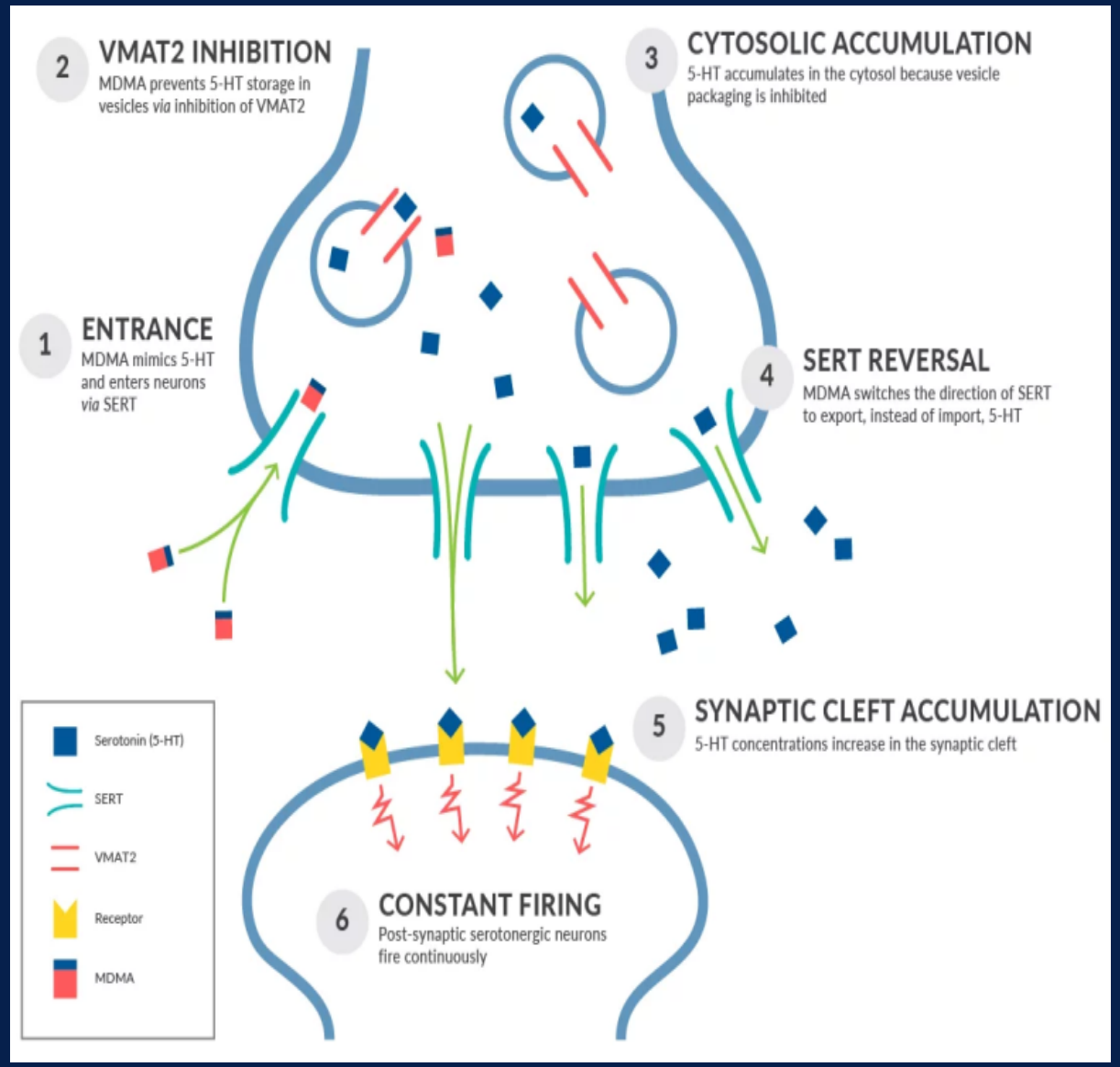
Increases transmission through pre-synaptic release and re-uptake blockade of:

- **norepinephrine (NE)**
- **dopamine (DA)**
- **serotonin (5-HT)**

***mild 5HT2a agonism: psychedelic-like effects**

Enhances release of hormones:

- **oxytocin - likely enhances pro-social and empathic effects**
- prolactin
- vasopressin
- cortisol



Why Study MDMA?

"We recommend individual, manualized trauma-focused psychotherapy over other pharmacologic and non-pharmacologic interventions for the primary treatment of PTSD."

- Psychotherapy is the definitive treatment, but doesn't always work
- Pharmacotherapies have limited efficacy (i.e. ability to induce remission), especially in patients with chronic, complex PTSD

What about a drug that could catalyze the psychotherapy?

VA/DoD Clinical Practice Guidelines (2017)

Psychoactive Effects of MDMA

- Increased compassion (for self and others)
- Increased capacity of introspection

- Feelings of closeness, ease of connection, trust
- Enhanced communication

- Reduced defense and fear of emotional injury
- Unpleasant memories present as less disturbing, more approachable

- Reduced anxiety
- Increased psychic energy, drive to engage

Carhart-Harris, et al., (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. International Journal of Neuropsychopharmacology, 17(4), 527-540.

Bedi, G., et al., (2014). A window into the intoxicated mind? Speech as an index of psychoactive drug effects. Neuropsychopharmacology, 39(10), 2340-2348.

MDMA –Potentiating the Therapeutic Process

Drug effects facilitate the therapeutic process by allowing the patient to **revisit trauma without feeling overwhelmed by the terror or shame** that have overwhelmed or paralyzed them in the past

- Penetrate the emotional numbing common to PTSD
- Allow more access to full range of emotions (e.g., grief, fear, rage, as well as joy, love, comfort, etc.) without the subjective feeling of emotional flooding
- Increased access and approachability of distressing thoughts and memories
- Give rise to novel thoughts about meaning/salience of events and memories
- Decreased self-blame, judgment

MDMA is expected to help ease the processing of feelings and memories, this does not mean, however, that the process will be easy

Task of the Therapist

*Is... **not to understand rationally** the problem the patient is facing in order to use some specific techniques to change the situation according to some preconceived plan,*

*but rather to mediate and facilitate the patient's access to a **deeper state of the psyche healing** than results from a dialectic interplay between the individual and the collective unconscious.*

*The objective is not a gradual exploration of various levels of the individual unconscious as in verbal western psychotherapies, but facilitation of a **powerful transformative experience** of a transcendental nature.*

Grof, S. (1988). The adventure of self-discovery: Dimensions of consciousness and new perspectives in psychotherapy and inner exploration. State University of New York Press.

Refining the Therapeutic Approach

Adaptation of foundation laid by Stanislav Grof MD and many others

A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder

-Michael C. Mithoefer, M.D.

Contributors: Annie Mithoefer, B.S.N., Lisa Jerome, Ph.D., June Ruse, Psy.D., Rick Doblin, Ph.D., Elizabeth Gibson, M.S., Marcela Ot'alora G., L.P.C., Evan Sola, Psy.D. candidate

Therapeutic Approach

- Supports an emerging experience
- Index trauma is targeted if it does not emerge
- Reclining, headphones with music, eyeshades
- Alternating inner focus & talking to therapists
- Allows for therapists' individual variation

***Importance of preparation and integration**

Elements of Other Treatments

- Imaginal exposure
- Cognitive restructuring
- Psychodynamic insights
  - transference/countertransference
- Somatic Experiencing

MDMA Toxicity

Stimulant-related medical toxicity

- Cardiac (i.e MI, arrhythmia)
- Neurologic (i.e. stroke, seizure)
- Rhabdomyolysis → renal failure
- Hyperthermia

Mortality

- Malignant hyperthermia
- CNS and cardiac events
- Hyponatremia due to excess fluid intake, solute loss, and vasopressin secretion

Adverse psychological & neuropsychological effects: acute and chronic (neurotoxicity?)

Adverse Effects: Psychological

Acute

- Anxiety/Panic
- Mania
- Psychosis

Sub-acute (i.e. 24-48 hours post ingestion)

- Depression, irritability, anxiety, difficulty concentrating, headache, fatigue, muscle aches

Chronic

- Depression
- Anxiety
- Insomnia
- Impulsivity
- Increased stress reactivity

***Note*: more likely to occur with co-occurring mental illness (i.e. psychosis, mania, depression, anxiety)**

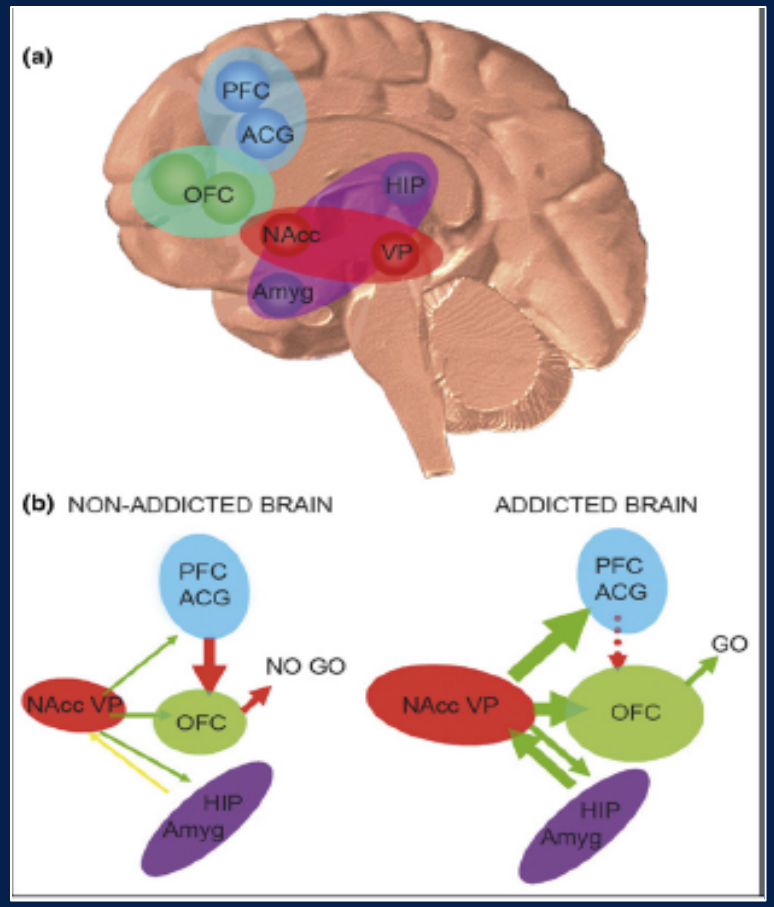
Concerns – MDMA & SUD

Addictive liability

- DA increases in mesolimbic pathway

Self-administered; induced CPP

Why would we give drug users drugs?

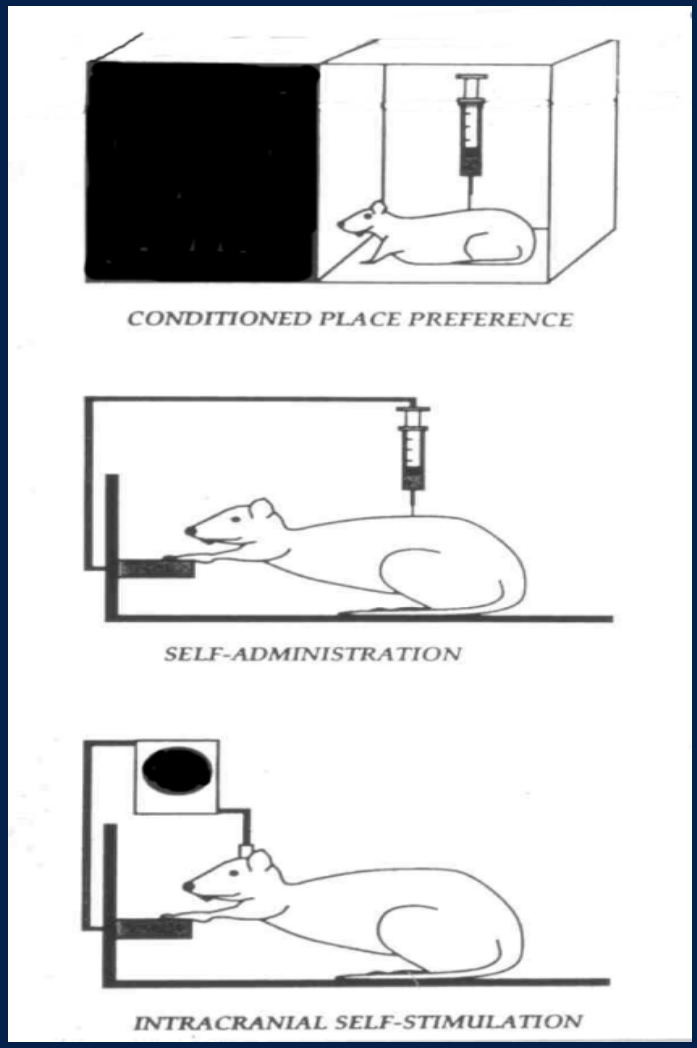


Addictive Liability

MUCH lower addictive liability compared to other DA-stimulants (e.g. cocaine, methamphetamine)

- **likely related to 5HT-mediated dampening of DA release**
- Low rates of MDMA addiction

Animal trials: some fail to self-administer MDMA



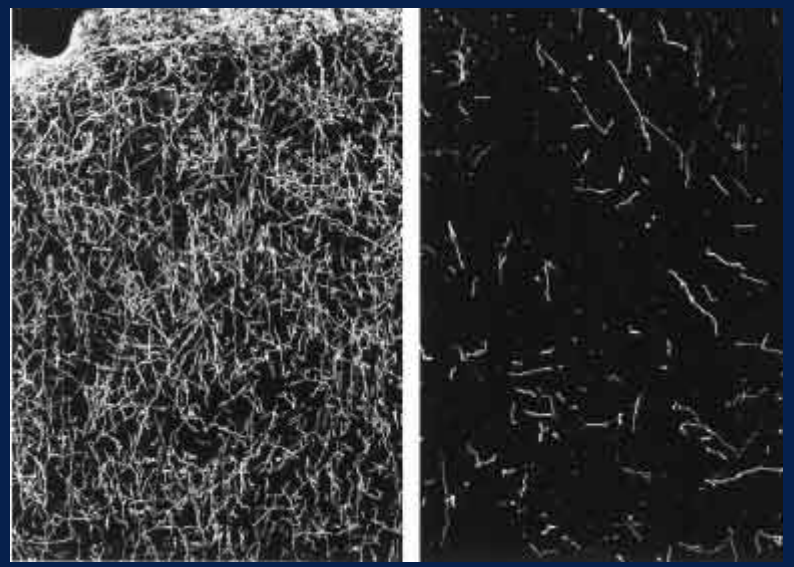
Schenk, S., & Highgate, Q. (2021). Methylenedioxymethamphetamine (MDMA): Serotonergic and dopaminergic mechanisms related to its use and misuse. *Journal of Neurochemistry*, *157*(5), 1714-1724.

Adverse Effects: Neuropsychological

Is MDMA neurotoxic?

Animal studies

- Reductions in 5-HT signaling, 5-HIAA, & 5-HT transporter (SERT) in cortex, hippocampus and striatum
- Neurodegenerative neurotoxicity vs neuroadaptations?



Adverse Effects: Neuropsychological

Human studies

- Neuroimaging: repeated MDMA use associating with chronic reductions in cortical 5HT signaling
    - Reductions in SERT
    - Up-regulation in 5HT2a receptors, increased neo-cortical excitability

- Functional studies in abstinent long-term users: <u>Neurocognitive impairment</u>
    - *Related to frontal and hippocampal regions*
    - *Deficits in verbal, visual, and working memory*
    - *Executive function impairment*

***Caveats: none of trials designed to establish causality and can't rule out effects of pre-existing differences, poly-drug use or other factors**

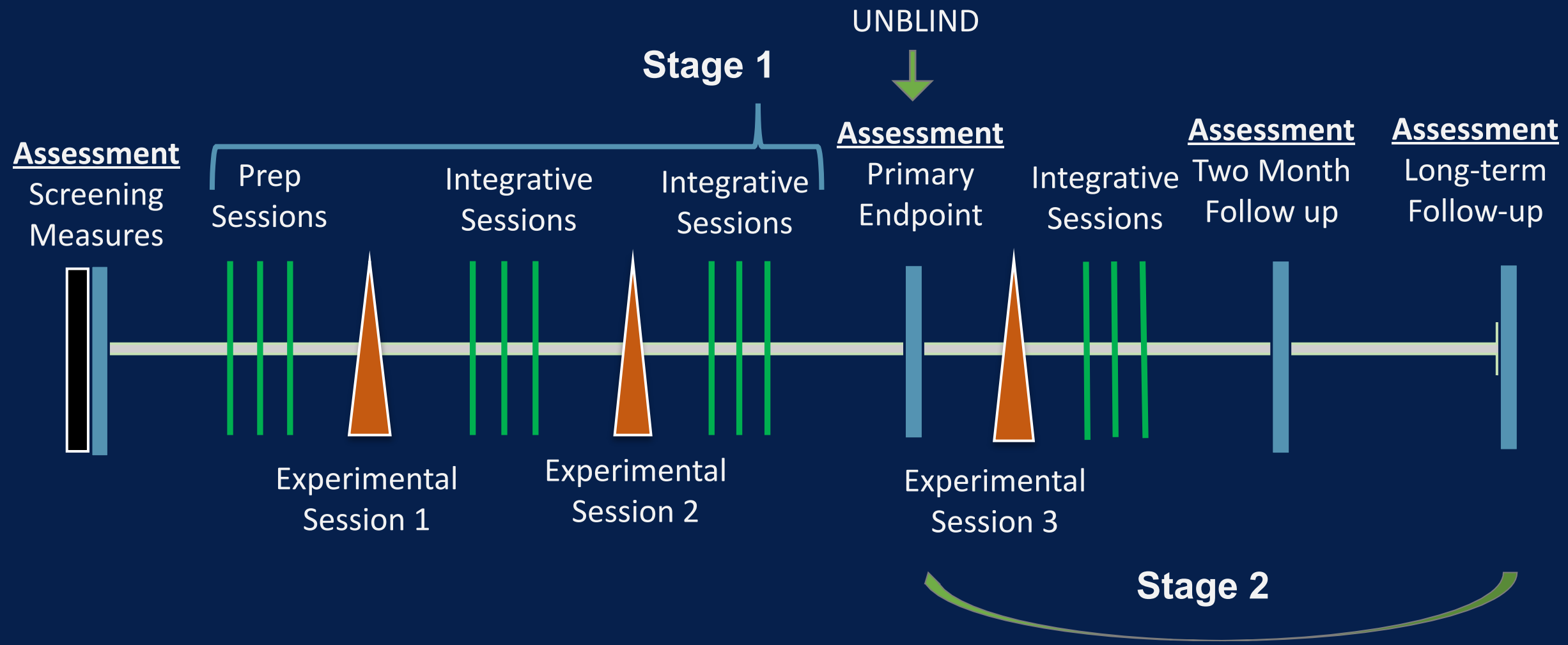
Cowan, R. L., Roberts, D. M., & Joers, J. M. (2008). Neuroimaging in human MDMA (Ecstasy) users: A cortical model. Annals of the New York Academy of Sciences, 1139(1), 291-298.

Resurgence of MDMA Clinical Research

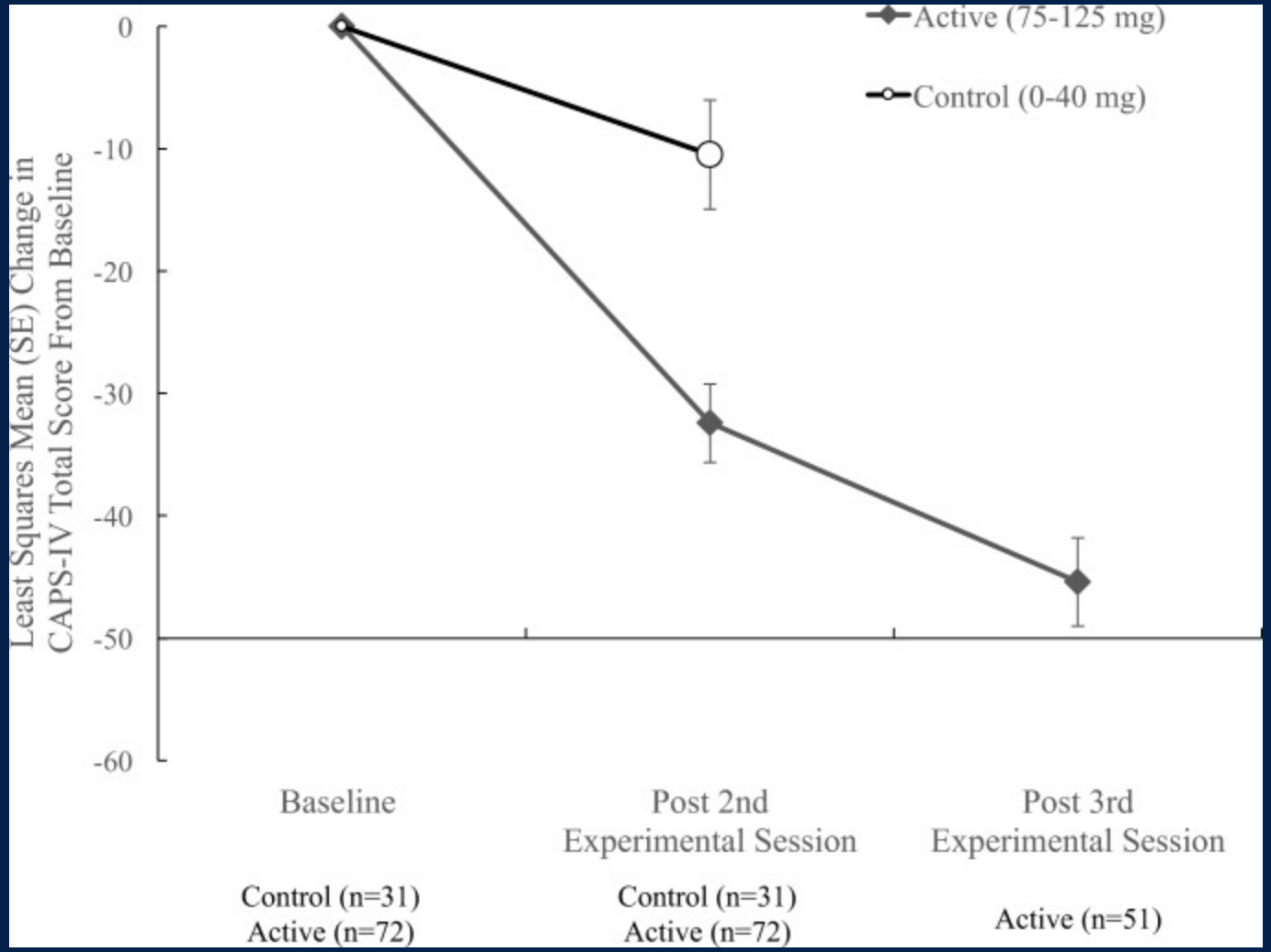
MAPS: Six Completed Phase 2 Studies

Study		Sample (N)	Dose Comparison	
Location	Code	Intent to Treat	Active	Comparator
Charleston, SC	MP-1	N=23	125 mg	0 mg
Switzerland	MP-2	N=14	125 mg	25 mg
Vancouver, BC	MP-4	N=6	125 mg	0 mg
Charleston, SC	MP-8	N=26	75 or 125 mg	30 mg
Tel Aviv, Israel	MP-9	N=8	125 mg	25 mg
Boulder, CO	MP-12	N=26	100 or 125 mg	40 mg
All Studies		**Intent to Treat N=103**	**Active (75-125 mg) vs. Comparator (0-40 mg)**	

Study Design: Chronic, Treatment-Resistant PTSD

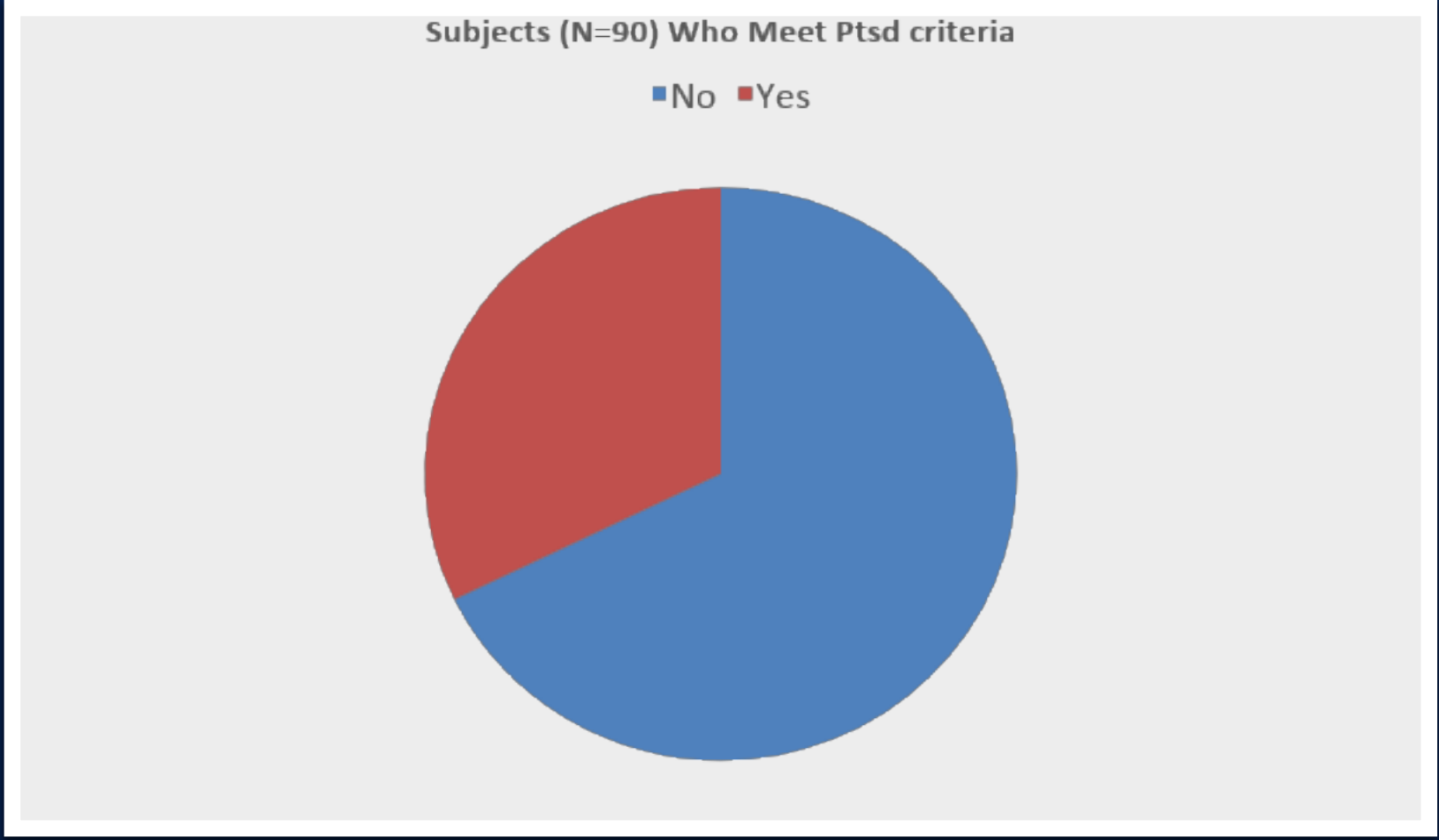


PTSD Outcome (6 MDMA/PTSD Studies)



Jerome, L., Feduccia, A. A., Wang, J. B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., ... & Doblin, R. (2020). Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology*, *237*, 2485-2497.

Phase 2: 12-Month Follow-up



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Serious Adverse Events

Dose	Comparator Dose (25-40 mg)	Active Dose (75-125 mg)	Open Label (100-150 mg)	
Subjects Per Dose Group	N=21 N (%)	N=74 N (%)	N=78 N (%)	
Cardiovascular Ventricular Extrasystoles (exacerbation)	--	--	1 (1.3%)	
Injuries Clavicle Fracture (auto accident) Lower Limb Fracture	-- --	1 (1.3%) 1 (1.3%)	-- --	
Nervous System Syncope	--	1 (1.3%)	--	
Psychiatric Suicidal Ideation	1 (4.8%)	--	--	

Phase 2 Trials

- Established **Safety** in controlled clinical settings
- Efficacy with **Large Effect Size**
- Cause/etiology of PTSD does not influence outcomes, MDMA-assisted psychotherapy can be used to treat anybody with chronic PTSD
- Successful End of Phase 2 meeting with FDA November 29, 2016
- **FDA Breakthrough Therapy Designation August 2017**

Phase 3 Trials

Two Studies: MAPP1 (2021) and MAPP2 (2023)

- Multi-site, randomized, double-blind, placebo-controlled
- Expanded Access/Compassionate Use
- DEA **re-scheduling?**

MAPP1: Treatment Response & Remission

nature medicine

ARTICLES

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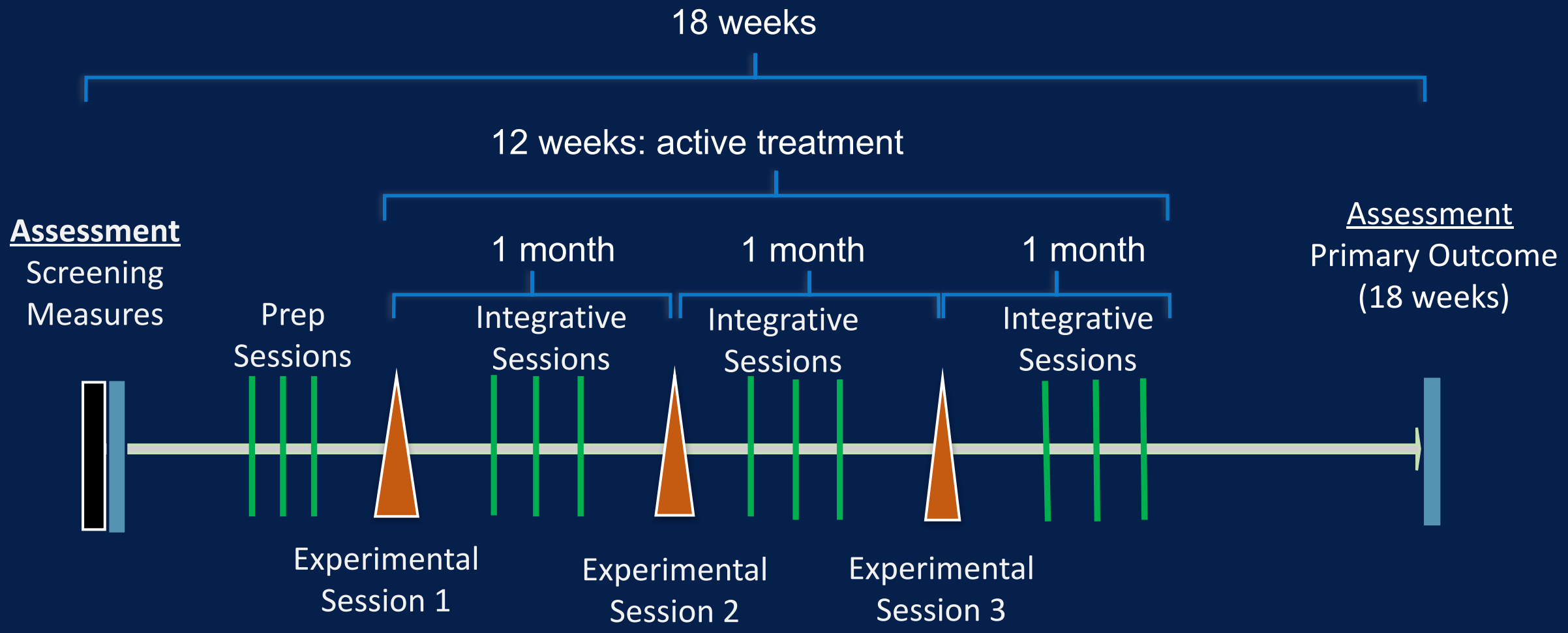
Check for updates

OPEN

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

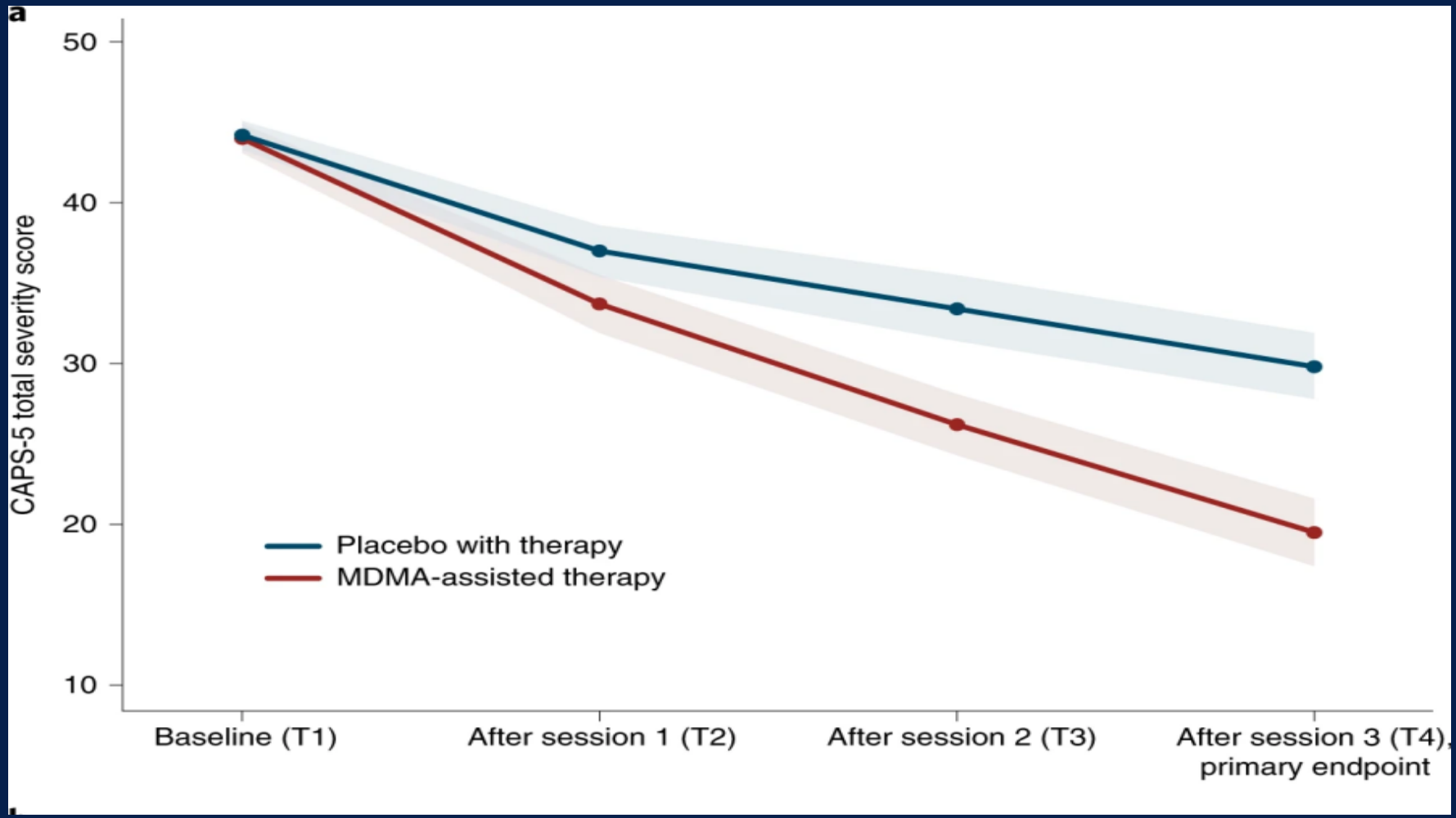
Jennifer M. Mitchell[1,2]✉, Michael Bogenschutz[3], Alia Lilienstein[4], Charlotte Harrison[5], Sarah Kleiman[6], Kelly Parker-Guilbert[7], Marcela Ot'alora G.[8,9], Wael Garas[8], Casey Paleos[10], Ingmar Gorman[11], Christopher Nicholas[12], Michael Mithoefer[5,9,13], Shannon Carlin[5,9], Bruce Poulter[8,9], Ann Mithoefer[9], Sylvestre Quevedo[2,14], Gregory Wells[14], Sukhpreet S. Klaire[15], Bessel van der Kolk[16], Keren Tzarfaty[9], Revital Amiaz[17], Ray Worthy[18], Scott Shannon[19], Joshua D. Woolley[2], Cole Marta[20], Yevgeniy Gelfand[21], Emma Hapke[22], Simon Amar[23], Yair Wallach[24], Randall Brown[11], Scott Hamilton[25], Julie B. Wang[5], Allison Coker[1,5], Rebecca Matthews[5], Alberdina de Boer[5], Berra Yazar-Klosinski[4], Amy Emerson[5] and Rick Doblin[4]

Phase 3 – MDMA vs Inactive Placebo



Experimental Session	Initial Dose	Supplemental Dose*	Min-Max Cumulative Dose
1	80 mg	40 mg	80 mg to 120 mg
2	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
3	80 or 120 mg	40 or 60 mg	80 mg to 180 mg
		Total Cumulative Dose	240 mg to 480 mg

MAPP1 Outcomes



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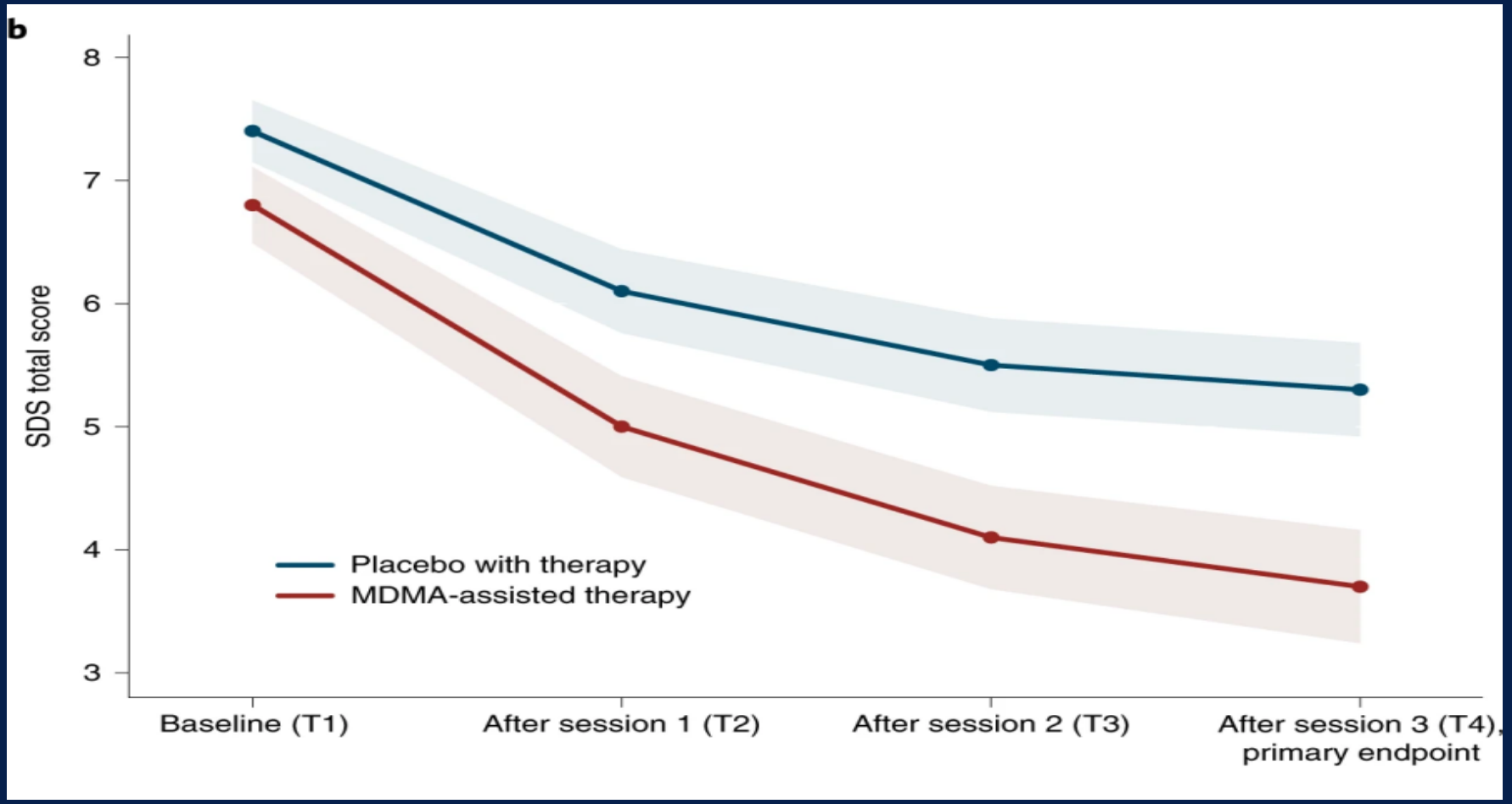
MAPP1 Outcomes



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MAPP2

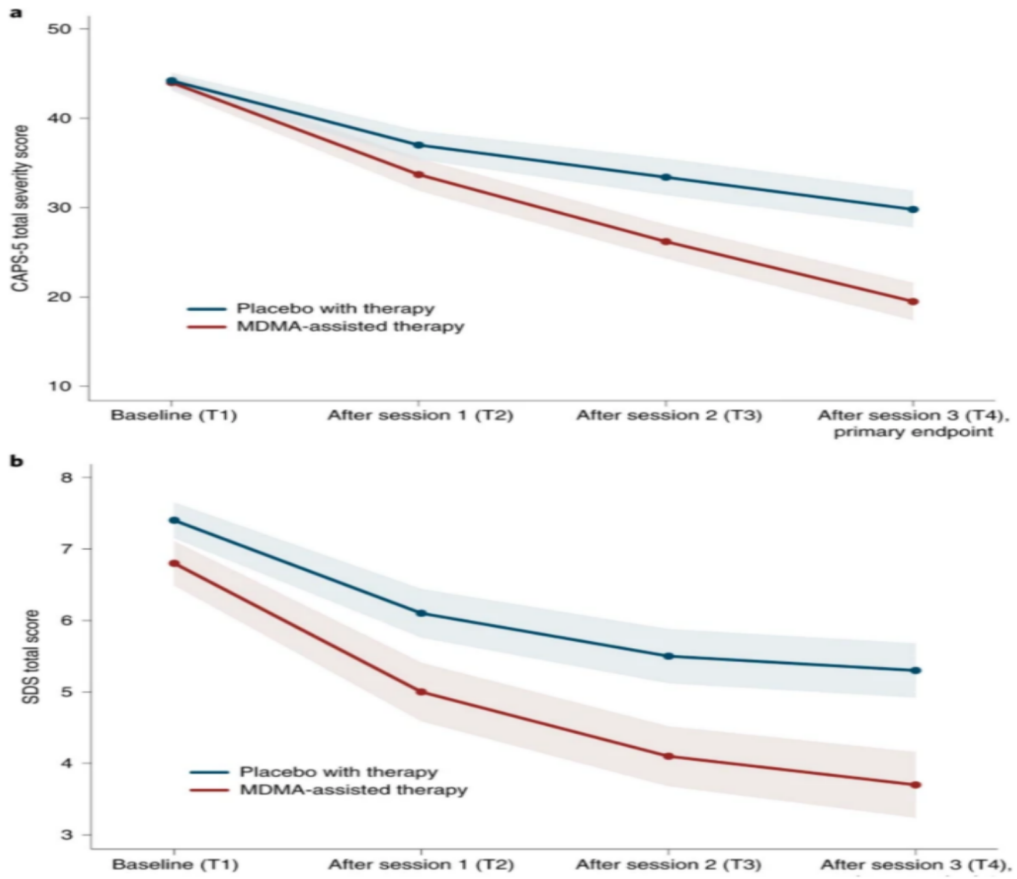
Protocol, design VERY similar to MAPP1

Significant Distinctions:

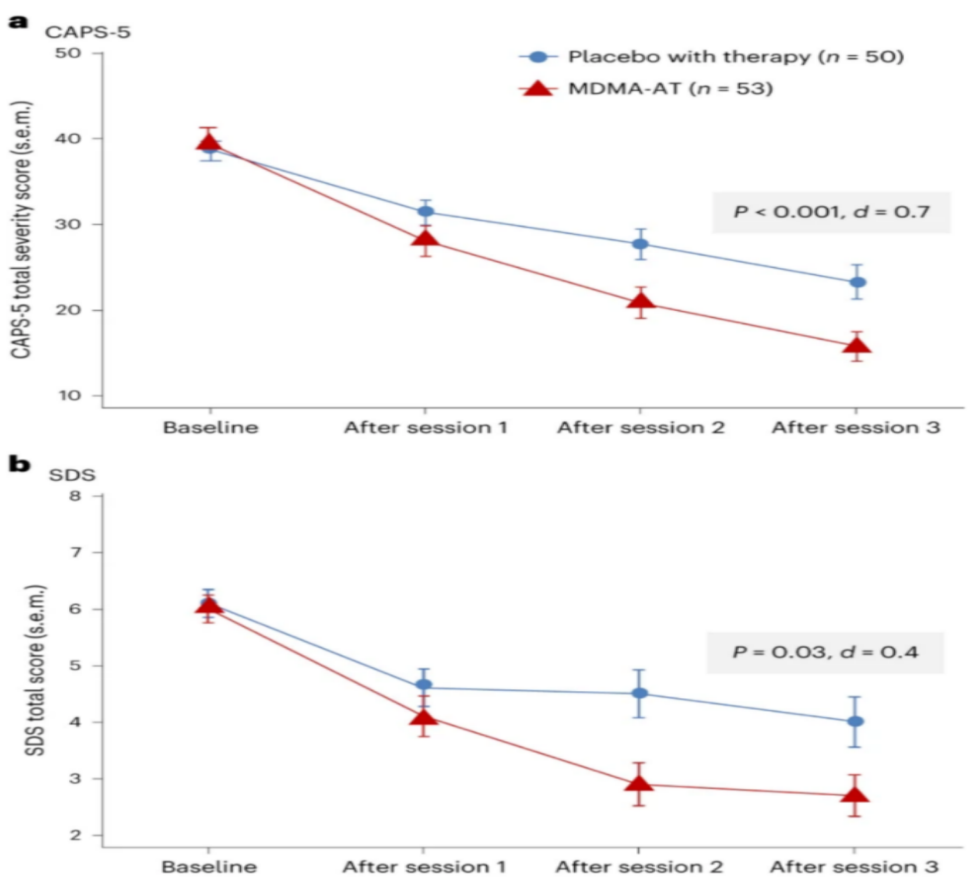
- MAPP1 enrolled only participants with severe PTSD, while MAPP2 enrolled participants with moderate PTSD and severe PTSD
- MAPP2 enrolled far more people of color: 35 of 104 (33.7%) participants identified their race as other than White, and 28 of 104 (26.9%) identified their ethnicity as Hispanic/Latino

Outcomes: MAPP1 and MAPP2

MAPP1
Mitchell et al., 2021



MAPP2
Mitchell et al., 2023



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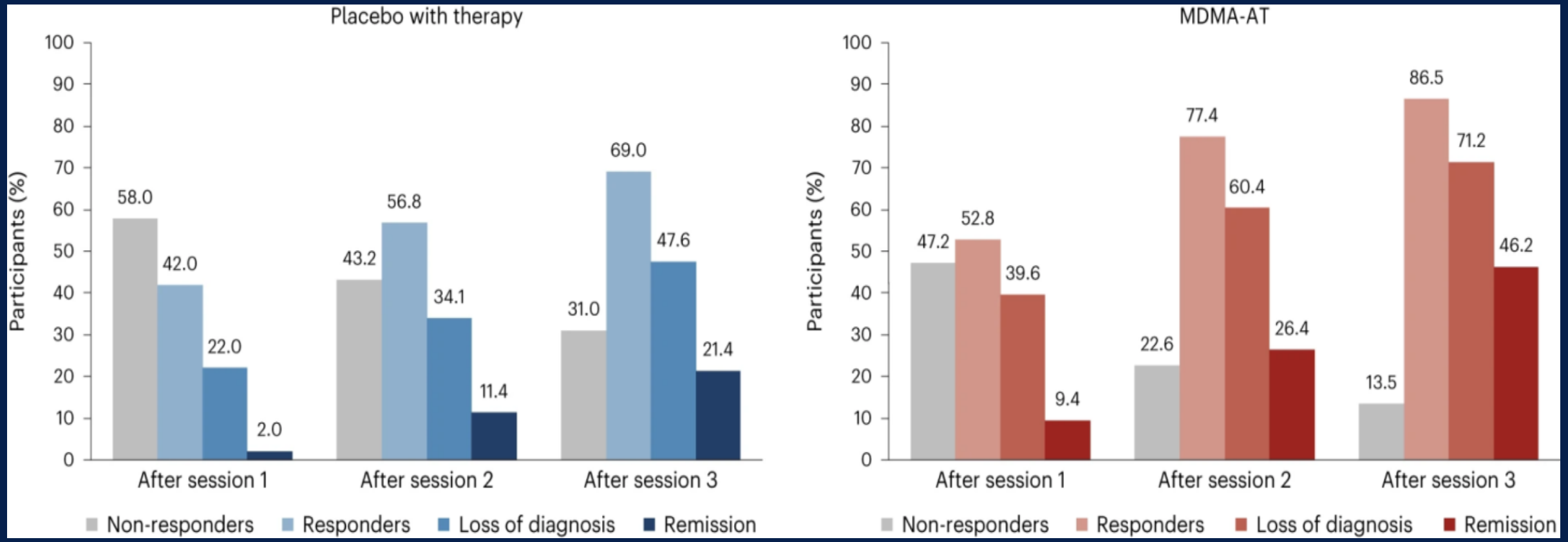
MAPP2: Treatment & Remission



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DEA Rescheduling?

- The results of MAPP2 supported submission of a new drug application (NDA) for MDMA in late 2023

- Feb. 2024 - FDA accepted the NDA for midomafetamine (MDMA) capsules (Lykos Therapeutics) "to be used in combination with psychological interventions, and other supportive services from a health care provider, for individuals with PTSD"

- The agency has also granted priority review to the NDA and assigned a target action date of August 11, 2024

Patient Experiences: During & After

During Treatment:

- “I was surprised that I was able to go so deeply into the trauma without fear”
- “I felt so connected and understood by my therapists”

After Treatment Completion:

- “I still can’t believe it but it has been over a year and I still have no PTSD symptoms.”
- “I’m so deeply grateful to have been able to participate in the study”

MDMA-AT: An Integrated Treatment Proposal

Study Design

- An open label pilot study to assess the feasibility, safety and effectiveness of MDMA-Assisted Therapy (MDMA-AT) for PTSD used in combination with a motivational/ behavioral psychotherapy for substance use disorder ("treatment as usual")

- Participants dually-diagnosed with PTSD and SUD in residential level of care

MDMA-AT: An Integrated Treatment Proposal

Both SUD and PTSD have as sequelae:

- the loss of engagement in fulfilling relationships and lifestyle
- isolation, self-loathing and avoidance

These factors are also part of the **high dropout rates** associated with current treatments, reducing the impact of interventions.

Inclusion of this facilitating medication, in the context of a residential setting that creates additional separation from avoidance strategies such as substance use:

- will facilitate fuller engagement with PTSD and SUD symptoms and sequelae
- allow for more engaged processing and integration.

Proposed Study Design

Study Design

- 11 week residential treatment (TAU + MDMA-AT)
  - MDMA-AT integrated with residential SUD protocol
- Prior to admission:
  - screening and study induction + medication washout if needed
- Post admission:
  - baseline evaluation, substance free window of 3 weeks minimum, TAU treatment and MDMA preparatory sessions
  - 3 eight-hour MDMA-AT sessions (weeks 4, 7, 10)
  - 3 preparatory, 9 integration sessions
- Pre-post data collection, includes F/U to 1 year

Proposed Study Schedule

Weeks 1 - 3:

- *Preparatory sessions + TAU sessions*

Week 4:

- *MDMA session (full day)*

Weeks 4-6:

- *Integration sessions + TAU sessions*

Week 7:

- *MDMA session (full day)*

Weeks 7-9:

- *Integration sessions + TAU sessions*

Week 10:

- *MDMA session (full day)*

Weeks 10-11:

- *Integration sessions + TAU sessions*

Potential Benefits in SUD/PTSD Clients

MDMA, as a monoamine releaser and reuptake inhibitor with indirect effects on neurohormone release produces combined neurobiological effects:

- reduce defenses and fear of emotional injury
- enhance communication and introspection
- increased empathy and compassion

The subjective effects of MDMA create a productive psychological state that enhances the therapeutic process:

- openness to considering new information
- ability to engage in a trusting manner (increased therapeutic alliance)
- potential profound shifts in views of self and other (perspective shifts)

Potential Benefits in SUD Clients

It is hypothesized that the use of MDMA-AT as part of a combined protocol for these 2 debilitating disorders will facilitate deeper and more persistent engagement in both the therapy process as well as the ongoing change process post-intervention, including the integration of new perspectives on self and other (connection and engagement)


thank you