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What's Therapy Got To Do With It?

Understanding the Conceptual Framework for the
Therapeutic Component of MDMA-Assisted Therapy in
Phase 3 Clinical Trials

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*MDMA-AT has not been approved by any regulatory agency.
The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.*



Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

Michael Alpert receives payments from Lykos Therapeutics, Inc. as an investigator to work on clinical trials and contracts with Lykos Therapeutics, Inc. to perform education and supervision services.

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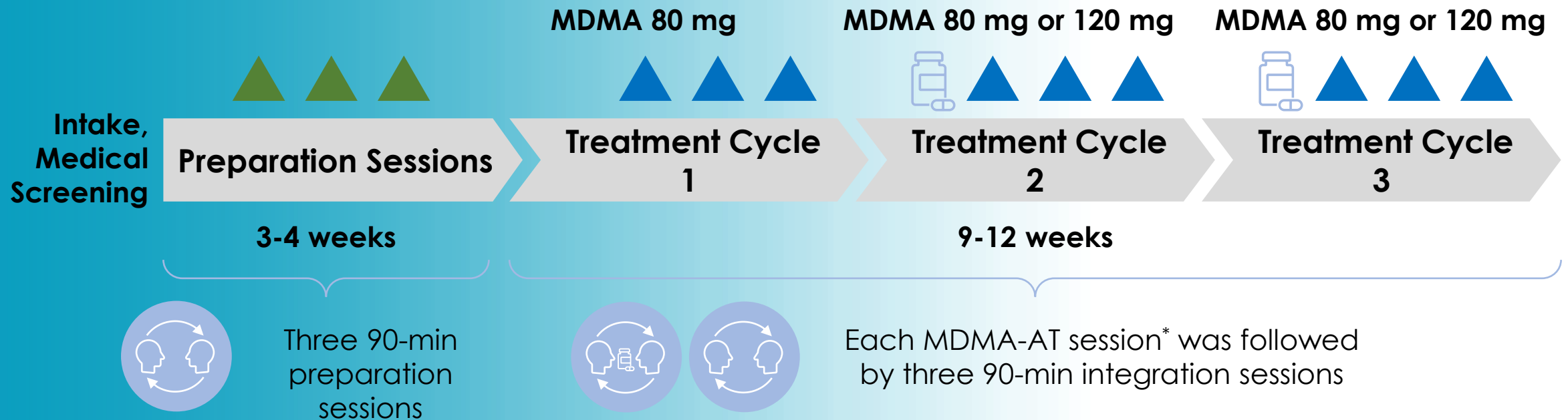
MDMA-assisted therapy is an integrated Investigational treatment



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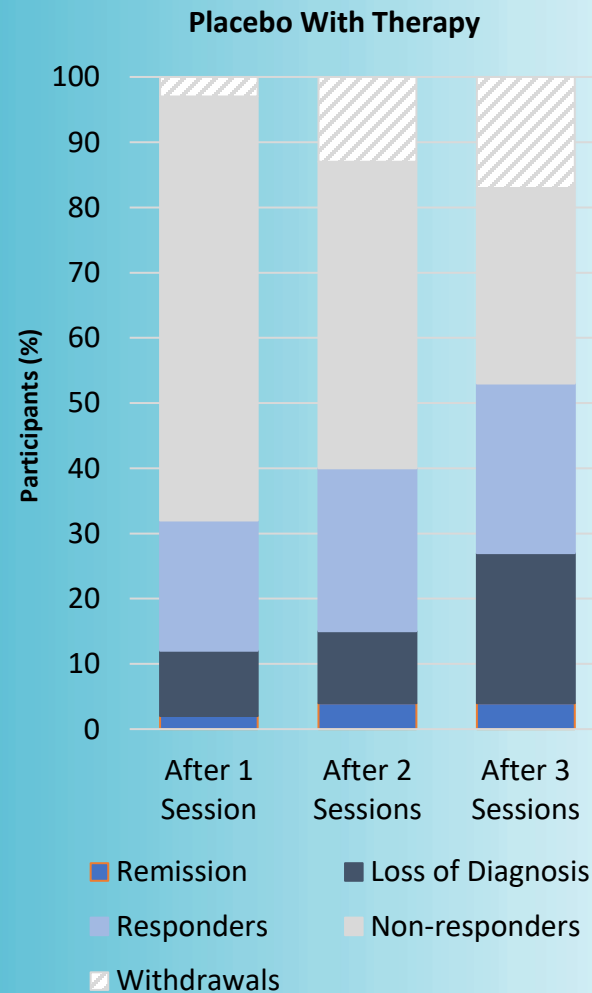
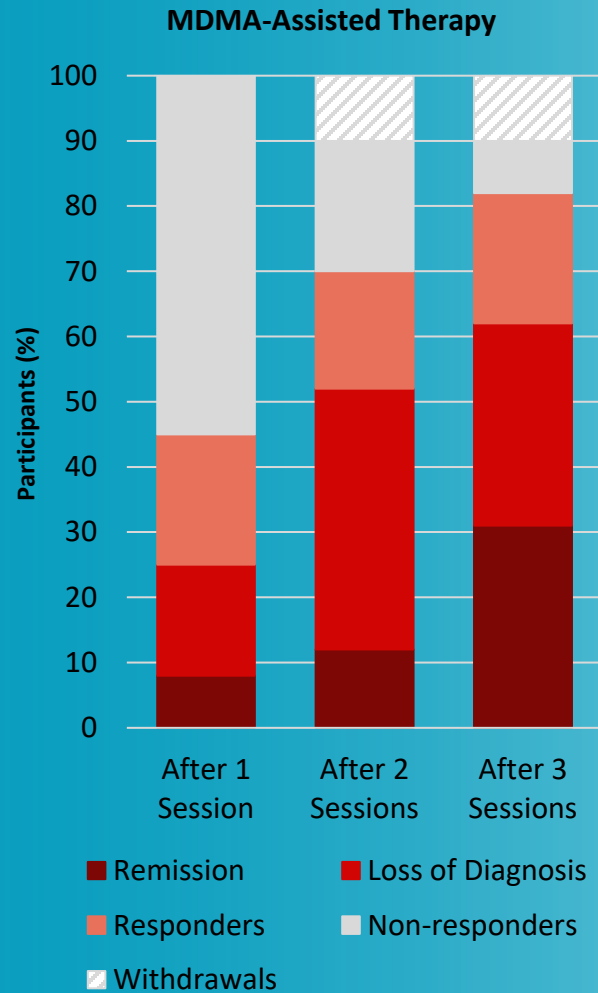
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Phase 3 Trial Design and Treatment Course



*Also called "Treatment Session," "Dosing Session," or "MDMA Session."
Mitchell JM et al. Nat Med. 2021 Jun;27(6):1025-1033.

Treatment response and remission by group and session: Phase 3



- **Clinically significant improvement** is defined as a decrease of ≥ 10 points on the CAPS-5
- **Loss of PTSD diagnosis** is defined as a specific diagnostic measure on the CAPS-5
- **Remission** is defined as a loss of PTSD diagnosis and a total CAPS-5 score ≤ 11

■ MDMA-AT (n=46)
■ Placebo (n=44)

Mitchell JM et al. *Nat Med.* 2021;27(6):1025-1033. This article is licensed under a Creative Commons Attribution 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.



Empirical Support for MDMA-AT

TYPE OF THERAPY	EFFECT SIZE	DROPOUT RATE
MDMA-AT TRIALS PLACEBO ARM (PHASE 3)	$d = 1.2, 1.25$	16%
PROLONGED EXPOSURE THERAPY	$g = 0.15 - 1.52$	56%
COGNITIVE PROCESSING THERAPY	$g = 1.24$	47%

Cogn Behav Ther, 48(1), 1-14.

Clinical Psychology Review, 91, 102115.



Why Use This Model?

- Maximize drug-specific effect size, minimize confounding variables
- Prior clinical knowledge and published evidence on psychedelic and MDMA-specific psychotherapy.

J Psychoactive Drugs, 18(4), 319-327 *Can J Psychiatry*, 50(7), 381-388.

J Psychoactive Drugs, 30(4), 371-379. *Drug Science, Policy and Law*, 3.



Core Conceptual Pillars of MDMA-AT

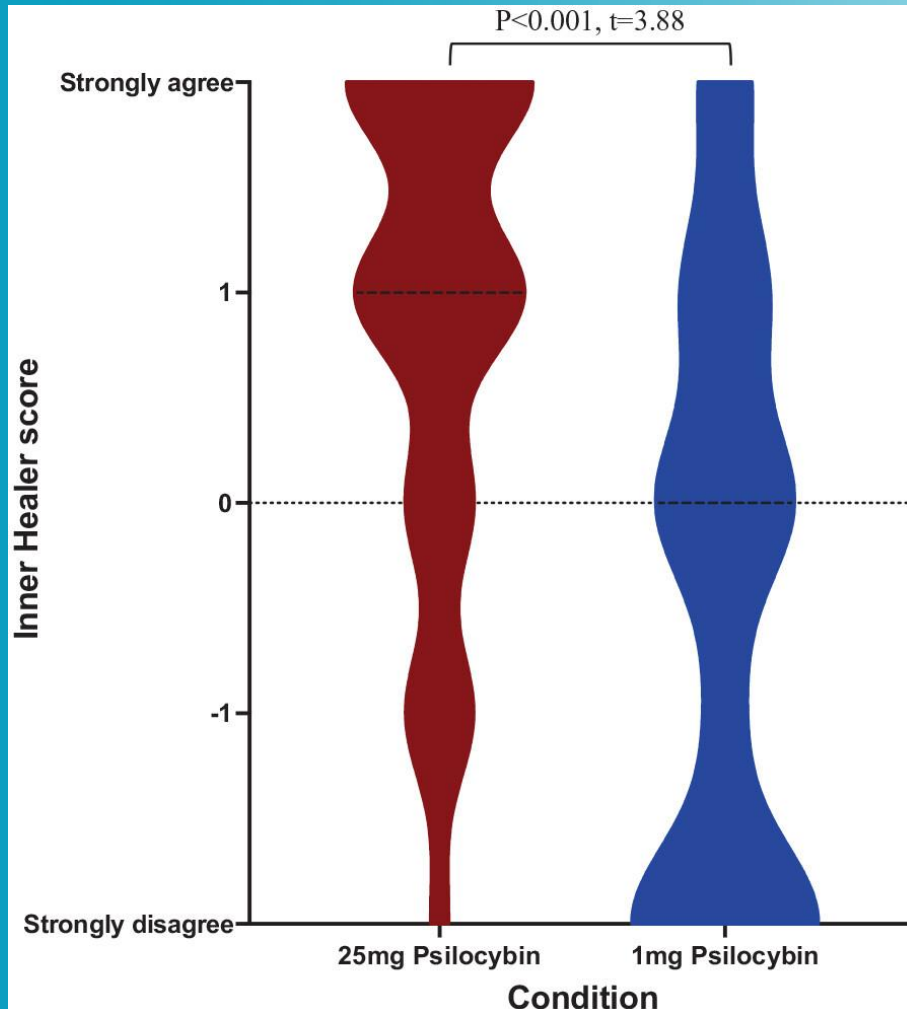
- Concept of the “inner healing intelligence”
 - Non-pathologizing of patient experience
 - Respect for patient autonomy
- Relationality and Intersubjectivity



“Inner healing intelligence”: a unifying construct

Therapeutic Modality	Conceptual overlap with IHI
Prolonged Exposure	Traumatic Recovery Capacity
Motivational Interviewing	Intrinsic motivation, self-efficacy
ACT	Psychological Flexibility
Psychodynamic/analytic therapy	Authentic self, insight
Hakomi	Organicity
Family Systems Therapy	Family homeostasis, systemic resilience
IFS	Self-energy, internal leadership
CBT	Natural recovery trajectory
Gestalt therapy	Gestalt awareness, organismic self-regulation
Narrative Therapy	Narrative Competence, Re-authoring power

Inner Healer: Myth or Mechanism



- Higher inner-healer scores at higher dose psilocybin
- Negative correlation between “inner-healer” score and BDI

Role of Therapist in MDMA-AT



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- Create facilitative conditions for healing
- Generate feeling of safety
- Non-pathologizing approach to:
 - Multiplicity of psyche
 - Transpersonal phenomena
 - Attention to all aspects of here-and-now experience

Image credit: Hunter McRae Lawrence.
Mithoefer MC. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. Version 8.1. Multidisciplinary Association for Psychedelic Studies; 2017.



Relationality and MDMA-AT

- Importance of Relational Field
- Influence of outside relationships on trauma and recovery
- Co-therapy model
- Transferences onto MDMA itself
- Sociocultural humility



Vulnerability

- *THERAPISTS* must create safety and trust
- Experience of vulnerability by therapists and patient



Creating and Maintaining Boundaries

- Increased vulnerability = increased potential for boundary violations
- Similarities with other medicines and therapies
- Importance of accountability



Ensuring Consistency and Adherence

- Training Program
- Clinical Consultation and Supervision
- Adherence Monitoring



Future Directions

- Head-to-head comparison between MDMA-AT therapy and current EBT's for PTSD
- Optimize therapeutic effect of MDMA
- Psychotherapy Process Research on MDMA-AT

Conclusion



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- Thank you for listening!
- www.mdmalpert.com
- @MDMAIpert

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