PSYCHEDELICS IN CLINICAL PRACTICE: CURRENT EVIDENCE

RENU GOEL, M.D., AND
ROBERT MCCLURE, M.D., L.F.A.P.A.

OBJECTIVES

1. Analyze the current state of evidence for clinical use of Psilocybin and MDMA in psychiatric practice

2. Examine other interventional strategies including Ketamine/Esketamine

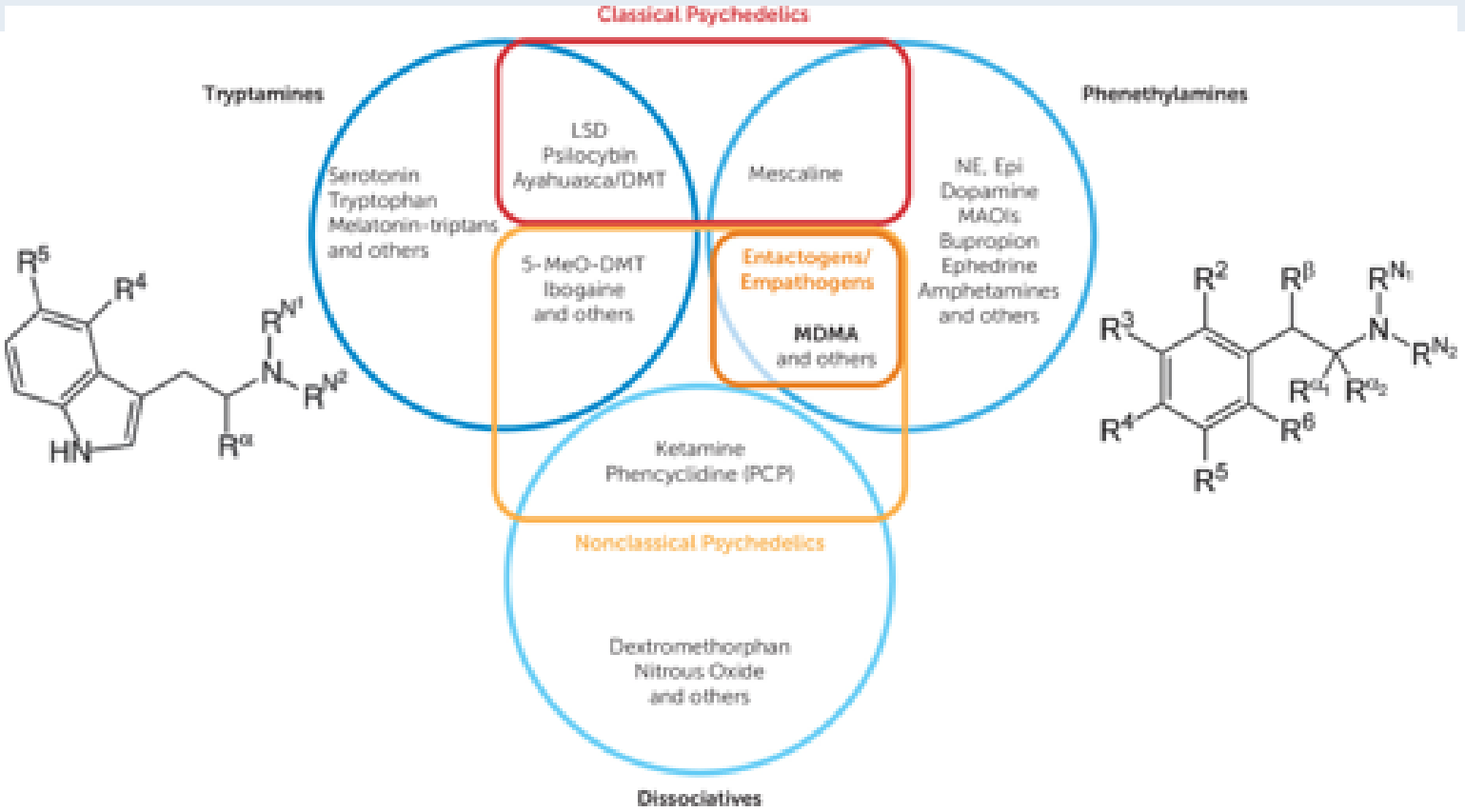
3. Develop expertise in managing patients receiving novel treatments and therapeutics

DISCLOSURE:
RENU GOEL
RECEIVED THE HEALTH EQUITY LEADERSHIP SCHOLARSHIP FOR MAPS MDMA ASSISTED THERAPY TRAINING

PSYCHEDELIC: MIND MANIFESTING/REVEALING

PSYCHEDELIC EFFECTS: PRODUCE ALTERED STATES OF CONSCIOUSNESS THAT CAN EFFECT BIOPSYCHOSOCIAL CHANGE

1. Anxiety/fear/panic
2. Dysphoria
3. Paranoia and hallucinations
4. "Bad trip" (recreational use) vs.
5. "Challenging experience" (psychedelic-assisted therapy)



aAdapted from Wolfgang and Hoge (14). DMT: dimethyltryptamine; 5-MeO-DMT: 5-methoxy-*N*,*N*-dimethyltryptamine; NE, norepinephrine; Epi, epinephrine; R: a carbon or hydrogen atom.

American Journal of Psychiatry January, 2025, Volume 182 (1), p. 81

DOI: (10.1176/appi.ajp.20230681)

CLASSIC PSYCHEDELICS

Tryptamines: primarily serotonergic 5HT2A agonism; Hallucinogens

- Ergot Fungus/LSD (ergotamine)
- Psilocybin
- Ayahuasca/ DMT
- Iboga/Ibogaine* (also SERT/DA/ opiate/NMDA Rec activity)

EFFECTS CAN BE BLOCKED BY KETANSERIN (5HT2 Antagonist) IN VARYING AMOUNTS

NON CLASSIC PSYCHEDELICS

Phenethylamines: Release of Serotonin, NE, DA and inhibits reuptake

- Peyote/Mescaline
- MDMA (efflux of serotonin at SERT)*

Dissociative:

- Ketamine (NMDA/Opiate action)
- PCP

PSYCHEDELICS CREATE CHANGE:
1. BRAIN STRUCTURE
2. CIRCUIT NETWORK/CONNECTIVITY
3. INDUCE NEUROPLASTICITY (MOLECULAR AND CELLULAR)
4. NEUROIMMUNO MODULATION

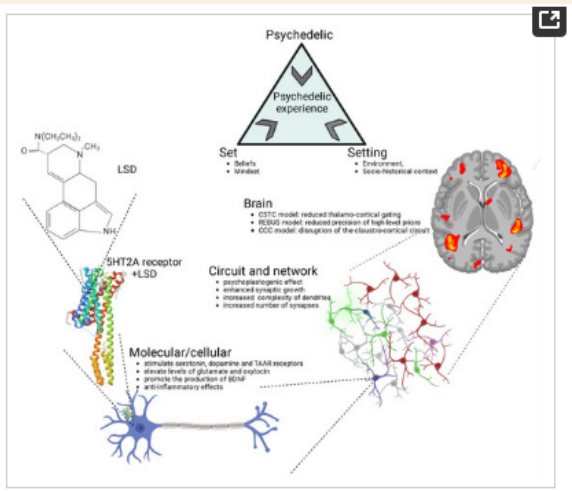
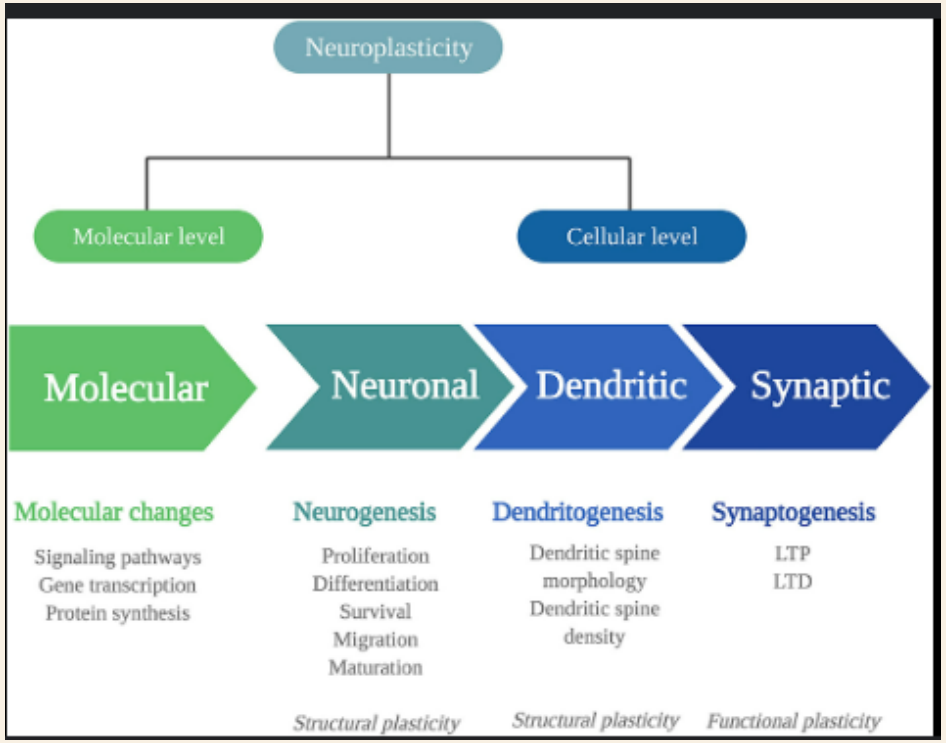
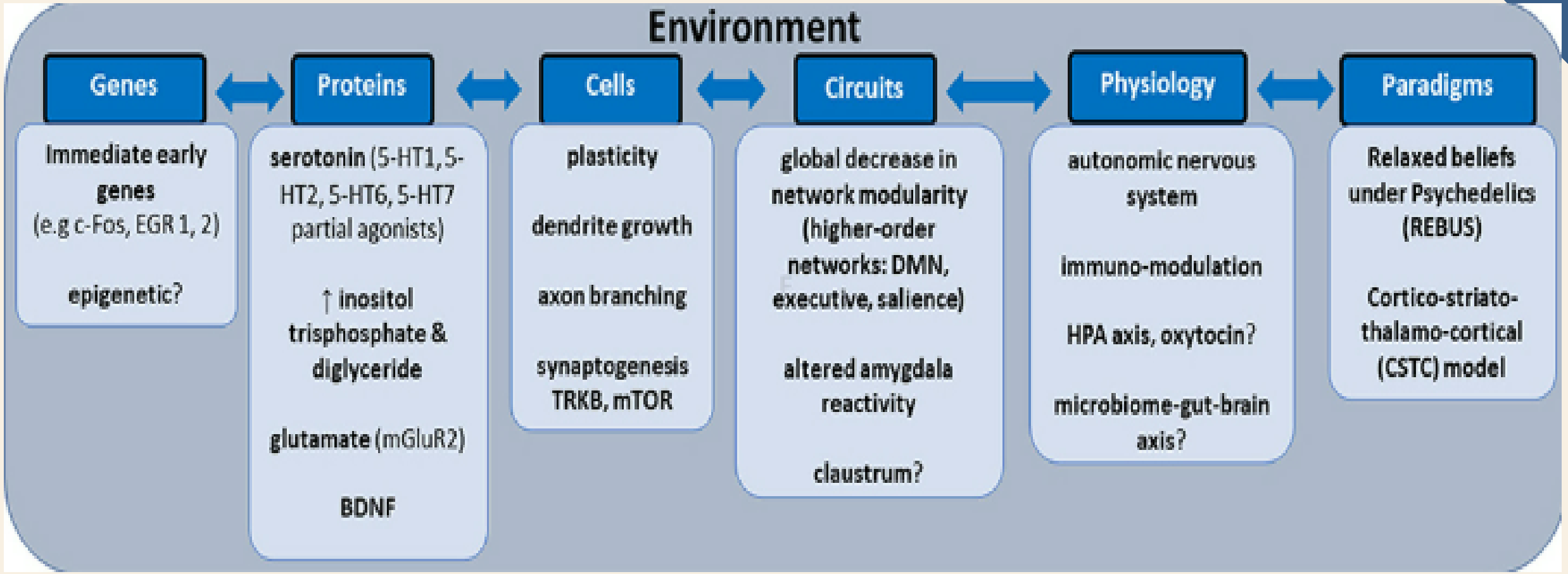


Figure 1. Psychedelics exert their effects through various levels of analysis, including the molecular/cellular, the circuit/network, and the overall brain. The crystal structure of serotonin 2A receptor in complex with LSD is sourced from the RCSB Protein Data Bank (RCSB PDB) [62]. LSD, lysergic acid diethylamide; 5-HT2A, serotonin 2A; CSTC, cortico-striato-thalamo-cortical [63]; REBUS, relaxed beliefs under psychedelics model [64]; CCC, claustro-cortical circuit [65]. Generated using Biorender, https://biorender.com/, accessed on 4 September 2023.



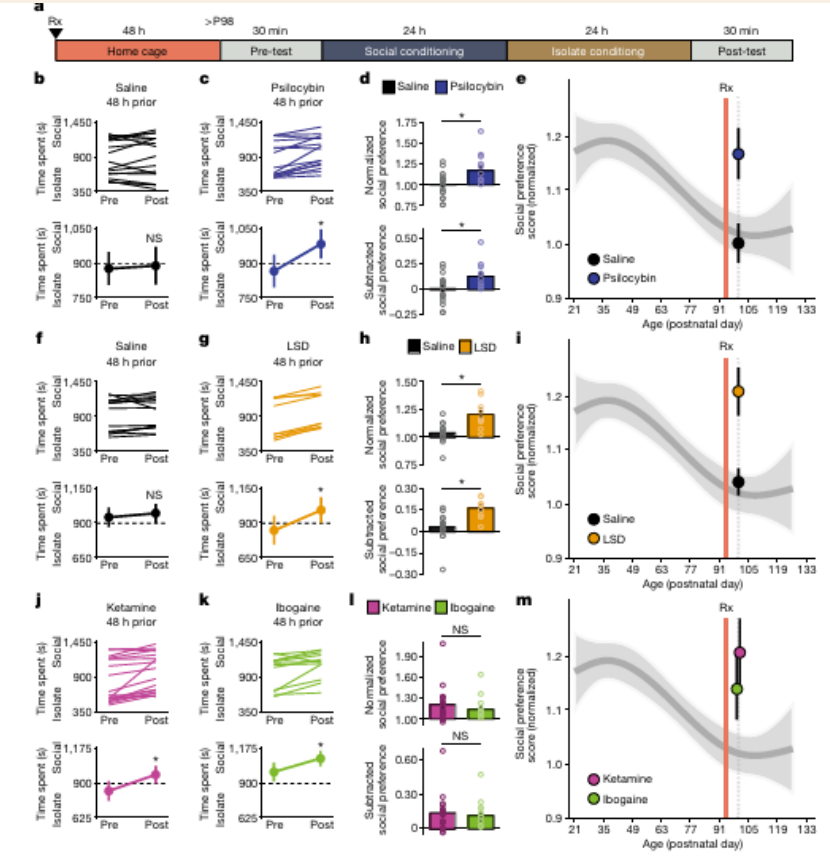
Biology, *12*(11), 1380. https://doi.org/10.3390/biology12111380



FRONTIERS IN PSYCHIATRY, DECEMBER 2021
VOL 12 - 2021 | HTTPS://DOI.ORG/10.3389/FPSYT.2021.800072

ALL PSYCHEDELICS MAY INDUCE METAPLASTICITY
THROUGH DOWNSTREAM GENETIC CHANGES MANY INFLUENCING GENES IN THE EXTRA-CELLULAR MATRIX (AT LEAST IN MICE)

ACCOUNTS FOR EFFECTS ON RE-OPENING CRITICAL SOCIAL LEARNING



In a rapid onset, context dependent (age), and durable fashion, the critical social learning period is open proportionally to the duration of effect in humans.

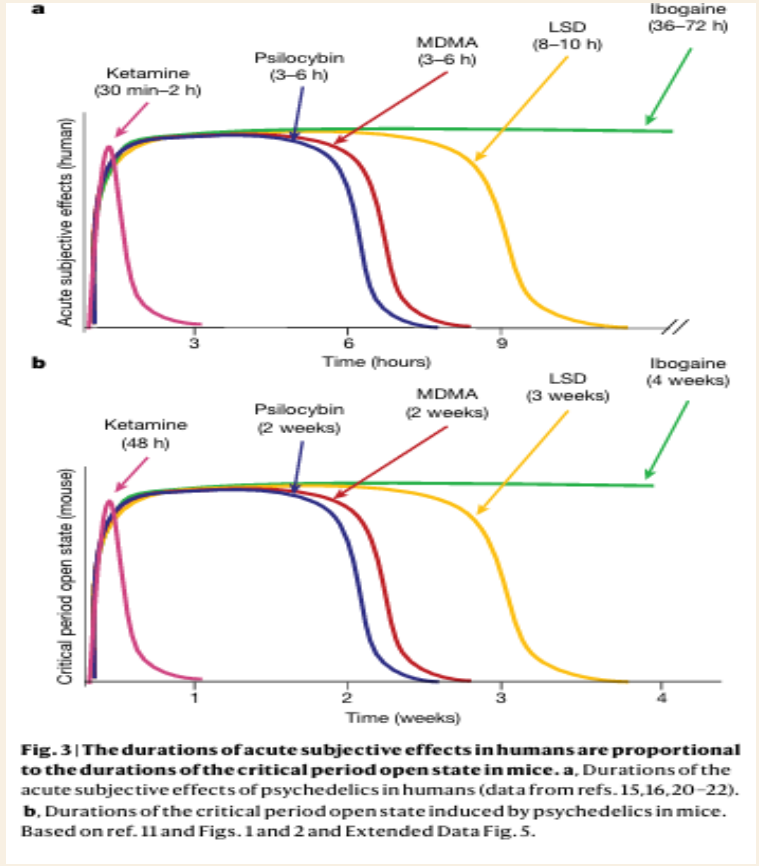


Fig. 3 | The durations of acute subjective effects in humans are proportional to the durations of the critical period open state in mice. a, Durations of the acute subjective effects of psychedelics in humans (data from refs. 15,16,20–22). **b**, Durations of the critical period open state induced by psychedelics in mice. Based on ref. 11 and Figs. 1 and 2 and Extended Data Fig. 5.

Nature June 2023, Issue 618, 790-798

HISTORY OF MDMA

3,4 methylenedioxymethamphetamine

- First synthesized by chemist Anton Kollisch working at Merck Pharmaceuticals in Germany in 1912, patent in 1914
- Rediscovered by Alexander "Sasha" Shulgin, eventually fired by DOW—self trials began in 1976 officially published in 1978
- MDA, patented in 1960 is used to treat anxiety in the 1960-1970s, used as adjunct to psychotherapy; recreational use too
- 1970s Controlled Substances Act makes MDA Schedule I. Soon after, MDMA confiscated in 1972 in a Chicago recreational setting by law enforcement
- 1973 US Army revealed that conducted animal toxicology studies at U of Mi to test phenylethylamines, including MDA. in the 1950s to establish safe doses
- September 27, 1976 Shulgin used 81 mg, and felt psychoactive effects

HISTORY OF MDMA

- Shulgin contacts Leo Zeff , PhD, and retired US Army Lt Colonel: *"stripped away the ego's defense mechanisms and returned the user to a primordial state of innocence*."
- Zeff goes onto train 150 therapists and legally treats 4000 patients with MDMA-AT until 1985
- 1980s over 1000 psychiatrists and therapists have used MDMA in their practices—estimated ½ million doses (no deaths reported)
- First clinical reports published in 1985, with pooled results and opinions of over 35 clinicians and researchers
- *Journal of Psychoactive Drugs*, Dec 1986 publishes paper George Greer, M.D., and his wife Requa Tolbert, RN "decrease the fear response to a perceived threat to a patient's emotional integrity, leading to a corrective emotional experience that probably diminishes the pathological effects of previous traumatic experiences"; 90% reported benefits at 1 year

HISTORY OF MDMA

- 1980s Raves and Deaths: Ecstasy, Molly, Vitamin E, ADAM
- Ralph Metzner, PhD: 1983, coined “Empathogen”—”a profound state of empathy in self and other”
- David Nichols, PhD: 1986 debated “Entactogen” Greek and Latin “producing a touch within”
- Petition made to have MDMA rescheduled and a DEA Administrative Law Judge presiding over the case determines Schedule III
- 1986 DEA decides it should be Schedule I
- 1986 MAPS founded by Rick Doblin, and MAPS PBC provides funding for all the randomized and PBO controlled Phase 2 and 3 studies
- Lykos Therapeutics submission for NDA in 2024

HISTORY OF MDMA

INITIAL STUDIES

- 1992 Approved Phase I Study: Charles Grob, M.D.
    - MDMA safe; Moderate increase in heart rate, blood pressure, body temperature; No negative effects

International Journal of Drug Policy (1998), vol 9 (3)

- 2017 Pooled analysis of 6 Double Blind Active/PBO controlled Phase II multi-site studies of 103 subjects with TR PTSD revealed 54% no longer met criteria for PTSD, compared to 23% in the control group. (Cohen's effect sizes d= 1.1-2.8)

FDA: Breakthrough Therapy Designation and helped design the Phase III trials

ECSTASY ≠ MDMA

MDMA purity tested in studies/ pharmaceutical grade

Adulterated with cocaine, amphetamines, opiates, ephedrine in various combinations >50% of pills; often taken with other substances

1-2 up to 10 pills at a time of 75 mg-300 mg

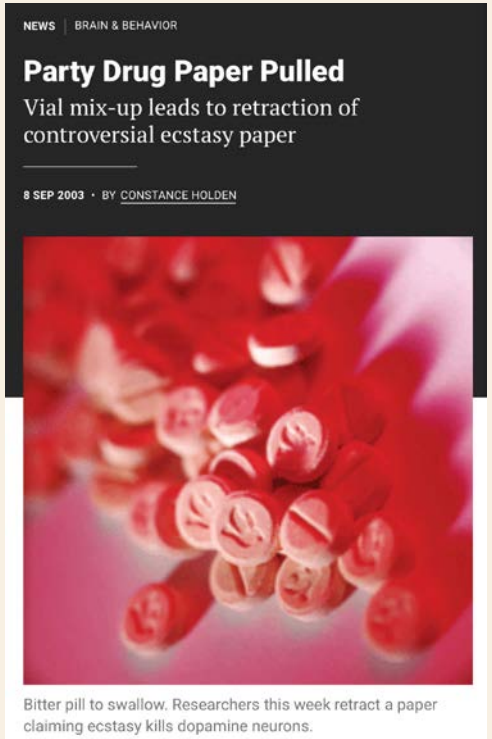
(LD50 of MDMA is 10-20 mg/kg)

Ecstasy typically taken in an uncontrolled, non-clinical environment

2001 study published CMAJ, 87 deaths reviewed:

Most Fatalities linked to Hyperthermia, hyponatremia, CV

CMAJ 2001 Oct 2; 165 (7); 917-928


NEWS | BRAIN & BEHAVIOR

Party Drug Paper Pulled

Vial mix-up leads to retraction of controversial ecstasy paper

8 SEP 2003 · BY CONSTANCE HOLDEN

Bitter pill to swallow. Researchers this week retract a paper claiming ecstasy kills dopamine neurons.

Reports of Neurotoxicity in 2002 study by George Ricuarte demonstrating fatal DA toxicity in 20% of primates retracted in 2003

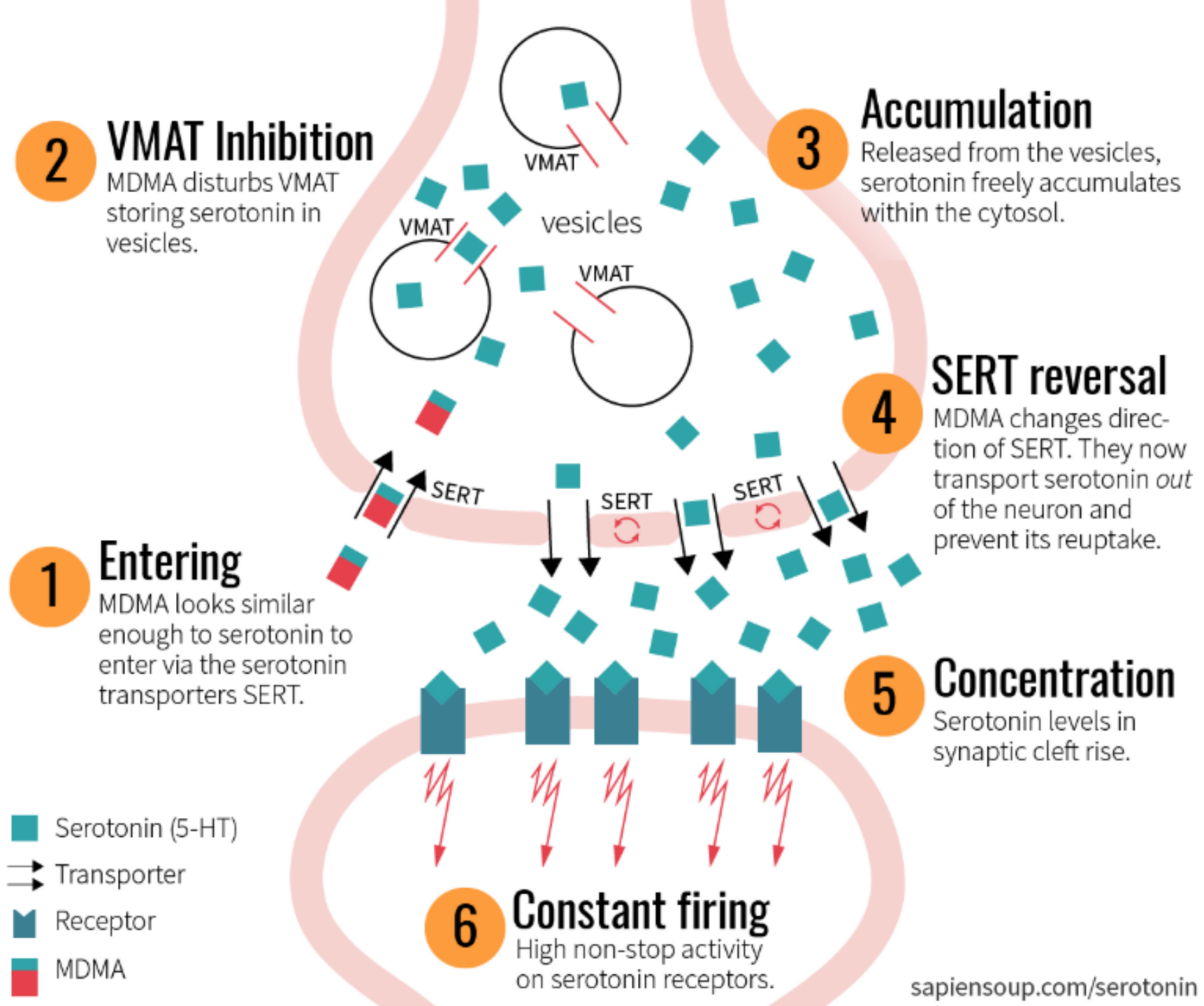
Chronic Lifetime use associated with decreased SERT density

VHD related to 5HT2B activity (LT use of over 300 tabs)

Estimates of death in 1st time use of ecstasy are 1/2000-1/50,000

MECHANISM OF ACTION

Risk of 5HT Syndrome is higher with MAOI; SSRI's decrease effect



MECHANISM OF ACTION

- Some Activity as 5HT2A agonist but primarily disrupts VMAT and SERT (some visuals)
- Blocks NE and DA as well, with less affinity than Serotonin
  - Sympathomimetic effects: increased heart rate, temp, BP hyperhidrosis
  - Help with attention and memory/reward
- Oxytocin plasma levels reach up to 4x greater than baseline
  - Accounts for some of the unique therapeutic actions:
    - Increased trust (therapeutic alliance) and empathy; decreased avoidance
    - Increased openness and connectedness; prosocialility is increased
    - Modulates encoding of stimuli as aversive vs. neutral /social and emotional processing shifts
    - Activation of Oxytocin Receptors , especially in NA reopens up previously closed critical learning period—resulting in neuroplasticity that temporarily enhances social reward learning (rats)

      Nature 2019; 569: 116-120
- Also demonstrates increases in Cortisol (extinction learning), Vasopressin, Prolactin

MECHANISM OF ACTION

Decreases acute amygdala activity
Anxiolytic, attenuated fear in memory recall, neutral valence while retrieving memories accurately, allowing positive emotions

Increased blood flow to the vmPFC
Hypoactive in PTSD, (inhibits amygdala); Combined with psychotherapy allows reconsolidation of memory for fear/threat extinction

Neuroscientist 2009 Apr 9; 15 (5) 540-548

Alterations in amygdala-hippocampal RSFC
Changes after treatment correlated with CAP5 responses

Decreased activity in the Insular Cortex
Modification of the Salience Network, interpretation of interoception, and cognitive control

Increased neuronal activity/BDNF (rats)
measured by c-fos+, rat studies correlated with increases in BDNF in the amygdala, PFC, NA, dentate gyrus region of the HC
Neuroplastogen/Psychoplastogen: increased dendritic spines and length after treatment/connectivity

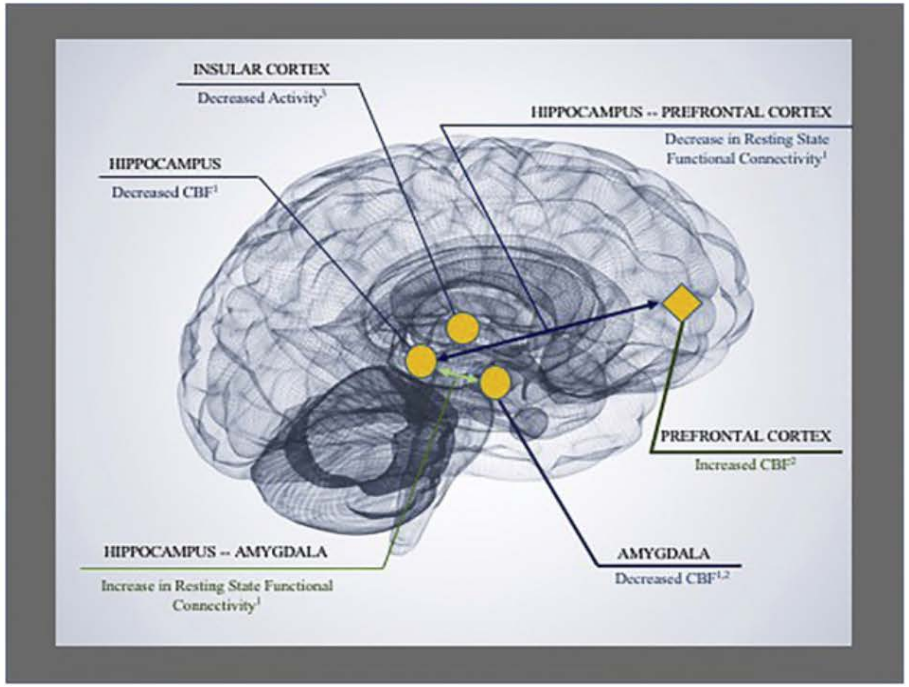


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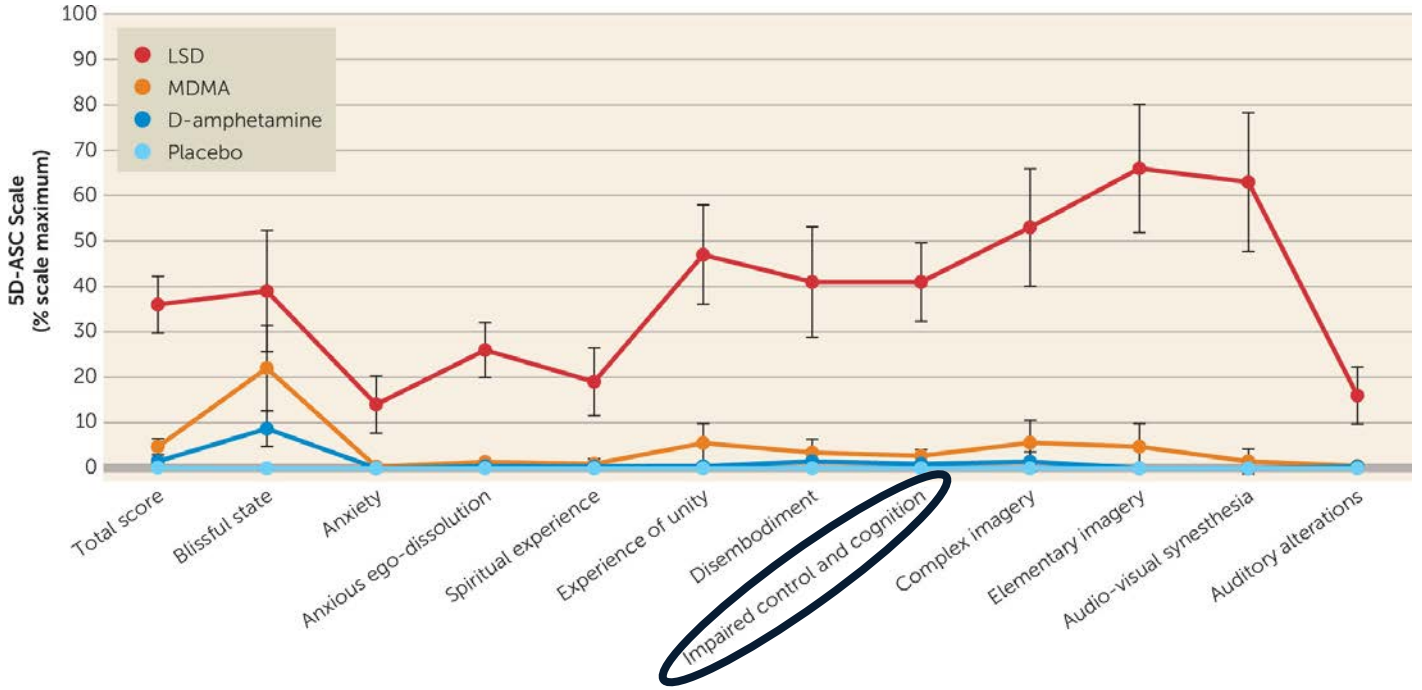
Fig. 1. MDMA modulates brain regions involved in Learning, Memory, Emotion, and Attention. In neuroimaging studies of healthy individuals, MDMA reduced cerebral blood flow (CBF) to amygdala (Carhart-Harris et al., 2015)[1] (Gamma et al., 2000)[2] and hippocampus (Carhart-Harris et al., 2015)[1]; decreased resting state connectivity between the medial prefrontal cortex (mPFC) and hippocampus (Carhart-Harris et al., 2015)[1]; decreased activity in the insular cortex (Walpola et al., 2017)[3]; and increased CBF in the ventromedial prefrontal cortex (Gamma et al., 2000)[2].

Progress in Neuropsychopharmacology & Biological Psychiatry,; 84 (2018) 221-228

MDMA IS EXHIBITS DIFFERENT PROPERTIES THAN AMPHETAMINES AND CLASSIC PSYCHEDELICS–WHILE THERE IS A BLISSFUL STATE, NO IMPAIRMENT TO COGNITION OR CONTROL OCCURS



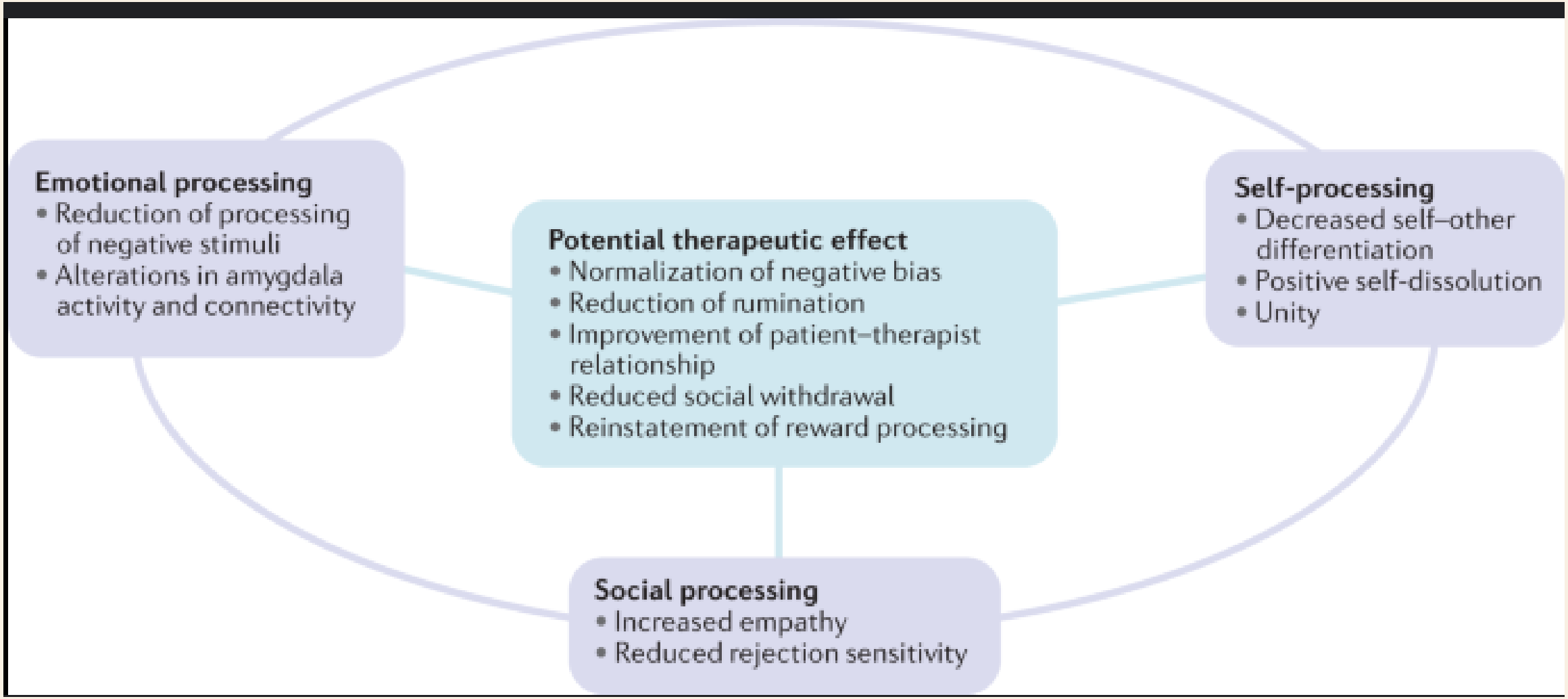
Ketanserin does not attenuate MDMA effects

aDoses were 100 μg oral for LSD, 125 mg oral for MDMA, and 40 mg oral for D-amphetamine versus inactive placebo. Data are presented as mean and 95% confidence intervals. Adapted from Holze et al. (20).

DOI: (10.1176/appi.ajp.20230681)

American Journal of Psychiatry January 2025, Volume 182 (1), p. 92

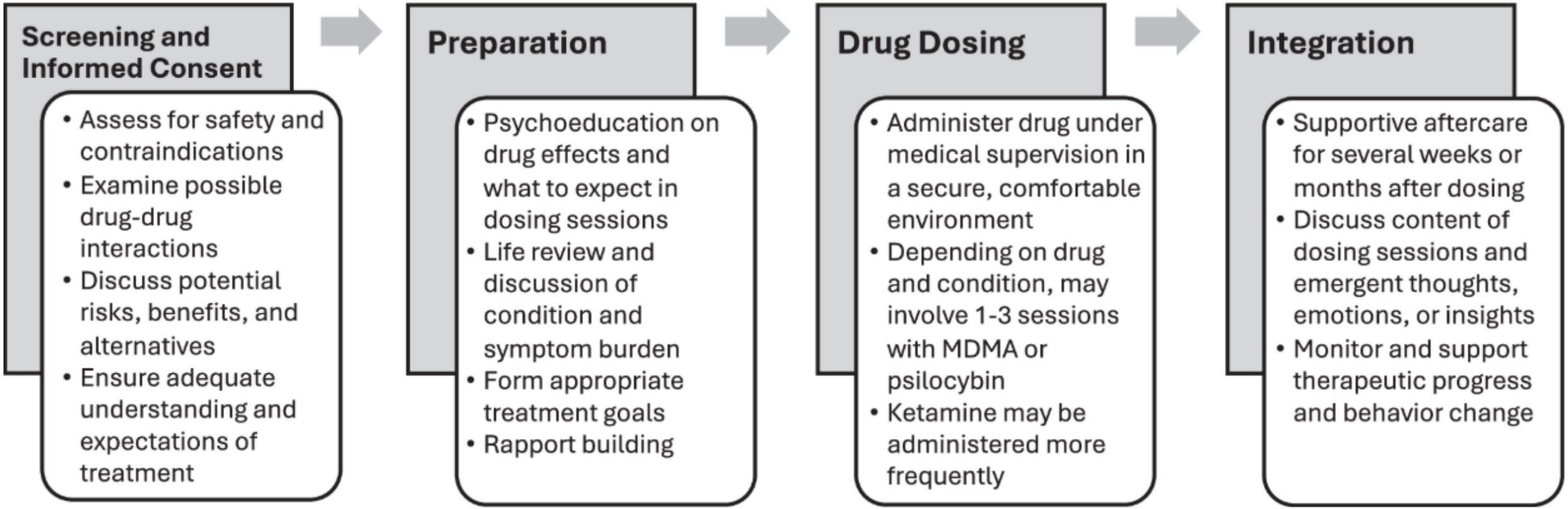
ALONG WITH THREAT REDUCTION, FEAR EXTINCTION and COGNITIVE CHANGES, SOCIAL-EMOTIONAL CHANGES OCCUR



Nat Rev Neurosci **21**, 611–624 (2020). https://doi.org/10.1038/s41583-020-0367-2

Fig. 1

From: Deconstructing the trip treatment: are hallucinogenic effects critical to the therapeutic benefits of psychedelics?



General Phases of Psychedelic Therapy.

NPP–Digit Psychiatry Neurosci **3**, 22 (2025). https://doi.org/10.1038/s44277-025-00043-y

WHY MDMA-AT?

"The basic premise of this treatment approach is that the therapeutic effect is not due simply to the physiological effects of the medicine; rather, it is the result of an interaction between the effects of the medicine, the therapeutic setting and the mindsets of the participant and the therapists."

MDMA is the CATALYST for the participant: Patient centered

Co-Therapists help establish the CONTAINER in Preparation/Dosing/Integration

- Psychoeducation
- Develop Rapport
- Set and Setting
- Therapeutic Attitude:
  - Safety and wellbeing for the participant are primary
  - Supportive approach during the sessions, especially during dosing sessions
  - Continued Development of therapeutic alliance and trust
  - **Nondirective approach—trusting the inner healing intelligence and inner wisdom of the participant to heal their own trauma**
  - "Invitation rather than direction": attitude of openness and curiosity, are encouraged (PAT "beginner's mind")
  - **Healing is derived from within the participant;** MDMA and the therapists facilitate process, but are not the source
  - **Intervention is via guidance or redirection, to facilitate the processing, vs. encouraging avoidance, allowing for respect for the defense mechanisms**
  - Non-invasive empathic witness, support the emotional experience, minimize distraction
  - Maximize the inner experience, ensuring the participant is safe and not re-traumatized by any internal conflicts
  - **Address somatic manifestations** (breathing, consented touch)
- Integration (Consolidation) is to reinforce learning and insights of dosing sessions, make meaning, decide applications to current day life

"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.

The successful use of MDMA in therapy depends on 'the sensitivity and talent of the therapist who employs [it]'…

'The relationship should be oriented toward a general healing for the client, who should feel safe enough in the therapists' presence to open fully to new and challenging experiences.'

Establishing these conditions requires that the therapists carefully set the parameters of treatment…prepare the participant before each…session, and…provide appropriate support following the session so that the experience can be successfully integrated."

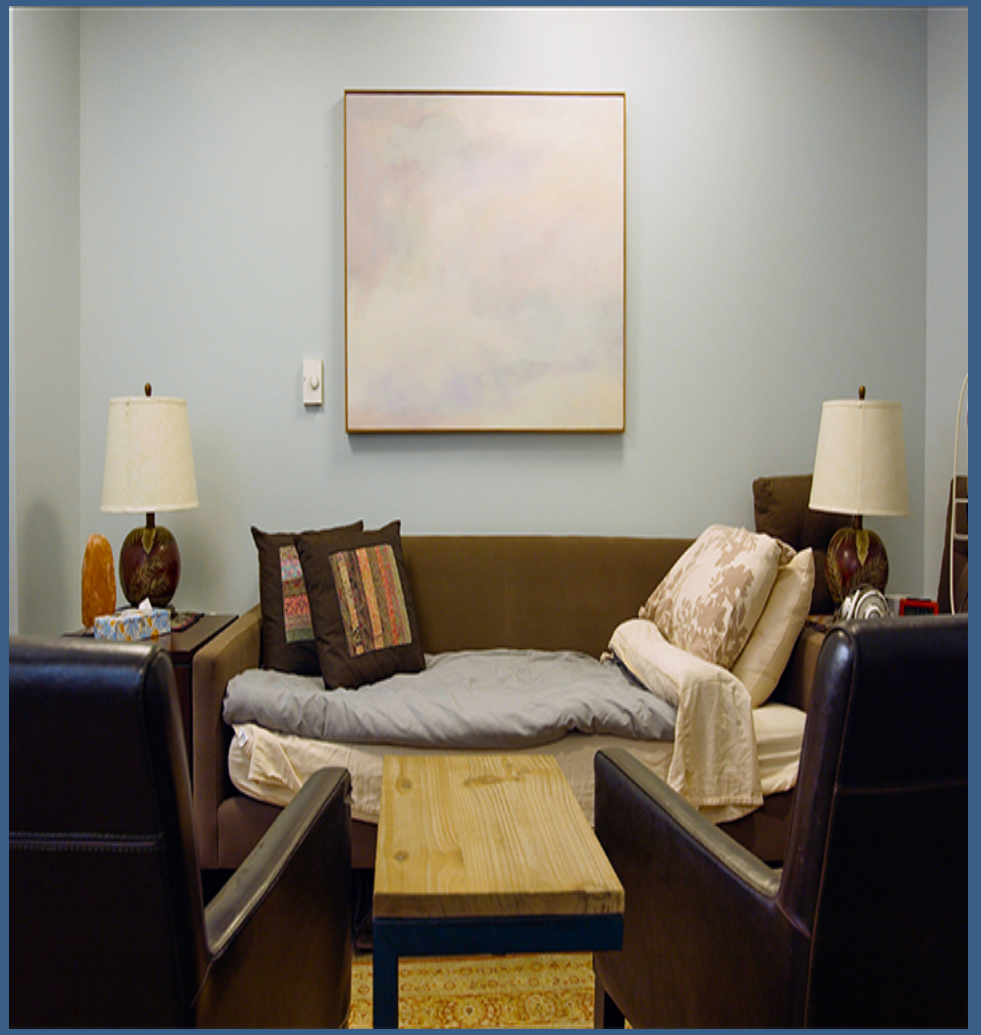
Mithoefer, M.; MAPS, A Manual for MDMA Assisted psychotherapy in the Treatment of Post Traumatic Stress Disorder v, 8.1 May 2017

PHASE III STUDY DESIGN MAPP1/MAPP2

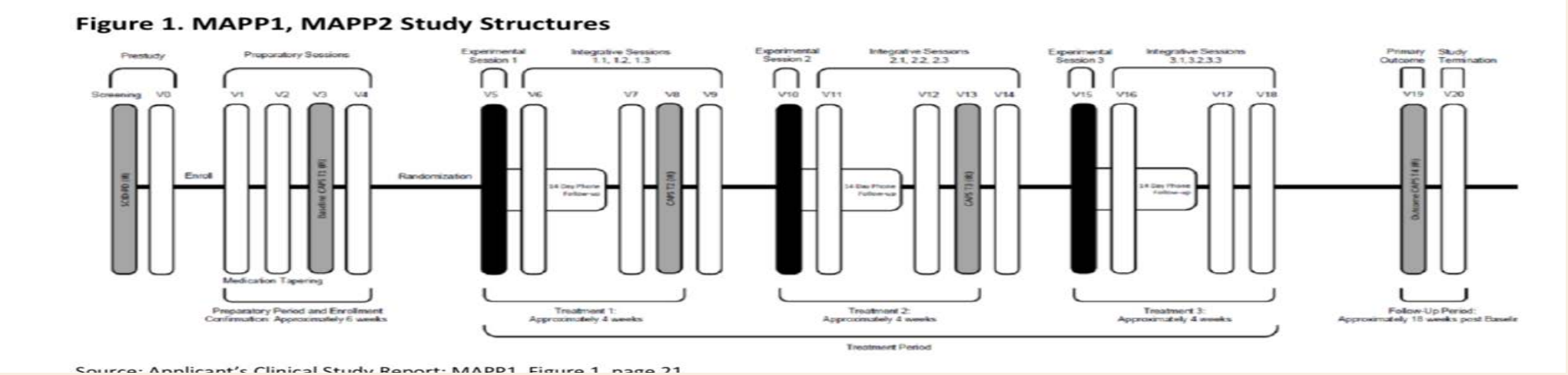
SCREENING: PCL-5 MAPP1 45/ MAPP2 40

EXCLUSIONARY CRITERIA:

Psychosis, BPI/Mania, DID
Current PD, ED with purging, MDD-Psychosis
Current Suicidality
Severe AUD/CUD (> 5 of 11 DSM5) in past 3 mos
(Mild/Mod A/C in past 3 mos OK)
Active Illicit or RX SUD in past 12 mos
CVD (including QTC prolongation)/Ablation 1yr Arr. free
Symptomatic Liver Dz or significant LFT elev
Hx of Hyponatremia or Hypothermia
Ketamine or KAT in past 12 weeks
No pain meds exc. 3 opiates (HC, M, C), gabapentin
Ongoing therapy or medication, incl. cannabis, STJW
MAPP2: MDMA/Ecstasy >10x/10 years or 1x in 6 mos
No prior MAPS study; no PTSD litigation



STUDY DESIGN MIDOMEFATAMINE



3 Preparation sessions, 90 minutes over 2 weeks
Dosing: (Fasting) standardized to 75 mg-125 mg po
Onset of action is 30-60 mins
Peak 75-120 mins (optional ½ dose)
Duration 3-6 hours with Baseline at 6 hours
Metabolism by CYP2D6 (auto inhibition), 2B6; T1/2 9 hours; MDA active
3 Integration sessions
Repeat dosing is done 1 month apart in studies
Phase 2 4 studies, under-powered to detect treatment effect
Phase 3 double blind, PBO controlled

<u>Primary Endpoint</u> CAPS-5
Baseline visit 3
Visits 8, 13, 19 (6, 10, 18 weeks after randomization)

<u>Secondary Endpoint</u> SDS

MAPP1: Severe PTSD (PCL ≥46/CAP-5 ≥35) **MAPP2:** Mod-Sev (PCL ≥40/CAP-5 ≥28)
MAPPUSX: All study participants given that were given PBO, offered Tx
MPLONG: Observational, LT F-up, anytime between 6 mos-2 years; assess durability, safety

Study (FDA phase)	Study design	Dose (mg)[b]	Group size (N)	Veterans/Combat trauma (N)	Clinical response at primary endpoint	Loss of PTSD diagnosis at primary endpoint	Loss of PTSD diagnosis at 12 months[c]	CAPS-IV/5 Between-group effect size of primary outcome (Cohen's d)
Mithoefer et al., 2011 (Phase 2) (106)	RCT; two closed-label MDMA sessions; open-label crossover of placebo arm for two more 125-mg sessions; primary outcome: CAPS-IV 2 months after second closed-label MDMA session.	125 and 0	125 mg: 12 0 mg: 8	125 mg: 1	125 mg: 10/12 (83%) 0 mg: 2/8 (25%)	125 mg: 10/12 (83%) 0 mg: 2/8 (25%)	All: 14/16 (88%)[d]	1.24
Oehen et al., 2013 (Phase 2) (108)	RCT; three closed-label MDMA sessions; open-label crossover of placebo arm for three more 125-mg sessions; primary outcome: CAPS-IV 3 weeks after third closed-label MDMA session.	125 and 25	125 mg: 8 25 mg: 4	None	125 mg: 4/8 (50%) 25 mg: 0/4 (0%)	125 mg: 0/8 (0%) 25 mg: 0/4 (0%)	All: 5/12 (42%)	
Mithoefer et al., 2018 (Phase 2) (86)	RCT; two closed-label MDMA sessions; 125-mg arm did one more open-label session; 75-mg and 30-mg arms crossed over and did three more 100–125-mg open-label sessions; primary outcome: CAPS-IV 1 month after second closed-label MDMA session.	125, 75, and 30	125 mg: 12 75 mg: 7 30 mg: 7	125 mg: 9 75 mg: 7 30 mg: 6	125 mg: 8/12 (67%) 75 mg: 7/7 (100%) 30 mg: 2/7 (29%)	125 mg: 7/12 (58%) 75 mg: 6/7 (86%) 30 mg: 2/7 (29%)	125 mg: 8/11 (72%) 75 mg: 5/7 (71%) 30 mg: 3/6 (50%)	1.1[e], 2.8[f]
Ot'alora et al., 2018 (Phase 2) (109)	RCT; two closed-label MDMA sessions; 125-mg and 100-mg arms did one more open-label session; 40-mg arm crossed over and did three more 100–125 mg open-label sessions; primary outcome: CAPS-IV 1 month after second closed-label MDMA session.	125, 100, and 40	125 mg: 13 100 mg: 9 40 mg: 6	[g]	125 mg: 6/12 (50%) 100 mg: 5/9 (56%) 40 mg: 1/6 (17%)	125 mg: 5/12 (42%) 100 mg: 4/9 (44%) 40 mg: 2/6 (33%)	All: 19/25 (76%)	1.12, 0.73[h]
Mitchell et al., 2021 (Phase 3) (2)	RCT; three closed-label MDMA sessions, no open-label cross-over; primary outcome: CAPS-5 1 month after third closed-label MDMA session.	80–120 and 0[i]	80–120 mg: 46 0 mg: 44	80–120 mg: 10 0 mg: 6	[j]	80–120 mg: 28/42 (67%) 0 mg: 12/37 (32%)		0.91
Mitchell et al., 2023 (Phase 3) (3)	RCT; three closed-label MDMA sessions, no open-label cross-over; primary outcome: CAPS-5 1 month after third closed-label MDMA session.	80–120 and 0[i]	80–120 mg: 53 0 mg: 51	80–120 mg: 9 0 mg: 7	80–120 mg: 45/52 (87%) 0 mg: 29/42 (69%)	80–120 mg: 37/52 (71%) 0 mg: 20/42 (48%)		0.70

	MAPP1			MAPP2		
Analysis Population	**Midomafetamine**	**Placebo**	**Total**	**Midomafetamine**	**Placebo**	**Total**
# Completed Visit 19	**42**	**37**	**79**	**53**	**43**	**96**
# Enrolled in MPLONG (analysis subset)	30	30	60	45	37	82
MPLONG Effectiveness subset	**27**	**29**	**56**	**44**	**37**	**81**
# completed MPLONG	26	29	55	43	37	80
# ongoing	0	0	0	0	0	0
# terminated MPLONG early	4	1	5	2	0	2

Source: Table 6 and Table 8 in MAPP1 CSR; Table 5 and Table 7 MAPP2 CSR; Table 14.1-1.1, Table 14.1-1.2, Table 14.1-2.1, and Table 14.1-2.2 in MPLONG ISE from durability update submitted to eCTD Seq 0047.

Table 4. Demographics and Baseline Characteristics of the Safety Set for MAPP1 and MAPP2

	MAPP1			MAPP2		
Variable	**Midoma-fetamine N=46**	**Placebo N=44**	**Total N=90**	**Midoma-fetamine N=53**	**Placebo N=51**	**Total N=104**
Sex						
Female	27 (58.7)	32 (72.7)	59 (65.6)	32 (60.4)	42 (82.4)	74 (71.2)
Male	19 (41.3)	12 (27.3)	31 (34.4)	21 (39.6)	9 (17.6)	30 (28.8)
Age (years)						
Mean (SD)	43.6 (12.9)	38.2 (10.4)	40.9 (11.9)	38.2 (11.0)	40.0 (9.6)	39.1 (10.3)
Ethnicity						
Hispanic or Latino	5 (10.9)	3 (6.8)	8 (8.9)	17 (32.1)	11 (21.6)	28 (26.9)
Not Hispanic or Latino	41 (89.1)	40 (90.9)	81 (90.0)	36 (67.9)	39 (76.5)	75 (72.1)
Missing	0	1 (2.3)	1 (1.1)	0	1 (2.0)	1 (1.0)

	MAPP1			MAPP2		
Variable	**Midoma-fetamine N=46**	**Placebo N=44**	**Total N=90**	**Midoma-fetamine N=53**	**Placebo N=51**	**Total N=104**
Race						
American Indian or Alaska Native	3 (6.5)	0	3 (3.3)	0	2 (3.9)	2 (1.9)
Asian	2 (4.3)	5 (11.4)	7 (7.8)	5 (9.4)	6 (11.8)	11 (10.6)
Black or African American	0	2 (4.5)	2 (2.2)	5 (9.4)	3 (5.9)	8 (7.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0	1 (2.0)	1 (1.0)
White	39 (84.8)	30 (68.2)	69 (76.7)	37 (69.8)	32 (62.7)	69 (66.3)
Multiple	2 (4.3)	6 (13.6)	8 (8.9)	6 (11.3)	7 (13.7)	13 (12.5)
Missing	0	1 (2.3)	1 (1.1)	0	0	0
Baseline CAPS-5 Total Severity Score						
Mean (SD)	44.0 (6.0)	44.2 (6.2)	44.1 (6.0)	39.4 (6.6)	38.7 (6.7)	39.0 (6.6)

Source: Adapted by Statistical Reviewer from Table 14.1.3.1 in MAPP1 study report and Table 14.1.3.1 in MAPP2 study report.
Abbreviation: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the Diagnostic and Statistical Manual for Mental Disorders Version 5

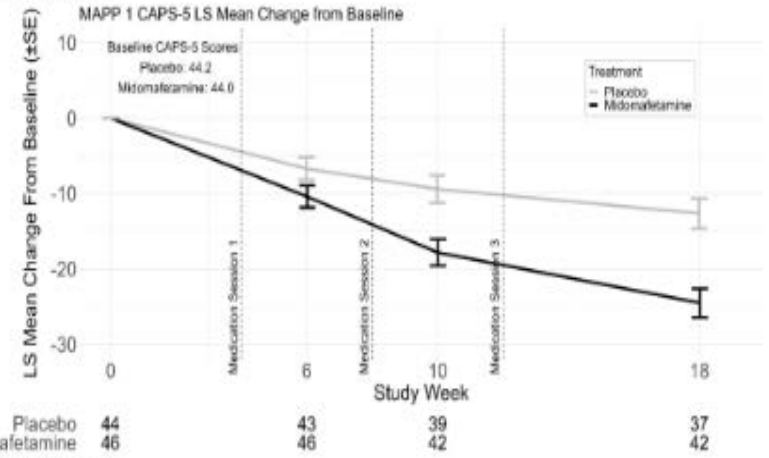
50% participants BIPOC in MAPP2

FDA.gov NDA/BLA Document 215455 June 4, 2024 p. 1-82

MIDOMAFETAMINE PHASE III RESULTS

Figure 2. LS Mean Change From Baseline in CAPS-5 Total Score Over Time

a) **Study MAPP1**



b) **Study MAPP2**

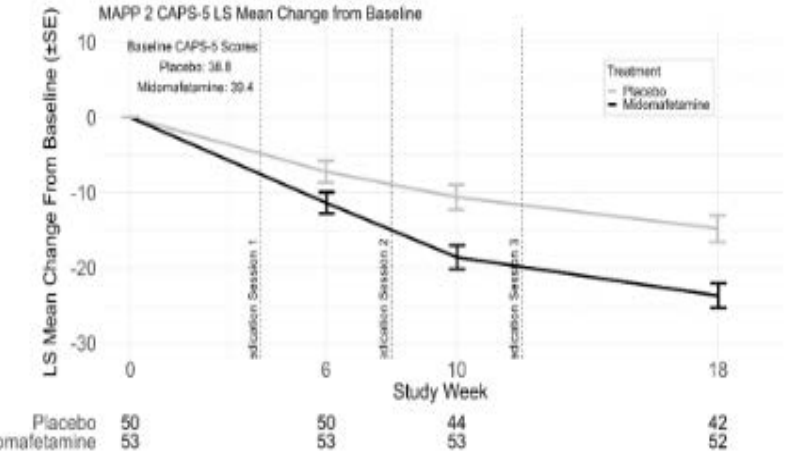


Table 5. Primary Endpoint: Change From Baseline in CAPS-5 Total Severity Score at Visit 19 (Week 18)—*De Jure* Estimand (mITT Population)

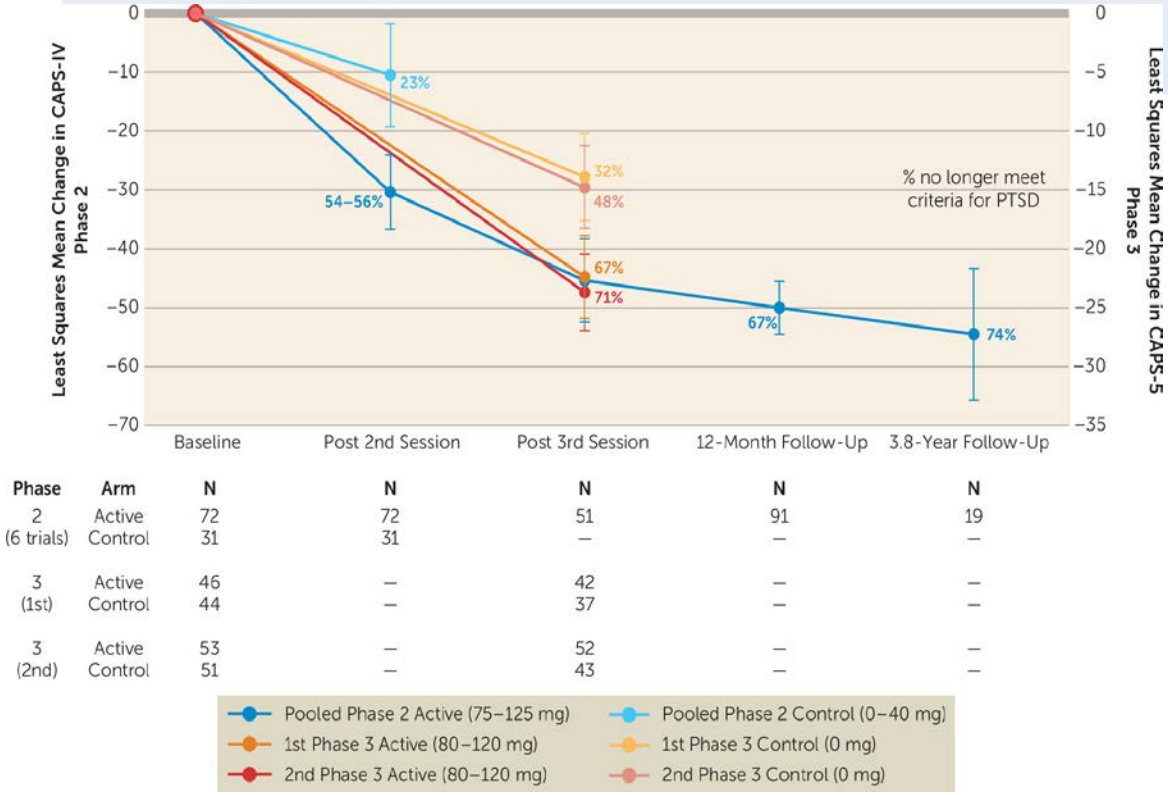
	MAPP1		MAPP2	
Variable	Midomafetamine (N=46)	Placebo (N=44)	Midomafetamine (N=53)	Placebo (N=50)
Mean baseline score (SD)	44.0 (6.01)	44.2 (6.15)	39.4 (6.64)	38.8 (6.63)
Visit 19				
N	42	37	52	42
Raw mean (SD)	19.5 (13.50)	29.8 (12.37)	15.8 (12.40)	23.3 (12.79)
LS Mean change from baseline (95% CI)[a]	-24.50 (-28.28, -20.71)	-12.64 (-16.61, -8.66)	-23.69 (-26.94, -20.44)	-14.78 (-18.28, -11.28)
Placebo-subtracted difference (95% CI)[a]	-11.86 (-17.41, -6.32)		-8.91 (-13.70, -4.12)	
p-value[a]	<0.0001		0.0004	

Source: MAPP1 CSR Table 17; MAPP2 CSR Table 16.
The *de jure* estimand does not include data after participants discontinued treatment.
[a] LS Mean, LS mean difference, 95% CI and p-value of treatment effect at Visit 19 were obtained from an MMRM model with treatment group, visit, treatment group by visit interaction, site, and dissociative subtype as fixed effect, and baseline CAPS-5 as a covariate.
Abbreviations: CAPS-5, Clinician-Administered Posttraumatic Stress Disorder Scale for the DSM-5; CI, confidence interval; CSR, clinical study report; DSM-5, Diagnostic and Statistical Manual of Mental Disorders version 5; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed models repeated measures; N, total number of participants in each group; PTSD, posttraumatic stress disorder

10 point drop in score is clinical meaningful change

MAPP1 M62%/PBO37% lose PTSD 1 month; d=0.91
MAPP2 M71%/PBO48% lose PTSD 1 month; d=0.70

FDA.gov NDA/BLA Document 215455 June 4, 2024 p. 1-82



Phase	Arm	N	N	N	N	N
2 (6 trials)	Active	72	72	51	91	19
	Control	31	31	–	–	–
3 (1st)	Active	46	–	42	–	–
	Control	44	–	37	–	–
3 (2nd)	Active	53	–	52	–	–
	Control	51	–	43	–	–

Remission rates (defined as no PTSD dx and CAP-5 ≤ 11:)
MAPP1 33% A vs 5% C
MAPP2 46% A vs 21% C

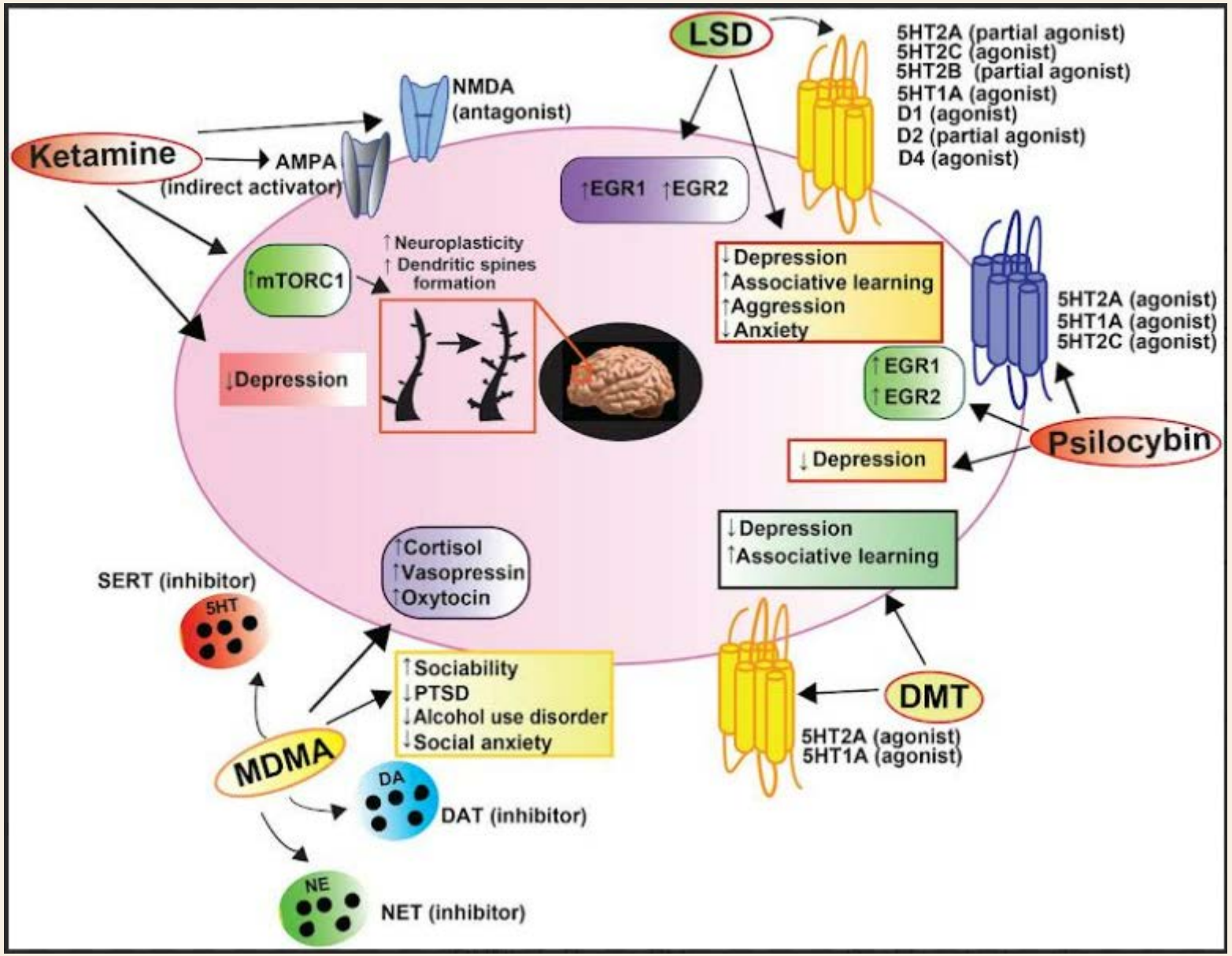
aResults pooled from all phase 2 and 3 clinical trials that used the Clinician-Administered PTSD Scale (CAPS-IV or CAPS-5) as the primary outcome. Data are presented as mean and 95% confidence intervals. Adapted from published data (1–3, 86, 106, 108, 109, 119, 129, 153, 154).

DOI: (10.1176/appi.ajp.20230681)

SO WHY DID FDA REJECT THE NDA?

1. EFFICACY/DURABILITY
2. MDMA assists a type of THERAPY
3. UNBLINDING/EXPECTANCY BIAS
4. SAFETY: AE, Ethics, Labs/EKG
5. ABUSE POTENTIAL

MECHANISM OF ACTION OF DIFFERENT PSYCHEDELICS:



Journal of Neuroscience Feb 2021, 41 (5) 891-900

DISCLOSURES

ROB MCCLURE, MD, DIRECTOR, UNC INTERVENTIONAL PSYCHIATRY SERVICE, ASSOCIATE PROFESSOR, UNC DEPARTMENT OF PSYCHIATRY, CHAPEL HILL, NC USA

UNC SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY

Foundation of Hope

Pilot Study of Psilocybin-Assisted Therapy in Treatment-Resistant MDD (2023)

Open Label Trial of rTMS in Post-Partum Depression (2010)

Schizophrenia & Genomic Regions Implicated in Human Evolution (2008)

UNC Healthcare

Open Label Trial of iTBS in Adolescents with MDD (2015)

NARSAD

Abnormal brain morphology in schizophrenia (2003)

Industry trials:

Neurolief

Trigeminal Occipital Neurostimulator Treatment-Resistant MDD (2022)

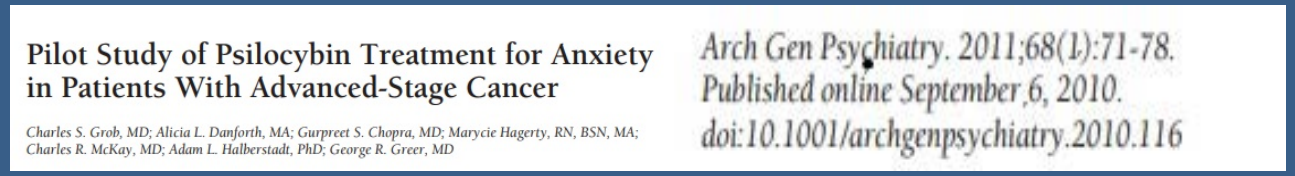
Janssen

Intranasal Esketamine MDD with SI adults and CAP (2017-2020)

Medtronics

Deep Brain Stimulation in Refractory OCD (2009)

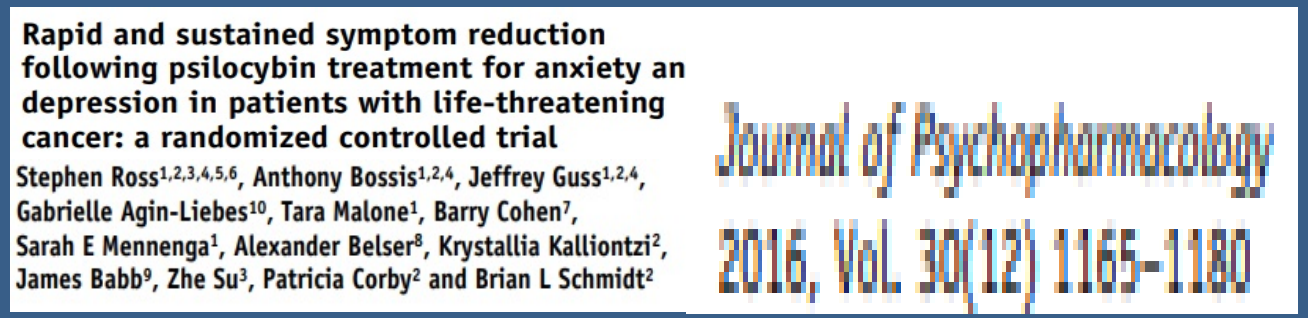
Psilocybin-assisted therapy and Cancer



Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer

Charles S. Grob, MD; Alicia L. Danforth, MA; Gurpreet S. Chopra, MD; Marycie Hagerty, RN, BSN, MA; Charles R. McKay, MD; Adam L. Halberstadt, PhD; George R. Greer, MD

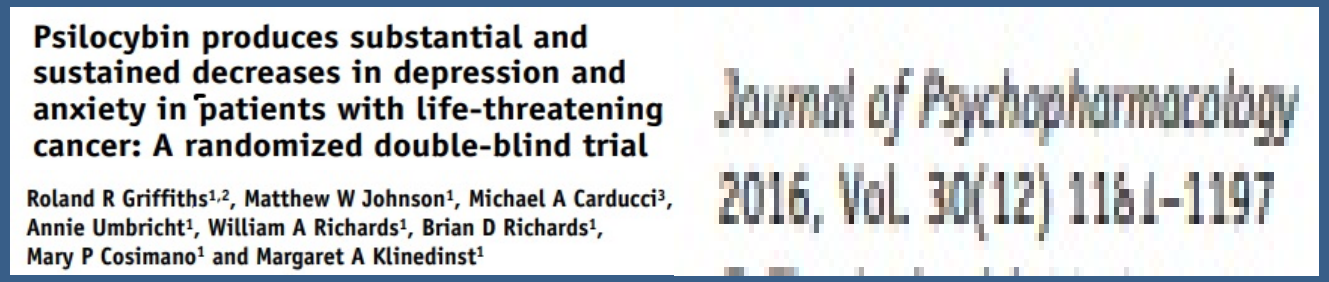
Arch Gen Psychiatry. 2011;68(1):71-78.
Published online September 6, 2010.
doi:10.1001/archgenpsychiatry.2010.116



Rapid and sustained symptom reduction following psilocybin treatment for anxiety an depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross[1,2,3,4,5,6], Anthony Bossis[1,2,4], Jeffrey Guss[1,2,4], Gabrielle Agin-Liebes[10], Tara Malone[1], Barry Cohen[7], Sarah E Mennenga[1], Alexander Belser[8], Krystallia Kalliontzi[2], James Babb[9], Zhe Su[3], Patricia Corby[2] and Brian L Schmidt[2]

Journal of Psychopharmacology
2016, Vol. 30(12) 1165–1180



Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths[1,2], Matthew W Johnson[1], Michael A Carducci[3], Annie Umbricht[1], William A Richards[1], Brian D Richards[1], Mary P Cosimano[1] and Margaret A Klinedinst[1]

Journal of Psychopharmacology
2016, Vol. 30(12) 1181–1197

Between 2010 and 2016, three RCTs of psilocybin at varying doses in terminal cancer patients diagnosed with adjustment disorder with anxiety showed

(Grob, 2011) A trend toward improvement in mood sustained after 6 months

(Ross, 2016) Improvement in anxiety and depression, sustained after at 6.5 months and 4.5 years

(Griffith 2016) Decreased depression and anxiety sustained for 6 months in 80% of participants (

Psilocybin assisted therapy alleviated anxiety and depression

MAJOR DEPRESSIVE DISORDER AND PSILOCYBIN

Promising results emerged supporting Psilocybin as a safe and effective treatment for MDD

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

JAMA Psychiatry. 2021;78(5):481-48
Published online November 4, 2020.

Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups

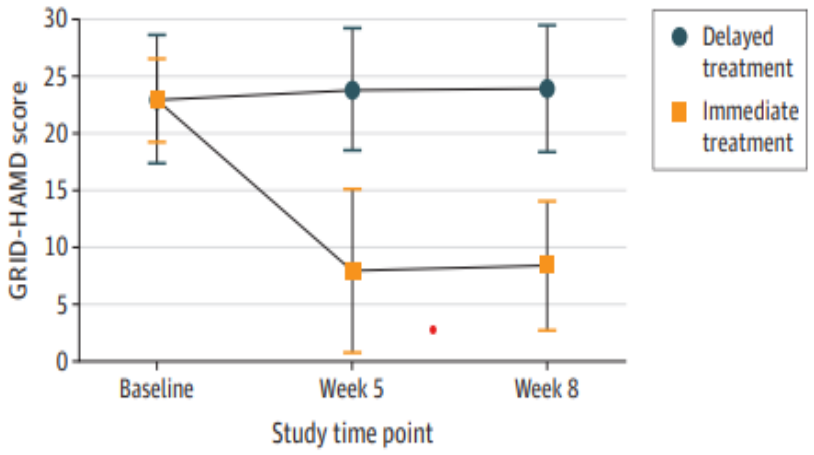
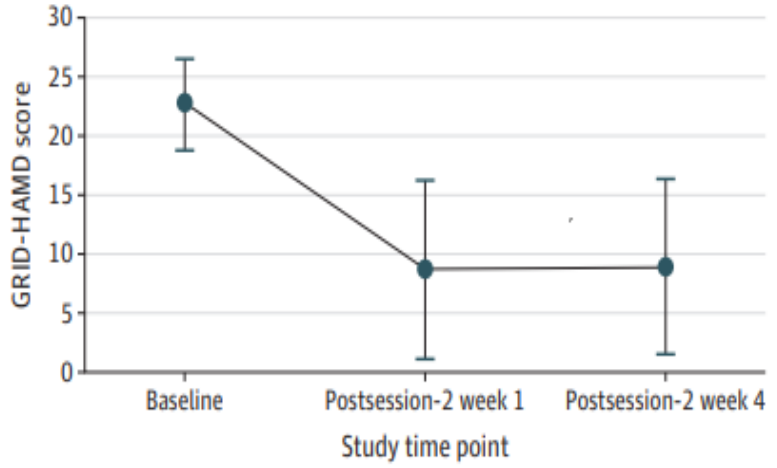


Figure 4. Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample

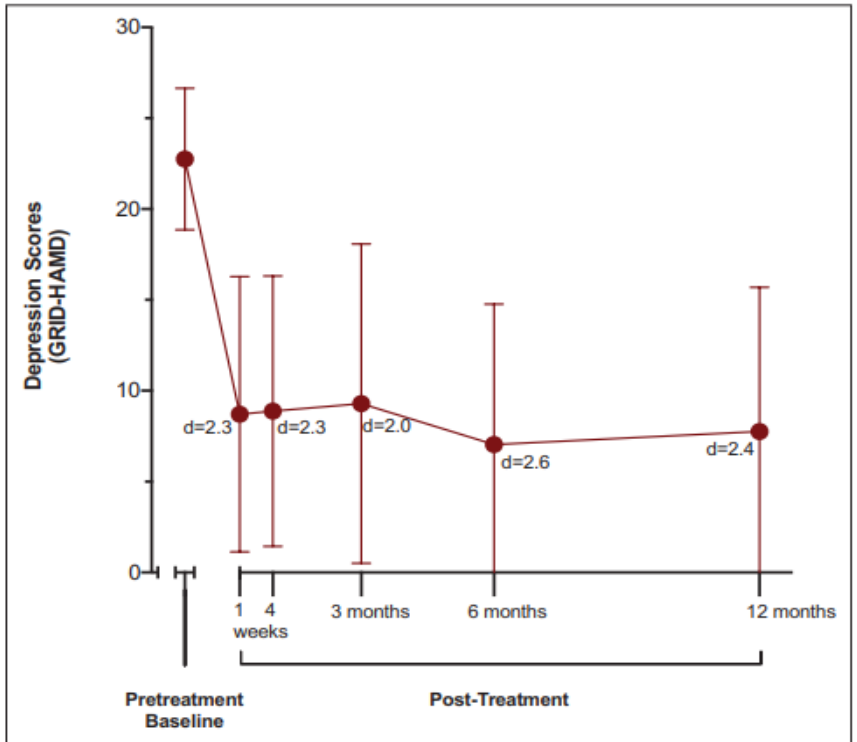


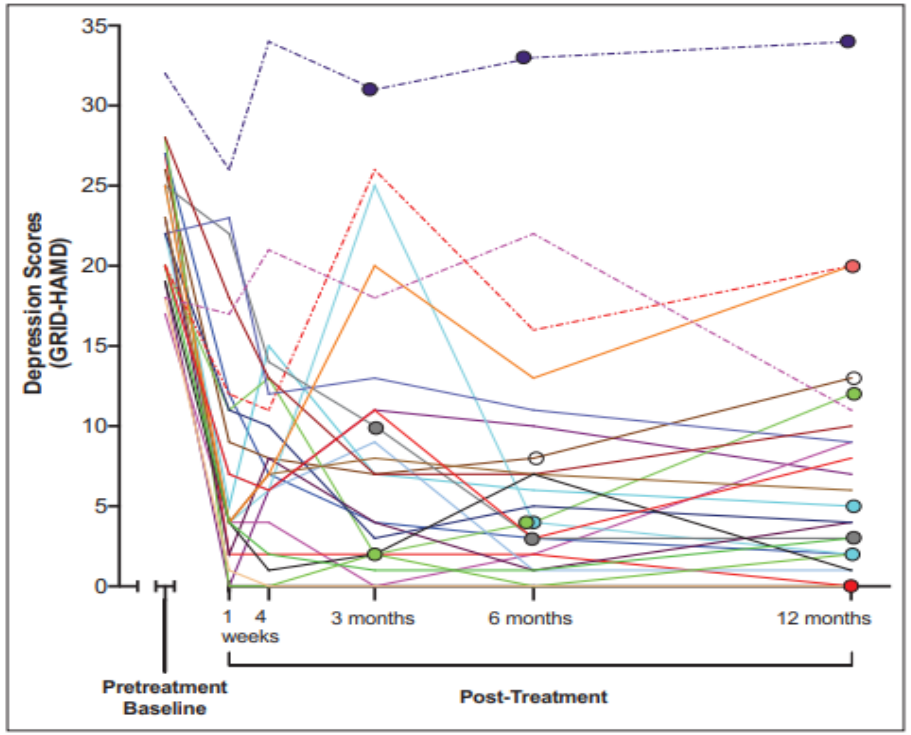
MAJOR DEPRESSIVE DISORDER AND PSILOCYBIN
12-MONTH FOLLOW UP:

Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up

Natalie Gukasyan[1], Alan K Davis[1,2], Frederick S Barrett[1], Mary P Cosimano[1], Nathan D Sepeda[1], Matthew W Johnson[1] and Roland R Griffiths[1,3]

Journal of Psychopharmacology
2022, Vol. 36(2) 151–158





MAJOR DEPRESSIVE DISORDER AND PSILOCYBIN

Trial of Psilocybin versus Escitalopram for Depression

N ENGL J MED 384;15 NEJM.ORG APRIL 15, 2021

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.

TREATMENT-RESISTANT MAJOR DEPRESSION AND PSILOCYBIN

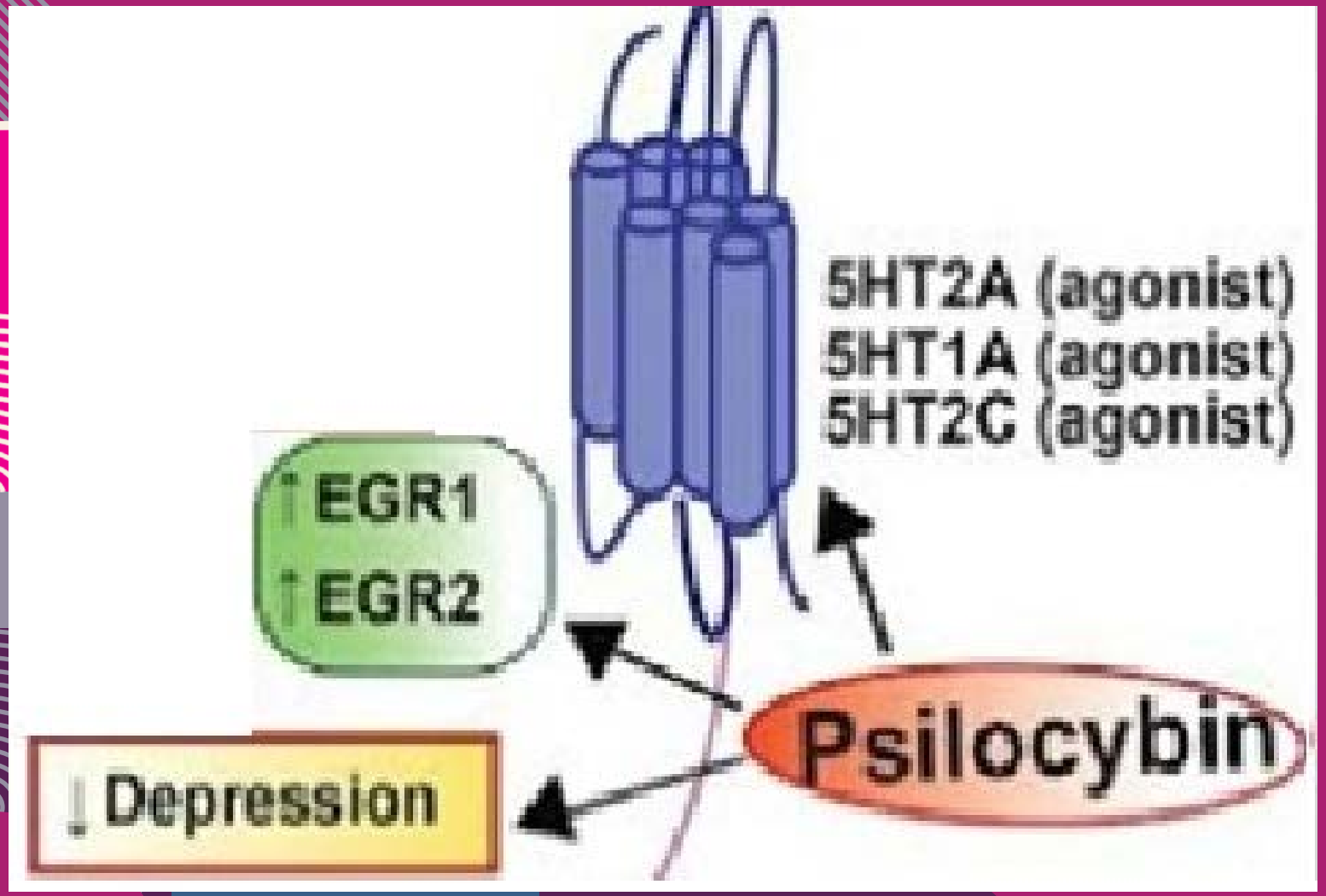
Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

Lancet Psychiatry 2016; 3: 619–27

Published Online May 17, 2016

Robin L Carhart-Harris, Mark Bolstridge, James Rucker, Camilla M J Day*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt*

TREATMENT-RESISTANT MAJOR DEPRESSION AND PSILOCYBIN :



Clinical studies and the definition of TRD

Two published reports from a small open-label study of the treatment of TRD with psilocybin

The first report (Carhartt-Harris, 2016) showed efficacy in 12 subjects, lasting 3 months

The second report (Carhart-Harris, 2018) showed efficacy in 19 subjects (12 + 7 more) subjects lasting 6 months

Journal of Neuroscience Feb 2021, 41 (5) 891-900

FIRST REPORT (2016)

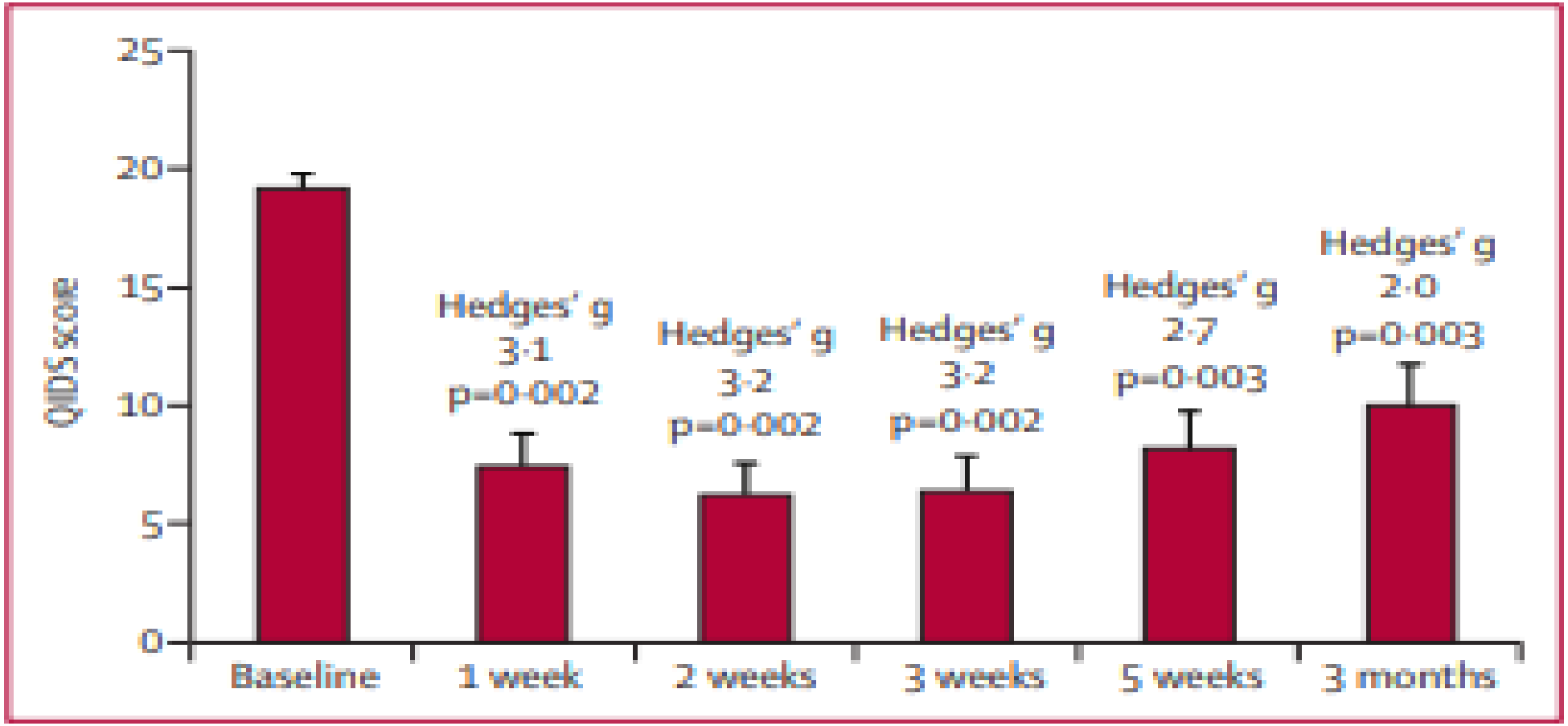


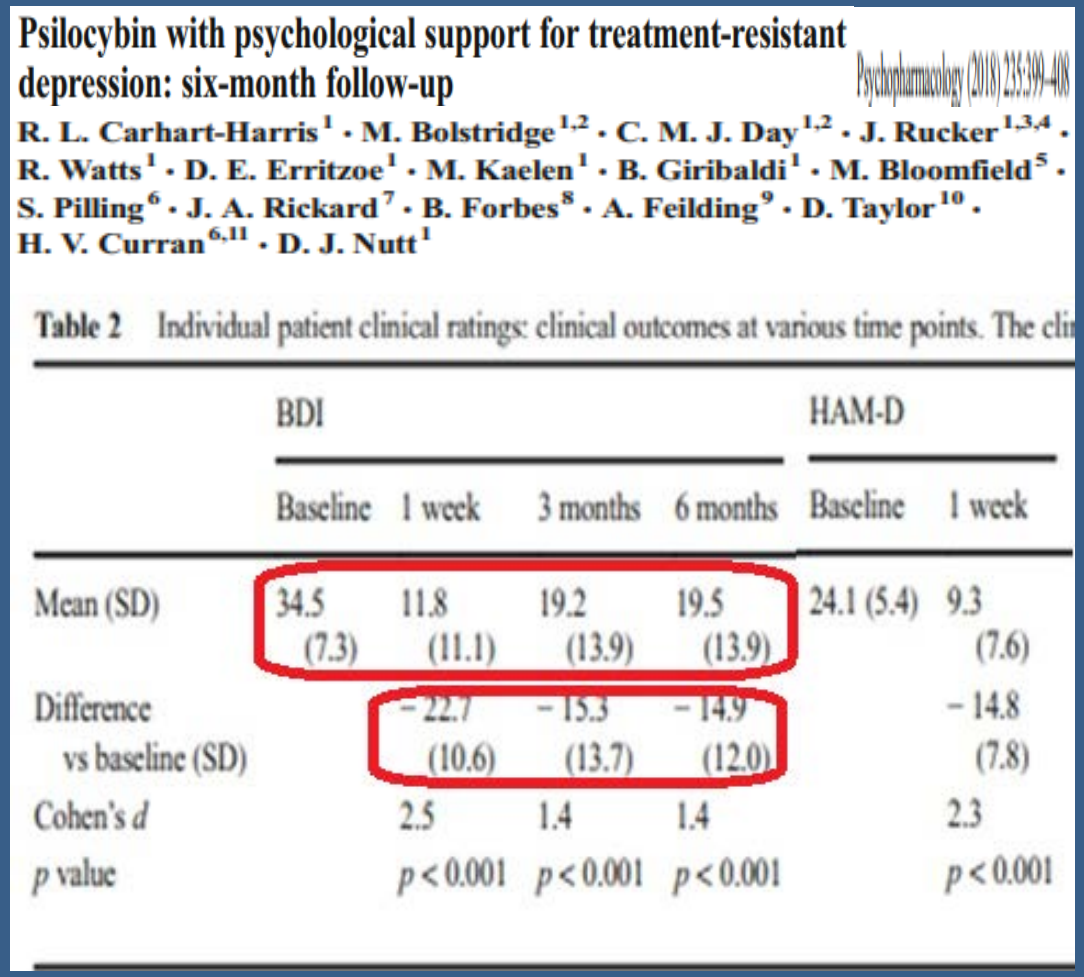
Figure 3: Mean depression severity (QIDS) over time

FIRST REPORT (2016)

	QIDS						BDI			HAM-D	
	Base-line	1 week	2 weeks	3 weeks	5 weeks	3 months	Base-line	1 week	3 months	Base-line	1 week
Mean (SD)	19·2 (2·0)	7·4 (4·9)	6·3 (4·6)	6·4 (5·1)	8·2 (5·4)	10·0 (6·0)	33·7 (7·1)	8·7 (8·4)	15·2 (11·0)	21·4 (4·5)	7·4 (6·9)
Difference versus baseline (95% CI)	–	−11·8 (−9·15 to −14·35)	−12·9 (−10·64 to −15·16)	−12·8 (−9·9 to −15·6)	−11·0 (−7·7 to −14·2)	−9·2 (−5·69 to −12·71)	–	−25·0 (−20·1 to −29·9)	−18·5 (−11·8 to −25·2)	–	−14·0 (−9·6 to −18·4)
Z	–	−3·1	−3·1	−3·06	−2·9	−3·0	–	−3·1	−3·1	–	−3·0
Hedges' g*	–	3·1	3·2	3·2	2·7	2·0	–	3·2	2·0	–	2·4
p value*	–	0·002	0·002	0·002	0·003	0·003	–	0·002	0·002	–	0·003

Table 3: Clinical ratings at baseline and follow-up

SECOND REPORT (2018)



Psilocybin with psychological support for treatment-resistant depression: six-month follow-up

Psychopharmacology (2018) 235:399–408

R. L. Carhart-Harris[1] · M. Bolstridge[1,2] · C. M. J. Day[1,2] · J. Rucker[1,3,4] · R. Watts[1] · D. E. Erritzoe[1] · M. Kaelen[1] · B. Giribaldi[1] · M. Bloomfield[5] · S. Pilling[6] · J. A. Rickard[7] · B. Forbes[8] · A. Feilding[9] · D. Taylor[10] · H. V. Curran[6,11] · D. J. Nutt[1]

Table 2 Individual patient clinical ratings: clinical outcomes at various time points. The cli

	BDI				HAM-D	
	Baseline	1 week	3 months	6 months	Baseline	1 week
Mean (SD)	34.5 (7.3)	11.8 (11.1)	19.2 (13.9)	19.5 (13.9)	24.1 (5.4)	9.3 (7.6)
Difference vs baseline (SD)		− 22.7 (10.6)	− 15.3 (13.7)	− 14.9 (12.0)		− 14.8 (7.8)
Cohen's *d*		2.5	1.4	1.4		2.3
p value		$p < 0.001$	$p < 0.001$	$p < 0.001$		$p < 0.001$

6-month follow-up

Additional 7 patients added

N = 19

BDI increases numerically at 3- and 6 months

NEUROBIOLOGY OF PSILOCYBIN:

- After psilocybin human imaging studies in healthy individuals show functional connectivity changes
  - reduced negative affect and amygdala response to emotional faces at 1 week;
  - decreased in resting state functional connectivity (RSFC) lasting 4 weeks;
  - reduced activity in the default mode network (DMN including subgenual cingulate cortex), and:
  - changes in synaptic plasticity.
- In TRD (contrary to the finding in healthy individuals):
  - increased resting state connectivity within the default mode network (DMN) between ventromedial prefrontal cortex and the bilateral inferior-lateral parietal cortex
  - It was predictive of clinical response 5 weeks

PSILOCYBIN AND TRD: PHASE 2 TRIALS

Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Bird, R.E. Blom, C. Brennan, D. Brusch, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, B.W. Dunlop, K. Eisen, D. Feifel, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, J. Kamphuis, J. Kawasaki, J.R. Kelly, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. Licht, J.L. Maples-Keller, J. Mars, L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirow, S. Mistry, T. Mletzko-Crowe, L.N. Modlin, R.E. Nielsen, E.M. Nielson, S.R. Offerhaus, V. O'Keane, T. Páleníček, D. Printz, M.C. Rademaker, A. van Reemst, F. Reinholdt, D. Repantis, J. Rucker, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. Somers, S.C. Stansfield, D. Sterling, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywema, S. Zisook, and E. Malievskaia

NOVEMBER 3, 2022

VOL. 387 NO. 18

PSILOCYBIN AND TRD: PHASE 2 TRIALS

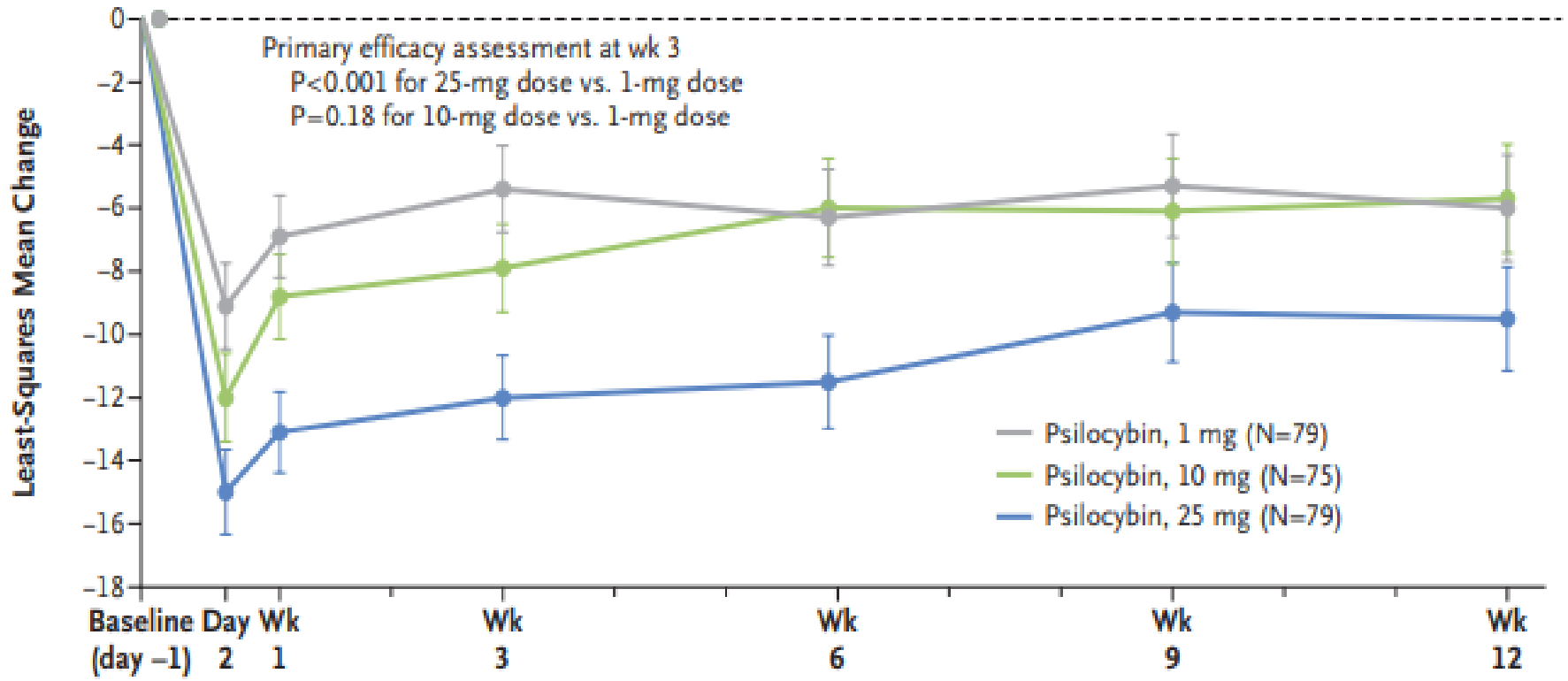


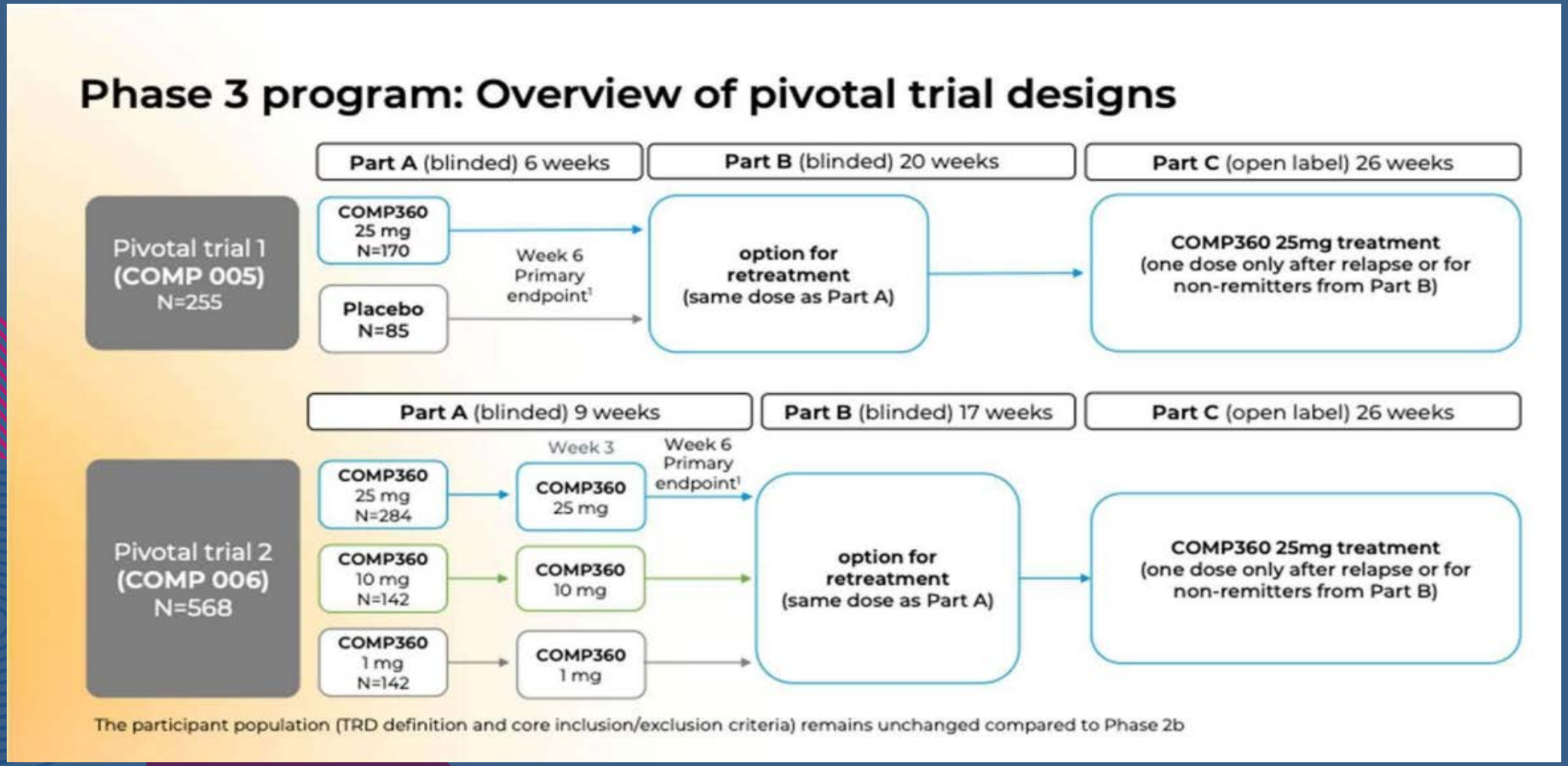
Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).

Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

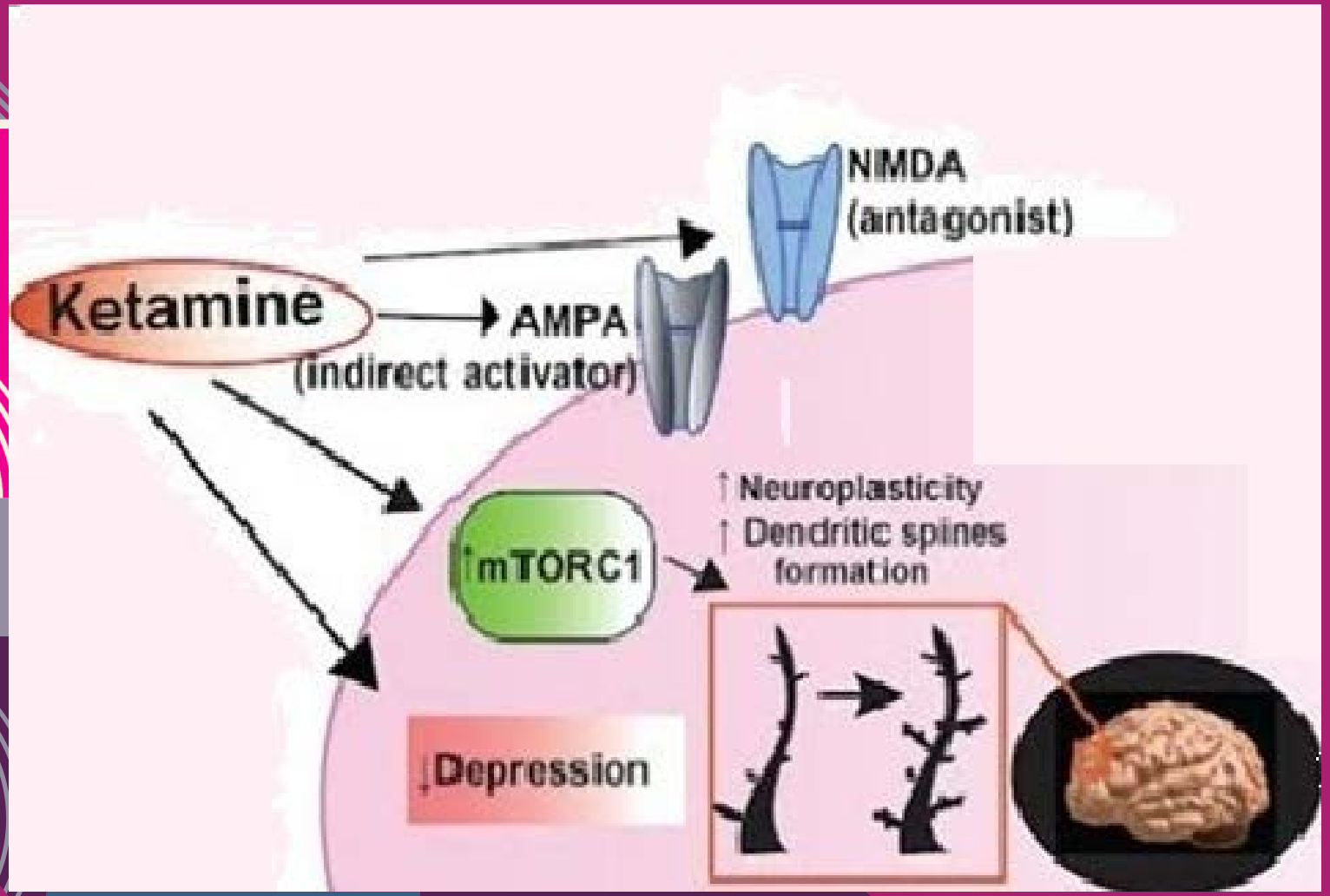
UNC
SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY

A PILOT STUDY OF PSILOCYBIN-ASSISTED THERAPY (PAT) FOR THE TREATMENT OF TRD:

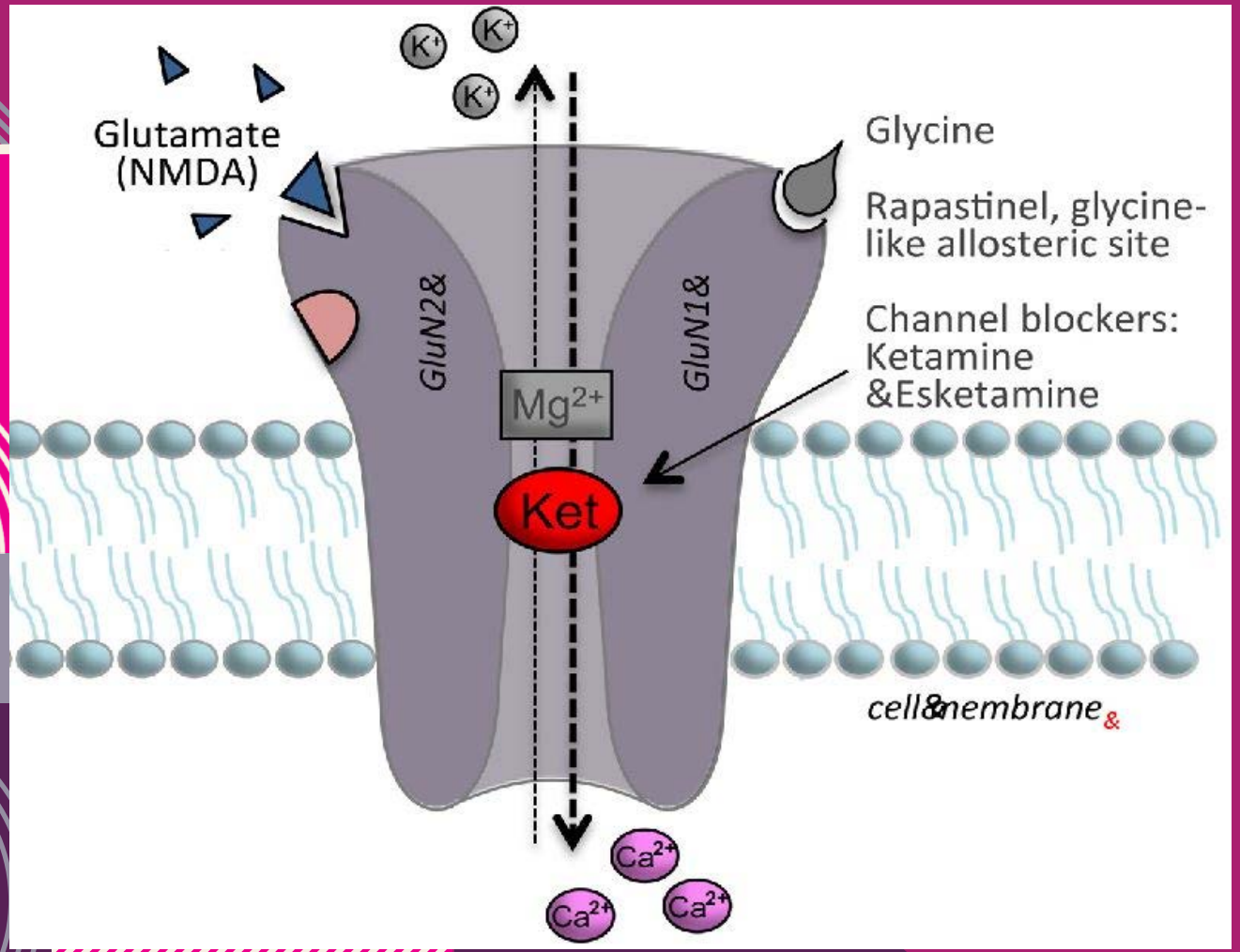
PSILOCYBIN AND TRD: PHASE 3 TRIALS



KETAMINE AND ESKETAMINE



KETAMINE: MECHANISM OF ACTION



Glutamate: major excitatory neurotransmitter in human CNS

Glutamate receptor types:

- ***ionotropic*** **(NMDA, AMPA, Kainite)**
- ***metabotropic*** **(mGluR, Groups 1-3)**

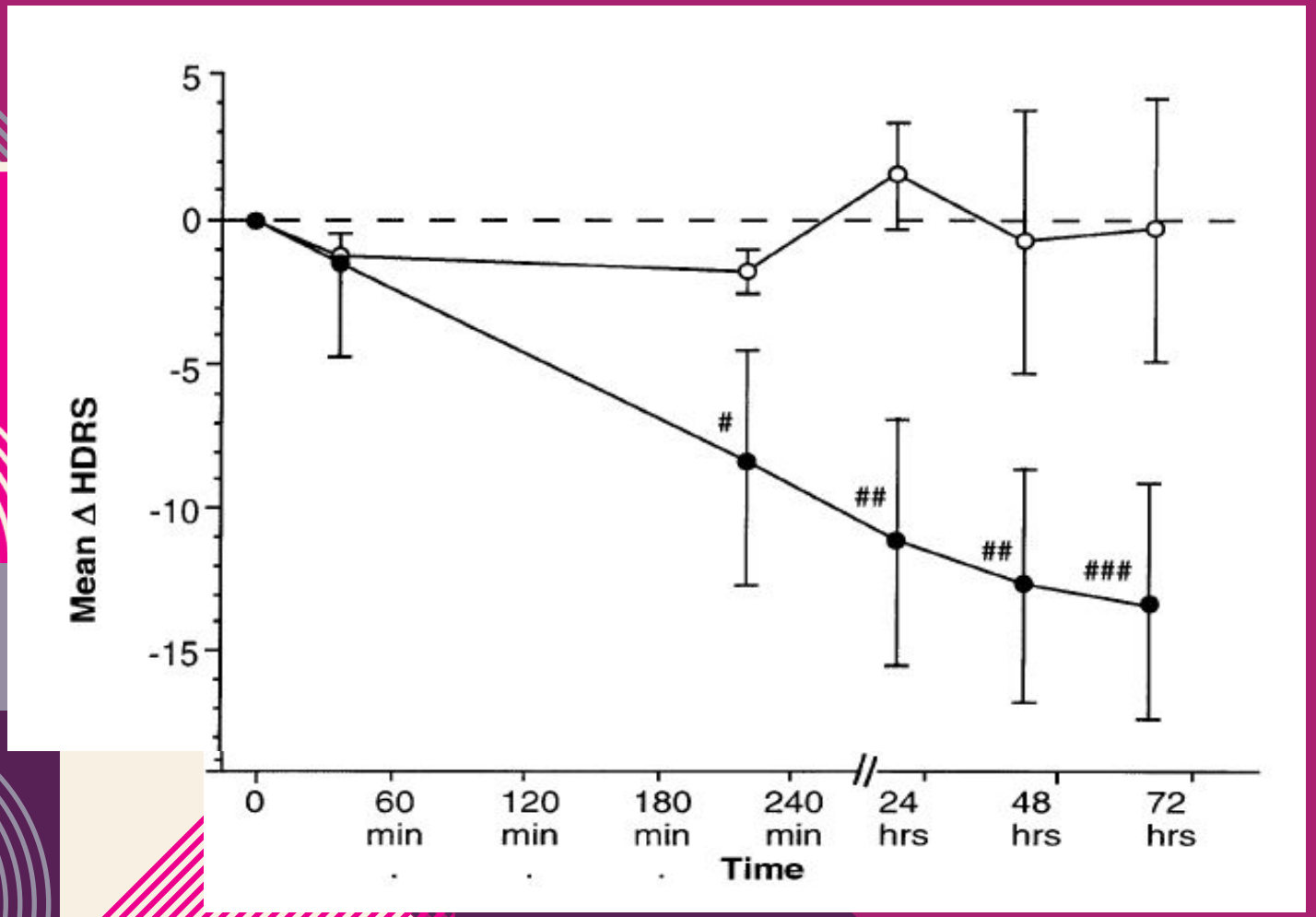
NMDA receptor activation requires binding of:

- **Glutamate to GluN2 receptor**
- **Glycine to GluN1 subunit**

NMDA receptors are the target for ketamine and esketamine.

Ketamine and Esketamine are antagonists at NMDA receptors

INTRANASAL ESKETAMINE: WHY?



Single dose IV ketamine reduced depression and SI in MDD over 24 hours (Berman, 2000).

Replication in several studies (Zarate, 2006).

KETAMINE META-ANALYSIS: MCGIRR ET AL, 2015

Table 1. *Characteristics of included studies*

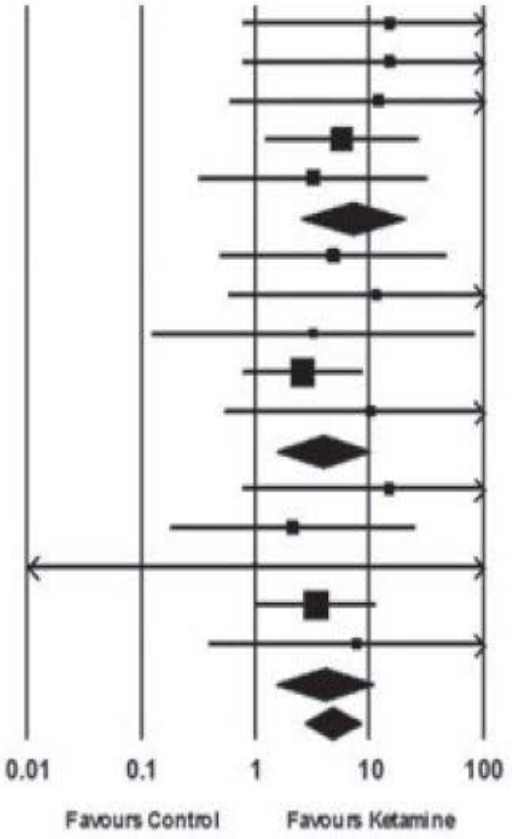
Study	Design	Diagnosis	Sample size	Instrument	Depression score	Placebo comparator	Ketamine dose	Follow-up period	Age (mean±S.D.)	Sex
Berman *et al.* (2000)	Cross-over RCT Double-blind	MDD(8)+BD(1)	9	HAMD-25	29.61±2.21	Saline	0.5 mg/kg 40 min infusion	3 days	37±10	5F/4M
Zarate *et al.* (2006)	Cross-over RCT Double-blind	MDD	18	HAMD-21	24.90±1.57	Saline	0.5 mg/kg 40 min infusion	7 days	45.86±11.80	12F/6M
Diazgranados *et al.* (2010)	Cross-over RCT Double-blind	BD	18	MADRS	32.60±1.09	Saline	0.5 mg/kg 40 min infusion	14 days	47.90±13.10	12F/6M
Zarate *et al.* (2012)	Cross-over RCT Double-blind	BD	15	MADRS	34.00±1.99	Saline	0.5 mg/kg 40 min infusion	14 days	53.90±3.27	8F/7M
Sos *et al.* (2013)	Cross-over RCT Double-blind	MDD	30	MADRS	23.06±0.93	Saline	0.54 mg/kg; 0.27 mg/kg bolus and 0.27 mg/kg 20 min infusion	7 days	43.72±2.26	15F/15M
Murrough *et al.* (2013)	RCT Double-blind	MDD	73	MADRS	32.07±0.69	Midazolam	0.5 mg/kg 40 min infusion	7 days (with additional 4 weeks in responders)	45.44±1.47	37F/36M
Lapidus *et al.* (2014)	Cross-over RCT Double-blind	MDD	20	MADRS	IDS-C 42.7±8.5	Saline	50 mg intranasal	7 days	48.0±12.8	10F/10M

RCT, Randomized controlled trial; MDD, major depressive disorder; BD, bipolar disorder; HAMD, Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; IDS-C, Inventory of Depressive Symptoms – Clinician rated; F, Female; M, Male.

KETAMINE META-ANALYSIS: MCGIRR ET AL, 2015

(a) *Remission*

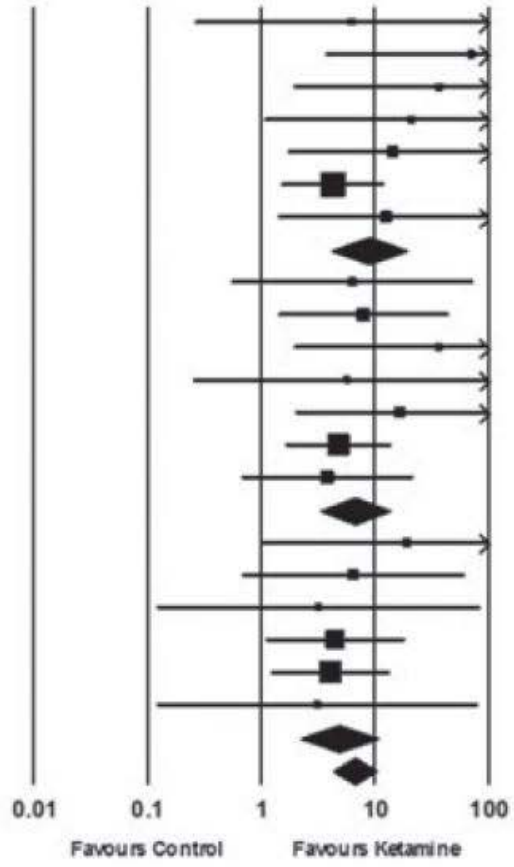
Group by Time point	Study name	Time point	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value	Remission / Total: Ketamine	Placebo	Relative weight
1 day	Zarate et al, 2006	1 day	15.07	0.77	296.44	0.074	5 / 18	0 / 18	12.13
1 day	Diazgranados et al, 2010	1 day	15.07	0.77	296.44	0.074	5 / 18	0 / 18	12.13
1 day	Zarate et al, 2012	1 day	12.13	0.59	248.49	0.105	4 / 15	0 / 15	11.81
1 day	Murrough et al, 2013	1 day	5.75	1.20	27.49	0.028	16 / 48	2 / 25	43.98
1 day	Sos et al, 2013	1 day	3.22	0.32	32.89	0.324	3 / 30	1 / 30	19.95
1 day			7.07	2.50	19.95	0.000			
3 days	Zarate et al, 2006	3 days	4.86	0.49	48.57	0.179	4 / 18	1 / 18	16.10
3 days	Diazgranados et al, 2010	3 days	11.48	0.57	230.99	0.111	4 / 18	0 / 18	9.48
3 days	Zarate et al, 2012	3 days	3.21	0.12	85.20	0.486	1 / 15	0 / 15	7.94
3 days	Murrough et al, 2013	3 days	2.63	0.77	8.95	0.123	16 / 48	4 / 25	56.79
3 days	Sos et al, 2013	3 days	10.36	0.53	201.45	0.123	4 / 30	0 / 30	9.69
3 days			3.87	1.54	9.75	0.004			
7 days	Zarate et al, 2006	7 days	15.07	0.77	296.44	0.074	5 / 18	0 / 18	10.50
7 days	Diazgranados et al, 2010	7 days	2.13	0.18	25.78	0.554	2 / 18	1 / 18	14.96
7 days	Zarate et al, 2012	7 days	1.00	0.00	6598.45	1.000	0 / 15	0 / 15	1.20
7 days	Murrough et al, 2013	7 days	3.44	1.02	11.60	0.046	19 / 48	4 / 25	63.04
7 days	Sos et al, 2013	7 days	7.76	0.38	157.14	0.182	3 / 30	0 / 30	10.30
7 days			4.00	1.53	10.51	0.005			
Overall			4.67	2.66	8.19	0.000			



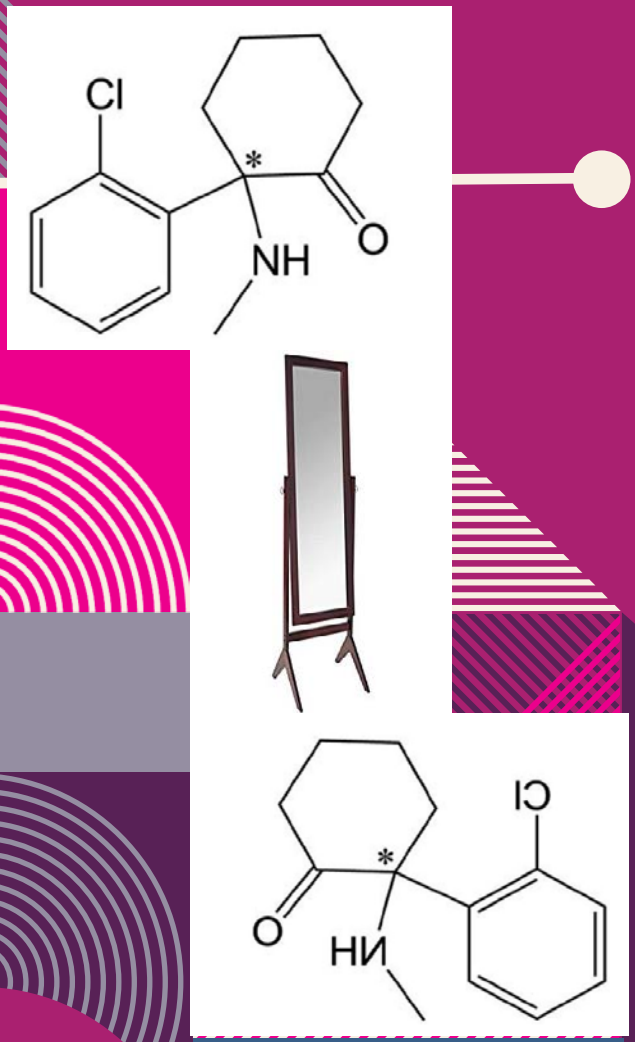
KETAMINE META-ANALYSIS: MCGIRR ET AL, 2015

(b) Response

Group by Time point	Study name	Time point	Statistics for each study: Odds ratio	Lower limit	Upper limit	p-Value	Response / Total: Ketamine	Placebo	Relative weight
1 day	Berman et al, 2000	1 day	6.33	0.26	152.86	0.256	2 / 9	0 / 9	5.57
1 day	Zarate et al, 2006	1 day	71.15	3.67	1379.46	0.005	12 / 18	0 / 18	6.42
1 day	Diazgranados et al, 2010	1 day	37.00	1.94	706.54	0.016	9 / 18	0 / 18	6.49
1 day	Zarate et al, 2012	1 day	21.21	1.07	420.80	0.045	6 / 15	0 / 15	6.32
1 day	Sos et al, 2013	1 day	14.50	1.72	122.40	0.014	10 / 30	1 / 30	12.40
1 day	Murrough et al, 2013	1 day	4.29	1.50	12.25	0.007	30 / 48	7 / 25	51.14
1 day	Lapidus et al. 2014	1 day	12.67	1.40	114.42	0.024	8 / 20	1 / 20	11.65
1 day			8.81	4.16	18.68	0.000			
3 days	Berman et al, 2000	3 days	6.40	0.55	74.89	0.139	4 / 9	1 / 9	7.82
3 days	Zarate et al, 2006	3 days	8.00	1.41	45.41	0.019	9 / 18	2 / 18	15.70
3 days	Diazgranados et al, 2010	3 days	37.00	1.94	706.54	0.016	9 / 18	0 / 18	5.44
3 days	Zarate et al, 2012	3 days	5.74	0.25	130.37	0.273	2 / 15	0 / 15	4.85
3 days	Sos et al, 2013	3 days	16.79	2.00	140.90	0.009	11 / 30	1 / 30	10.46
3 days	Murrough et al, 2013	3 days	4.83	1.63	14.30	0.004	29 / 48	6 / 25	40.21
3 days	Lapidus et al. 2014	3 days	3.86	0.67	22.11	0.130	6 / 20	2 / 20	15.52
3 days			6.63	3.33	13.18	0.000			
7 days	Zarate et al, 2006	7 days	19.24	0.99	373.01	0.051	6 / 18	0 / 18	6.78
7 days	Diazgranados et al, 2010	7 days	6.54	0.68	62.99	0.104	5 / 18	1 / 18	11.62
7 days	Zarate et al, 2012	7 days	3.21	0.12	85.20	0.486	1 / 15	0 / 15	5.54
7 days	Sos et al, 2013	7 days	4.50	1.09	18.50	0.037	10 / 30	3 / 30	29.83
7 days	Murrough et al, 2013	7 days	4.08	1.22	13.72	0.023	21 / 48	4 / 25	40.61
7 days	Lapidus et al. 2014	7 days	3.15	0.12	82.16	0.490	1 / 20	0 / 20	5.61
7 days			4.80	2.22	10.38	0.000			
Overall			6.58	4.31	10.06	0.000			



INTRANASAL ESKETAMINE:



Stereoisomers are two molecules are that are mirror images but not superimposable: R and S enantiomers

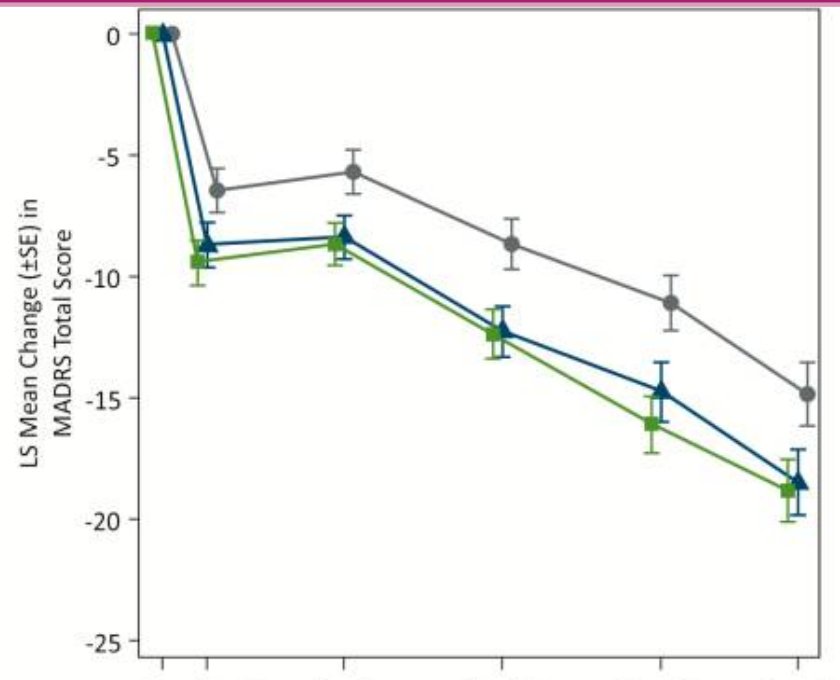
Racemic mixture = R and S enantiomers together

R and S enantiomers differ in pharmacokinetics and pharmacodynamics

R, S and the racemic mixture (both enantiomers) have different affinities/binding strength for the NMDA Receptor

S *(Ki = 0,2μM) >* ***R,S*** *(Ki = 0,54 μM) >* ***R*** *(Ki = 1,2 μM)*

INTRANASAL ESKETAMINE:



No. of Patients :	Baseline	Day 2 (24hrs)	Day 8	Day 15	Day 22	Day 28
Esketamine 56 mg/Oral Antidepressant	115	105	114	110	107	111
Esketamine 84 mg/Oral Antidepressant	114	104	107	99	96	98
Oral Antidepressant/Placebo	113	101	111	106	105	108
LS mean (SE) treatment difference vs. placebo:						
Esketamine 84 mg		-2.2 (1.29)	-2.7 (1.26)	-3.6 (1.48)	-3.7 (1.65)	-3.6 (1.86)
Esketamine 56 mg		-3.0 (1.29)	-3.0 (1.24)	-3.8 (1.45)	-5.0 (1.61)	-4.0 (1.81)

Esketamine 56 mg/Oral Antidepressant Esketamine 84 mg/Oral Antidepressant Oral Antidepressant/Placebo

GOALS:

1. Analyze the current state of evidence for clinical use of Psilocybin and MDMA in psychiatric practice

2. Examine other interventional strategies including Ketamine/Esketamine

3. Develop expertise in managing patients receiving novel treatments and therapeutics