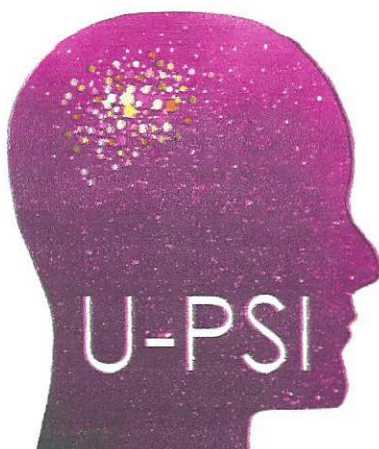


U-PSI June 7, 2021



1

**nature
medicine**

ARTICLES

<https://doi.org/10.1038/s41591-021-01336-3>

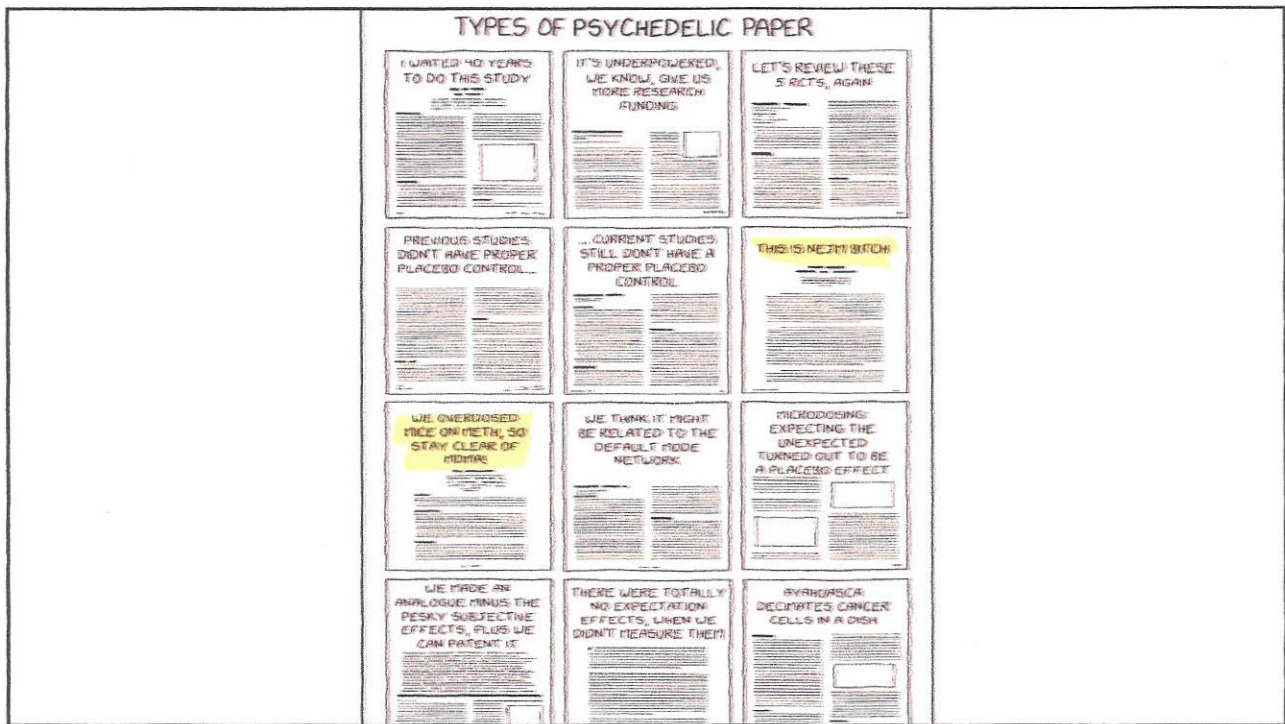
Check for updates

OPEN

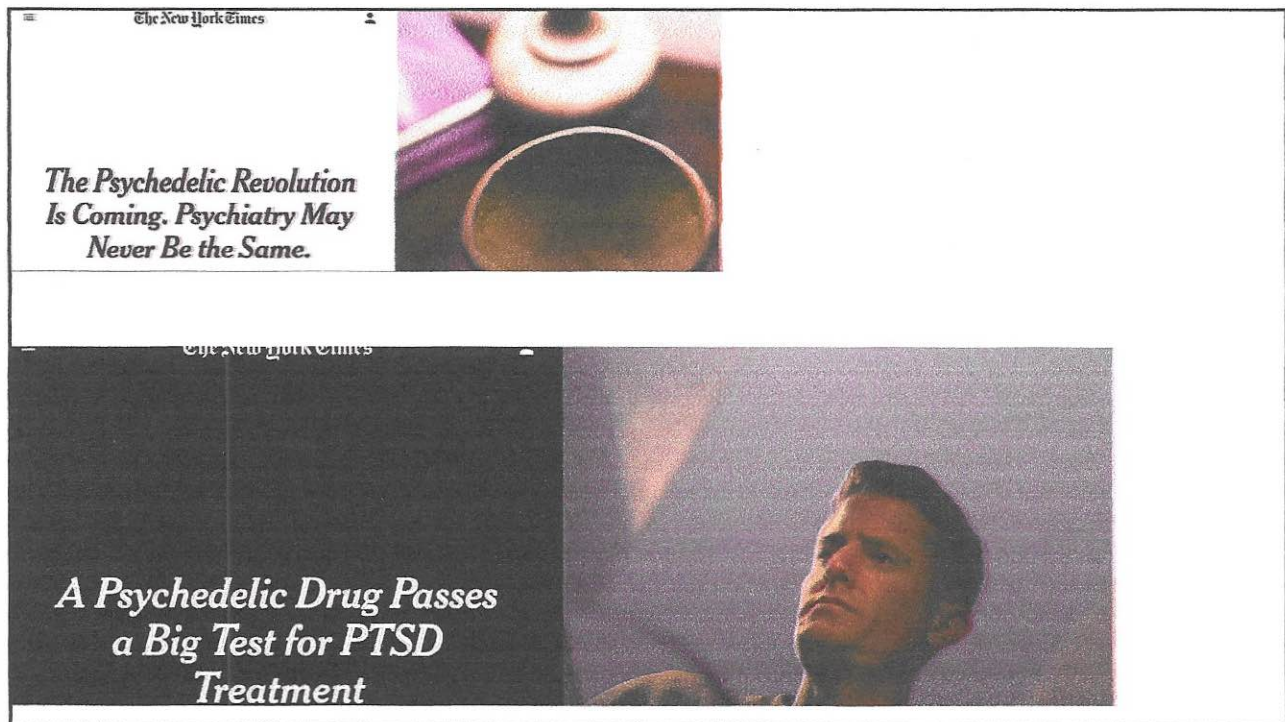
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell^{1,2}✉, Michael Bogenschutz³, Alia Lilienstein⁴, Charlotte Harrison⁵, Sarah Kleiman⁶, Kelly Parker-Guilbert⁷, Marcela Ot'alora G.^{8,9}, Wael Garas⁸, Casey Paleos¹⁰, Ingmar Gorman¹¹, Christopher Nicholas¹², Michael Mithoefer^{5,9,13}, Shannon Carlin^{5,9}, Bruce Poulter^{8,9}, Ann Mithoefer⁹, Sylvestre Quevedo^{2,14}, Gregory Wells¹⁴, Sukhpreet S. Klaire¹⁵, Bessel van der Kolk¹⁶, Keren Tzarfaty⁹, Revital Amiaz¹⁷, Ray Worthy¹⁸, Scott Shannon¹⁹, Joshua D. Woolley², Cole Marta²⁰, Yevgeniy Gelfand²¹, Emma Hapke²², Simon Amar²³, Yair Wallach²⁴, Randall Brown¹¹, Scott Hamilton²⁵, Julie B. Wang⁵, Allison Coker^{1,5}, Rebecca Matthews⁵, Alberdina de Boer⁵, Berra Yazar-Klosinski⁴, Amy Emerson⁵ and Rick Doblin⁴

2



3



4



5

Background

- 2017: MDMA granted breakthrough therapy status following preliminary Phase II results
- 6 phase II double-blind RCTs: N=105, pooled remission rate of >66%, drop of 47.7 points on the CAPS (Bousu et al, Mithoefer et al)
- MAPS: non-profit research and educational organization. Goal of MDMA being FDA approved by 2022/2023

6

PTSD

- 4 symptom clusters (DSM 5): re-experiencing, avoidance, negative alterations in cognition/mood, alterations in arousal or reactivity
- 1st line treatments = trauma focused psychotherapies (CBT, TFEBT, CPT, EMDR). Response in approx. 40%. High drop out rate (>30%).
- 2nd line treatments= pharmacotherapies (SSRIs- sertraline, paroxetine). Response in 20-30%

7

MDMA

- 1st synthesized in 1912 (Merck). Shelved until 1950s, emerged in MK-ULTRA.
- Limited use in the 1960s (vs. MDA)
- Shulgin (mid-1970s)
- Therapeutic use in late 1970s-1980s.
- 1977: first paper on psychoactive properties (Nichols, Shulgin)
- 1980s: rave culture, "ecstasy"
- 1985: schedule 1
- 1995: first phase I study (Grob)
- 2010: 1st controlled study for treatment resistant PTSD (Mithoefer)

8

MDMA



- 3,4-Methylenedioxymethamphetamine
- Monoamine releaser (5HT, DA, NE).
- Complex pharmacology 5HT1a, 1b, 2a. Alpha-2. DA.
- Oxytocin release.
- Increase in cortisol
- Entactogen/empathogen
- 3-6 hr duration
- 125mg + possible booster of 62.5mg @ 2 hrs.

9

Practices

- Core Principles:
- Safety, Support, Inner Healing Intelligence, Inner-directed process, Beginner's Mind, Trusting the Process, Somatic Manifestation, Therapeutic Alliance and Trust.
- 3 Preparatory Sessions (90min)
- MDMA sessions (2-3) 8 hr.
- Integration sessions (90min)(3 between each MDMA session)

10

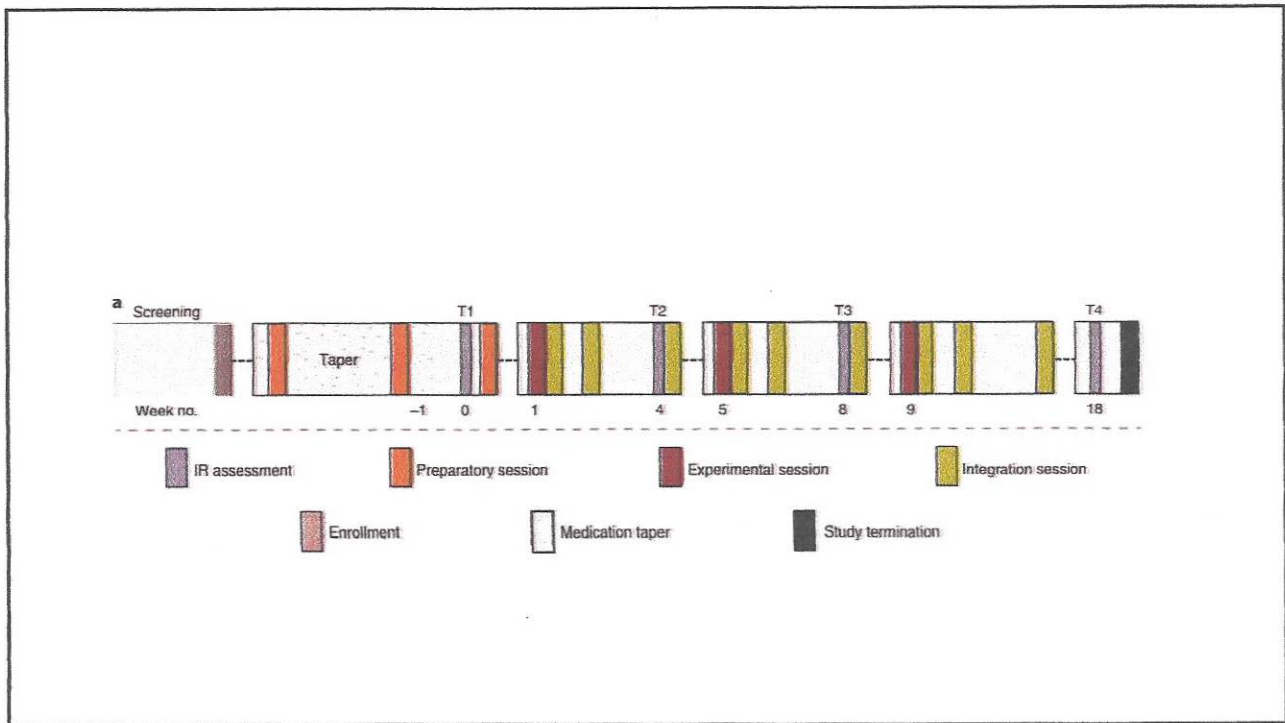


11

Study overview

- N=90 (US, Canada, Israel). 44 placebo, 46 MDMA. Mean duration of PTSD dx 14.8 yrs. (6 in MDMA group, 13 in placebo group with dissociative subtype).
- Primary outcome measure CAPS-5
- Secondary outcome measure SDS (blinded, independent assessors), 18 week time course.

12

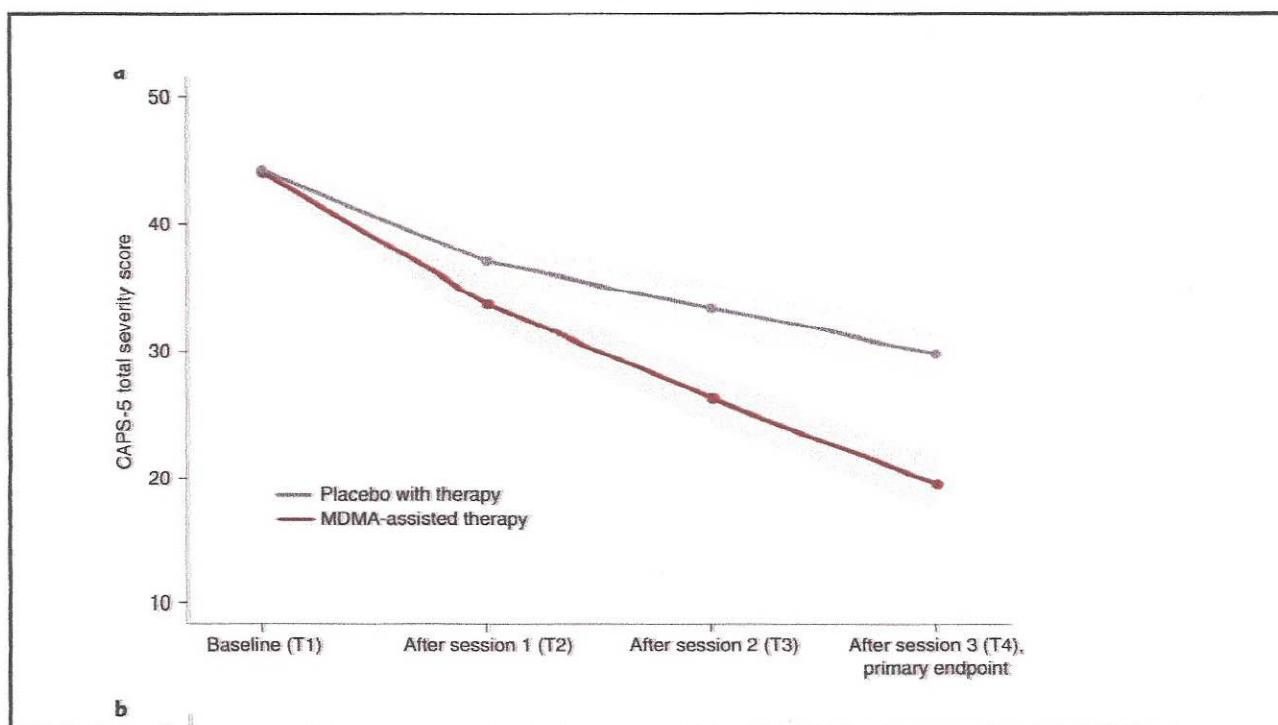


13

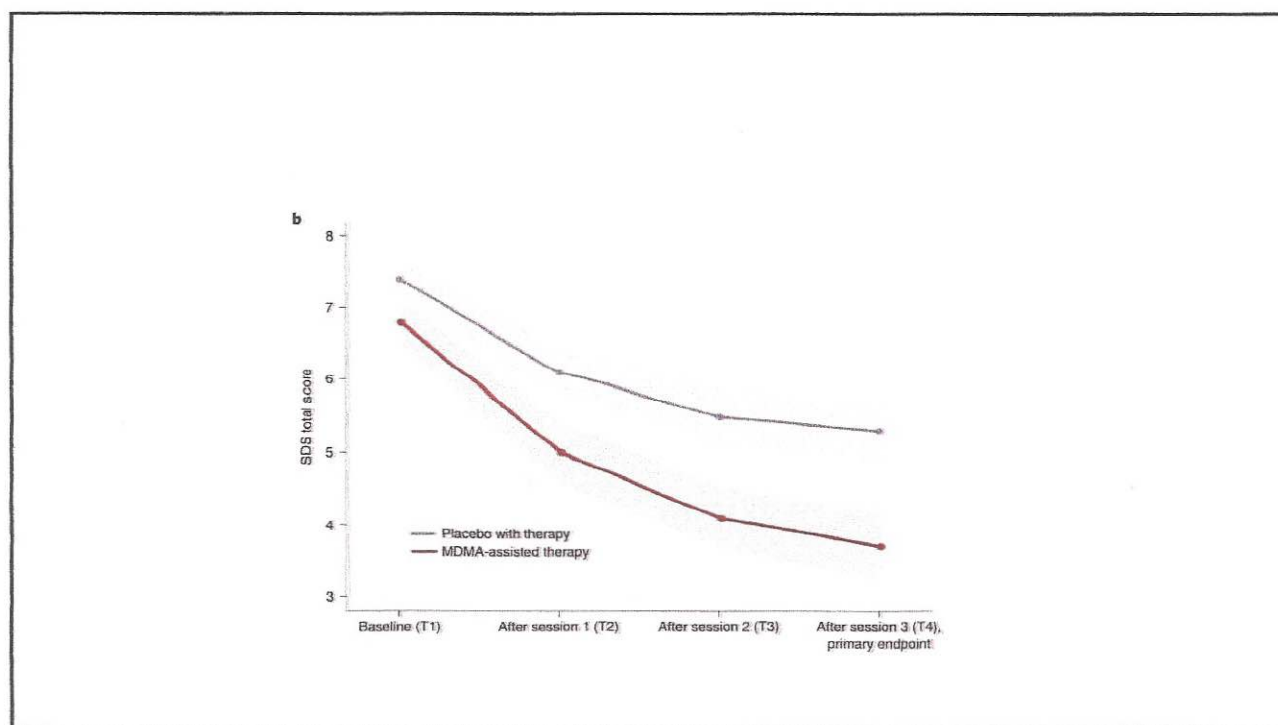
Table 1 | Demographics and baseline characteristics

	MDMA-assisted therapy (n=46)	Placebo with therapy (n=44)	Total (n=90)
Age (years), mean (s.d.)	43.5 (12.9)	38.2 (13.3)	41.3 (13.1)
Sex assigned at birth, n (%)			
Male	18 (40.3)	12 (27.3)	30 (33.4)
Female	27 (58.7)	32 (72.7)	59 (65.6)
Ethnicity, n (%)			
Hispanic or Latino	5 (10.8)	3 (6.8)	8 (8.9)
Not Hispanic or Latino	40 (88.1)	40 (90.9)	80 (90.1)
Race, n (%)			
American Indian or Native Alaskan	3 (6.5)	0 (0.0)	3 (3.3)
Asian	2 (4.3)	5 (11.4)	7 (7.8)
Black or African American	0 (0.0)	2 (4.5)	2 (2.2)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	39 (84.8)	30 (68.2)	69 (76.7)
Multiple	2 (4.3)	6 (13.6)	8 (8.9)
BMI (kg/m ²), mean (s.d.)	26.3 (6.8)	24.8 (6.2)	25.6 (6.5)
Duration of PTSD (years), mean (s.d.)	16.8 (17.4)	13.2 (17.4)	15.1 (17.5)
Disorder subtype of PTSD, n (%)	6 (13.0)	12 (27.3)	18 (20.1)
Current or major depression, n (%)	42 (91.3)	40 (90.9)	82 (91.1)
Veteran	10 (21.7)	6 (13.6)	16 (17.8)
Trauma history, n (%)			
Developmental trauma	40 (87.0)	36 (81.8)	76 (84.4)
Combat exposure	6 (13.0)	5 (11.4)	11 (12.2)
Multiple trauma	41 (89.3)	39 (88.4)	79 (87.8)
Pre-study PTSD medications, n (%)			
Sertraline	8 (17.4)	11 (25.0)	17 (19.0)
Paroxetine	3 (6.5)	3 (6.8)	6 (6.7)
Pre-study therapies, n (%)			
CBT	12 (26.1)	22 (50.0)	34 (37.9)
EMDR	11 (23.9)	13 (29.5)	24 (26.7)
Group therapy	19 (41.3)	14 (31.8)	33 (36.7)
Pharmacological or psychotherapy	1 (2.2)	0 (0.0)	1 (1.1)
Psychodynamic	1 (2.2)	10 (22.7)	11 (12.2)
Other	41 (89.3)	39 (88.4)	79 (87.8)
None	1 (2.2)	1 (2.3)	2 (2.2)
Baseline CAPS-1 total score, mean (s.d.)	44.0 (10.0)	44.2 (10.5)	44.1 (10.3)
Baseline SES total score, mean (s.d.)	4.6 (2.0)	4.4 (2.0)	4.5 (2.0)
Baseline C-SSRS, n (%)			
Positive lifetime suicidal ideation	42 (91.3)	40 (90.9)	82 (91.1)
Serious lifetime suicidal ideation	20 (43.5)	17 (38.6)	37 (41.3)
Positive lifetime suicidal behavior	16 (34.8)	13 (29.5)	29 (32.2)
Baseline BDI-II total score, mean (s.d.)	39.5 (12.7)	34.9 (12.4)	37.2 (12.5)
Auditory mean (s.d.)	41.4 (8.2)	41.3 (8.2)	41.3 (8.2)
Visual mean (s.d.)	27.6 (4.3)	25.4 (4.5)	26.5 (4.4)
ACE Questionnaire score, mean (s.d.)	5.0 (2.7)	5.0 (2.9)	5.0 (2.8)
Previous report of MDMA use, n (%)	18 (39.1)	11 (25.0)	29 (32.2)
Reported use in the past 12 years	9 (19.6)	10 (22.7)	19 (21.1)

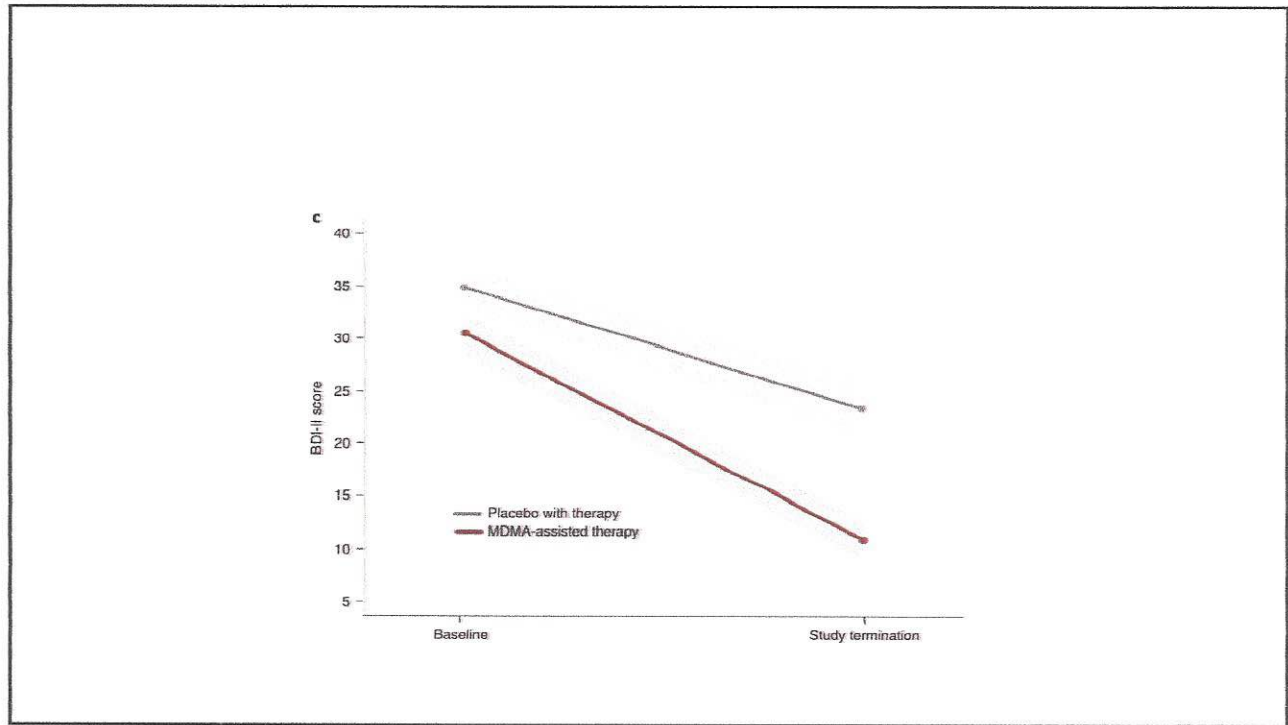
14



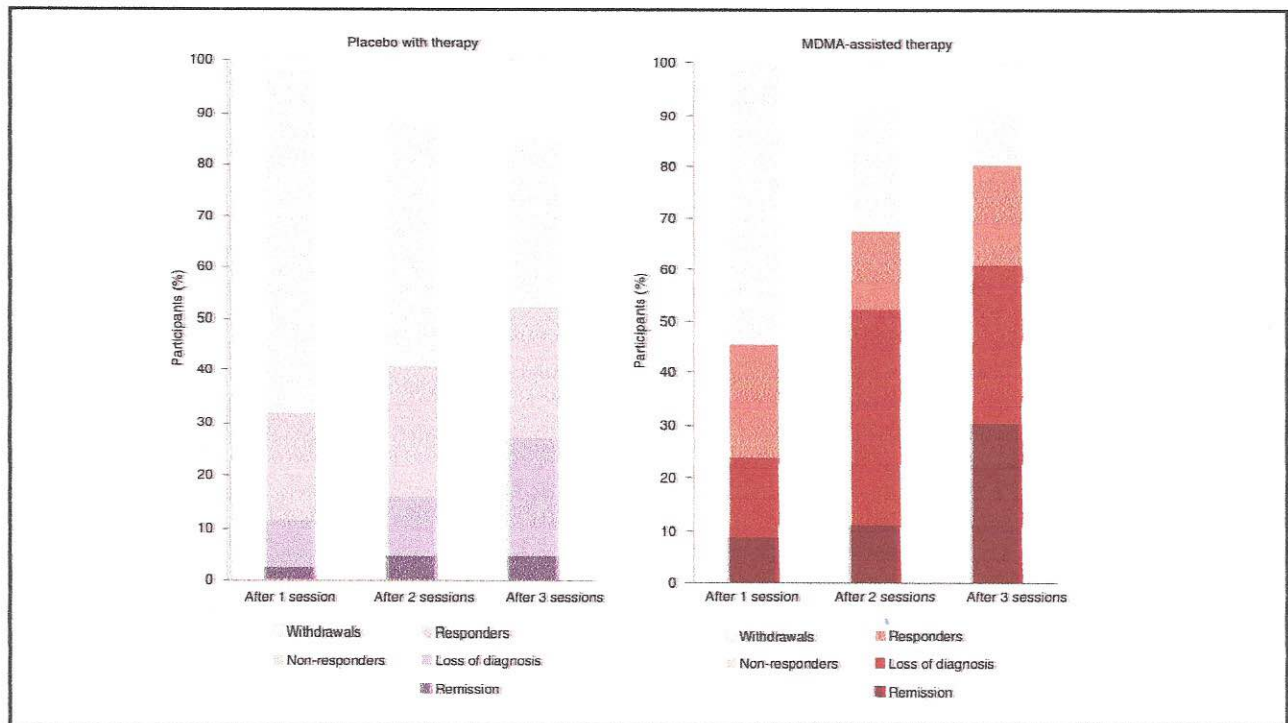
15



16



17



18

Notable findings

- MDMA equally effective in participants with comorbidities typically associated with treatment resistance.
- Large effect size for MDMA on primary outcome measure (CAPS-5) ($d=0.91$)
- No clear impact of SSRI hx on effectiveness
- 67% of participants in MDMA group no longer met criteria for PTSD (vs. 32% in placebo group). 14/42 in MDMA group met criteria for remission (vs. 2/37)
- Safety: only 2 SAE (both in placebo group). Minimal SI.
- Results consistent across all 15 study sites

19

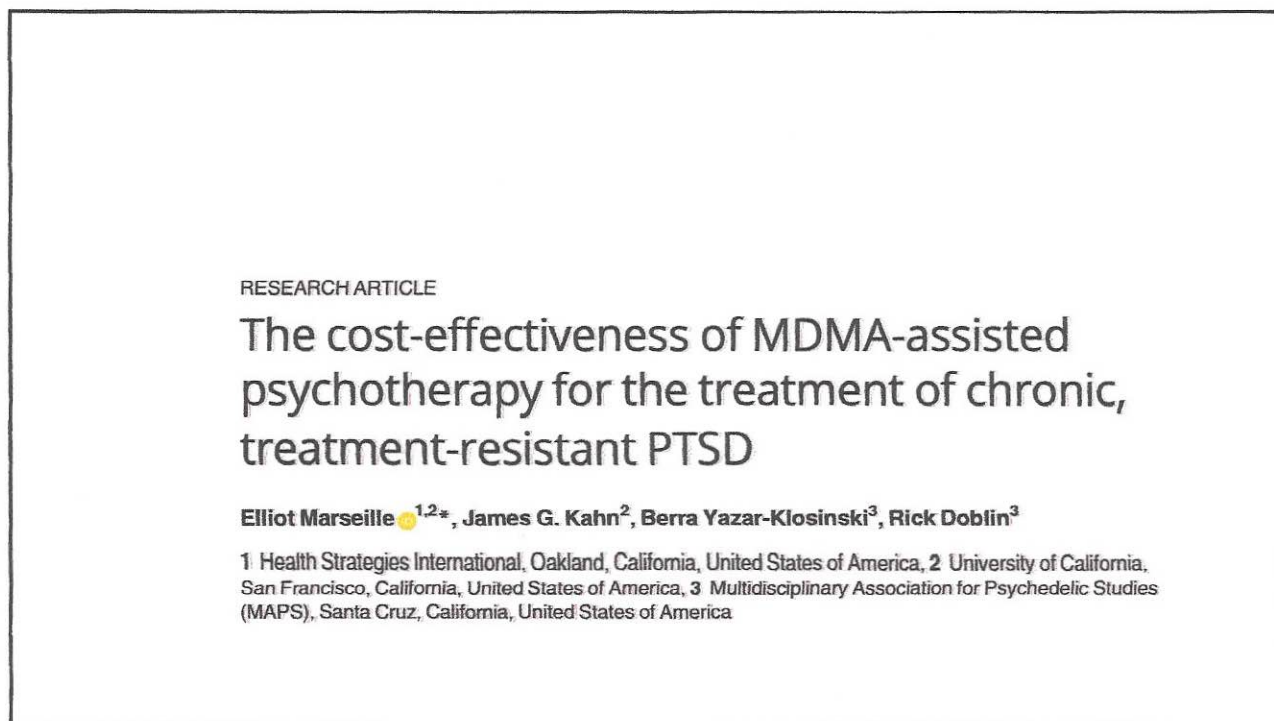
Limitations

- Placebo control
- Robust placebo condition
- Heterogeneous PTSD diagnoses
- Selection bias
- Expectancy bias
- Non-diverse sample

20



21



22

