MDMA Therapy for PTSD

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Disclosures

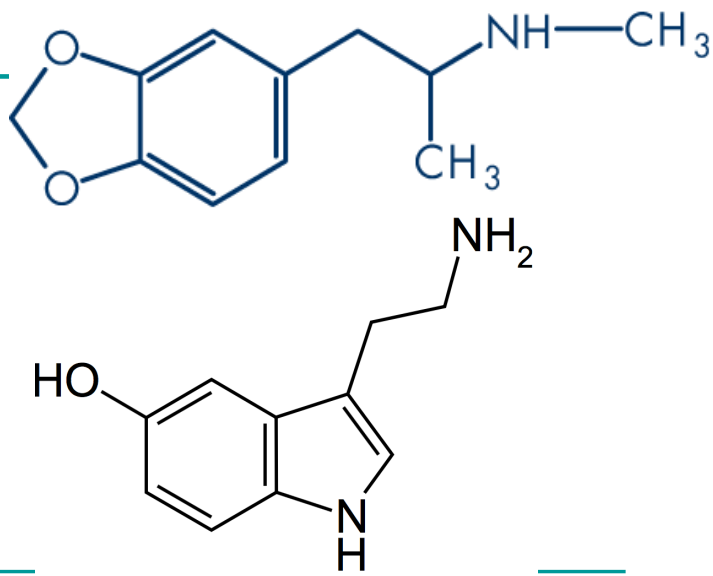
- Employed by King's College London.
- Honorary Consultant - Maudsley Hospital National Affective Disorders Service (NHS)
- Paid advisory boards for Clerkenwell Health (past), Beckley PsyTech (past) and Delica Therapeutics (past). Paid articles (Janssen). No investments or share holdings in any pharma or any company developing psychedelics
- Principal Investigator for clinical trials Sponsored/Funded by MAPS, Beckley PsyTech & Compass Pathways.
- Grant funding (past and present): NIHR (UK), Wellcome Trust (UK), NIHR Maudsley BRC (UK), Compass Pathways, Beckley PsyTech, MAPS

Participant Perspective

“Maybe one of the things the drug does is let your mind relax and get out of the way because the mind is so protective about the injury.”

US veteran and MAPS study participant

3,4-Methylenedioxymethamphetamine



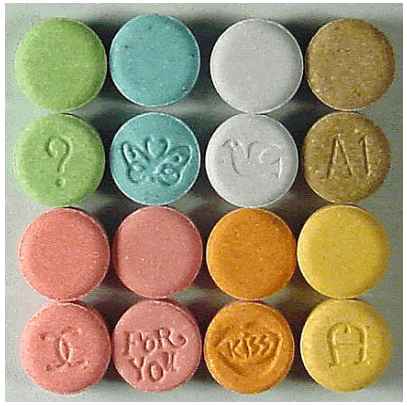
Monoamine releaser and re-uptake inhibitor

Increases release of

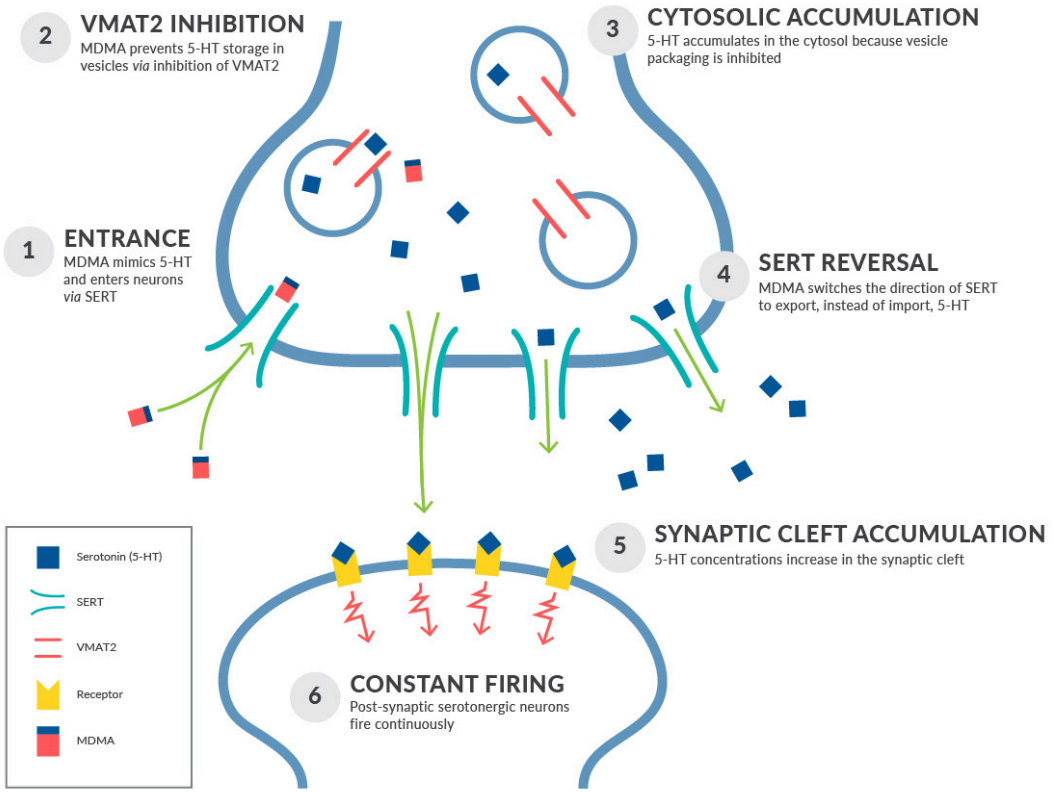
- Serotonin (5-HT)
- Norepinephrine (NE)
- Dopamine (DA)

Enhances release of hormones

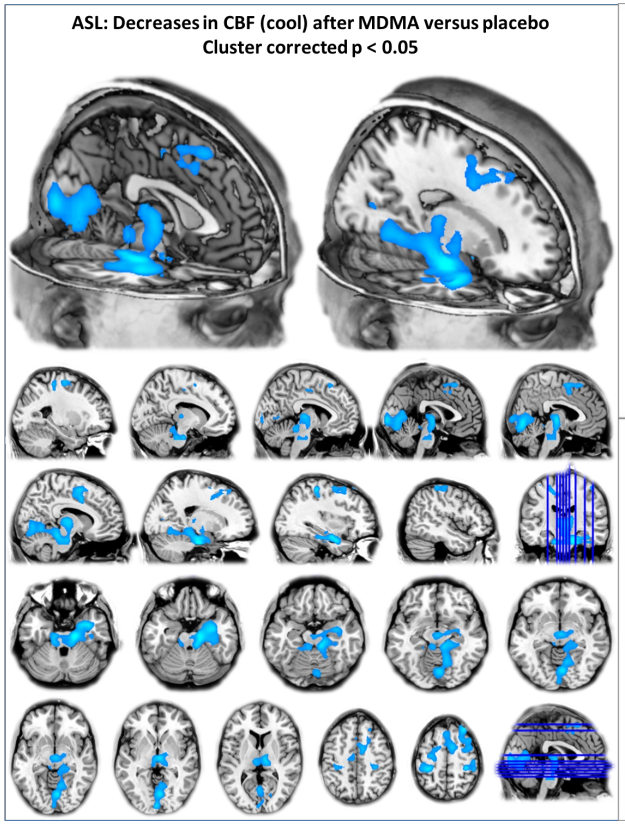
- Oxytocin
- Prolactin
- Vasopressin
- Cortisol

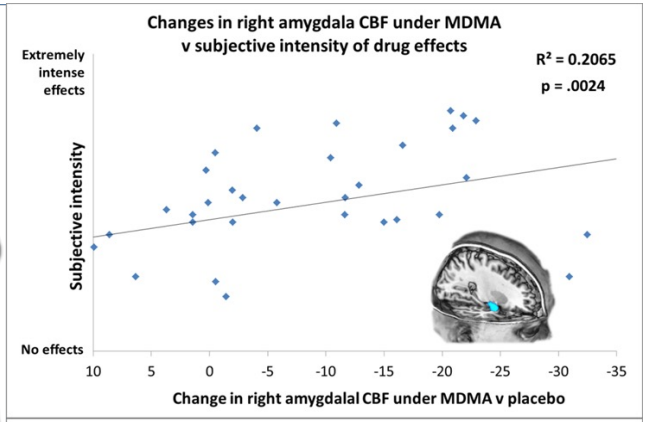


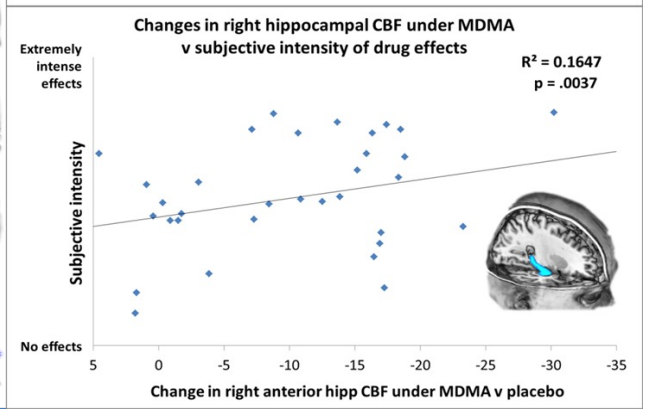
Effects of MDMA on Neurotransmission



fMRI Changes MDMA vs Placebo





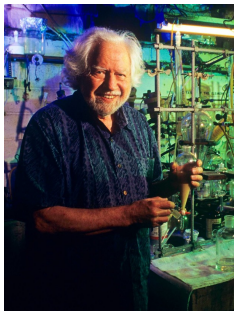


- Reductions in activity in amygdala and hippocampus
- Amygdala is seat of 'fight or flight' response
- Robust evidence shows overactivity here in PTSD
- Explains reduction in fear responses reported by PTSD patients under MDMA therapy

Carhart-Harris RL, Biol Psychiatry. 2015;78(8):554. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4578244

A Brief Timeline of MDMA Therapy

1912 — First synthesis of MDMA by the company Merck

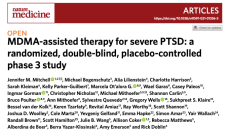


1965 — Re-synthesis of MDMA by Alex Shulgin

1977 — First use of MDMA therapy by Leo Zeff

1984 — ~ 500,000 MDMA therapy sessions given

1986 — Rick Doblin creates 'MAPS'



2022 — First Phase 3 trial of MDMA therapy for PTSD published in Nature Medicine

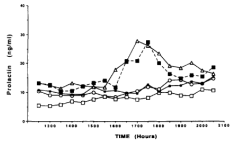
1950s — Testing of MDMA on animals by CIA

1976 — Shulgin self-experiments with MDMA

1982 — MDMA appears on the streets

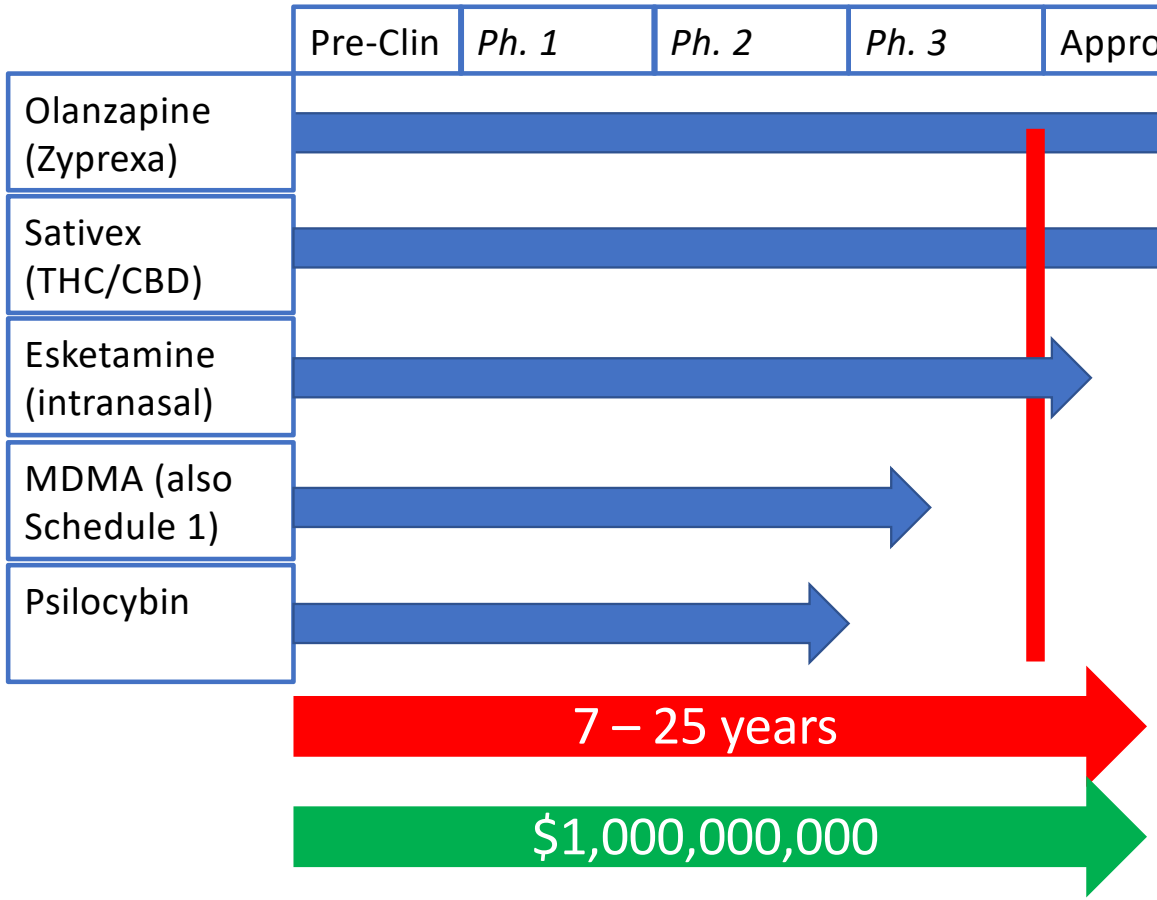
1985 — MDMA placed in Schedule 1

1996 — Charles Grob completes first phase 1 study in humans



2023 — First patient with PTSD dosed with MDMA in the UK at King's College London

Drug Development & Clinical Trials



Drug development questions

1. Is the drug **safe** (relative to the disease)?
2. Is the drug **efficacious** (relative to placebo)?

Main obstacles to MDMA:

1. **Money**
2. GMP source of drug
3. Stigma
4. Schedule 1

MDMA for PTSD – A Phase 3 Trial (2021)

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

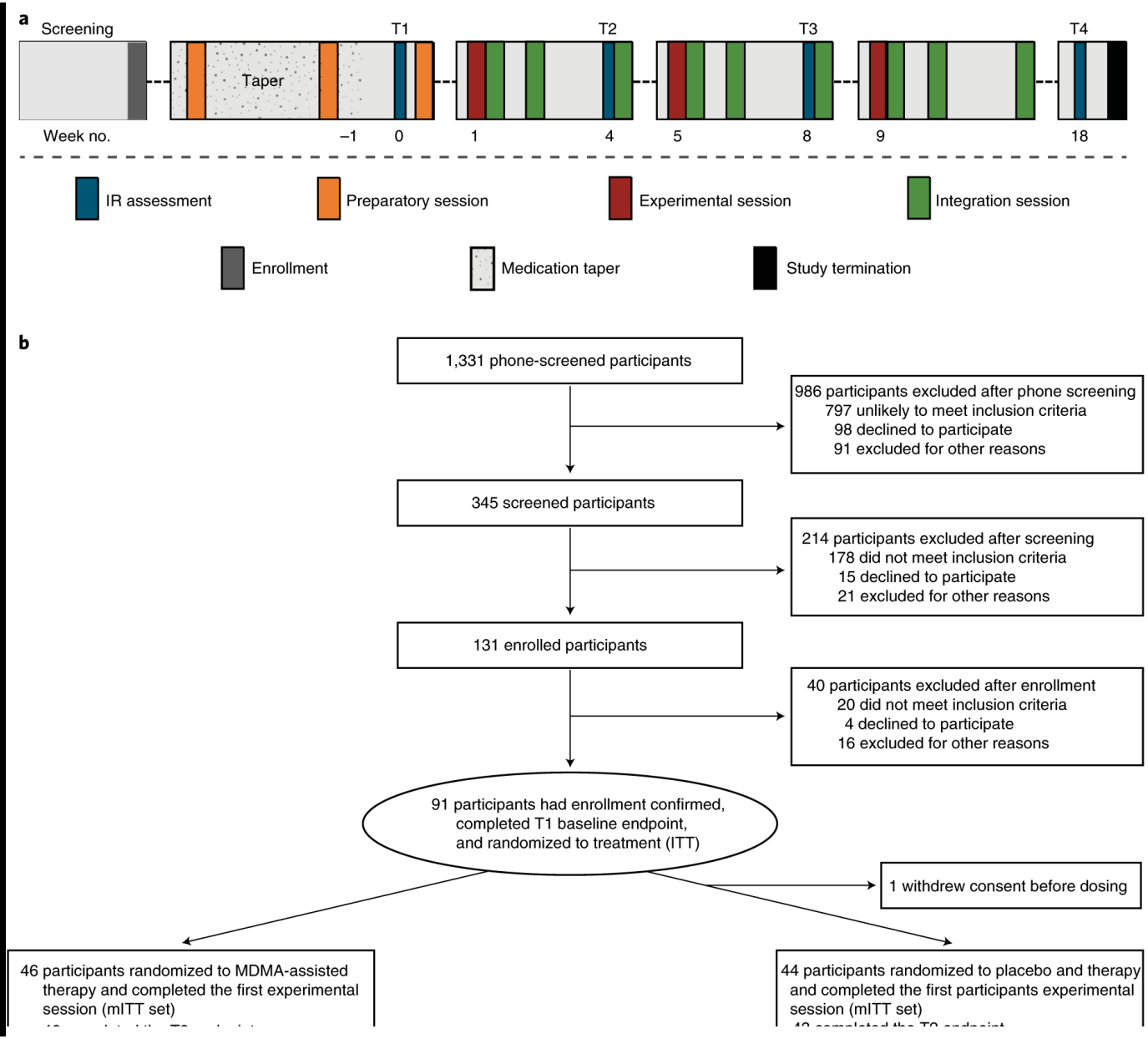
Jennifer M. Mitchell[1,2]✉, Michael Bogenschutz[3], Alia Lilienstein[4], Charlotte Harrison[5], Sarah Kleiman[6], Kelly Parker-Guilbert[7], Marcela Ot'alora G.[8,9], Wael Garas[8], Casey Paleos[10], Ingmar Gorman[11], Christopher Nicholas[12], Michael Mithoefer[5,9,13], Shannon Carlin[5,9], Bruce Poulter[8,9], 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]

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

MDMA P3 Trial - Recruitment

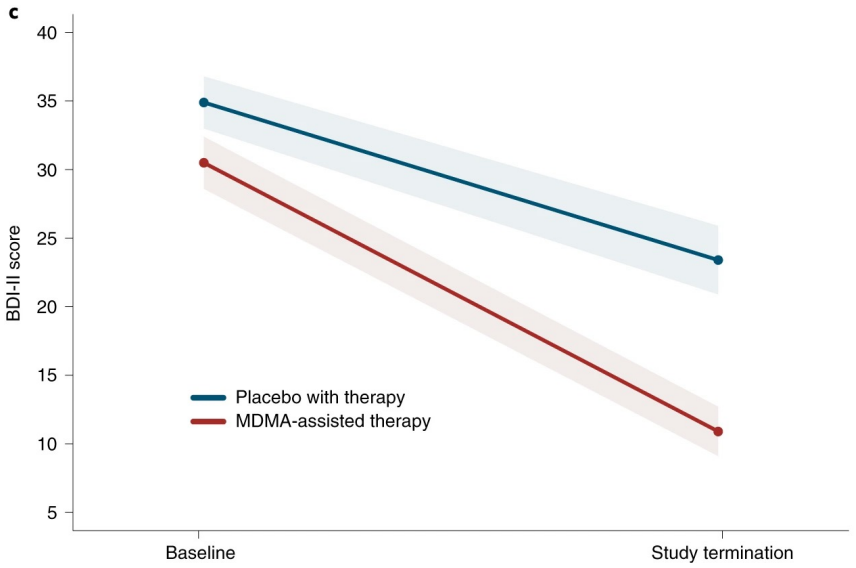
- 90 participants recruited
- Severe PTSD
- 2 groups – A) 3 x MDMA sessions vs B) 3 placebo sessions
- All given extensive psychotherapy regardless
- Primary outcome – CAPS5
- Taper off Adx beforehand (Adx likely to reduce effects of MDMA)

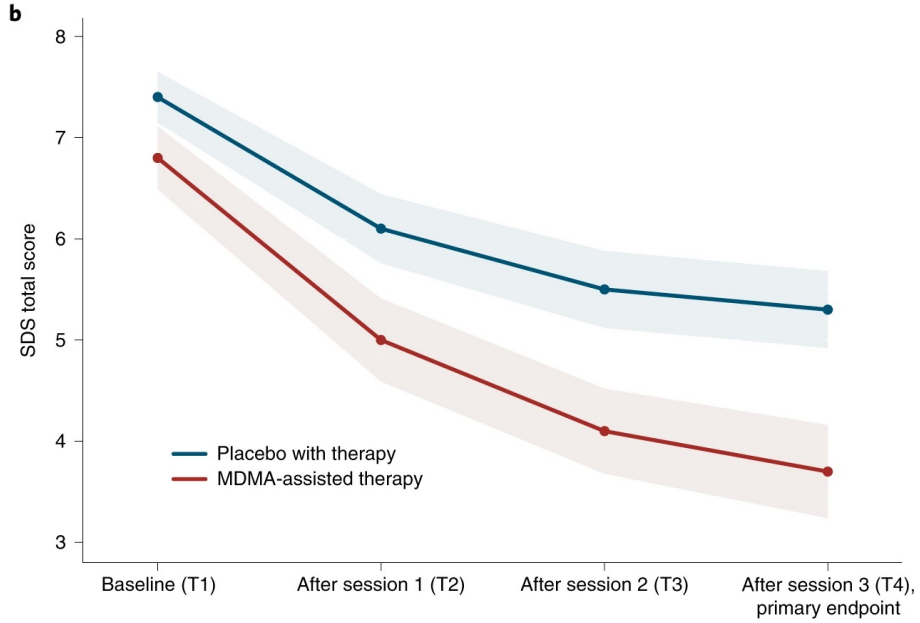
- **https://doi.org/10.1038/s41591-021-01336-3**

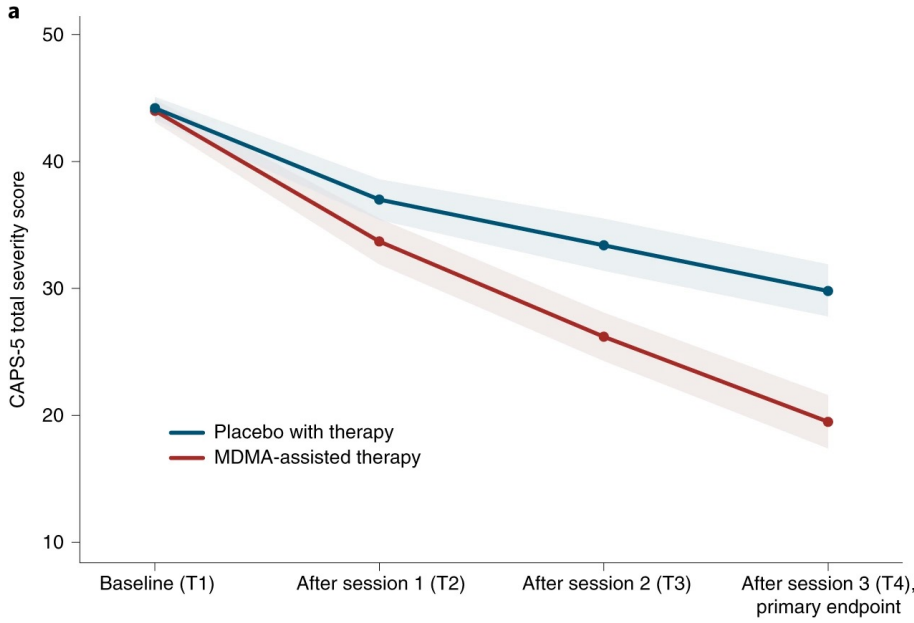


MDMA P3 Trial Results - CAPS5, BDI & SDS

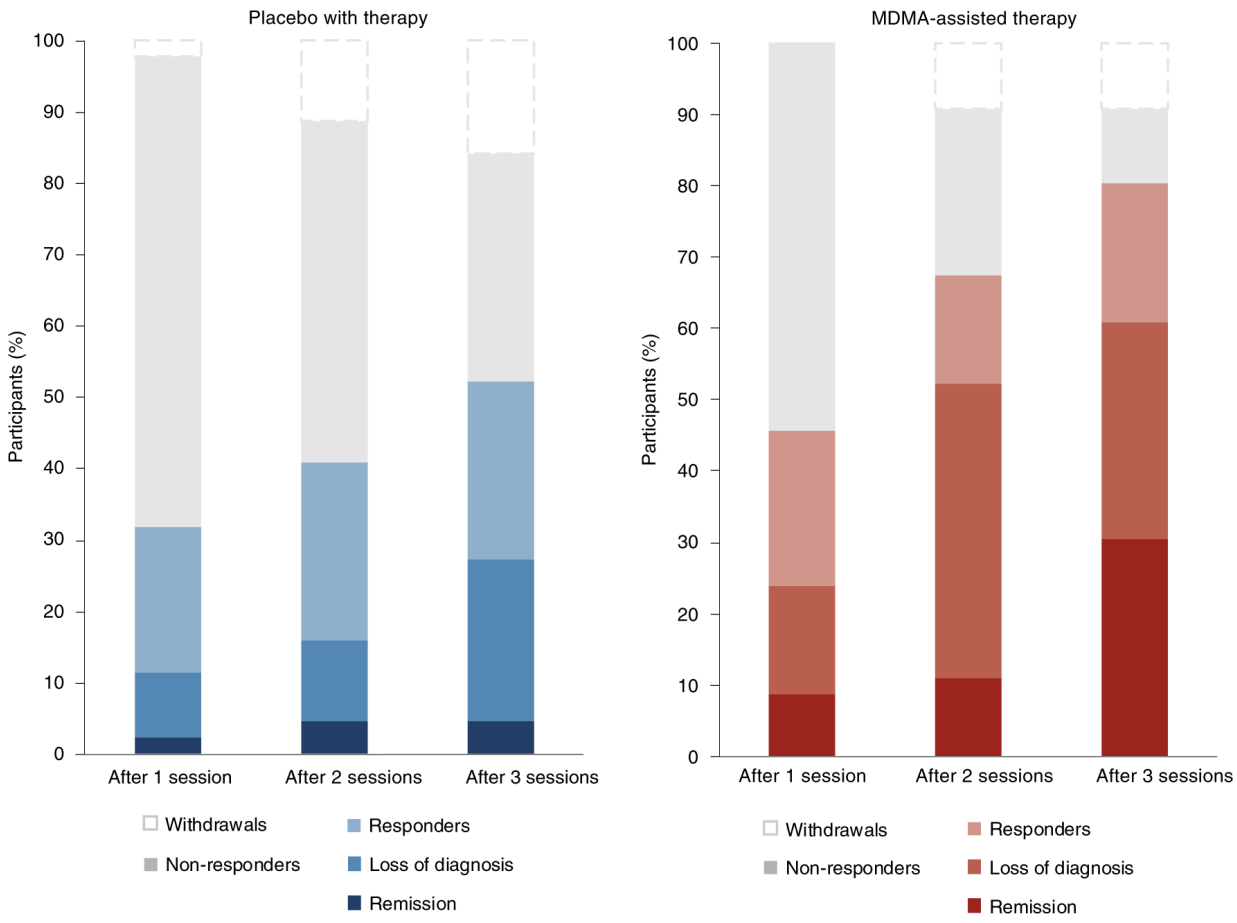
https://doi.org/10.1038/s41591-021-01336-3







MDMA P3 Trial Results – Withdrawal, Non-Response, Response, LoD, Remission



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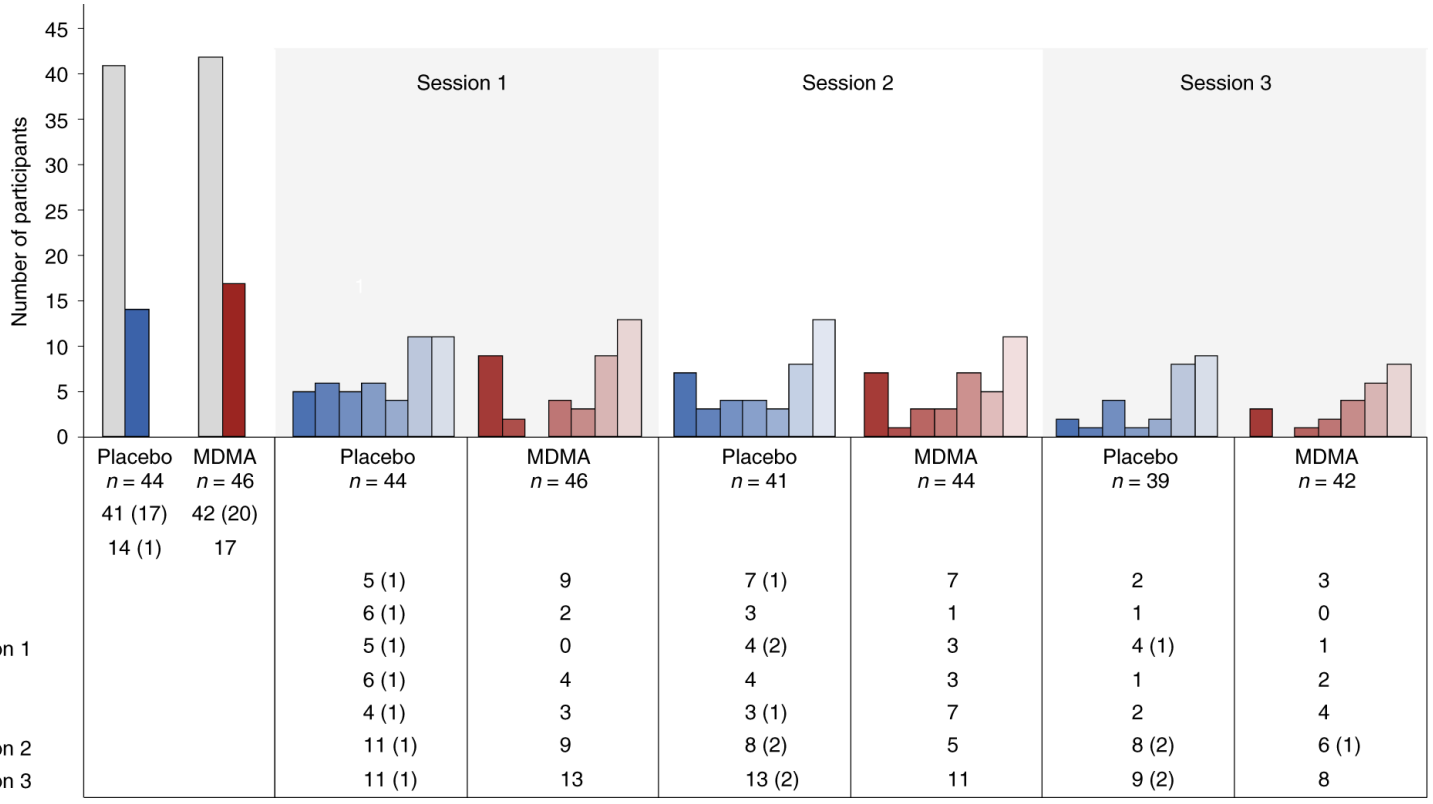
MDMA P3 Trial - Suicidality



Assessment timeline	Placebo *n* = 44	MDMA *n* = 46	Placebo *n* = 44	MDMA *n* = 46	Placebo *n* = 41	MDMA *n* = 44	Placebo *n* = 39	MDMA *n* = 42
Lifetime	41 (17)	42 (20)						
Baseline	14 (1)	17						
Before drug			5 (1)	9	7 (1)	7	2	3
After drug			6 (1)	2	3	1	1	0
Integrative session 1			5 (1)	0	4 (2)	3	4 (1)	1
Call day 2			6 (1)	4	4	3	1	2
Call day 7			4 (1)	3	3 (1)	7	2	4
Integrative session 2			11 (1)	9	8 (2)	5	8 (2)	6 (1)
Integrative session 3			11 (1)	13	13 (2)	11	9 (2)	8

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

Progress of Phase 3 Clinical Trials: Safety & Tolerability

AE	MDMA	Placebo
Muscle Tightness	30 (65.2%)	6 (13.6%)
Decreased Appetite	24 (52.2%)	5 (11.4%)
Hyperhidrosis (sweating)	10 (21.7%)	1 (2.3%)
Feeling Cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis (dilated pupils)	7 (15.2%)	0
Bruxism (teeth grinding)	6 (13%)	1 (2.3%)
Nystagmus (eye wiggling)	6 (13%)	0
Dizziness Postural	6 (13%)	2 (4.5%)
Blood Pressure Increased	6 (13%)	0
Feeling Jittery	6 (13%)	0
Non-Cardiac Chest Pain	5 (10.9%)	1 (2.3%)
Dry Mouth	5 (10.9%)	2 (4.5%)

Most frequent non-serious adverse events for the MDMA group:

- Muscle tightness
- Decreased appetite

Mitchell, J.M., Bogenschutz, M., Lilienstein, A. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med 27, 1025–1033 (2021). https://doi.org/10.1038/s41591-021-01336-3

Progress of Phase 3 Clinical Trials

Safety of MDMA Therapy: Participants with Adverse Events of Special Interest

- Suicidality (Suicidal thoughts, behavior, self-harm)
  - 3 participants in MDMA group
  - 5 participants in placebo group

- Serious Adverse Events of Suicidal ideation and/or attempt
  - 0 participants in MDMA group
  - 2 participants in placebo group, 1 attempted suicide twice, other self-hospitalized

Mitchell, J.M., Bogenschutz, M., Lilienstein, A. et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med 27, 1025–1033 (2021). https://doi.org/10.1038/s41591-021-01336-3

Overview of Psychotherapeutic Method

The therapists prepare the participant for the likelihood that revisiting their trauma and experiencing their PTSD symptoms might be part of the therapeutic process.

Therapists encourage participants to be as open as possible to fully exploring, expressing, and understanding the PTSD symptoms and the other impacts the trauma has had on their life.

The therapists explicitly agree to provide support, safety, and guidance for the participant in working with any emotions and memories that may arise.

MDMA Therapy Training

Psychotherapeutic Rationale

- MDMA produces an experience that appears to temporarily reduce fear, increase the range of positive emotions toward self and others, and increase interpersonal trust without clouding the sensorium or inhibiting access to emotions.

- MDMA may catalyse therapeutic processing by allowing participants to stay emotionally engaged while revisiting traumatic experiences ***without being overwhelmed*** by anxiety or other painful emotions. It can be intensive, challenging, and often painful therapeutic work.

- MDMA can enable a heightened state of empathic rapport that ***facilitates the therapeutic process*** and allows for a corrective experience of secure attachment and collaboration with the therapists.

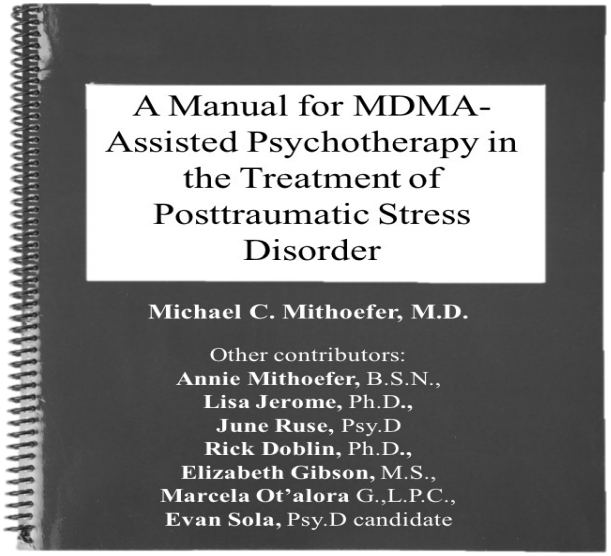
- At some point during the MDMA experience feelings of empathy, trust, and deep appreciation often emerge in conjunction with a clearer perspective of the trauma as a past event and a heightened awareness of the support and safety that exist in the present.

Greer, G.R. and R. Tolbert, A method of conducting therapeutic sessions with MDMA. Journal of Psychoactive Drugs, 1998. 30(4): p. 371-379.

Grob, C. and R.E. Poland, MDMA, in Substance Abuse: A comprehensive textbook: Third Edition, Lowinson J. H., P. Ruiz, and R.B. Millman, Editors. 1997, Williams and Wilkins: Baltimore, MD. p. 269-275

FDA-Approved Manualised Therapeutic Method

- The basic premise is that the therapeutic effect is not due simply to the physiological effects of MDMA; rather, it is the result of an interaction between the effects of the MDMA, the therapeutic setting/alliance and the mindsets of the participant and the therapists.
- The therapists work with the participant to establish a sense of safety, trust, and openness, as well as to emphasise the necessity of trusting the participant's innate resilience, intelligence and ability to recover.
- Establishing these conditions requires that the therapists prepare the participant before each MDMA-assisted session, stay with them, at all times, throughout the drug dosing-day, and then provide support following the session so that the experience can be successfully integrated.
- Participant safety and wellbeing are always prioritised ahead of any scientific goals of the study.



MDMA P3 Trial – What's Next?

2 further Phase 3 trials

1 in US, underway

1 in Europe, started 2022 (we have dosed 2 in UK so far)

At least 2 positive phase 3 trials required for licensing

Pitfalls of Psychedelia: Exceptionalism & Evangelism

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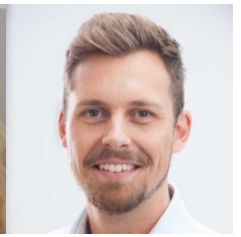

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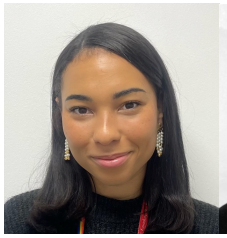

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Thank you…

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