A History of Psychedelics in 15 Minutes

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Disclosures

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”
A very brief cultural history of psychedelics in the (non-native) USA

- Popularity in intellectual and salon circles in late 1950s
- Leary, Alpert, Metzner
- 1966: LSD illegal
- Counterculture: anti-war, civil rights, women’s rights, environmentalism
- Nixon: congressional address 1969: “war on drugs”
- 1970-71: under heavy American pressure, psychedelics criminalized worldwide
- 1970s-1990s: psychedelics go underground, rising use of mushrooms (vs LSD)
- 1994: first new study since 1960s
Psychedelics are not new

- Psychedelics are not “novel agents”
- Used across cultures and continents for thousands of years
- Generally used as medicines within a sacred context combining elements of therapy, medicine, and religion
- Broader context of elevating non-ordinary states of consciousness as integral aspects to the human experience
Mescaline

• Peyote buttons found in Rio Grande valley, 3700 BC

• San Pedro cactus in Peru from 1300 BC

El Seedi, J Ethnopharmacol, 2005; Davis Botanical Museum Leaflets, 1983
• Many diverse plants contain DMT
• Ayahuasca (at least 1,000 years ago in Bolivia), *Banisteriopsis caapi* and *Psychotria*
• Jurema (northeastern Brazil) - *Mimosa*
• Tepezcohuite (Mexico) – *Mimosa*
• Cohoboa or yopo (Caribbean) - *Anadananthera*
Psilocybin

- Extensively used and deeply embedded within Mesoamerican cultures
- Various names, teonanacatl (flesh of the gods), temicxoch (dream flowers)
- Aztecs also consumed morning glory seeds (ololiuqui)
- Brutally suppressed by invading Europeans
Psilocybin
Ibogaine

- Shrub native to central and western Africa
- Used likely for millenia
- Primarily used in large doses in coming of age rituals
Sacred use in the 20th century

- Religious Crimes Code 1883 bans religious ceremonies and rituals, punishable by imprisonment
- Indian Citizenship Act 1924
- American Indian Religious Freedom Act 1978 allows right to practice some religion
- Religious Freedom Restoration Act 1993
- States and federal governments continue to make arrests
- Santo Daime, União de Vegetal, Native American Church
- Psychedelic tourism
Psychedelics in western medicine

- Hashish, chloroform, ether (1890s)
- Narcoanalysis (barbiturates, 1920s)
- Confessions in Mescaline Inebriation (1931)
- First clinical study with LSD (1947)
- First use of LSD in therapy (1950)
Psycholytic therapy

• Arose in context of psychoanalysis-dominated era
• Goal to use LSD as an adjunct to therapy, rather being a cure itself
• Amplification of psychodynamic processes and reduction of ego defenses
• Many, frequent, moderate dose LSD sessions embedded within extensive, traditional psychotherapy paradigm
• Predominant model in Europe
Psychedelic therapy

• Inadvertent discoveries that LSD led to significant patient improvement in cancer and alcoholism by way of inducing mystical and religious experiences

• Concurrent refocus within psychology on transcendent states (Maslow, head of APA)

• Growing awareness of indigenous practices using psychedelics in ritual context
Psychedelic therapy

- Dominant form in North America by latter 1960s
- Explicit purpose to induce mystical or transcendent experience
- Manipulation of expectation and environment to prime this occurrence
The return of psychedelics

- 1994: DMT study by Rick Strassman with unexpected results
- 2006: “psilocybin can occasion mystical type experiences” (Griffiths, Johns Hopkins)
- 2010s-present: Research grows, primarily in USA, UK, Switzerland, Brazil
- 2019-present: starting with Imperial College (UK) and Johns Hopkins (USA), psychedelic research centers open
- 2021: first Phase III study results reported (MDMA-assisted therapy for PTSD)
Ethical-cultural issues

• Cultural tourism
  – Dilution of indigenous customs
  – Lack of access for actual indigenous peoples

• Who determines right to use?
  – FDA, DEA vs millennia of tradition

• Cultural appropriation and neocolonialism
The Pharmacology of Psychedelics

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What are psychedelics?

• Psychedelic, 1956 = “mind-manifesting”
• Change in consciousness, experience often described as profound, transformative, with spiritual or mystical importance, and/or personal meaning
• “Ego dissolution” – decreased boundary between self and world, increased connectedness
• Increased sensory experiences: synesthesia, visual imagery and/or hallucinations
Psychological effects

• Effects often long lasting: increased well being, enhanced appreciation, increased openness

• Majority of subjects in controlled settings report experience as enriching or meaningful, even if the session was marked by dysphoria

• 14-month follow-up of non-clinical study: among 5 most personally meaningful (58%) and spiritually significant (67%) experiences in their lives

Griffiths 2018 J Psychopharmacol.
How do psychedelics differ?

• Time: LSD and mescaline (8-12 hours), psilocybin and ayahuasca (4-6 hours), DMT and 5-MeO DMT (10-20 minutes)

• Quality:
  – Measures: ASC, MEQ, HRS
  – Visual aspects
  – Ego dissolution/consciousness change
  – Prosociality (MDMA, MDA - “empathogens”)

• Oral bioavailability: DMT – 100% metabolized by gut monoamine oxidase, most others with good oral bioavailability
Classes of Psychedelics

**Tryptamines**

![Tryptamine structure]

**Phenethylamines**

![Phenethylamine structure]

**Benzofurans**

![Benzofuran structure]

**Cathinones**

![Cathinone structure]
Tryptamines

- All based on structural backbone of serotonin (5-hydroxytryptamine)
- Psilocybin (4-phosphoryloxy-DMT)
- N,N-DMT, 5-MeO-DMT
- LSD
Tryptamines

Bufotenin

N,N-Dimethyltryptamine

5-Methoxy-dimethyltryptamine

Serotonin

Psilocybin

Psilocin

Idole-3-acetic acid

Melatonin
Phenethylamines

- Substituted phenethylamines include a wide array of drug classes
- Psychedelics include mescaline, MDMA, 2-CB
- Other than MDMA, less well-researched CNS stimulants, decongestants, antidepressants, anti-Parkinson agents, vasopressors, bronchodilators, and neurotransmitters epinephrine, norepinephrine and dopamine
Phenethylamines

• “2C” compounds, eg, 2C-B (psychedelic + empathogenic)

• Also include psychedelic agents with higher risk for adverse effects
  – DOM: “STP”, extremely potent, long lasting, mistakenly taken as LSD in late 1960s
  – NBOMe’s: group of compounds highly potent, sometimes misrepresented as LSD -> overdose
    • Toxicity: tachycardia, fever, hypertension, seizures, hyperthermia

Wood et al, Clin Toxicol, 2015
Pharmacology

- Primary effect via agonist or partial agonist activity at 5HT-2A receptor
- Blocked by pretreatment with 5HT-2A antagonists
- Widely varying duration (LSD, mescaline 10-12 hours; psilocybin, ayahuasca 4-6 hours; DMT, 5-MeO DMT 10-20 minutes)
The 5HT-2A receptor

- Excitatory (G-protein coupled receptor, causes neuron to depolarize, release cortical glutamate)
- Expressed throughout the brain, but some populations are more sensitive to depolarization than others (PFC and claustrum)

Neuroplasticity

• Role of 5HT-2A receptor – evolutionary mechanisms to promote neuroplasticity as a stress response?

• 5HT-2A agonists promote neuroplasticity (growth of dendritic spines, synaptic proteins)
  – This effect is blocked by ketanserin
  – Increase in BDNF: “window” of neuroplasticity
  – Enhancement of suggestibility?

5HT-2C and 5HT-1A

• 5HT-2C: psychedelics also potent 5HT-2C agonists
  – Unclear significance, 5HT-2C antagonism does not block psychedelic effect
• 5HT-1A: inhibitory receptors (hyperpolarize the cell) in median raphe nuclei and cortical pyramidal cells
  – Buspirone, 5HT-1A partial agonist, caused reduced visual effects of psilocybin
  – Pretreatment with 5HT-1A agonist may intensify psychedelic (pindolol, DMT)

Pokorny et al, Eur Neuropsychopharmacol, 2016; Strassman, Behav Brain Res, 1996
Drugs interactions

- Two ways of increasing extracellular monoamines
  - Re-uptake inhibitors:
    - Bind to transporter protein and block transporter-mediated re-uptake of monoamines from extracellular space
  - Substrate-type releasers:
    - Disrupt intracellular vesicles, leading to monoamine release into cytoplasm
    - Promote monoamine release via exchange
    - Can be blocked by re-uptake inhibitors
Psychedelics and psychiatric medications

• Theoretical risk for serotonergic excess with SRI’s, but...
• In practice, SSRIs have long been thought to blunt the effects of psychedelics
• Recent research claims otherwise but results not yet published
• Duration of drug therapy may matter (secondary vs acute effects of SRIs)
Psychedelics and psychiatric medications

• MDMA is more reliably known to be nearly fully blocked by SSRIs and SNRIs
• All published trials to date have employed a washout period
• Ayahuasca: contains MAOI 🎃
• Ibogaine: QT prolongation <-> methadone et al.
• Lithium: increased risk of seizure?
• Bupropion: possible increased intensity of MDMA
• Second generation antipsychotics fully antagonize psychedelic,* partial blocking of effect with haloperidol
Ibogaine

- Shares tryptamine structure w/ classical psychedelics
- Multiple pharmacologic targets
  - NMDA-R antagonist
  - SRI
  - kappa opioid agonist and (weak) mu opioid receptor agonist/partial agonist
- Cardiac risk: bradycardia, QTc prolongation
  - 19 fatalities reported 1998 — 2008*
  - Harm reduction: CV disease, EKG, LFTs

*Nature 2020
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*Nature 2020
The pharmacology of MDMA

- Methylenedioxyphenethylamines
  - MDMA, MDA, MMDA, MDEA, MBDB
- Primary effect is by inducing release of serotonin and thus indirect agonism of post-synaptic 5HT receptors
- Also causes release of dopamine and norepinephrine although clinical significance unclear
- Mild direct 5HT-2A agonist activity
- 5HT-2B agonist (cardiac valves)
- Increased oxytocin, needs more research
Tachyphylaxis

- Tachyphylaxis occurs within 3-4 days of daily administration
- Cross-tolerance between different agents
- Correlates with downregulation of 5HT-2A receptors in animal models
- Biological dependence on psychedelics is not possible
- Implications for microdosing
Safety & physiologic effects

- Subjective physical effects:
  - Headache, nausea, fatigue most common (<50%)
- Sympathetic changes:
  - ↑BP, ↑HR (mild), ↑temperature (mild)
  - Mydriasis, increased reflexes
- Well tolerated in medically ill subjects (terminal cancer, geriatric patients)
- Toxicity: no LD50 established for humans, likely in grams or kilograms
- No evidence for mutagenic effects or neurotoxicity, including high dose exposures
Autonomic effects

Psilocybin

LSD

Bogenschutz *Psychopharmacology* 2015, Holze *Neuropsychopharmacology* 2021
Autonomic effects

Distinct acute effects of LSD, MDMA, and d-amphetamine
F Holze et al.

Holze Neuropsychopharmacology 2019
48 healthy older adults (55-75 yo; mean = 62.9)
Randomly assigned to placebo or 5µg, 10µg, or 20µg LSD Q4days for 6 doses, monitored for 8-12 hours post-dosing
No statistical difference between groups on measures of cognition, balance or proprioception
Only adverse effect = headaches in 10µg group
Psychological safety: the bad trip

• Anxiety, fear/panic, dysphoria, and/or paranoia
• Variety of modalities:
  • Sensory: frightening illusions
  • Somatic: hyperawareness of body processes
  • Personal: distressing thoughts about oneself
  • Metaphysical: fearful thoughts about the world, society, evil forces
• In clinical settings, primary intervention is interpersonal support (pharm rescue usually not needed)

Johnson 2008, Studerus 2011
Microdosing

- Use of very small doses (≤0.05 typical dose) with minimal acute drug effects
- Schedule varies, usually taken only a few days each week
- LSD, psilocybin most commonly used
- Observational study: increased mood, attention, well being, creativity on dosing days but no residual effects
- Benefits may correlate with expectation

Kaertner, Sci Reports, 2021
Psychological safety: post-acute effects and screening

- Prolonged psychosis?: 1/1200 subjects experienced psychosis > 48h
  - Subject’s twin had schizophrenia
- No cases of prolonged psychosis in modern studies
  - Screening: personal or family history of bipolar or schizophrenia contraindicated
  - HPPD has not been reported following any clinical studies
- Catastrophic behaviors (eg suicide) rare, but have occurred in non-controlled settings
  - Preparation, controlled settings, psychological support

Cohen 1960, Krebs 2013, Studerus 2011
PSYCHEDELICS IN DEPRESSION, ANXIETY AND PTSD

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Psilocybin-assisted psychotherapy for treatment resistant depression

• Open label
• 20 participants with treatment-resistant depression
• 2 oral doses of psilocybin, 7 days apart (10mg, 25mg) (open label)
• Preparatory sessions, psychological support during psilocybin, integration session post treatment
• Followed at weeks 1-5, 3 months and 5 months
• Depression scores significantly reduced at all time points

Carhart Harris, Psychopharmacol 2018
Psilocybin-assisted psychotherapy for treatment resistant depression

Table 2

Individual patient clinical ratings: clinical outcomes at various time points. The clinician administered ratings were completed at baseline and 1 week post-dosing only

<table>
<thead>
<tr>
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<th>BDI</th>
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<td>Baseline</td>
<td>1 week</td>
<td>3 months</td>
<td>6 months</td>
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<tr>
<td>Mean</td>
<td>34.5</td>
<td>11.8</td>
<td>19.2</td>
<td>19.5</td>
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<td>44.8</td>
<td>56.5</td>
<td>53.8</td>
<td>6.6 (4.1)</td>
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<td>(SD)</td>
<td>(7.3)</td>
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<td>Difference vs baseline</td>
<td>– 22.7</td>
<td>– 15.3</td>
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<td>Cohen’s $d$</td>
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Carhart Harris, *Psychopharmacol* 2018

Results: Significant response rate in intervention group at Day 1, 2 and 7. Remission rate showed trend toward significance at Day 7 ($p = 0.054$).
Effects of psilocybin-assisted therapy on major depressive disorder

- Waitlist control, 27 subjects enrolled
- Waitlist controlled
- 2 psilocybin sessions
- Significant reductions in depression scores from baseline
- Remission from depression in 58% at week 1 and 54% at week 4

Davis et al, 2020
Psilocybin versus Escitalopram for Depression

**Phase 2, Double-Blind, Randomized, Controlled Trial**

59 Adults with moderate-to-severe major depressive disorder

Psilocybin (two 25-mg doses 3 wk apart) + placebo (microcrystalline cellulose)

N = 30

Escitalopram (10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1-mg doses 3 wk apart)

N = 29

Change in QIDS-SR-16 depressive symptom score at 6 wk (range, 0–27; higher score = greater depression)

- Psilocybin: -8.0±1.0
- Escitalopram: -6.0±1.0

Difference, -2.0 points (95% CI, -5.0 to 0.9)

Overall incidence of adverse events was similar in the two groups.

No significant difference between psilocybin and escitalopram in QIDS-SR-16 score change from baseline.

R. Carhart-Harris et al. 10.1056/NEJMoa2032994
Use in end of life-related depression and anxiety

- Grob et al 2011/UCLA: 30% decrease in BDI, significant decrease in trait anxiety sustained at 6 months
  - N=12, dx=advanced stage cancer/acute stress, GAD, adjustment disorder, or anxiety secondary to cancer
  - Psilocybin 14 mg/70 kg vs niacin placebo
- Gasser et al 2014/University of Bern: trend toward decreased state anxiety sustained at 12 months
  - N=12, dx=life threatening medical illness/anxiety associated with medical illness
  - Randomized, open-label crossover; 200 µg vs 20 µg LSD
- Griffiths et al 2016/Hopkins: 80% of subjects with significant decreases in anxiety and depression at 6 months
  - N=51, dx=life threatening cancer/depression or anxiety
  - Randomized crossover design; 22 mg/70 kg psilocybin vs 1 mg (placebo)
- Ross et al 2016/NYU: 60-80% response rate for anxiety and depression at 6 months
  - N=29, dx=cancer (2/3 with advanced cancer)/anxiety disorder (GAD 10%, adjustment 90%)
  - Randomized, crossover design; psilocybin 21 mg/70 kg vs niacin placebo
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MDMA-ASSISTED PSYCHOTHERAPY
History

• Synthesized and patented by Merck, 1912, then shelved ("Safrylmethylamin")

• Military research (CHATTER, MK ULTRA) into mescaline for "behavior manipulation" and "ego depressant" effects

• Mescaline derivatives re-synthesized by Army 1950-1952, shelved when Army research swung towards LSD exclusively
History

• 1976, rediscovered by chemist Alexander Shulgin

• By early 1980s, emerging case reports using MDMA within psychotherapy for PTSD and social anxiety

• Rapid popularity as "club drug"

• Emergency DEA meeting in 1985 led to Schedule I classification, effectively shutting down research for two decades
History

• 1986 – Multidisciplinary Association for Psychedelic Studies (MAPS) founded by Rick Doblin, PhD

• 2004 – MAPS, along with renewed interest in "prosocial" drugs, led to FDA's approval of MDMA as an IND, leading to several small trials

• Aug 2017 – Breakthrough Therapy designation by FDA for 2 Phase III clinical trials
Effects

• Usually taken orally
• Study doses usually 80 – 125mg (recreational doses usually within similar range)
• Time to onset ~30 min
• Average duration of effect 2-6 hours, with peak effect around 1-2 hours after ingestion
• Mild elevations in BP, HR, and core temp
Effects

• Euphoria
• Increased well-being
• Increased feelings of connectedness to others
• Self-confidence
• Extroversion
• Heightened sensory experience
Why PTSD?

• For effective psychotherapy in PTSD, patient must be engaged but not overwhelmed
• PTSD patients suffer from both under-arousal (numbing) and over-arousal (intense emotions, anxiety, dissociation)
• MDMA may widen this window by reducing fear response and increasing capacity for tolerating negative emotions and memories
Why PTSD?

Correspondence

It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD). The clinical, social, and financial burden of ineffectively treated PTSD is enormous (1–6). The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace, and societal contexts (7). For the Department of Veterans Affairs (VA) and Department of Defense (DoD), i.e., institutions that are vehicles for the expression of the national debt to military personnel who developed PTSD as a consequence of their military service, the need to help these people has taken on significant priority. One in 10 VA healthcare users have the diagnosis of PTSD, which includes one in four treatment-seeking veterans of the recent wars in Iraq and Afghanistan (8). The prevalence of PTSD in the general population for lifetime is approximately 8% (8) and just under 4% for the current year, making it the fifth most prevalent mental disorder in the United States (9–11). Despite this high prevalence and costly

• FDA approval only for sertraline and paroxetine, most treatment is off label
• Psychotherapy efficacy (CPT, exposure) 49-70% show improvement, but in military populations 60-72% retain PTSD diagnosis
• Treatment, when successful, takes weeks to months
MDMA - Pharmacology

Methylenedioxyphenethylamines

MDMA, MDA, MDEA, MBDB, MMDA

Binds to SERT, NET, and DAT (reuptake inhibition)
Also substrate for monoamine transporters (releasing agent)
Mild 5HT-2A agonism

Effects

Euphoria, enhanced well-being, extraversion, connection to others, trust

Toxicity (?)

Early studies focused exclusively on neurotoxicity in animals, extremely high doses
Neurocognitive effects from recreational use?
Retracted article (Ricaurte et al, Science, 2003)
MDMA-assisted psychotherapy for PTSD

2018 study (Mithoefer, *Lancet Psychiatry*)
- 26 veterans and 1st responders with treatment-resistant PTSD
- CAPS mean = 86.5
- Randomized to 30mg/75mg/125mg. Each received 2 rounds of MAP
- Significant reduction in CAPS, with sustained reduction at 12 month follow up (71% no longer met criteria for PTSD)

2021 study (Mitchell, *Nature Medicine*)
- 90 participants with severe PTSD
- Randomized to either 3 rounds of MAP versus placebo with therapy
- Significant reductions in CAPS (MDMA= -24.5; placebo = -13.9)
Informed written consent and screening with SCID, CAPS-IV, neuropsychological measures, physical exam, blood tests, and ECG

Three 90-min preparatory sessions with co-therapy team

Two 8-h MDMA or comparator experimental sessions, approximately 1 month apart; overnight stay with attendant; 90-min integration session morning after; and daily phone contact during following week

Two non-drug integration sessions after each experimental session, approximately weekly

Primary endpoint (1 month after second experimental session)

Blind broken

125 mg group

One open-label (125 mg) session with three integration sessions

Stage 1 (double-blind)

30 mg and 75 mg groups

Preparatory session: two open-label (100–125 mg) sessions with three integration sessions

Secondary endpoint (1 month after second experimental session)

One open-label experimental session with three integrative sessions

End of stage endpoint (2 months after third MDMA session)

Stage 2 (open-label crossover)

12-month follow-up

### Primary efficacy measure

<table>
<thead>
<tr>
<th></th>
<th>30 mg MDMA plus psychotherapy (n=7)</th>
<th>75 mg MDMA plus psychotherapy (n=7)</th>
<th>125 mg MDMA plus psychotherapy (n=12)</th>
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</thead>
<tbody>
<tr>
<td>Mean CAPS-IV total score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87·4 (14·1)</td>
<td>82·4 (17·3)</td>
<td>89·7 (17·3)</td>
</tr>
<tr>
<td>After two experimental sessions of MDMA</td>
<td>76·0 (23·4)</td>
<td>24·1 (17·2)</td>
<td>45·3 (33·8)</td>
</tr>
<tr>
<td>Change†</td>
<td>-11·4 (12·7)</td>
<td>-58·3 (9·8)</td>
<td>-44·3 (28·7)</td>
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<tr>
<td>p value‡</td>
<td>NA</td>
<td>0·0005</td>
<td>0·004</td>
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### Secondary efficacy measures

<table>
<thead>
<tr>
<th>Number of participants who met CAPS-IV PTSD diagnostic criteria (primary endpoint)</th>
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<tbody>
<tr>
<td>Yes</td>
<td>5 (71%)</td>
<td>1 (14%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>No</td>
<td>2 (29%)</td>
<td>6 (86%)</td>
<td>7 (58%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of participants who had more than 30% decrease in CAPS-IV total score (primary endpoint)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2 (29%)</td>
<td>7 (100%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (71%)</td>
<td>0</td>
<td>4 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean BDI-II score</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30·4 (13·7)</td>
<td>24·7 (12·6)</td>
<td>36·6 (10·5)</td>
</tr>
<tr>
<td>After two experimental sessions of MDMA</td>
<td>25·9 (11·2)</td>
<td>9·3 (6·8)</td>
<td>12·0 (9·0)</td>
</tr>
<tr>
<td>Change†</td>
<td>-4·6 (8·8)</td>
<td>-15·4 (9·5)</td>
<td>-24·6 (10·6)</td>
</tr>
<tr>
<td>p value‡</td>
<td>NA</td>
<td>0·052</td>
<td>0·0003</td>
</tr>
</tbody>
</table>
- No difference in efficacy for dissociative vs non-dissociative subtypes of PTSD

- Equally effective in participants with comorbidities a/w treatment resistance (eg AUD, SUDs, severe childhood trauma)
Fig. 3: Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, n = 46; placebo, n = 44).

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

Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of <11) were tracked in both groups. Non-response is defined as a <10-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.
Thank you!