



Novel & Emerging Therapeutics in the DoD

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Agenda

- Personal Background
- BLUF
- Political Landscape
- Legal Considerations
- Potential Therapies: Overview
- MDMA
- MDMA-Assisted Therapy for PTSD



Personal Background

- Background with Psychedelic-Assisted Therapy (PAT)
 - Certified in PAT with MDMA and Psilocybin
 - Experienced in delivering PAT (while in fellowship at Yale)
- PAT-related Activities
 - Deputy Psychiatry Consultant, Novel & Emerging Therapeutics– Army OTSG
 - Consultant – DARPA
 - Consultant – Several PAT studies
 - Leading several PAT review papers
 - PI on a series of meta-analyses of MDMA-AT for PTSD



BLUF

- Political climate is supportive: Texas state legislature, Congress, White House, & VA all with efforts towards increasing access to these treatments.
- There is a clear legal pathway to conduct DoD research and/or treatment protocols today.
- MDMA-Assisted Therapy (MDMA-AT) is safe & highly efficacious for PTSD. All Phase 2 & 3 studies complete. FDA-approval is >90% likely in 2024. Expanded Access (“Compassionate Use”) now initiated.
- MDMA-AT has a favorable clinical/safety profile for Service Members.



Current Political Landscape

- MDMA-AT Expanded Access (“Compassionate Use”) now initiated
- At least 5 VA medical centers conducting MDMA-AT clinical trials
- White House (2021)
 - “The Biden-Harris Administration *strongly supports expanding the research of Schedule I substances* to help advance evidence-based public policy.”
- Texas HB 1802 (2021)
 - TX passed bill (25-5) to study PAT in Veterans
 - Rick Perry (Republican Former Texas Gov.) w/ support of Democrats & Navy SEAL Team 6 Veterans
- Maryland Senate Bill 709 (2022)
 - MD passed bill allocating \$1M for Walter Reed (and other civilian MD academic centers) to study psychedelics
- NDAA 2023
 - 2 amendments passed House (but not Senate) to study PAT specifically in Active Duty Service Members (Sec 743 & 782)
 - Rep. Dan Crenshaw (R-TX) & Rep. Alexandria Ocasio Cortez (D-NY)
 - Congress requested Sec. Def. to brief Congress on novel therapeutics before 1 Mar 2023



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Legal Considerations

- No serious legal barriers (verified by legal review)
 - Can conduct Schedule I research in DoD (AR 40-7).
 - Schedule I substance administered in the context of command-approved participation in a clinical trial is a legal prescription. Would not be “wrongful” (UCMJ 112a), “illegal,” or “improper” for Active Duty (AR 635-200) or National Guard/Reserve (AR 135-178).
 - Schedule I substances legally administered in an appropriate setting would not affect security clearance (AR 380-67).
 - UAs not a concern if adhere to regulations (AR 600-85).



Potential Therapies: Evidence Overview

Medication	PTSD RCT Data	Depress-ion RCT Data	Pain RCT Data	TBI RCT Data	Projected FDA Approval (Indication)	Note
Ketamine	✓	✓	✓✓	-	1970 (Analgesia)	Used off-label for depression
Esketamine	-	✓✓	✓	-	2019 (Depression)	Primarily used for depression
MDMA	✓✓	✓	✓	-	2024 (PTSD)	Strongest evidence for PTSD
Psilocybin	-	✓	✓	-	~2026 (Depression)	Positive depression and headache RCTs
LSD	-	-	✓	-	~2030 (Anxiety)	Primarily anxiety (modern RCTs) and alcohol use disorder (1960s)
DMT (Ayahuasca)	-	✓	-	-	~2030+ (Unknown)	
Ibogaine	-	-	-	-	~2030+ (Unknown)	PTSD/TBI data from uncontrolled trials
5-MeO-DMT	-	-	-	-	~2030+ (Unknown)	Undergoing Phase 1 safety studies
Cannabinoids (Various)	✓	-	✓	-	1985 (Nausea, Vom.) 2018 (Seizures)	PTSD and pain data is overall equivocal, but strongest evidence is null for both

✓✓ Phase 3 RCT (+)
✓ Strongest Phase 2 RCT (+)
✓ Strongest Phase 2 RCT null
- No RCT



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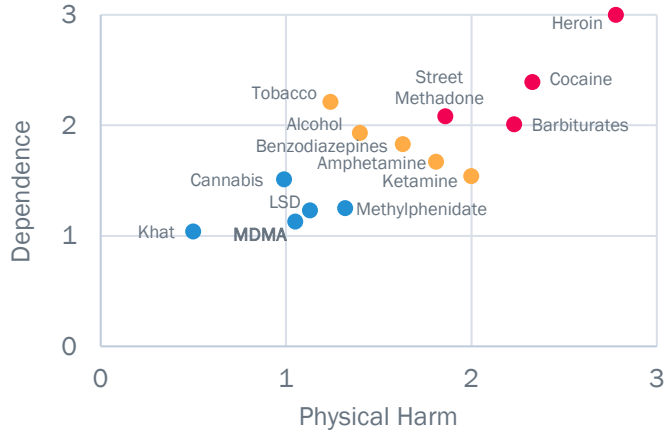


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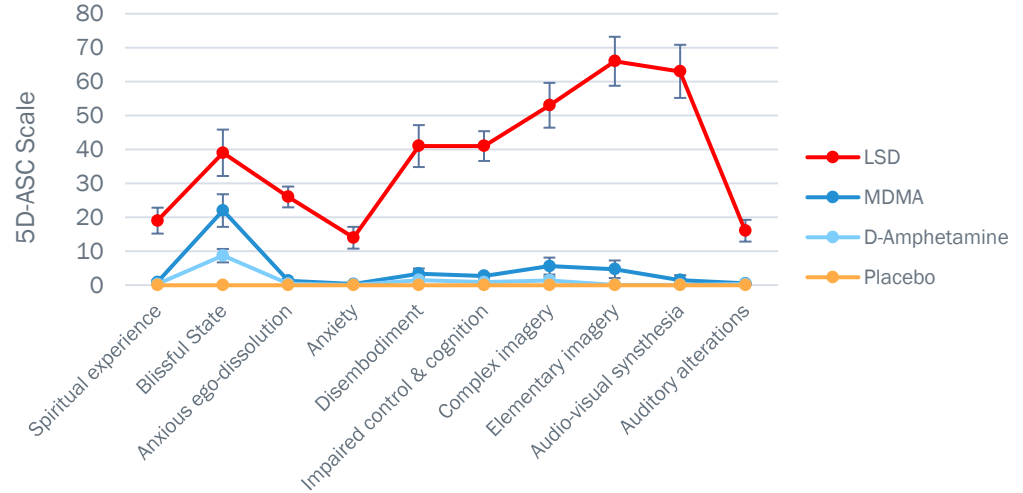


MDMA

Physical Harm & Dependence of Recreational Substances



Subjective Effects of LSD, MDMA, D-Amphetamine, & Placebo



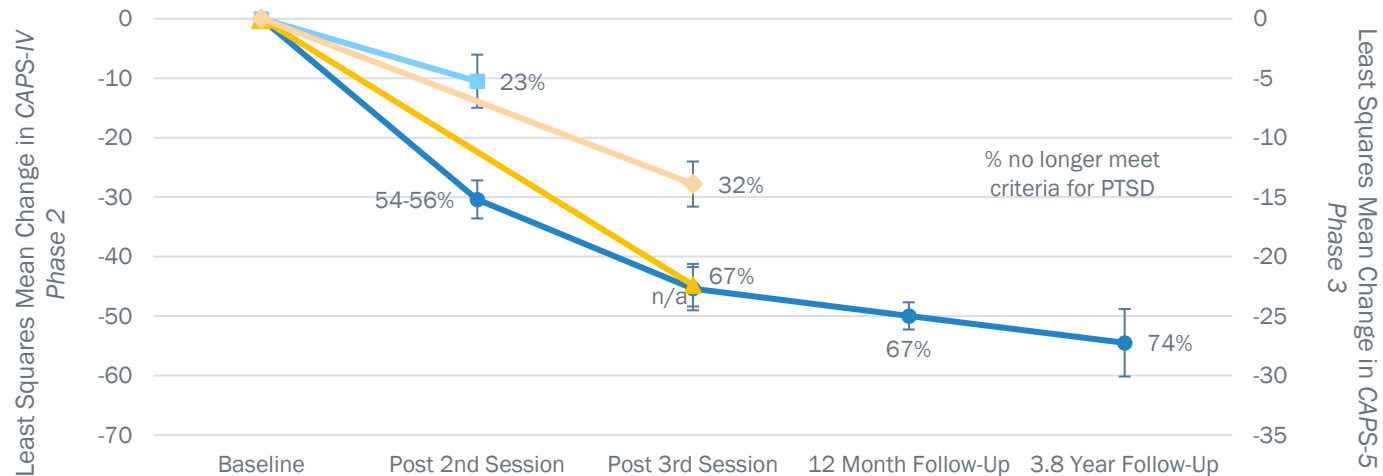
- MDMA has a low risk of dependence and harm.
- Subjective effects of MDMA ≠ other psychedelics. With MDMA, cognitive & perceptual lucidity remain intact.
- Overall profile of MDMA effects conducive for AD SMs (whereas other psychedelics more questionable).

(Wolfgang in submission; Holze 2021; Nutt 2007)



MDMA-AT for PTSD

Pooled Results from All Phase 2 & 3 Trials of MDMA-AT for PTSD



Phase	Arm	n	n	n	n	n
2 (6 trials)	Active	72	72	51	91	19
	Control	31	31	-	-	-
3 (1 trial)	Active	46	-	42	-	-
	Control	44	-	37	-	-

● Active (75-125 mg) ■ Control (0-40 mg) ▲ Phase 3 Active (80-120 mg) ◆ Phase 3 Control (0 mg)

(Mitchell 2021, Jerome 2020, Mithoefer 2019, Mithoefer 2018, Ot'alora 2018, Oehen 2013, Mithoefer 2011, Kotler unpub., Pacey unpub., Wolfgang in prep)

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PTSD: Gold Standards Vs MDMA-AT

	Current Gold Standard PTSD Treatments (PE & CPT)	MDMA-Assisted Therapy (MDMA-AT) for PTSD
Loss of PTSD Diagnosis Rate	~34% (28-40%) ¹	~67% (54-86%) ^{3,5,6}
Tx Effect Size (Cohen's d)	~0.38 (0.27-0.49) ²	0.91 ⁶
Dropout Rate	~40% (27-55%) ^{3,4}	~7.7% (7.6-7.8%) ^{5,6}
Therapist-Hours per Tx Course	~12	~80*

* Research settings: 40+ therapist-hours per therapist & 2 therapists. Real-world implementation: likely to be much more efficient & less therapist-hours.

(1. Steenkamp 2015; 2. Huang 2020; 3. Mithoefer 2018; 4. Schnurr 2022; 5. Mithoefer 2019; 6. Mitchell 2021)



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Summary

- Political climate favorable towards increased access to PAT
- Clear legal pathway to conduct DoD PAT research and/or treatment protocols
- MDMA ≠ Other Psychedelics
- MDMA-AT using pharmaceutical-grade MDMA in a controlled clinical setting is safe and highly efficacious for PTSD
- 67% with treatment-resistant PTSD no longer meet criteria for PTSD after MDMA-AT
- Effects are durable at nearly 4 years (current longest follow-up)
- MDMA-AT more efficacious than current gold standard treatments
- >90% likelihood FDA approval, projected for 2024
- Expanded Access (“Compassionate Use”) is available now
- DoD underprepared



Conclusion

The time for MDMA-AT is now.



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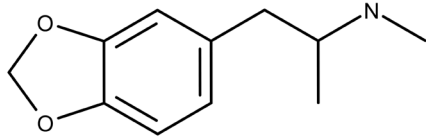




Back-up Slides

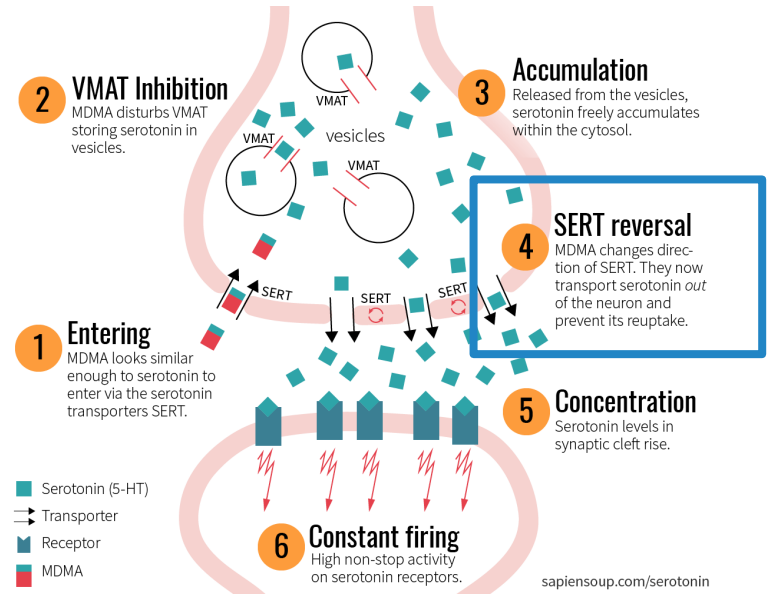
MDMA Pharmacology

- 3,4-methylenedioxymethamphetamine (MDMA)



- Effects

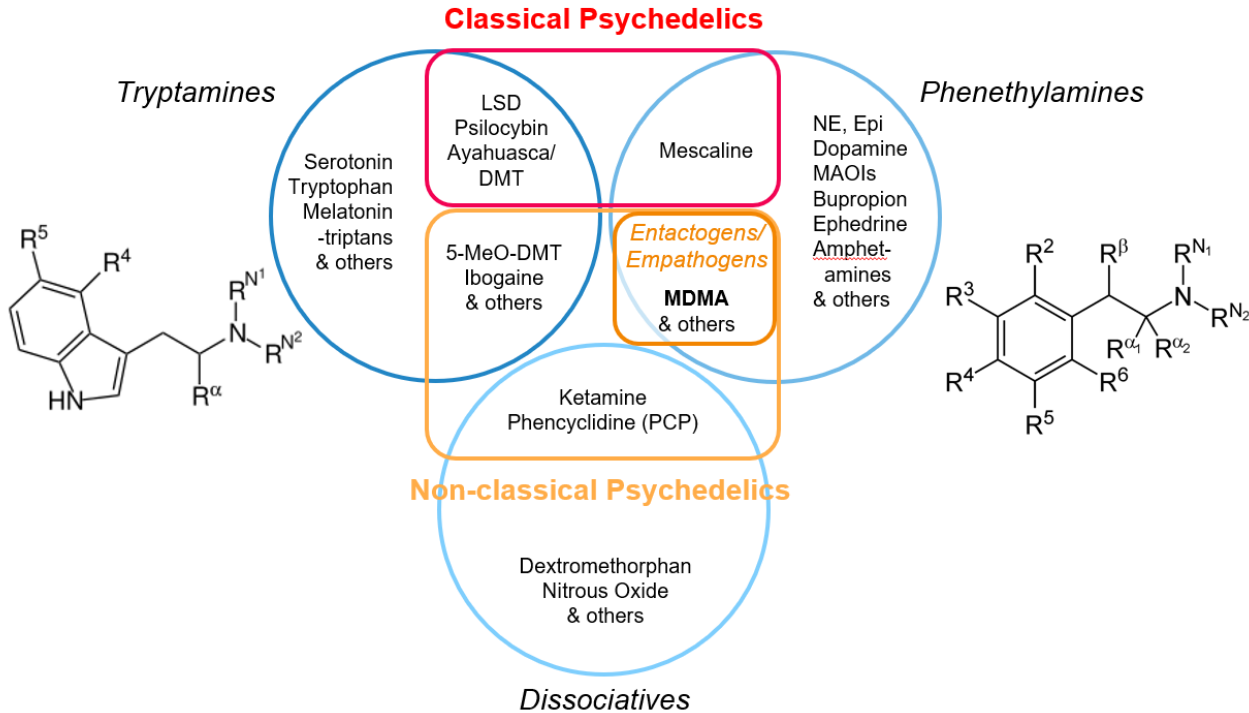
- ↑↑↑ Serotonin
- ↑↑ Oxytocin
- ↑ Norepinephrine
- ↑ Dopamine



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MDMA vs Other Psychedelics



(Wolfgang in prep)

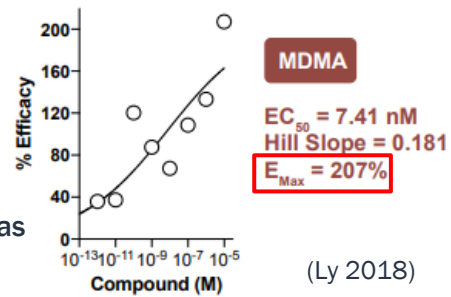
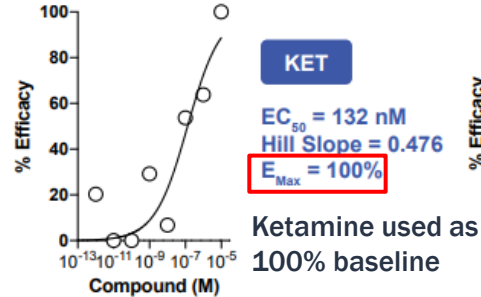
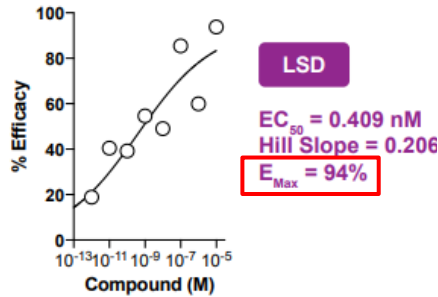
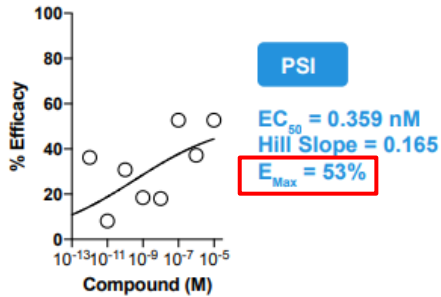
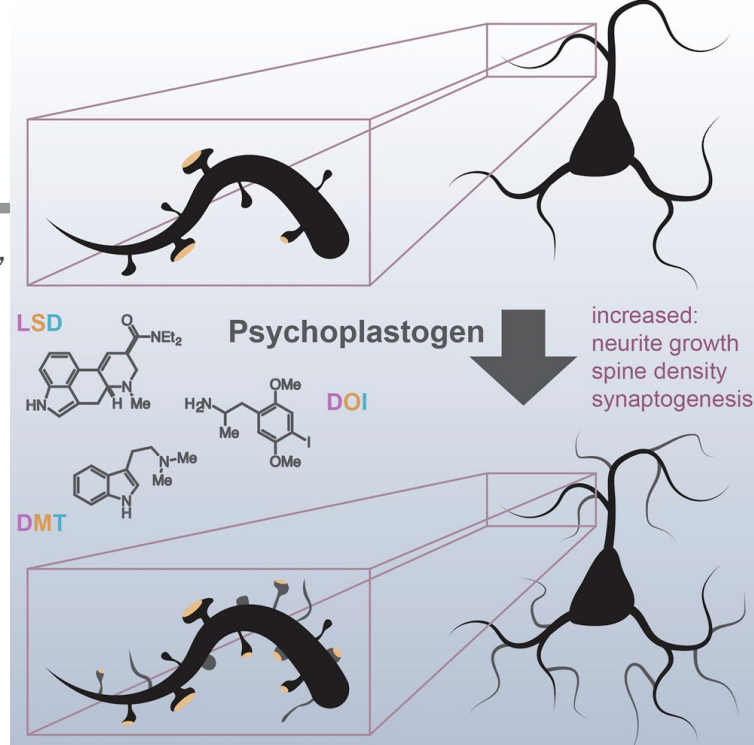
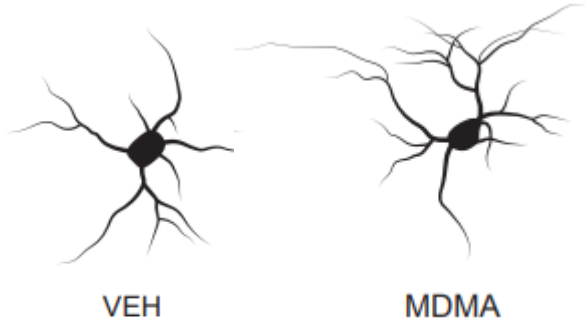


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Neuritogenesis

- Psychedelics “...capable of robustly promoting neuritogenesis.”
- Potential for TBI?



History of MDMA-Assisted Therapy

- 1970-1986
 - ~4000 MDMA therapists & ~500k *legal* MDMA therapy sessions
- 1986
 - DEA Administrative Law Judge recommends *Schedule III* (accepted medical use & moderate to low potential for abuse)
 - DEA still designates MDMA as *Schedule I* (no accepted medical use & high potential for abuse)
- 2010-Present
 - Multidisciplinary Association for Psychedelic Studies (MAPS) conducts 6x phase 2 studies and 2x phase 3 studies of MDMA-AT for PTSD
 - 4+ Clinical Trials ongoing at VAs
- 2017
 - FDA Breakthrough Therapy Designation
- 2022
 - FDA Expanded Access (“Compassionate Use”) approved
- 2024
 - >90% likelihood of FDA Approval






MDMA-AT Treatment Course

Jan						
		Preparatory Session				
		Preparatory Session				
		Preparatory Session	MDMA-AT Session	Integration Session		

Feb						
				Integration Session		
				Integration Session		
			MDMA-AT Session	Integration Session		

Mar						
				Integration Session		
				Integration Session		
			MDMA-AT Session	Integration Session		

Apr						
				Integration Session		
				Integration Session		

-  Preparatory Session (90 min)
-  MDMA-AT Session (6-8 hours)
-  Integration Session (90 min)



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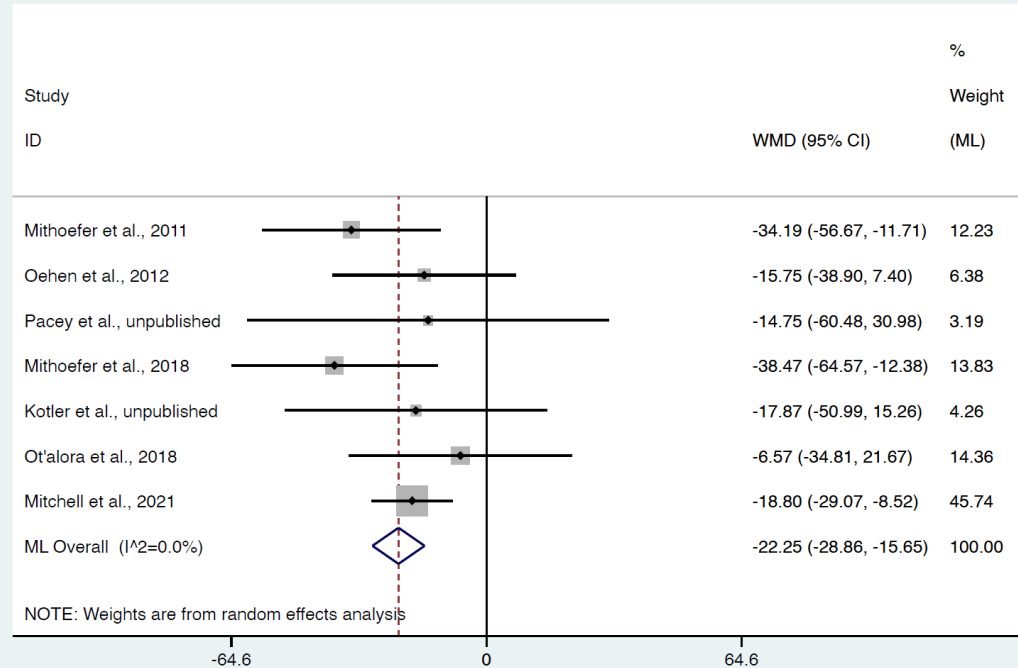




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PTSD (CAPS-IV/5) Significantly Improves



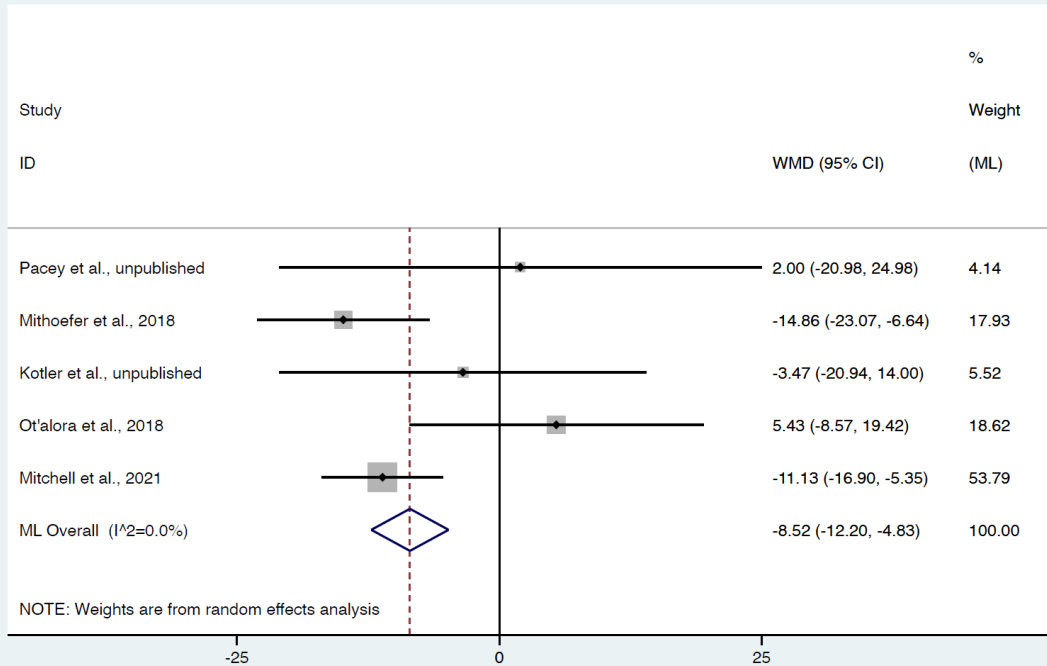
(Wolfgang et al. in prep)



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Comorbid Depression (BDI-II) Significantly Improves



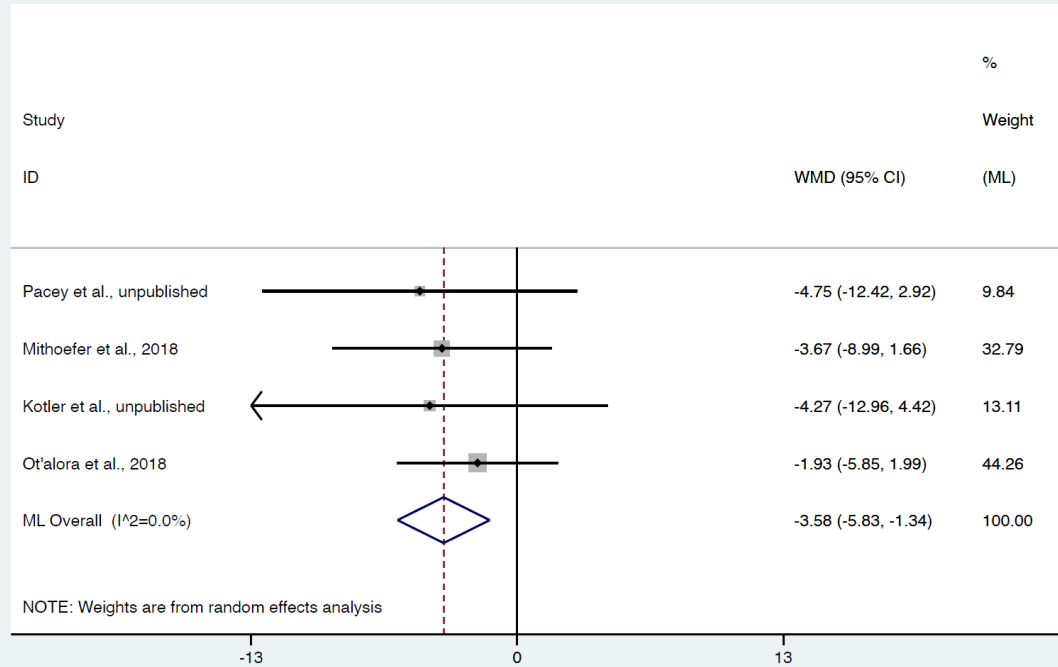
(Wolfgang et al. in prep)



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Comorbid Insomnia (PSQI) Significantly Improves



(Wolfgang et al. in prep)



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Post-treatment Substance Use

Substance	Between Study Exit & 12-mo Follow-up	Notes
Ecstasy/MDMA	8/83 (10%)	6/8 had used before the study. 2/2 with no previous use used in non-approved therapeutic setting, found it to be non-therapeutic, and did not use MDMA again.
Alcohol	2/55 (3.6%) Increased 17/55 (31%) No change 22/55 (40%) Decreased	
Marijuana	10/55 (18%) Increased 6/55 (11%) No change 10/55 (18%) Decreased	

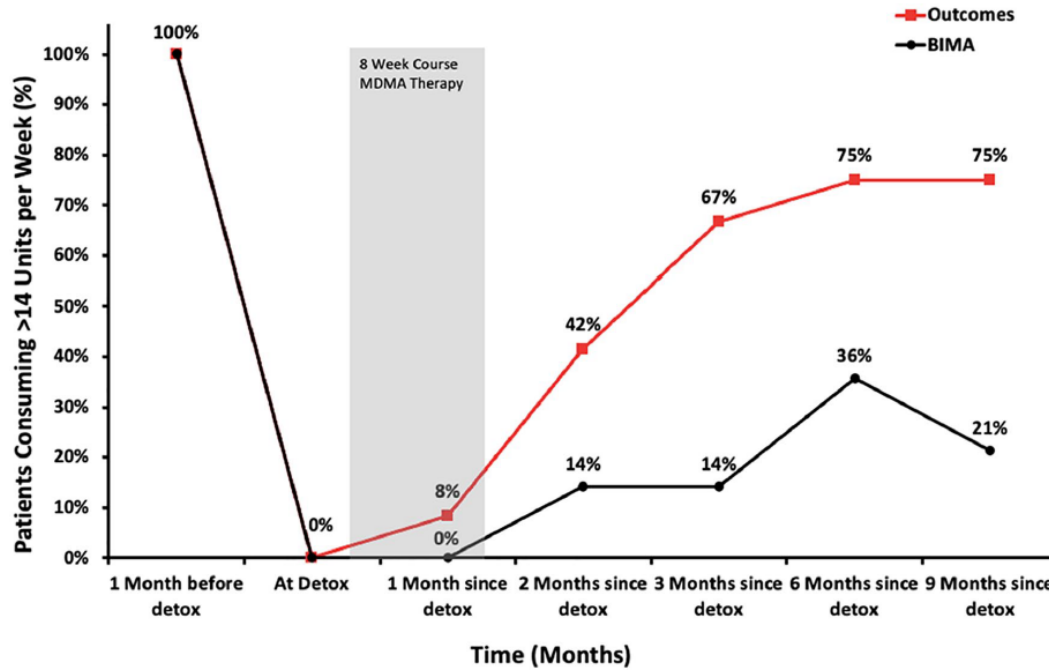
(Jerome 2020)



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MDMA-AT Treatment of Alcohol Use Disorder



(Sessa 2021)



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Cost-effectiveness

- Residential Treatment Program (4 weeks): \$30k
- 3-session course of MDMA-AT in research setting: \$~10-40k*
depending on degree of in-kind support
 - *Costs yet unclear in post-approval clinical implementation
- MDMA-AT “provided to patients with **severe or extreme, chronic PTSD** appears to be **cost-saving** while delivering substantial clinical benefit.”¹
- “Third-party payers are likely to **save money** within **three years** by covering this form of therapy.”¹

(Marseille 2021)

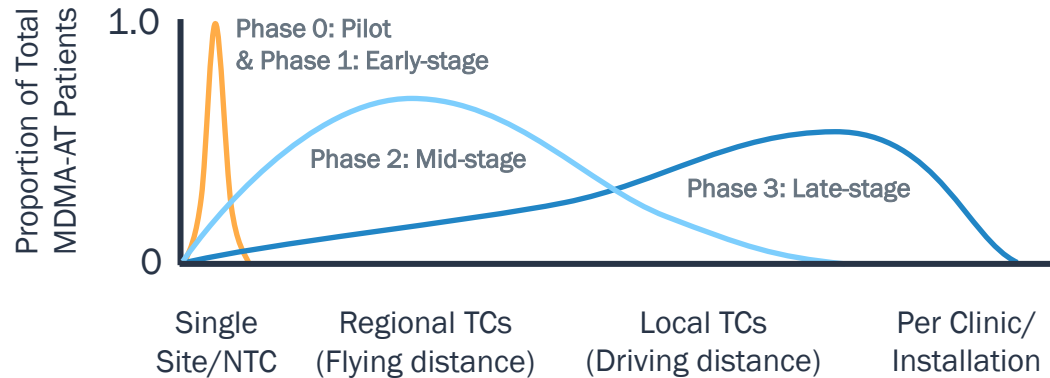


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DoD Implementation Phases

Distribution of Total MDMA-AT Patients in the DoD
Phases of Implementation



*TC = Treatment Center

(Wolfgang, in-prep)



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