Psychedelics and their therapeutic potential

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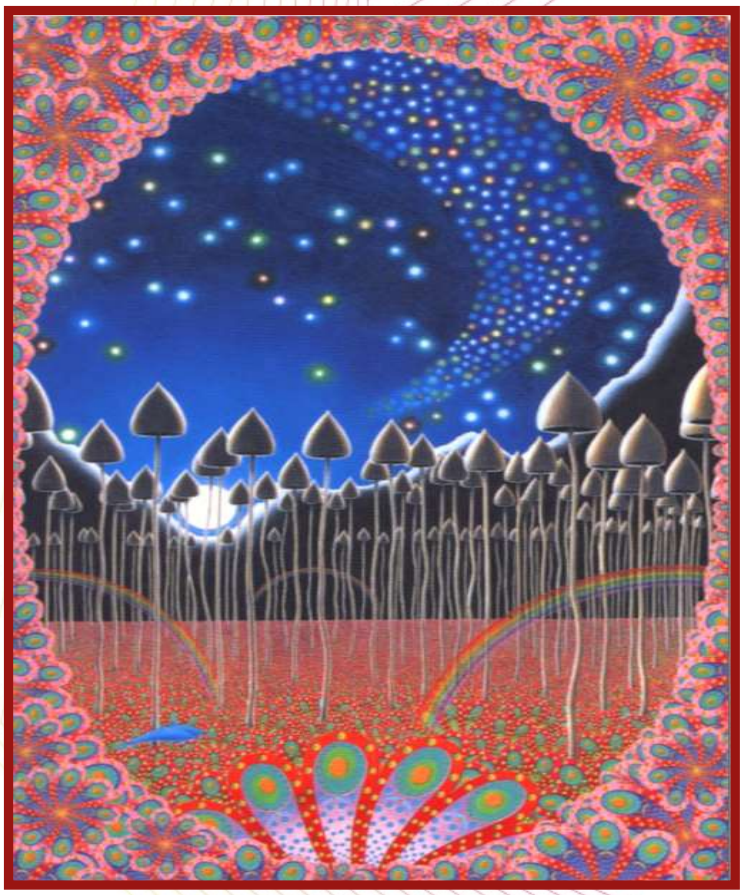
PSYRES a psychedelic research foundation and PSYON clinic

PSYCHEDELICS *(OSMOND, 1957)*



ψυχή *(psyché)* + **δηλείν** *(deleín)*

=

soul-manifesting

Fantastica ***(Louis Lewin, 1964)***

Psychotomimetics **(Hoffer, 1964)**

Entheogens **(Rock, 1979)**

Hallucinogens **(Rock, 1979)**

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Psychedelics

Classical serotonergic psychedelics

- **Tryptamines** (psilocybin, DMT, 5-MeO-DMT, AMT, 5-MeO-DIPT…)
- **Ergolines** (LSD, LSA)
- **Phenethylamines** (mescaline, DOB, DOM, TMA, 2C-B, MDMA…

Dissociative anesthetics (ketamine, PCP, MXE, DXM, DXE)

Delirogens (atropine, scopolamine, hyosciamine, muscimol)

Salvinorins (Salvinorin A)

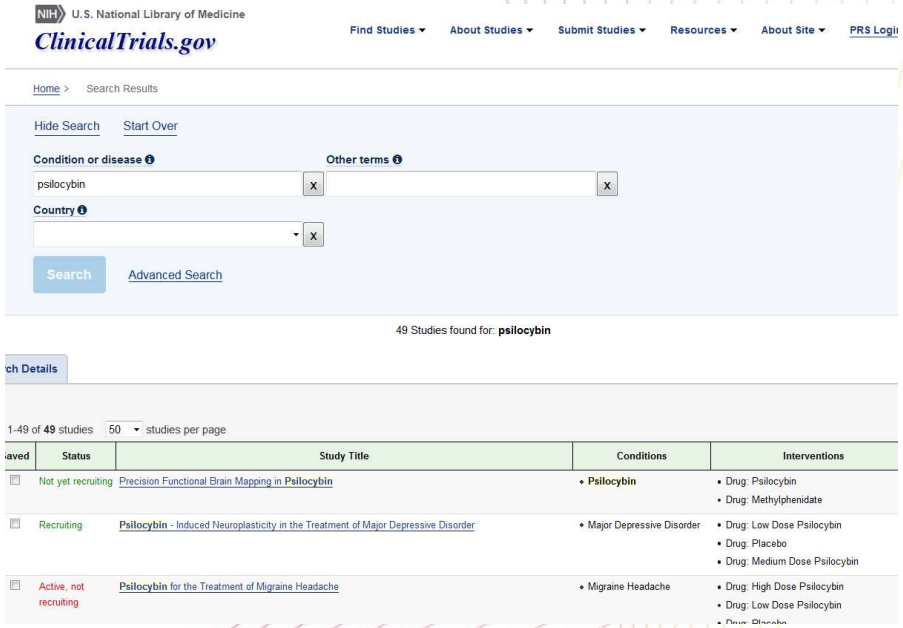
Cannabinoids (THC, CBN, synthetic cannabinoids)

Psychedelics in @ www.clinicaltrials.gov

- **Psilocybin**
  - **49 registered** trials
  - Neuroimaging studies, spirituality, pharmacokinetics, MDD, OCD, various headaches, distress and anxiety associated with cancer, AIDS, anorexia nervosa, treatment of tobacco, cocaine, alcohol addiction etc.

- **LSD**
  - **11 registered** trials
  - Neuroimaging studies, pharmacokinetics and pharmacodynamics, MDD, anxiety etc.

- **Ayahuasca & DMT**
  - **2 registered** trials
  - Effects in healthy volunteers and treatment of MDD



ACUTE EFFECTS

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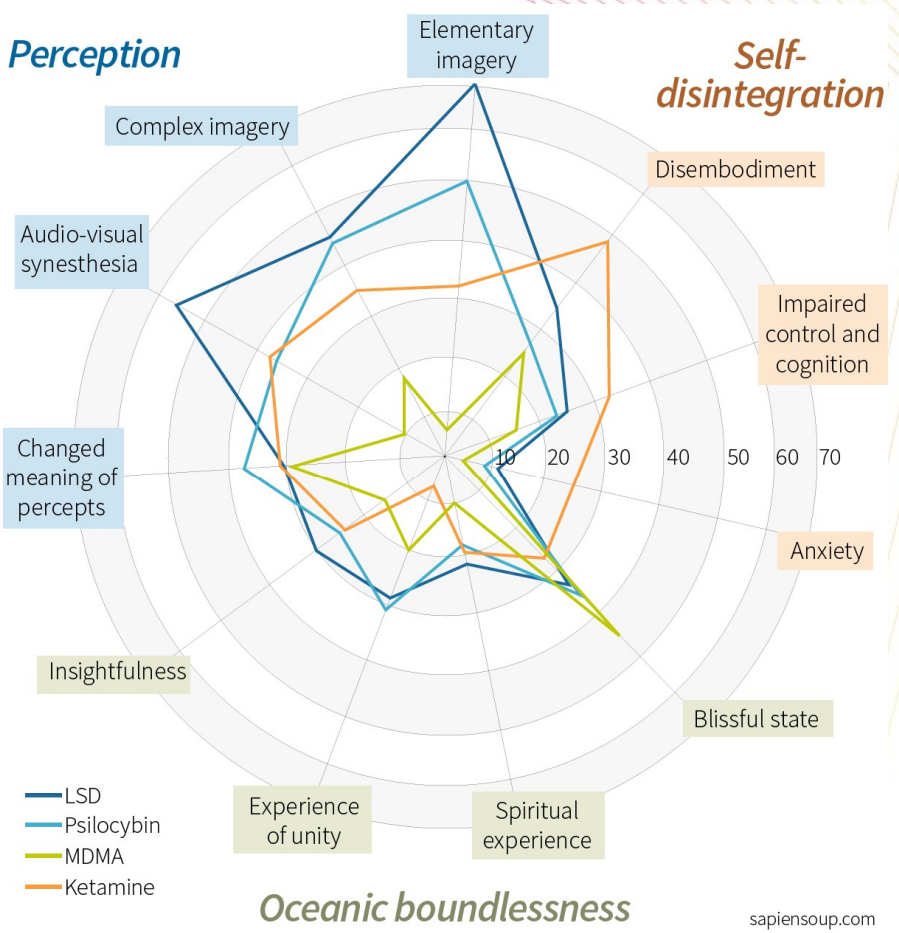
5D-ASCs

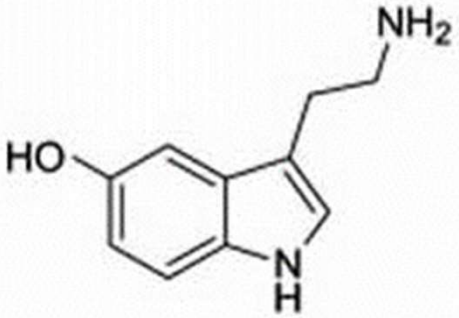
11 dimensions of responders and non-responders at 5 weeks.

OAV - 11 factors		
OBN	**Experience of Unity**	EOU
OBN	**Spiritual Experience**	SE
OBN	**Blissful State**	BS
OBN/VRS	**Insightfulness**	IF
OBN	**Disembodiment**	DB
DED	**Impaired control and cognition**	ICC
DED	**Anxiety**	AX
VRS	**Complex Imagery**	CI
VRS	**Elementary Imagery**	EI
VRS	**Audio-Visual Synesthesiae**	AVS
VRS	**Changed Meaning of Percepts**	CMP

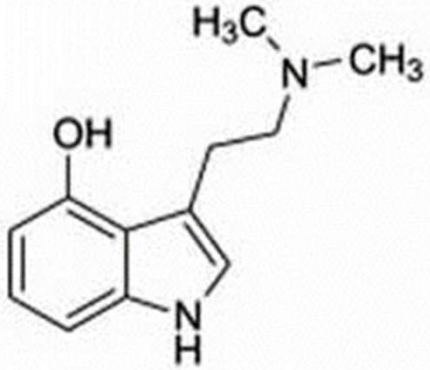


MECHANISMS OF ACTION

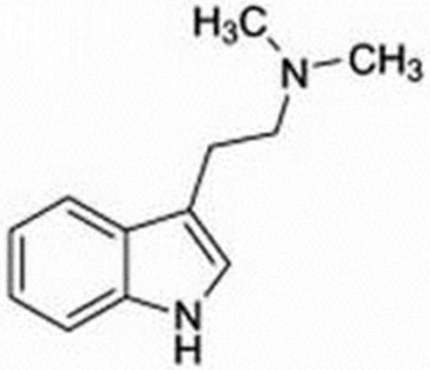
Structure activity relationship



Serotonin

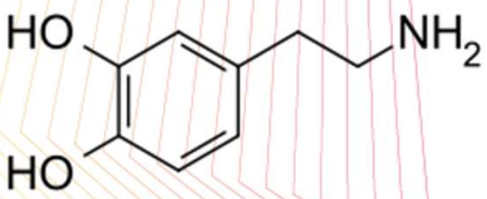


Psilocin

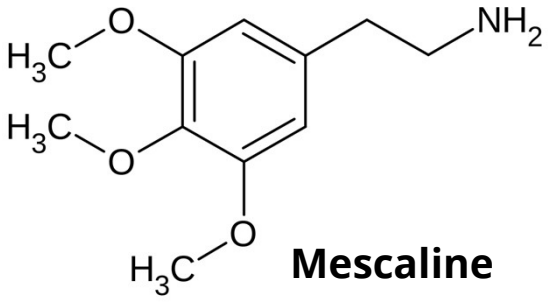


N,N-Dimethyltryptamine (DMT)

LSD



Dopamine



Mescaline

5-HT receptor modulation

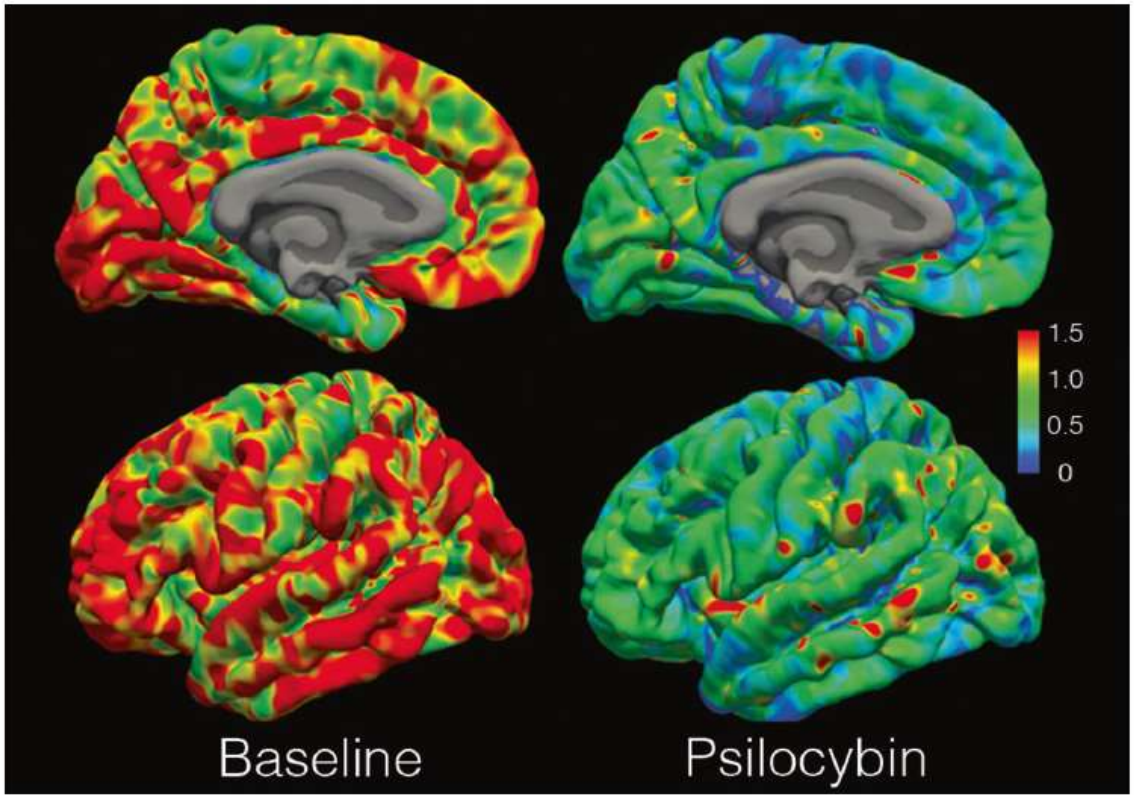
Table 3 Affinity of psilocin to serotonin receptors. x=missing data.

Constant	Subtypes of serotonin receptors														Study
	$5HT_{1A}$	$5HT_{1B}$	$5HT_{1D}$	$5HT_{1E}$	$5HT_{1F}$	$5HT_{2A}$	$5HT_{2B}$	$5HT_{2C}$	$5HT_{3}$	$5HT_{4}$	$5HT_{5A}$	$5HT_{5B}$	$5HT_{6}$	$5HT_{7}$	
Ki (nM)	49, [3H] 8-OH-DPAT	x	x	x	x	25, [125I] DOI	x	10, [125I] DOI	x	x	x	x	x	x	Blair et al. (2000)
Ki (nM)	190, [3H] 8-OH-DPAT	x	x	x	x	6, [125I] DOI	410, [3H] ketanserin	x	x	x	x	x	x	x	McKenna et al. (1990)
npKi[a]	2.88	2.19	3.4	3.03	x	2.14	4	2.52	x	x	2.83	x	2.82	2.82	Ray (2010)
Ki (nM)	567.4	219.6	36.4	x	x	107.2	4.6	97.3	>10000	x	83.7		57	3.5	Halberstadt and Geyer (2011)

[a]npKi is logarithmated and normalized value of Ki. It is calculated as follows: npKi=4+pKi−pKiMax, where pKi=−log 10(Ki).

Tyls et al. European Neuropsychopharmacology(2014) 24, 342–356

psilocin 5-HT2A receptor binding

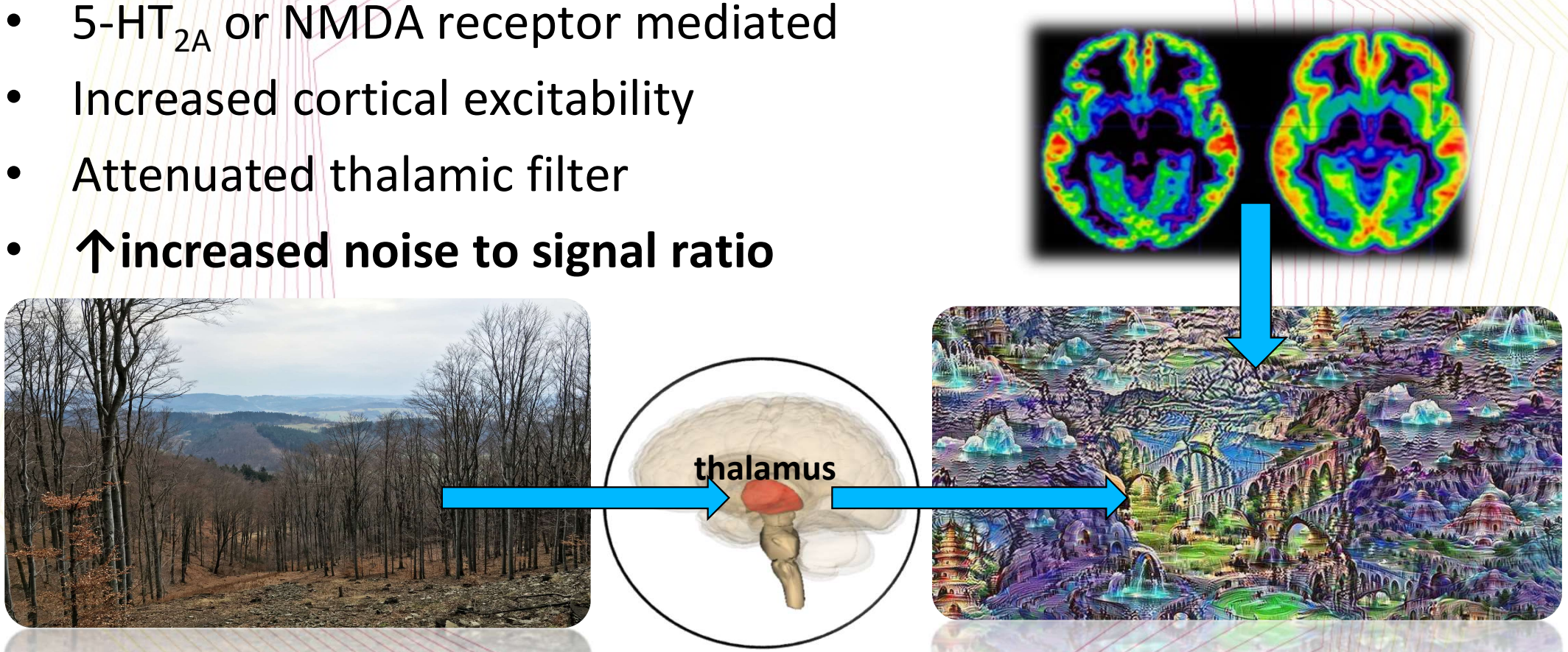


Madsen et al. Neuropsychopharmacology (2019) 0:1–7;

Fig. 3 Psilocybin occupancy of 5-HT2AR. [^{11}C]Cimbi-36 BP_{ND} map of the cortical surface of the left hemisphere of Subject 5 at baseline and at the first post-psilocybin intervention scan. Color bar in units BP_{ND}

Acute mechanism of action

- 5-HT_{2A} or NMDA receptor mediated
- Increased cortical excitability
- Attenuated thalamic filter
- **↑increased noise to signal ratio**



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THERAPUTIC POTENTIAL OF PSYCHEDELICS

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Clinical experiments in 50-60´s

1950 - chlorpromazine *(marketed in 1954)*
1951 - imipramine *(marketed in 1957)*
1960 - amitriptyline *(marketed in 1961)*

HERMAN C.B. DENBER, M.D., Ph.D.

"I was persuaded that by using such drugs one could penetrate into the cavernous darkness of mental illness and come to the ultimate hidden cause of these many strange and different illnesses which by custom have come to be designated as "madness".

So wrote Joseph Moreau de Tours in 1845[1,2]

thylamide[9-13], and mescaline[14-16]. It is generally agreed that the effects of these two drugs are similar, with perhaps some minor variations of a pharmacological and clinical nature[17]. Their relationship to the schizophrenic psychosis is disputed[18], although Keeler[19] maintains a re-

Psychiatric patients including acute schizophrenics, implanted electrodes – treated with LSD or mescaline

350 psychiatric patients – each 500mg of mescaline
Some patients were shouting I became crazy, some had panic attacks, some had regression into the childhood….

59 schizophrenics – mescaline or LSD
Hallucinating, anxiety….

ADDICTION

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LSD for addcition 1960-70´s

	Follow-up (months)	LSD (n/N)	Control (n/N)	Weight	Odds Ratio (95% CI)
First follow-up					
Smart *et al.*, 1966	6	[a]/10	[a]/20	7.2%	1.41 (0.36-5.60)
Hollister *et al.*, 1969	2	18/36	11/36	14.7%	2.27 (0.87-5.94)
Ludwig *et al.*, 1969	1	94/132	25/44	27.3%	1.88 (0.93-3.81)
Bowen *et al.*, 1970	12	9/22	7/22	8.9%	1.48 (0.43-5.10)
Pahnke *et al.*, 1970	6	34/73	13/44	21.6%	2.08 (0.94-4.60)
Tomsovic & Edwards, 1970	3	30/52	17/45	20.4%	2.25 (0.99-5.10)
Total		**325**	**211**	**100%**	**1.96 (1.36-2.84)**

Test for heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.65$, df = 5 ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 3.59$ ($P = 0.0003$)

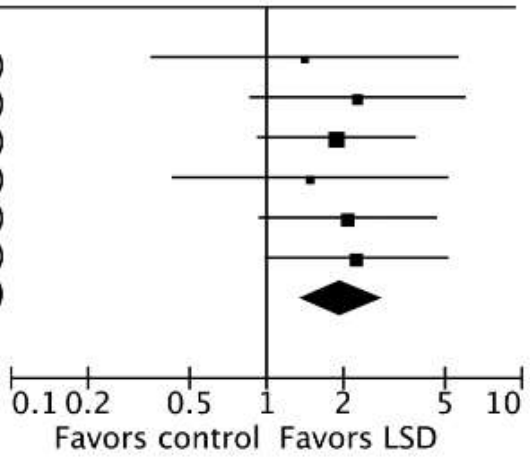


Figure 2. Improvement on alcohol misuse at the first available follow-up after LSD versus control treatments.

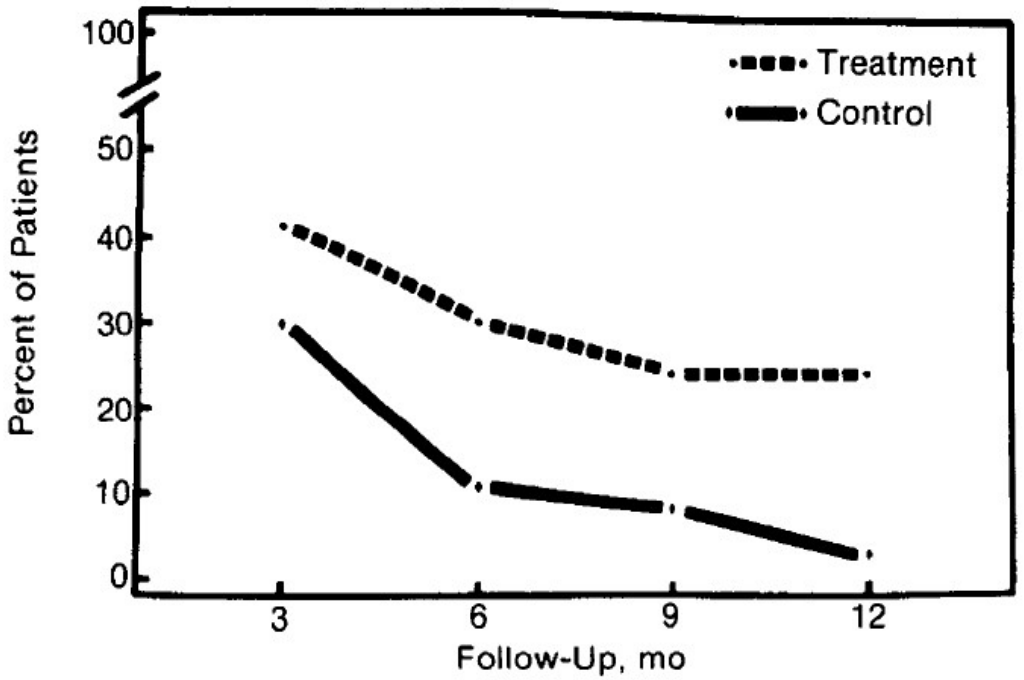
[a]Continuous outcome data.

Krebs, Johansen. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol;26(7):994-1002.

LSD in heroine dependence

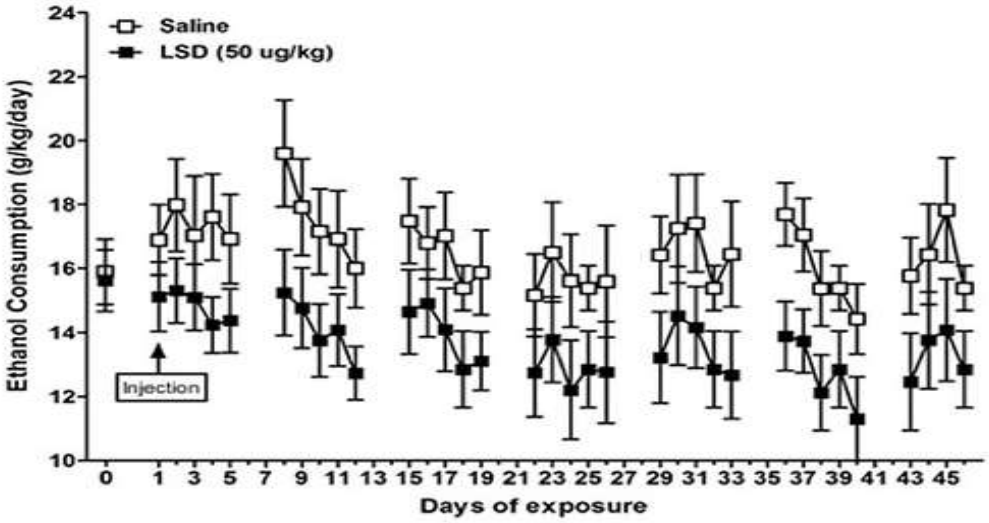
1. **Control group:**
   - **4-6 weeks outpatient group therapy with everyday urine check for opioids**
2. **LSD group:**
   - **Resident treatment (4-6 weeks)**
   - **300–500 µg LSD**
   - **24 h preparatory sessions**
   - **~ 1 week of integration**

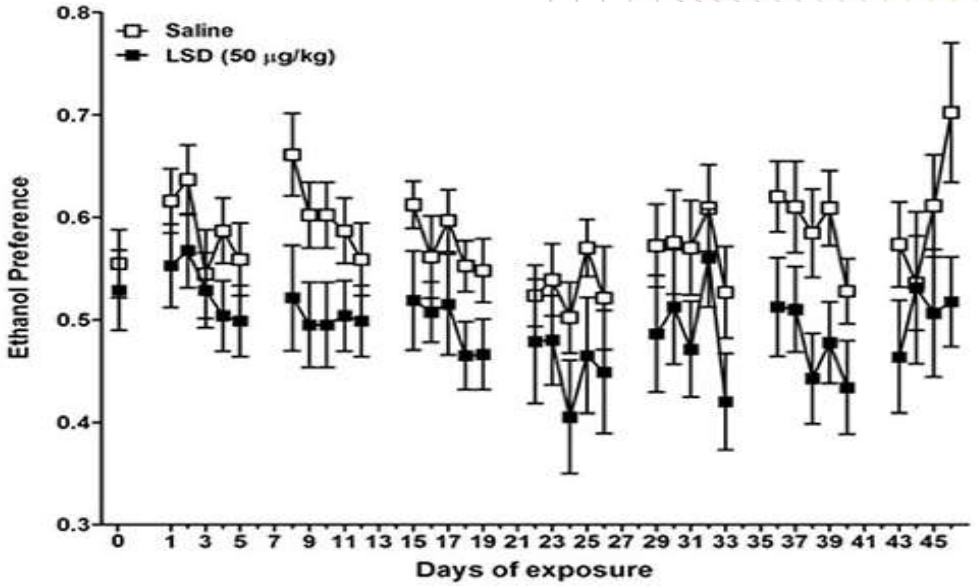
Fig 1.—Percent of patients maintaining total abstinence at 3-, 6-, 9-, and 12-month follow-up.



Savage C, McCabe OL. Arch Gen Psychiatry. 1973 Jun;28(6):808-14.

LSD Administered as a Single Dose Reduces Alcohol Consumption in C57BL/6J Mice





In the group treated with 50 µg/kg LSD, MLM for repeated measures indicated significant reductions versus saline-treated controls in ethanol consumption ($p = 0.0035$) and preference ($p = 0.0024$).

Alper et al. Front. Pharmacol., 31 August 2018 | https://doi.org/10.3389/fphar.2018.00994

Ketamine for heroin addiction

KPT influence on craving, anxiety, and depression

Scales	Dose of ketamine		Before KPT	After KPT	1 month	3 months	6 months	12 months	18 months	24 months
Visual Analog Scale of Craving	High	Mean	29.24	3.97***,+++	7.72*,+++	5.40**,+++	9.25++	3.17+++	0.57+++	1.71+++
		SD	27.32	5.04	13.25	13.35	15.67	4.52	0.98	4.53
	Low	Mean	36.34	15.06+++	20.18++	28.33	19.75	27.00	12.50	0.00[a]
		SD	24.88	16.54	22.41	27.93	14.54	24.04	2.12	—[a]
Spielberger State Anxiety Scale	High	Mean	41.17	35.71+	35.81+	36.36	38.00	37.00	33.57	37.14
		SD	11.55	8.64	9.69	7.46	9.3	10.75	11.98	9.37
	Low	Mean	45.11	38.06++	35.26+++	37.17+	35.88+	28.50+	25.00++	31.00[a]
		SD	11.86	10.62	8.38	7.49	7.83	7.78	2.83	—[a]
Spielberger Trait Anxiety Scale	High	Mean	45.97	42.23+	39.54++	38.71+	37.33++	37.44+	38.86	40.86
		SD	9.9	9.12	9.21	7.17	5.68	8.45	9.99	7.77
	Low	Mean	46.69	40.74++	40.13++	37.58++	36.50++	33.50+	36.50	34.00[a]
		SD	8.73	8.35	8.09	7.05	7.50	3.54	4.95	—[a]
Zung Depression Scale	High	Mean	46.20	42.66	39.88+	39.57+	40.50	39.44+	35.00++	37.66+
		SD	8.96	9.21	9.81	8.10	9.40	10.63	9.45	6.89
	Low	Mean	49.31	41.71+++	40.87+++	38.00+++	37.50+++	35.00+	37.00	30.00[a]
		SD	9.26	10.28	6.81	9.02	6.41	1.41	1.41	—[a]

Notes: 1. Statistical significance of differences between the scores before KPT and later scores: + - $p < .05$; ++ - $p < .01$; +++ - $p < .001$.
2. Statistical significance of differences between the high dose and low dose group: * - $p < .05$; ** - $p < .01$; *** - $p < .001$.
3. SD - Standard Deviation.
4. [a] - There is only one subject in this group.

for 24 months decreased craving !!!

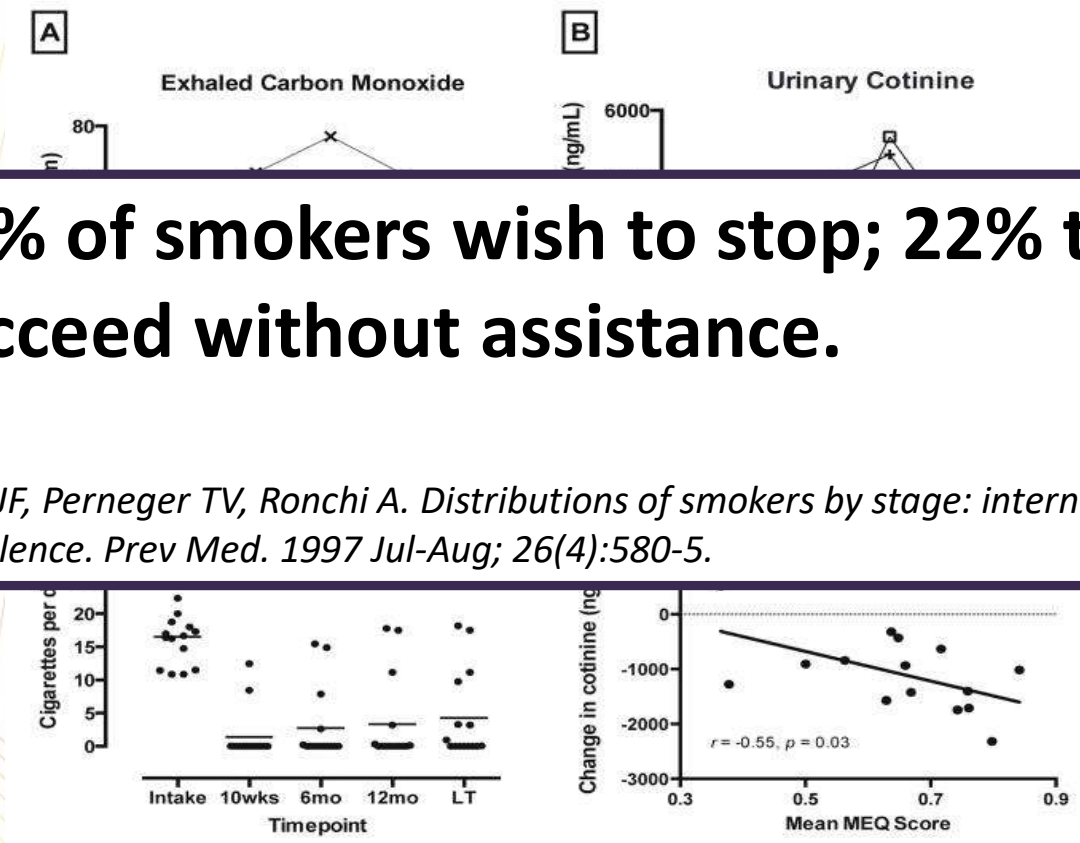
Months of follow up

Krupitsky et al.

Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up.

Journal of Substance Abuse Treatment. 2002

Psilocybin-facilitated smoking cessation



73% of smokers wish to stop; 22% try and less than 5% succeed without assistance.

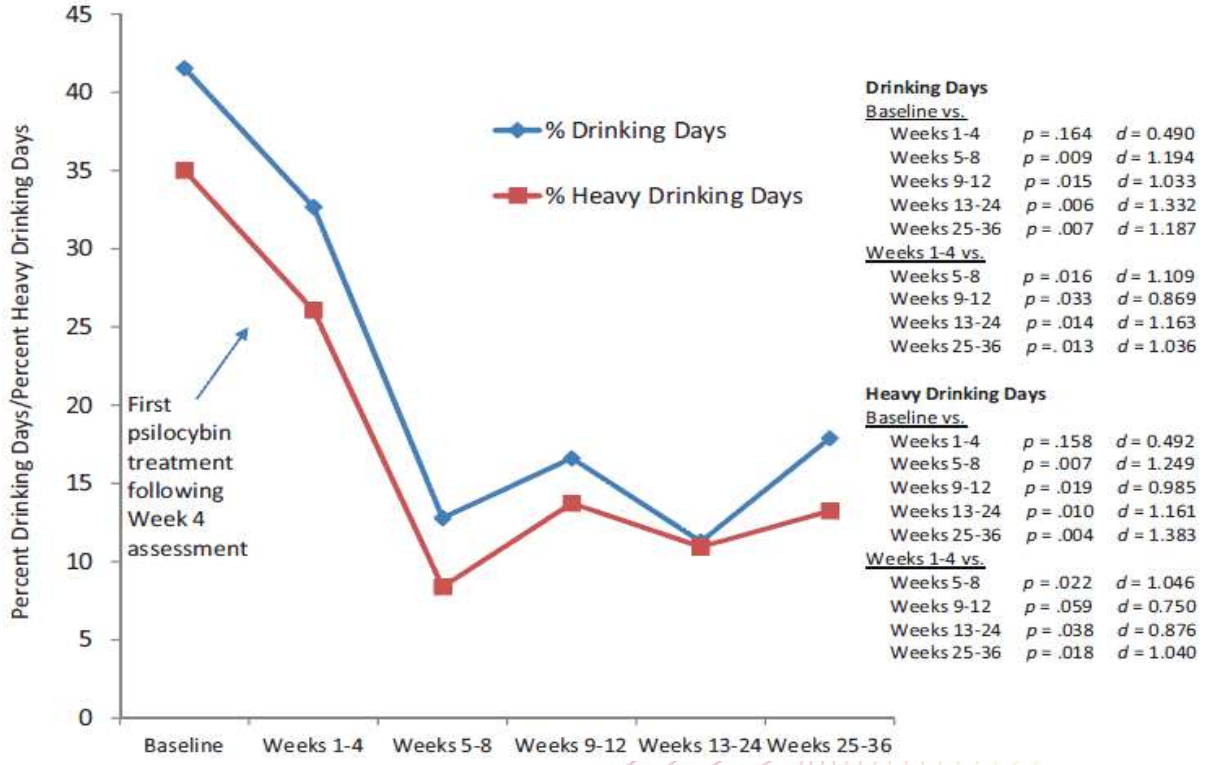
Etter JF, Perneger TV, Ronchi A. Distributions of smokers by stage: international comparison and association with smoking prevalence. Prev Med. 1997 Jul-Aug; 26(4):580-5.

12-month follow-up

- All 15 participants completed
- 12 (80%) participants completed
- 9 participants (60%) were confirmed as smoking abstinent.

Psilocybin for alcohol dependence

- psilocybin 0.3 mg/kg or 0.4 mg/kg
- 1-2 supervised sessions 4 weeks apart
- 12 weeks (motivational enhancement therapy + preparatory and integrative sessions)
- Intensity of effects correlated with the decrease of drinking and craving 5 weeks after treatment



Bogenschutz et al., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol, 29 (3) (2015), pp. 289-299

Psilocybin in alcohol addiction

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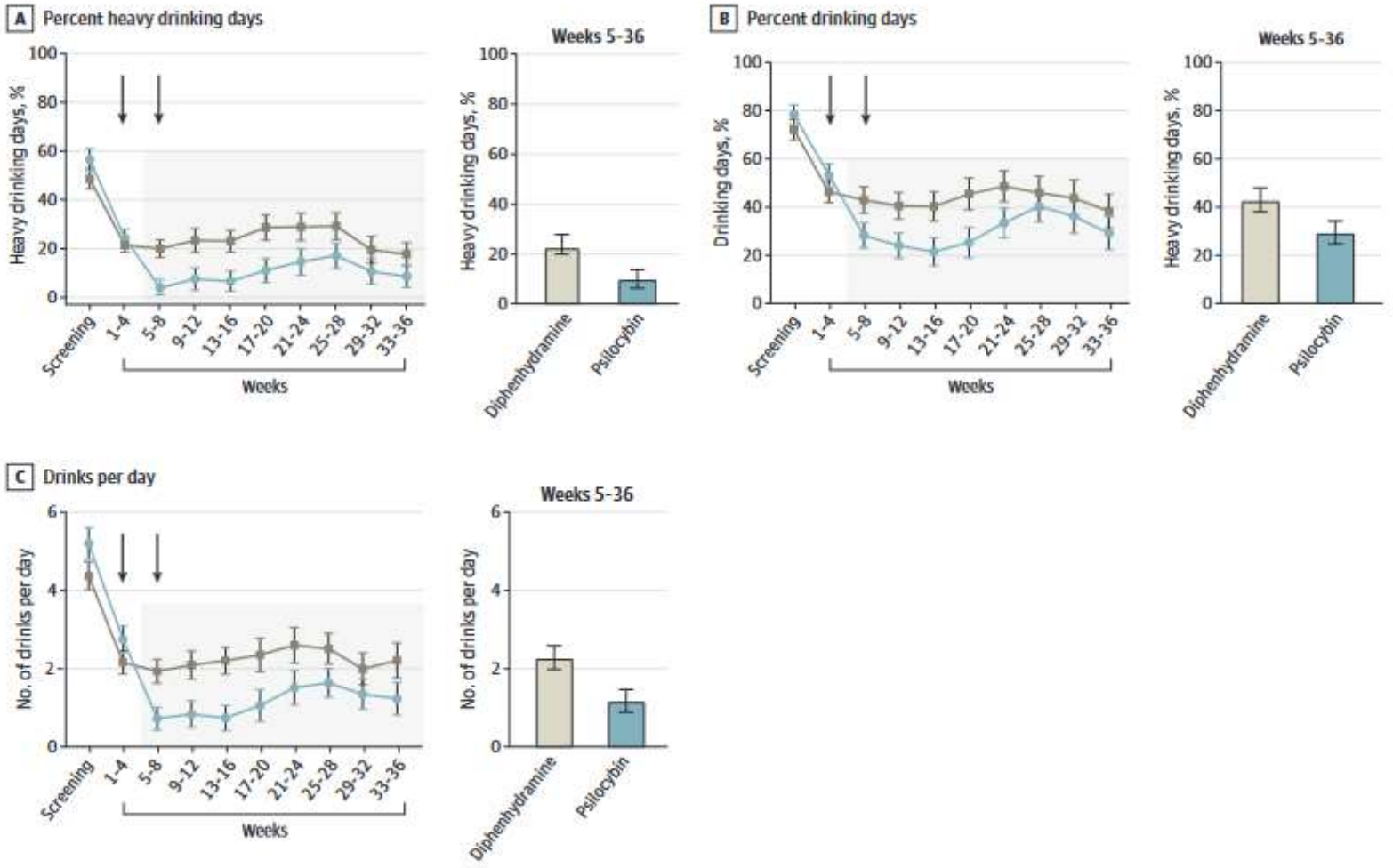

Mean (SE) estimates for screening (84 days prior to screening), weeks 1-4 (28 days prior to first double-blind medication session; covariate in the model), and eight 28-day bins following the first double-blind medication session (shaded area: weeks 5-8, 9-12, 13-16, 17-20, 21-24, 25-28, 29-32, and 33-36). Arrows represent double-blind medication sessions 1 and 2.

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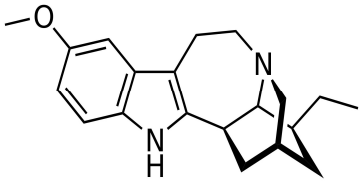
t of CZECH PSYCHEDELIC SOCIETY

Ibogain

- Tabernanthe Iboga (tropical west Africa)
- Roots of the plant
- 100 - > 1g
- Long-lasting mixed psychedelic and dissociative effect
- Ca^{2+} channel blockade – prolonged QT



Ibogaine (and metabolite)[28][29]

Site	Ibogaine	Noribogaine
MOR	2,000–100,000	700–3,000
DOR	>100,000	5,000–25,000
KOR	2,000–4,000	600–1,000
5-HT_{2A}	16,000	>100,000
5-HT_{2C}	>10,000	>10,000
5-HT_3	2,600	>100,000
σ_1	2,500–9,000	11,000–15,000
σ_2	90–400	5,000–19,000
NMDA	1,000–3,000	6,000–15,000
nACh	20	1,500
SERT	500	40
DAT	2,000	2,000

Values are K_i (nM). The smaller the value, the more strongly the drug binds to the site.

Ibogain for heroin and cocaine

heroin craving questionnaire (HCQ-29)

Subscale	Pre-Ibogaine (*N* = 75)	Discharge (*N* = 74)	1 Month (*N* = 37)	*F*	*P*
HCQ-NOW Factor 1: Emotionality (Negative mood state)	3.51 (0.22)	2.02 (0.14)	1.69 (0.19)	26.53	0.0001
HCQ-NOW Factor 2: Purposefulness (Desire or intent to use drug now)	4.10 (0.23)	2.21 (0.15)	2.04 (0.22)	33.36	0.0001
HC (La usi					
HCQ-NOW Factor 4: Expectancy (Expected positive benefits of drug use)	4.51 (0.20)	3.74 (0.19)	2.90 (0.29)	11.47	0.0001

IBOGAINE reduced craving in opioid and cocaine dependent users

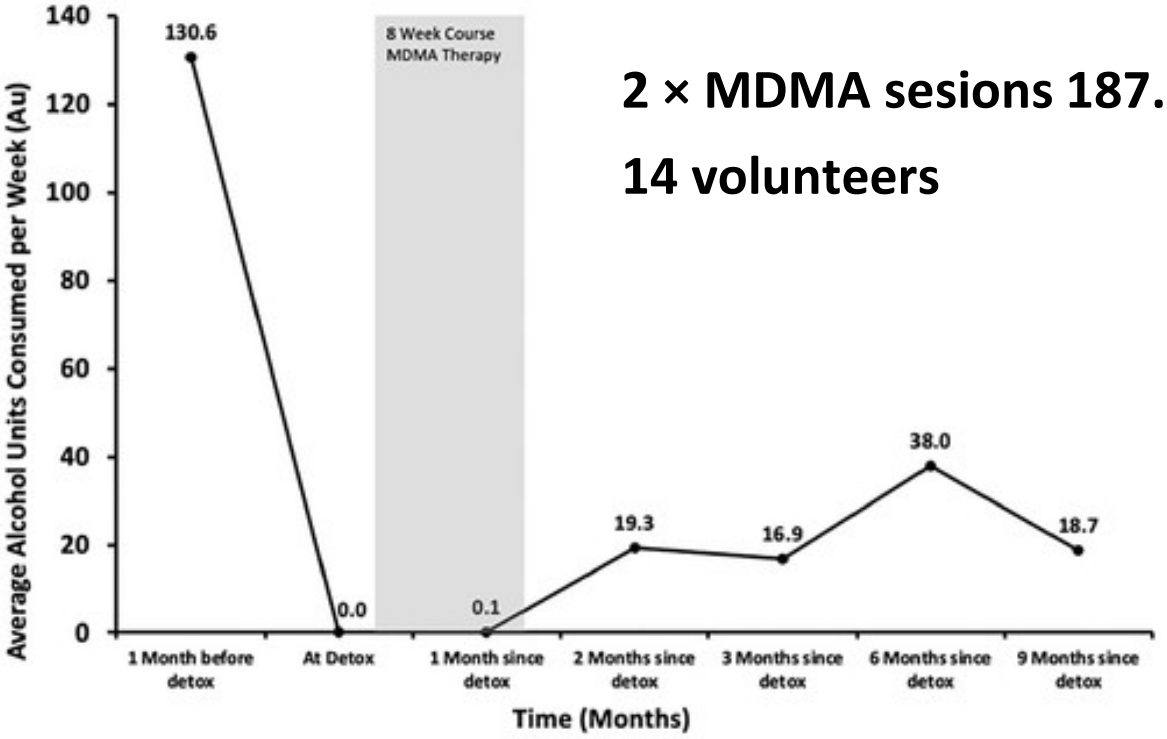
Cocaine craving questionnaires (CCQ-29)

Subscale	Pre-Ibogaine (*N* = 81)	Discharge (*N* = 79)	1 Month (*N* = 32)	*F*	*p*
CCQ-NOW Factor 1: Emotionality (Negative mood state)	1.85 (0.13)	1.09 (0.03)	1.19 (0.05)	22.11	0.0001
CCQ-NOW Factor 2: Purposefulness (Desire or intent to use drug now)	2.60 (0.14)	1.54 (0.20)	1.57 (0.09)	28.37	0.0001
CCQ-NOW Factor 3: Compulsivity	4.27 (0.16)	2.95 (0.13)	3.15 (0.20)	24.44	0.0001
Minnesota Cocaine Craving Scale (MCCS)	Pre-Ibogaine	Discharge	1 Month	*F*	*p*
MCCS Factor 1: Craving Intensity	5.51 (0.38) (*n* = 83)	1.47 (0.14) (*n* = 74)	1.96 (0.23) (*n* = 25)	56.35	0.0001
MCCS Factor 2: Craving Frequency	2.28 (0.19) (*n* = 83)	0.29 (0.10) (*n* = 75)	0.52 (0.51) (*n* = 25)	46.42	0.0001
MCCS Factor 3: Craving Duration	2.51 (0.24) (*n* = 81)	1.36 (0.14) (*n* = 73)	1.21 (0.12) (*n* = 24)	10.75	0.0001

Deborah C et al. **Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes.** Front Pharmacol. 2018; 9: 529

MDMA in alcohol dependence

Open-Label Proof of Concept Feasibility Study



2 × MDMA sesions 187.5 mg each

14 volunteers

Ben Sessa et al. 2021

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder.

Journal of Psychopharmacology

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PSYCHEDELICS AND EXISTENTIAL DISTRESS

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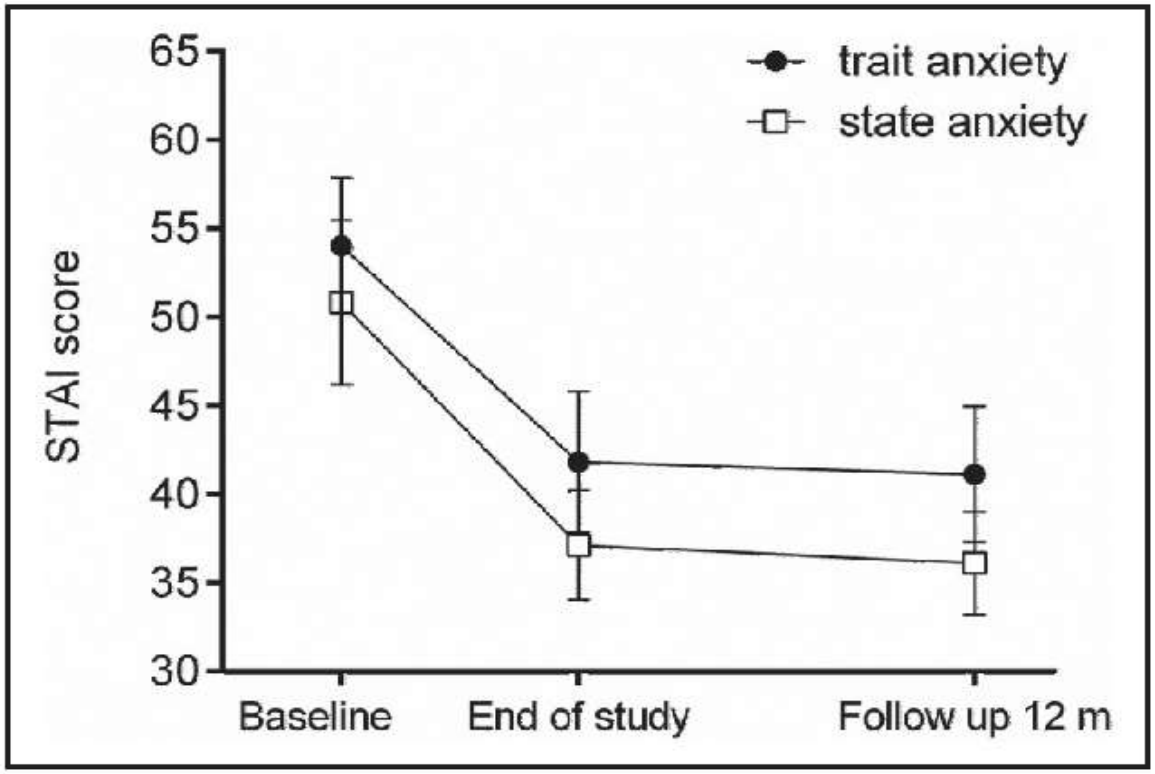
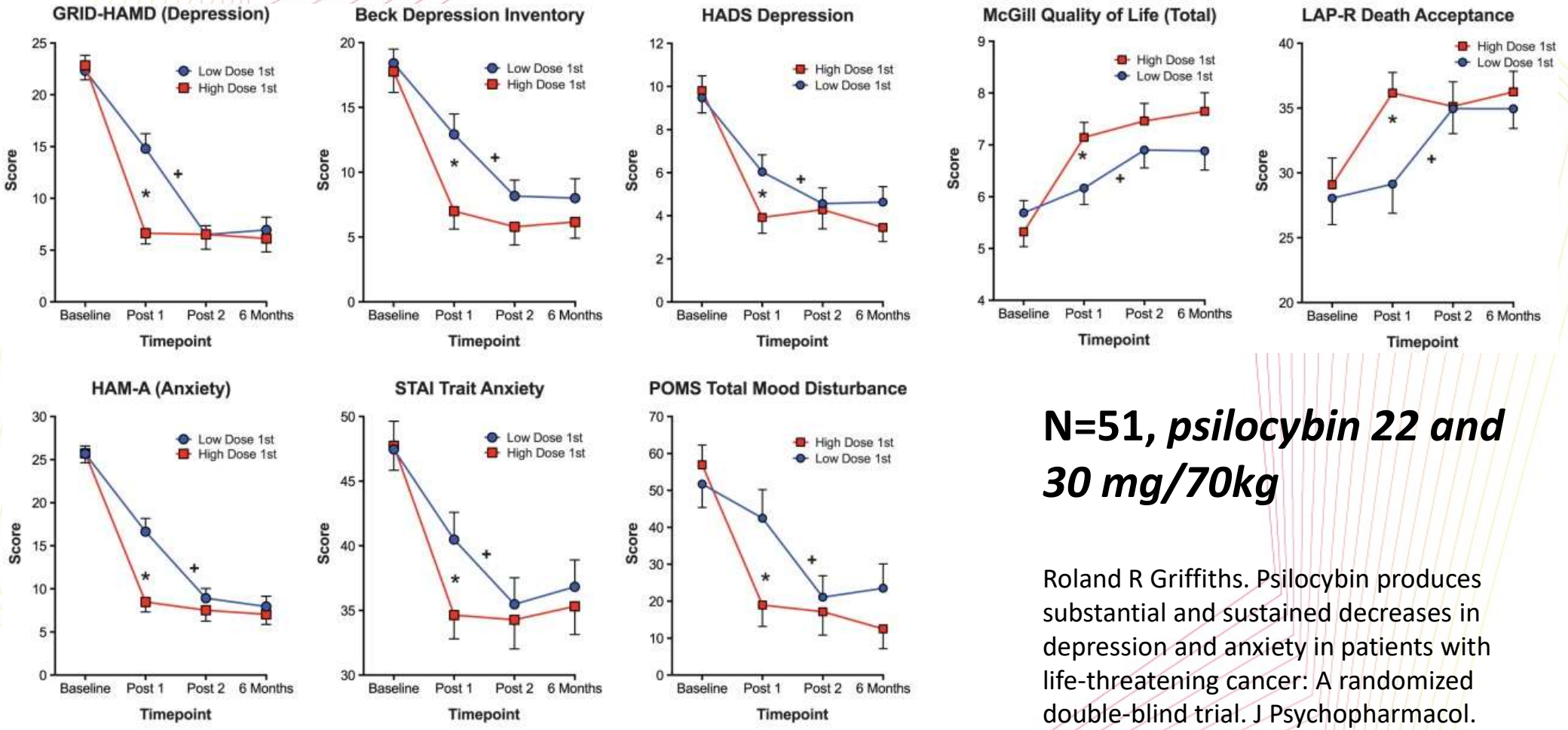
LSD in cancer

- **Placebo controlled cross-over study**
- **N = 12 (3 drop out – 1 died, 1 missing STAI, 1 did not want full LSD dose)**
- **LSD 200µg vs placebo (LSD 20µg)**

Gasser P, et al. (2015) J Psychopharmacol 29: 57-68



Psilocybin cancer study



N=51, *psilocybin 22 and 30 mg/70kg*

Roland R Griffiths. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016 Dec; 30(12): 1181–1197.

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FAST ACTING ANTIDEPRESSANTS ???

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PSYCHEDELICS IN DEPRESSION AND ANXIETY IN 1960-70´s

Table 1. Summary of studies included in the systematic review.

Author	Year	Sample size (*n*)	Population	Dose range	Frequency of sessions	Number of sessions	Percentage improvement (*n*)
Condrau	1949	5	'Depressives'	'Daily increasing'	Daily	Several	40% (2)
Busch and Johnson	1950	5	'Psychoneuroses'	30–40 µg	*Unknown*	*Unknown*	40% (2)
Savage	1952	15	'Depressives'	20–100 µg	Daily	Up to 30	47% (7)
Sandisonet a							
Sloane and L							
Langner and							
Martin							
Sandison and							
Lewis and Slo							
Eisner and Co							
Chandler and							
Maclean et al							
Sherwood et							
Martin							
Geert-Jörgen							
Whitaker							
Savage							
Savage et al.	1967	36	'Psychoneurotic depressive reaction'	200–300 µg LSD ± 200–400 mg Mescaline	Once	1	81% (29)
Baker	1967	11	'Depressives'	100–2000 µg	Weekly	1–10	91% (10)
Leuner	1967	11	'Depressive reactions'	30–200 µg	Biweekly–weekly	2–16	82% (9)
Savage et al.	1973	63	'Severe chronic neuroses'	50 µg or 350 µg	Once	1	*Unclear*

*There are overlapping populations in the studies of Sandison 1954 and 1957.

- Doses: 25 – 1500 µg LSD

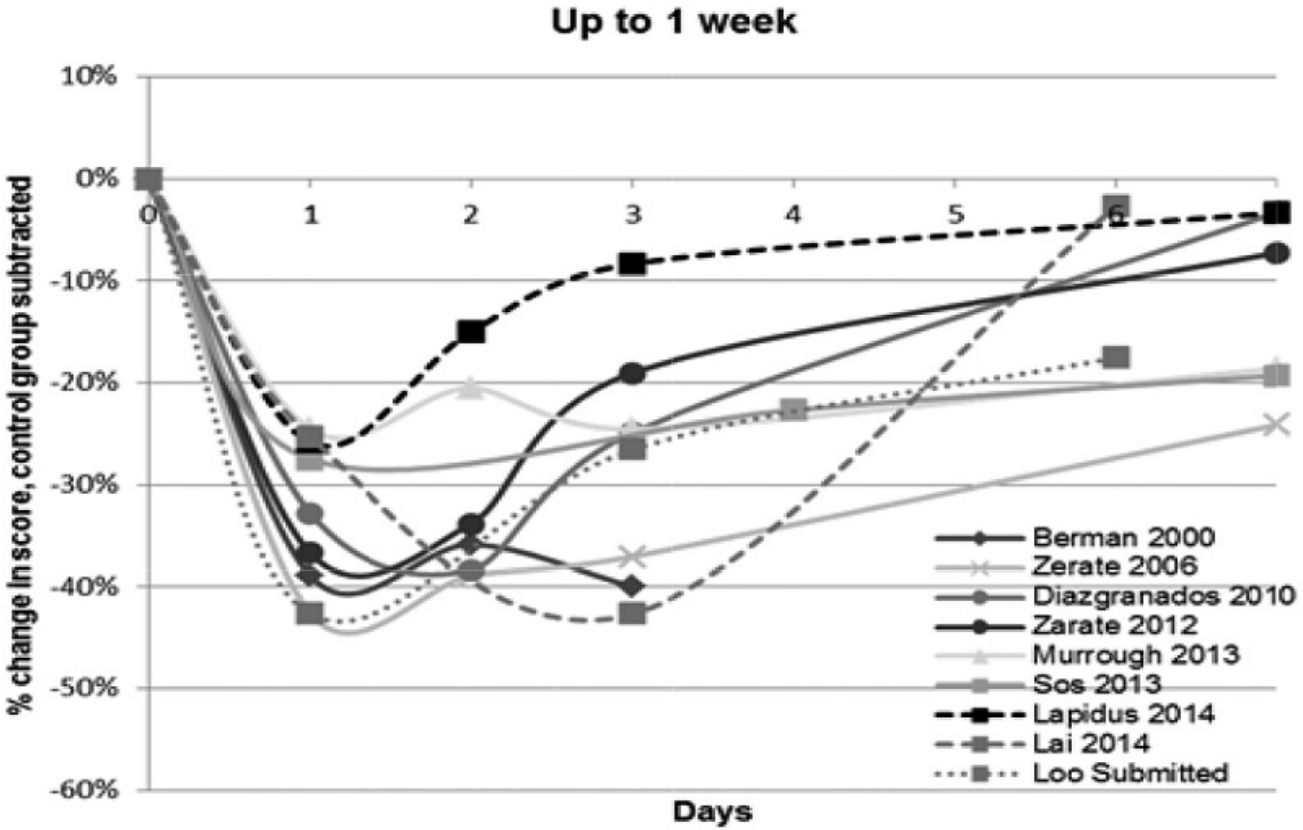
  200 – 400 mg mescaline
- Sessions: 1 – 58
- Improvement: 40 – 91% of patients

Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH.

Psychedelics in the treatment of unipolar mood disorders: a systematic review.

J Psychopharmacol. 2016 Dec;30(12):1220-1229. Epub 2016 Nov 17.

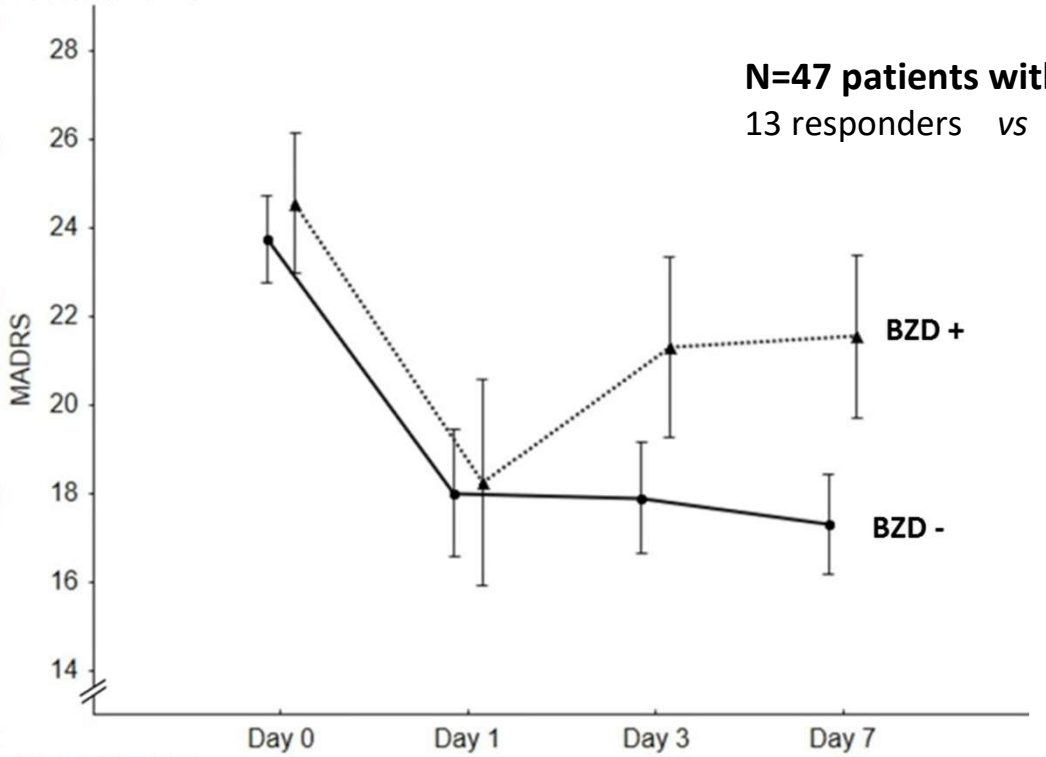
Antidepressant effects of ketamine



Gianluca Serafini et al. The Role of Ketamine in Treatment-Resistant Depression: A Systematic Review. Curr Neuropharmacol. 2014 Sep; 12(5): 444–461.

Placebo-corrected percentage changes in HAM-D/MADRS.

Antidepressant effects of ketamine

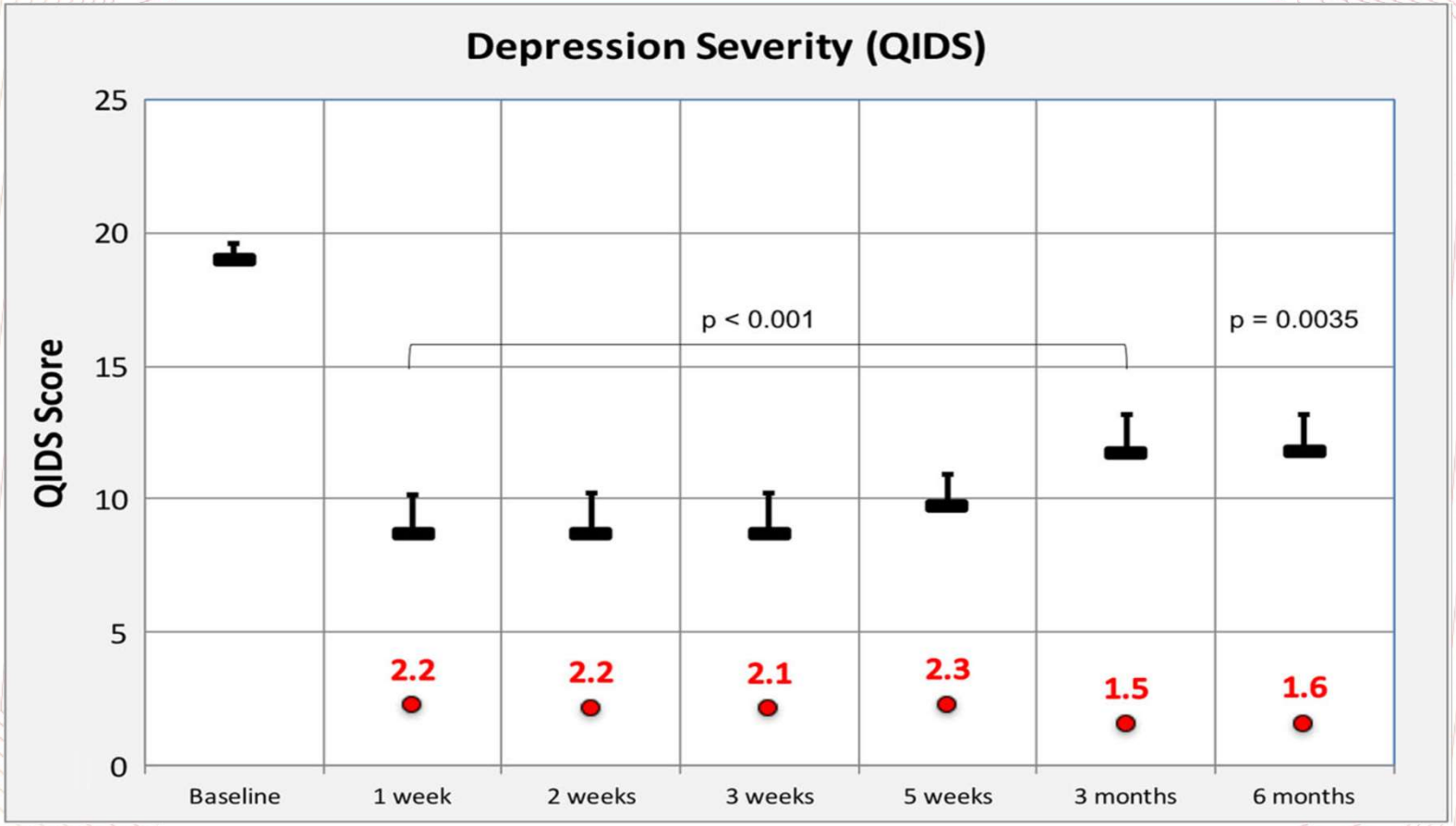


N=47 patients with MDD
13 responders *vs* 34 non-responders

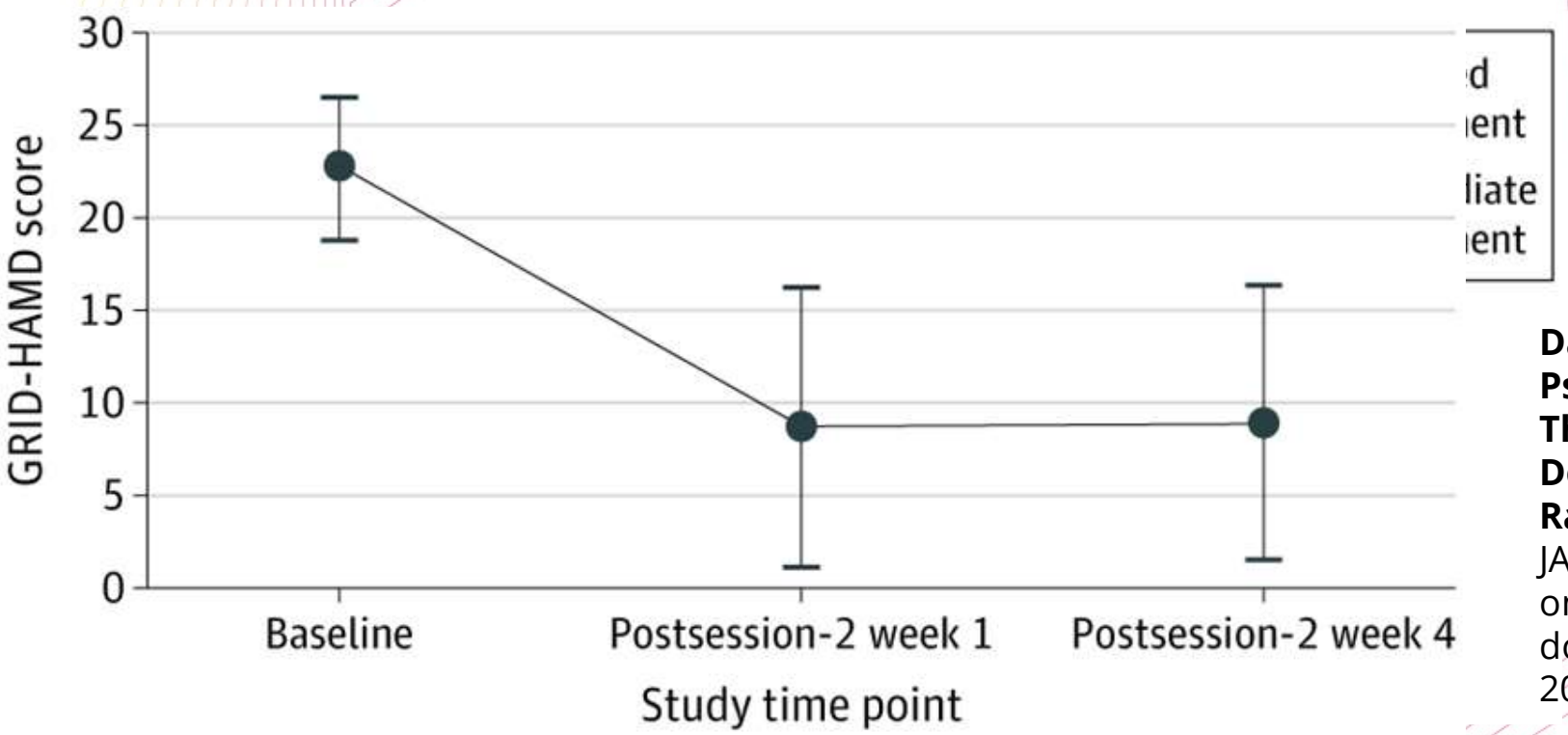
Andrashko V. et al. **The Antidepressant Effect of Ketamine Is Dampened by Concomitant Benzodiazepine Medication.** Front Psychiatry. 2020; 11: 844.

Psilocybin in depression

Robin L Carhart-Harris et al. The Lancet Psychiatry 2016 and Psychopharmacology 2018



Psilocybin in depression

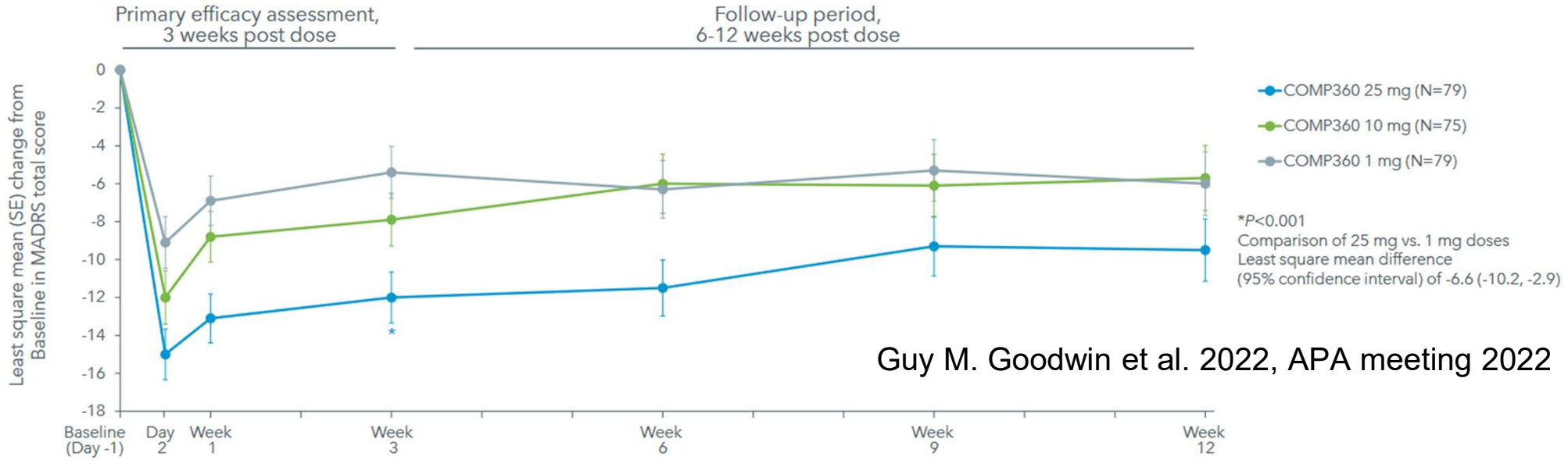


Davis et al. Effects of Psilocybin-Assisted Therapy on Major Depressive DisorderA Randomized Clinical Trial
JAMA Psychiatry. Published online November 4, 2020. doi:10.1001/jamapsychiatry.2020.3285

Psilocybin in depression

Psilocybin versus Escitalopram for Depression

Figure 2. Mean change from Baseline in MADRS total score over time (full analysis set)



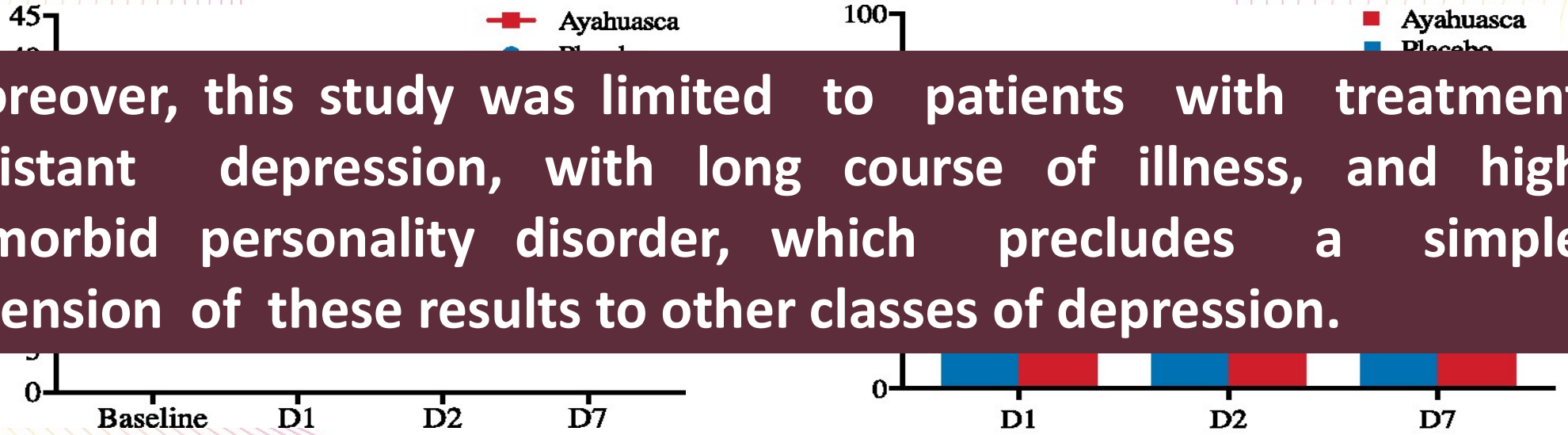
Guy M. Goodwin et al. 2022, APA meeting 2022

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

R. Carhart-Harris et al. 10.1056/NEJMoa2032994

Ayahuasca antidepressant effect

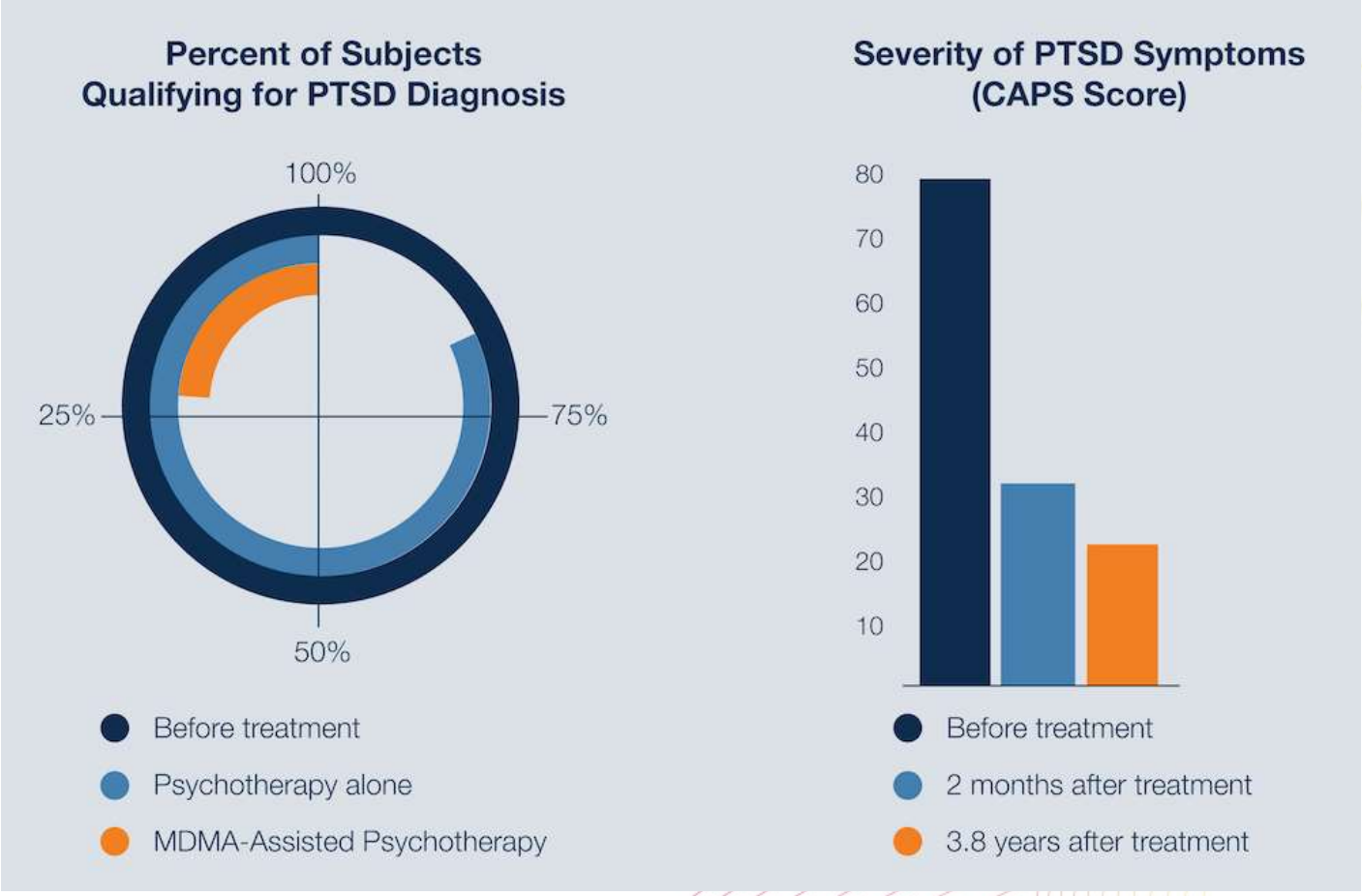
- placebo controled trial (n=29)
- 0.36±0.01 mg/mL DMT, 1.86±0.11 mg/mL harmine, 0.24±0.03 mg/mL harmaline, and 1.20±0.05 mg/mL tetrahydroharmine
- 0.36 mg/kg DMT cca 25 mg DMT in 70 kg man



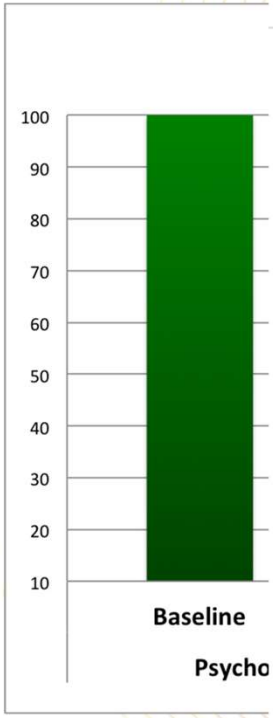
Moreover, this study was limited to patients with treatment resistant depression, with long course of illness, and high comorbid personality disorder, which precludes a simple extension of these results to other classes of depression.

Palhano-Fontes et al. BiorXiv, preprint, 2017, https://doi.org/10.1101/103531

MDMA in postrautmatic stress disorder



MDMA for postraumatic stress disorder



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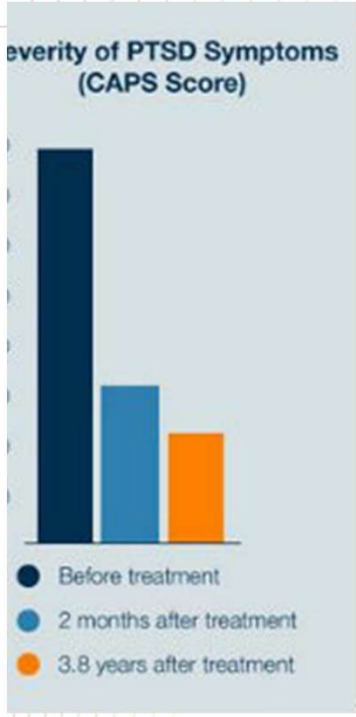
Written on August 26, 2017.

PRESS RELEASE: FDA Grants Breakthrough Therapy Designation for MDMA-Assisted Psychotherapy for PTSD, Agrees on Special Protocol Assessment for Phase 3 Trials

Key highlights

- *Breakthrough Therapy Designation ensures that FDA will work closely with MAPS to complete Phase 3 trials as efficiently as possible*
- *MAPS and FDA have also reached agreement on design, primary endpoint, and statistical approach for Phase 3 trials*
- *Posttraumatic stress disorder (PTSD) is a serious and life-threatening psychiatric condition with unmet medical need despite available treatments*
- *MAPS is sponsoring two Phase 3 clinical trials of MDMA-assisted psychotherapy in patients with severe PTSD starting in 2018*
- *MAPS, a non-profit research organization, has raised or pledged half of the $25 million estimated cost of these trials, with $12.5 million still needed*

CONTACT:
Brad Burge, Director of Strategic Communications, MAPS
brad@maps.org



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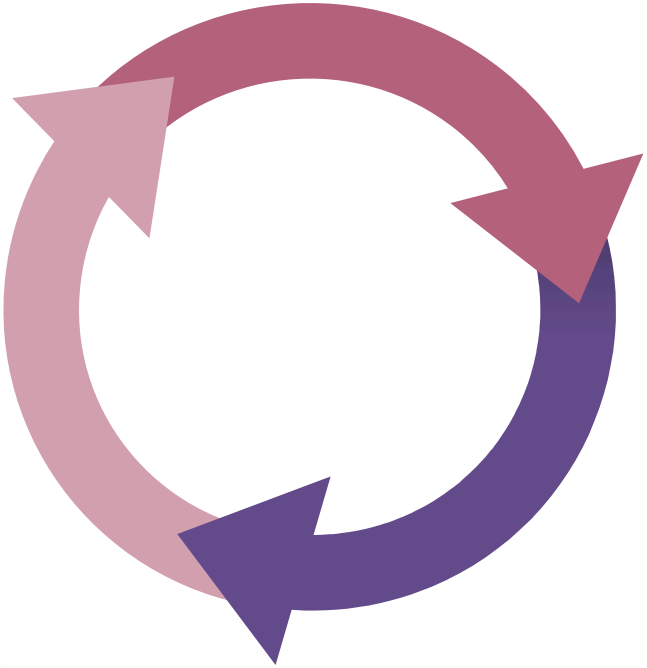

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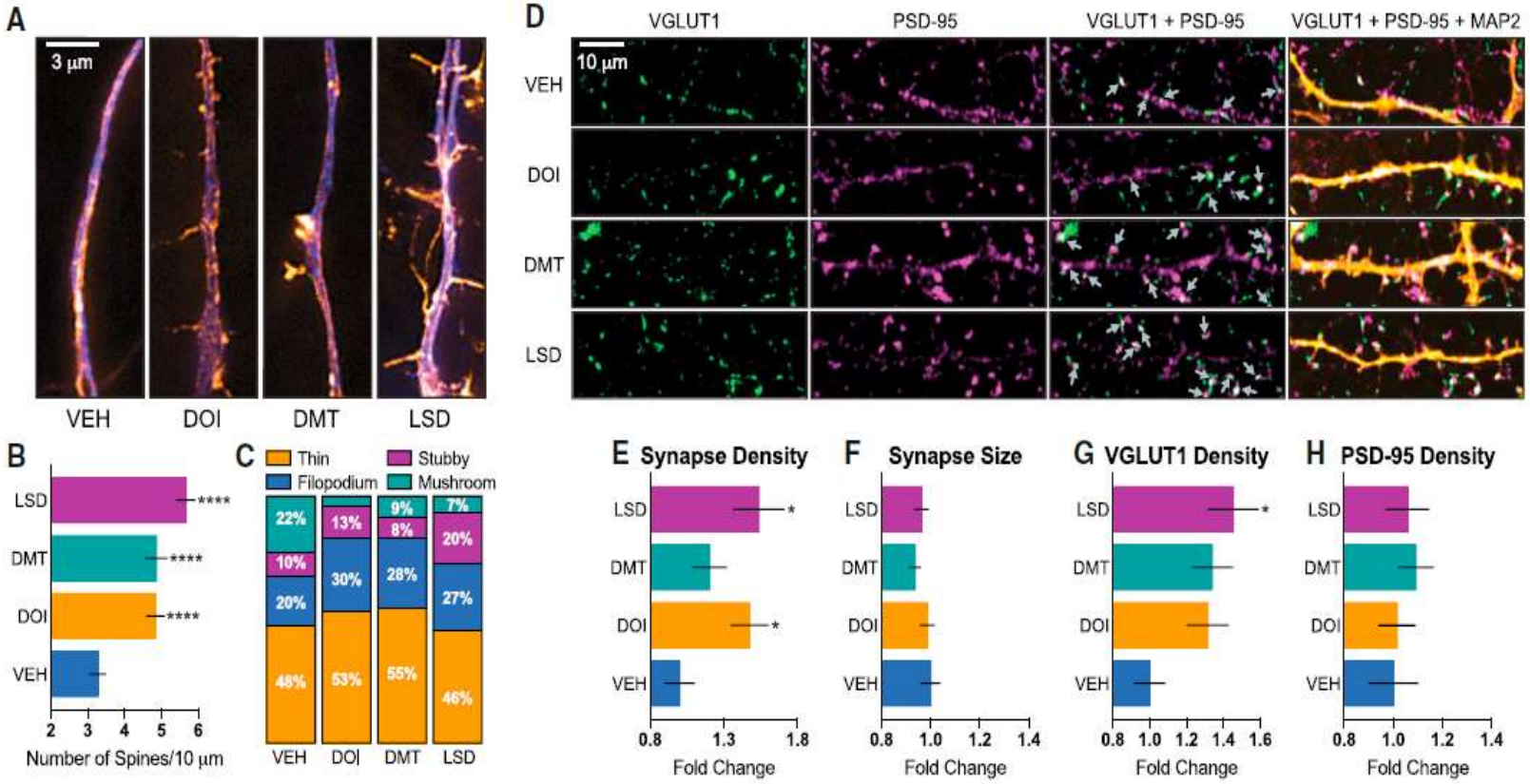
5-HT PSYCHEDELICS & SYNAPTIC PLASTICITY



Neuritogenesis, spinogenesis, synaptogenesis induced via TrkB, mTOR, and 5-HT2A signaling

ARTICLE

Psychedelics Promote Structural and Functional Neural Plasticity

Calvin Ly, Alexandra C. Greb, Lindsay P. Cameron, Jonathan M. Wong, Eden V. Barragan, Paige C. Wilson, Kyle F. Burbach, Sina Soltanzadeh Zarandi, Alexander Sood, Michael R. Paddy, Whitney C. Duim, Megan Y. Dennis, A. Kimberley McAllister, Kassandra M. Ori-McKenney, John A. Gray, David E. Olson[10]

[10] Lead Contact

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DOI: https://doi.org/10.1016/j.celrep.2018.05.022 | CrossMark

Open access funded by National Institutes of Health

Article Info

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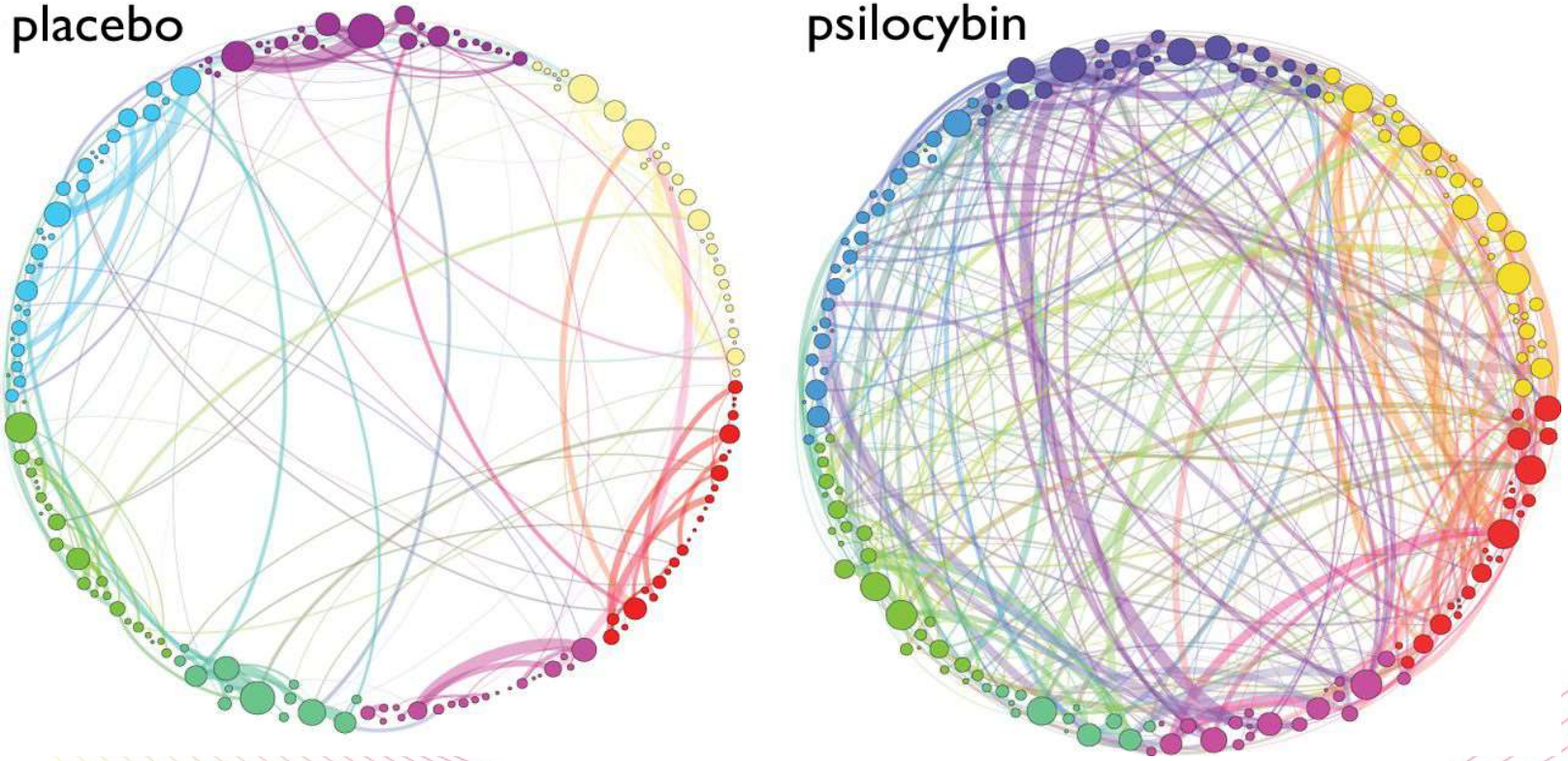
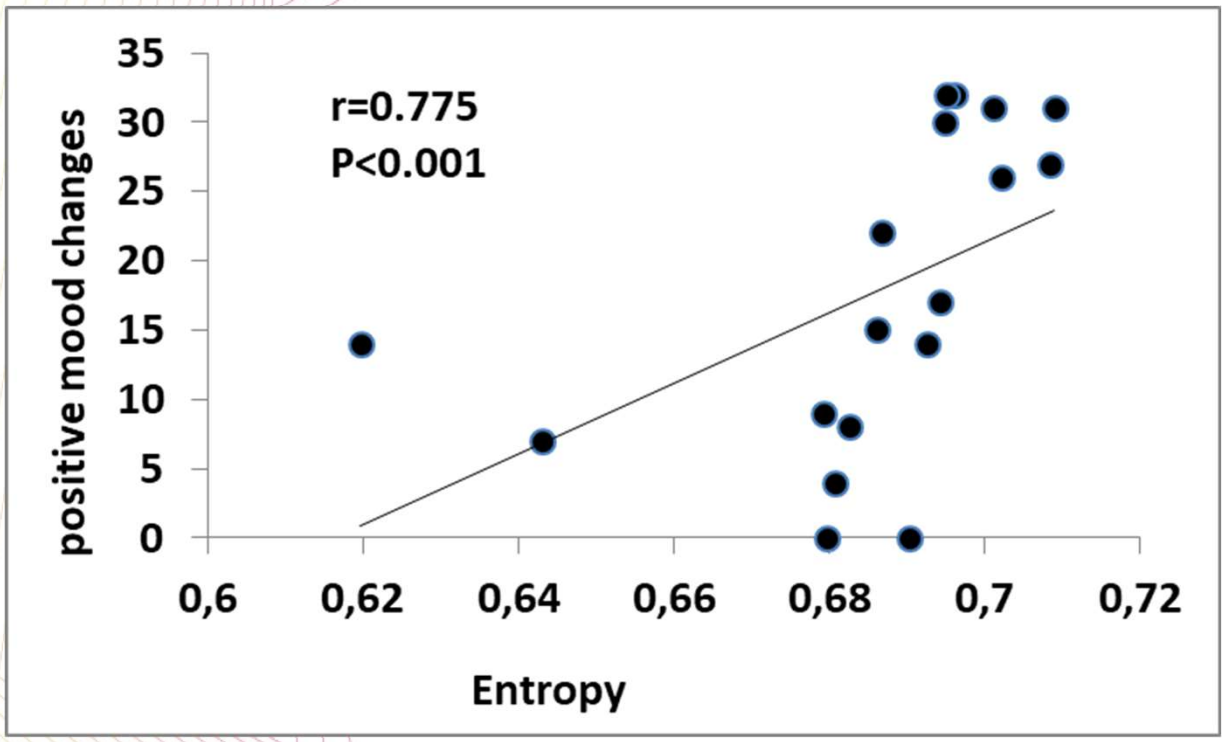
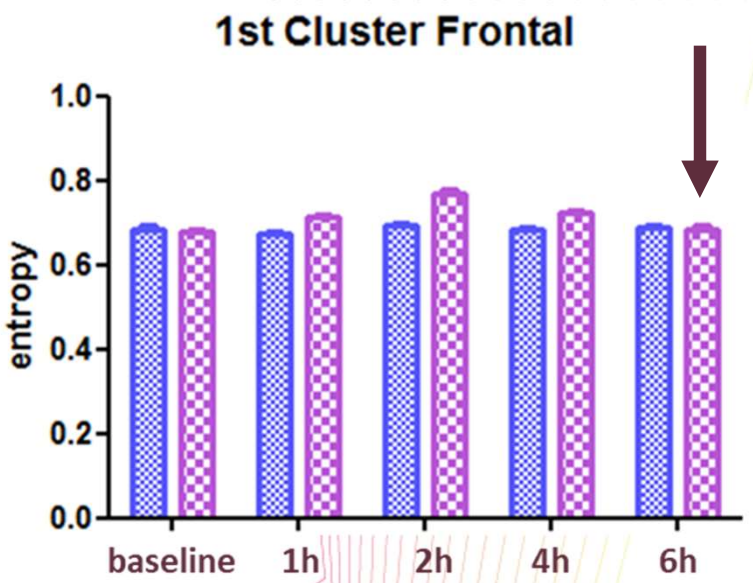


G. Petri, P. Expert, F. Turkheimer, R. Carhart-Harris, D. Nutt, P. J. Hellyer, F. Vaccarino. 2014.

Homological scaffolds of brain functional networks

ENTROPY AND PERSISTING EFFECTS





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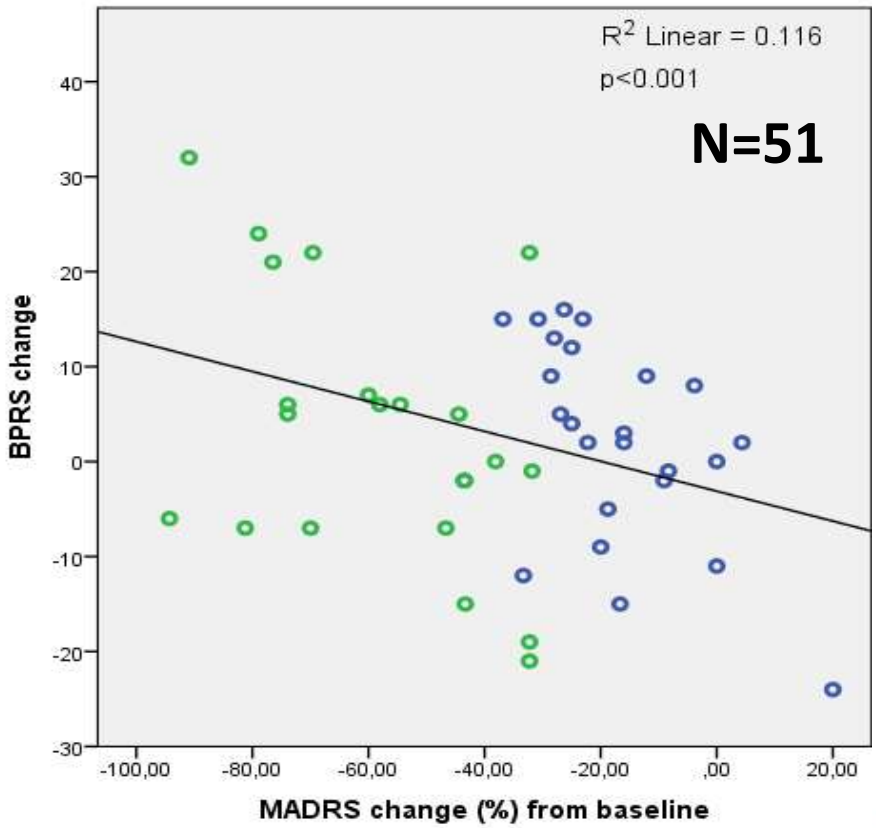
PSYCHOTOMIMETIC EFFECT *vs* THE THERAPEUTIC OUTCOME (KETAMINE)

responders

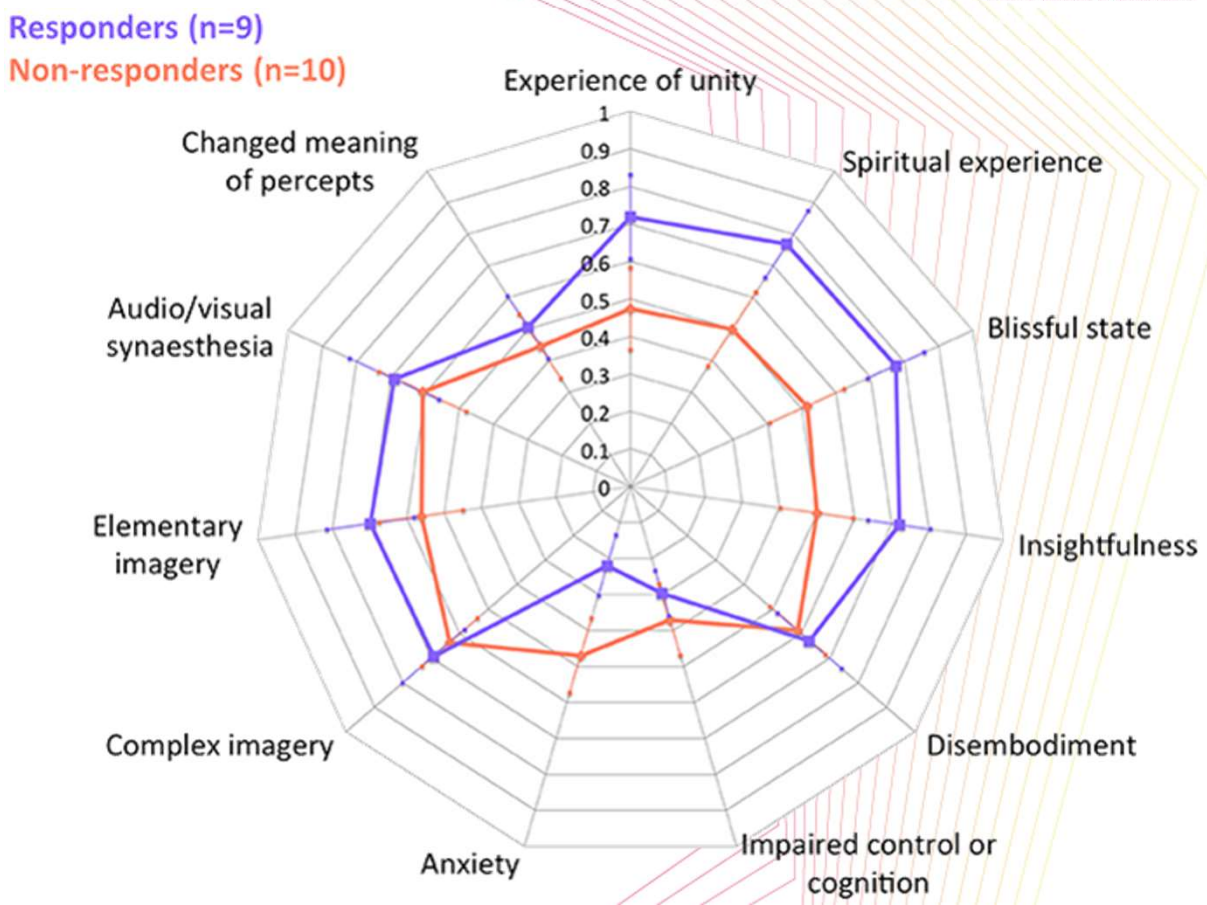


non-responders

PREDICTION OF ANTIDEPRESSANT RESPONSE

ASCs (11 dimensions) of responders and non-responders at 5 weeks.

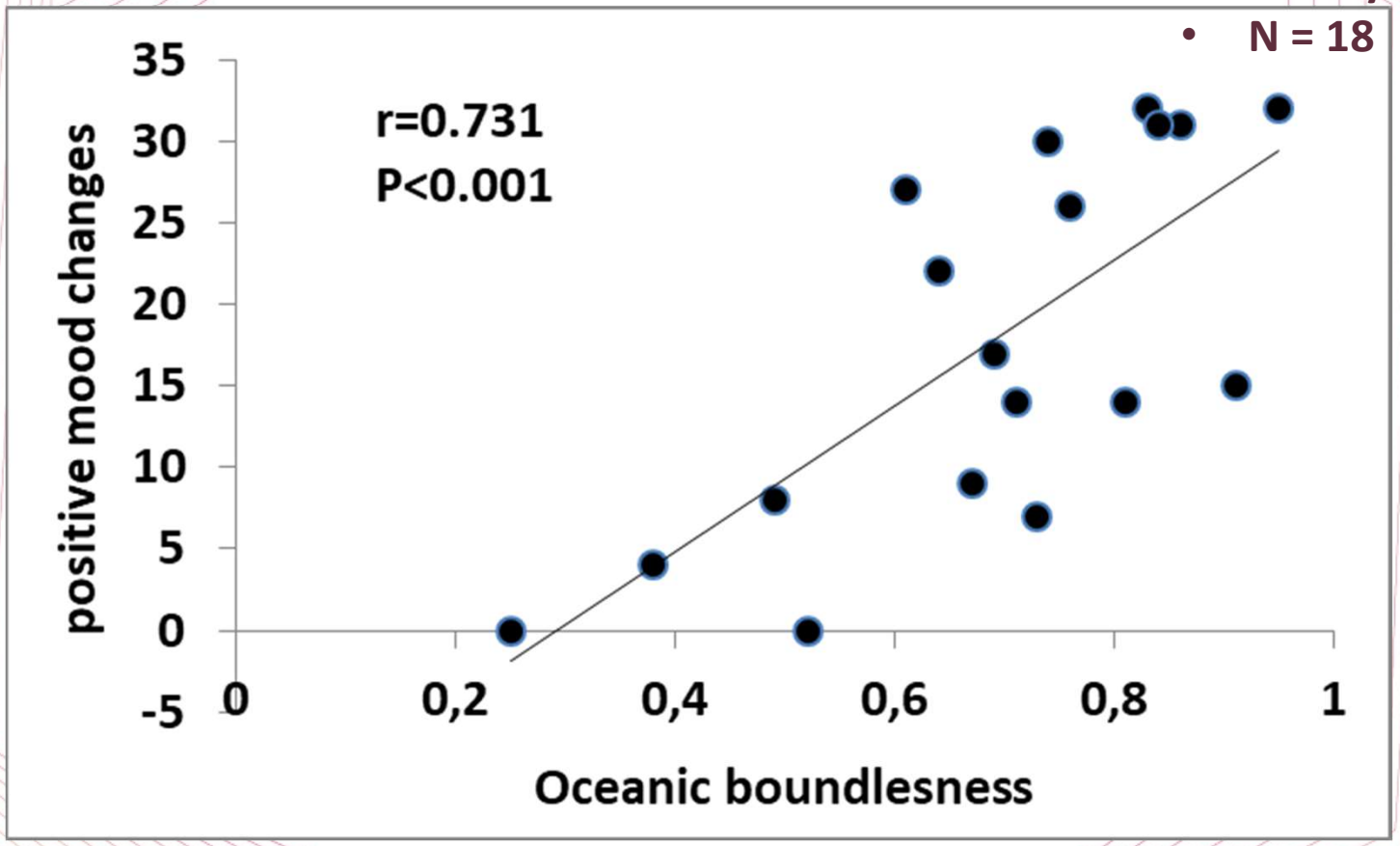
OAV - 11 factors		
OBN	**Experience of Unity**	EOU
OBN	**Spiritual Experience**	SE
OBN	**Blissful State**	BS
OBN/VRS	**Insightfulness**	IF
OBN	**Disembodiment**	DB
DED	**Impaired control and cognition**	ICC
DED	**Anxiety**	AX
VRS	**Complex Imagery**	CI
VRS	**Elementary Imagery**	EI
VRS	**Audio-Visual Synesthesiae**	AVS
VRS	**Changed Meaning of Percepts**	CMP



Roseman L. et al. *Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression.* Front. Pharmacol., 17 January 2018 | https://doi.org/10.3389/fphar.2017.00974

PSILOCYBIN IN HEALTHY VOLUNTEERS – ONGOING CZECH STUDY

- Psilocybin 0.26 mg/kg
- N = 18



CLINICAL STUDIES AT NIMH

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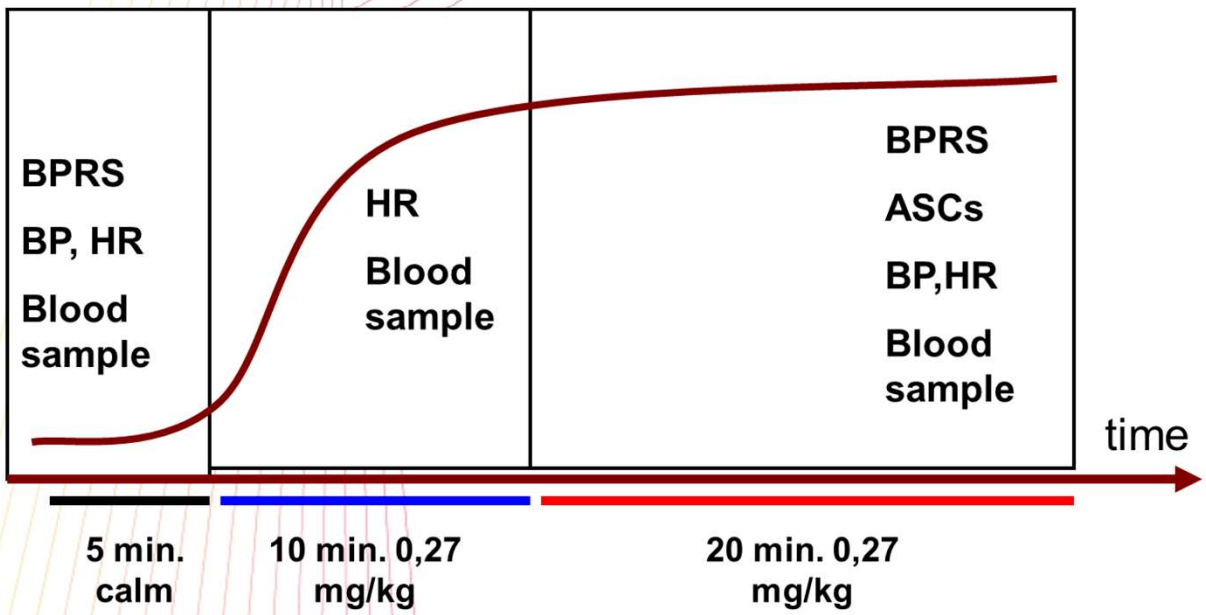
1st study with ketamine in healthy



- **ketamine: i.v.** 0.27 mg/kg for 10 minutes → maintenance dose 0.27 mg/kg for 20 min. (total 0.54 mg/kg in 30 min.)
- **placebo: i.v.** physiological saline for 30 min.

Psychological Medicine, Page 1 of 9. © Cambridge University Press 2009
doi:10.1017/S0033291709991619

ORIGINAL ARTICLE

Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect

J. Horacek[1,2,3*], M. Brunovsky[1,2], T. Novak[2], B. Tislerova[3], T. Palenicek[2,3], V. Bubenikova-Valesova[1,2], F. Spaniel[1,3], J. Koprivova[2,3], P. Mohr[1], M. Balikova[4] and C. Hoschl[1,2,3]

[1] *Prague Psychiatric Centre, Prague, Czech Republic*
[2] *Centre of Neuropsychiatric Studies, Prague, Czech Republic*
[3] *Third Medical Faculty of Charles University, Prague, Czech Republic*
[4] *Institute of Forensic Medicine and Toxicology, First Medical Faculty, Charles University, Prague, Czech Republic*

Background. Theta cordance is a novel quantitative electroencephalography (QEEG) measure that correlates with cerebral perfusion. A series of clinical studies has demonstrated that the prefrontal theta cordance value decreases after 1 week of treatment in responders to antidepressants and that this effect precedes clinical improvement. Ketamine, a non-competitive antagonist of *N*-methyl-D-aspartate (NMDA) receptors, has a unique rapid antidepressant effect but its influence on theta cordance is unknown.

Method. In a double-blind, cross-over, placebo-controlled experiment we studied the acute effect of ketamine (0.54 mg/kg within 30 min) on theta cordance in a group of 20 healthy volunteers.

Results. Ketamine infusion induced a decrease in prefrontal theta cordance and an increase in the central region theta cordance after 10 and 30 min. The change in prefrontal theta cordance correlated with ketamine and norketamine blood levels after 10 min of ketamine infusion.

Conclusions. Our data indicate that ketamine infusion immediately induces changes similar to those that monoaminergic-based antidepressants induce gradually. The reduction in theta cordance could be a marker and a predictor of the fast-acting antidepressant effect of ketamine, a hypothesis that could be tested in depressive patients treated with ketamine.

Received 27 January 2008; Revised 3 September 2009; Accepted 28 September 2009

Key words: Depression, healthy volunteers, ketamine, QEEG, theta cordance.

PI – Prof. MUDr. Jiří Horáček, PhD

1st study with ketamine in depression

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Trials with a EudraCT protocol (1) | Paediatric studies in scope of Art45 of t

1 result(s) found for: 2009-010625-39. Displaying page 1 of 1.

EudraCT Number: 2009-010625-39	**Sponsor Protocol Number:** MZ09-PCP-SosPeter	**Start Date*:** 2010-04-21
Sponsor Name: Prague Psychiatric Center		
Full Title: QEEG cordance and EEG connectivity changes after administration of subanesthetic ketamine doses in depressive disorder patients		
Medical condition: INCLUSION CRITERIA: 1. Men and women at the age between 18 to 65 years, with dextromanual dominance. 2. Patients have to answer DSM IV criteria for the major depressive episode, without psychotic s...		
Disease:		
Population Age: Adults		**Gender:** Male, Female
Trial protocol: CZ *(Completed)*		
Trial results: *(No results available)*		

PI – MUDr. Peter Šoš, PhD

Neuroendocrinology Letters Volume 34 No. 4 2013

ORIGINAL ARTICL

Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression

Peter Sos, Monika Klirova, Tomas Novak, Barbora Kohutova, Jiri Horacek, Tomas Palenicek

1 Prague Psychiatric Centre, Prague, Czech Republic

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Ústavní 91, CZ–181 03 Praha 8, Czech Republic.
TEL: +420 266 003 364; FAX: +420 266 003 366; E-MAIL: sos@pcp.lf3.cuni.cz

Submitted: 2013-06-04 *Accepted: 2013-06-06* *Published online: 2013-06-25*

Key words: **ketamine; nor-ketamine; antidepressant; psychotomimetic; NMDA; major depressive disorder**

Neuroendocrinol Lett 2013; **34**(4):287–293 **PMID:** 23803871 NEL340413A06

Abstract

OBJECTIVES: Ketamine and other NMDA (N-methyl-D-aspartate) antagonists produce fast-acting antidepressant-like effects, although the underlying mechanism is unclear. Furthermore, high affinity NMDA antagonists such as ketamine are associated with psychotomimetic effects. To date the link between the antidepressant and psychotomimetic effects of ketamine has not been explored. We examined the relationship between the antidepressant and psychotomimetic effects of a single ketamine infusion in subjects diagnosed with major depressive disorder.

METHODS: In a double-blind, cross-over, placebo-controlled, two weeks clinical trial we studied the effects of ketamine (0.54 mg/kg within 30 min) in a group of 27 hospitalized depressive patients.

RESULTS: Higher intensity of psychotomimetic symptoms, measured using BPRS, during ketamine administration correlated with alleviation in mood ratings during the following week with maximum on day seven. Ketamine was superior to placebo in all visits (day 1, 4, and 7) assessed by MADRS with effect size (Cohen´s d) of 0.62, 0.57, and 0.44 respectively. There was no significant correlation between ketamine and nor-ketamine plasma levels and MADRS score change at any study time point.

CONCLUSION: The substantial relationship between ketamine's antidepressant and psychotomimetic effects was found. This relationship could be mediated by

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1st study with ketamine in depression

Tab. 1. Demo

Age (years)
Gender (M : F
Duration of d
Duration of c
Number of pr
Baseline MAD
Treatment be

[a] Student's t-t
Noradrenergic
AD augm. – au

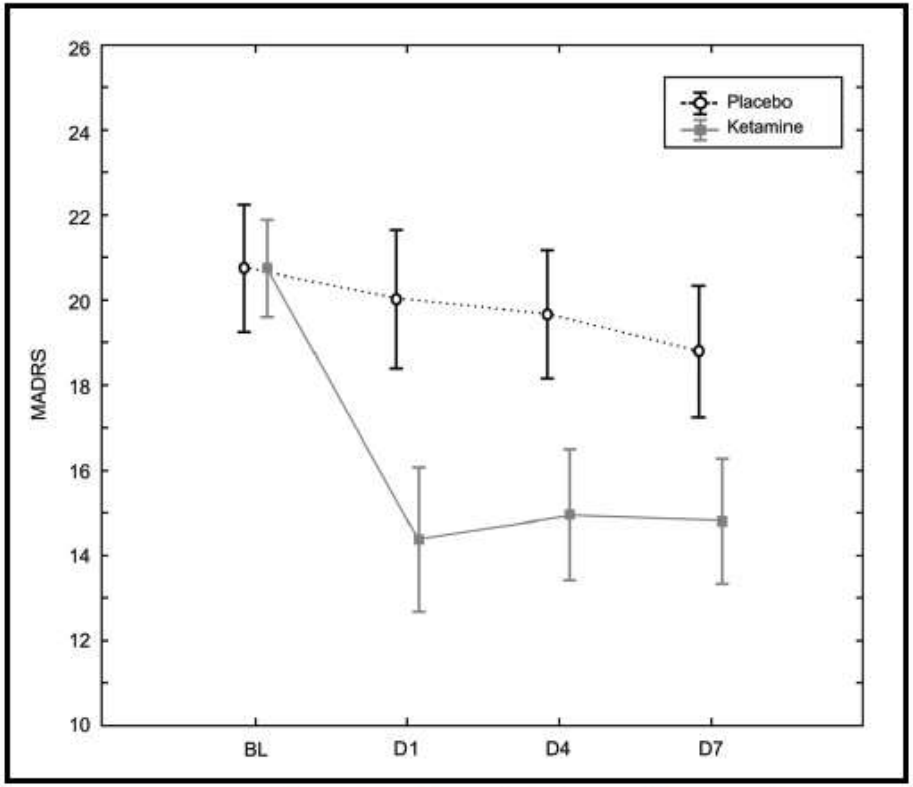

Fig. 2. Superiority of ketamine over placebo at all post-infusion visits was found (day 1: $p<0.001$ day 4: $p=0.002$; day 7: $p=0.02$).

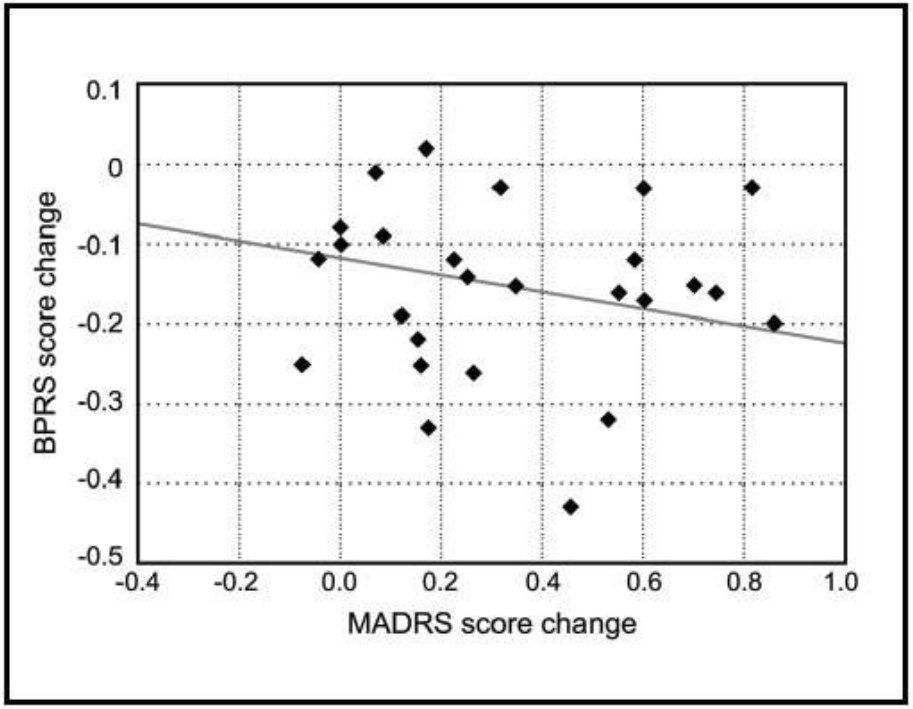

Fig. 3. Association between BPRS score change during acute administration of ketamine and MADRS score change at day seven, analysed by Pearson's correlation coefficient (r=–0.40, $p=0.04$).

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decision)
= 8

solution)

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ebo response)

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Oral ketamine in intelectually disabled

Tab. 1. Mean values (±SEM) of scores on PAS subscales. The last line shows *p*-values of Mann-Whitney comparisons between the treatment groups.

	Aberant vocalization	Motor agitation	Aggressive behavior	Resisting care
KM group	0.06±0.06	0.06±0.06	0	0.12±0.12
KCM group	0.5±0.19	0.08±0.08	0	0.5±0.19
KM vs KCM	*p*=0.11	*p*=0.71	NA	*p*=0.39

PI – Doc. MUDr. Ladislav Hess, DrSc

KM = ketamine 5 mg/kg + midazolam 0,3 mg/kg
KCM = ketamine 5 mg/kg + clonidine 2 µg/kg + midazolam 0,3 mg/kg

Neuroendocrinology Letters Volume 33 No. 4 2012

ORIGINAL ARTI

The influence of clonidine on oral ketamine-midazolam premedication in intellectually disabled patients indicated for dental procedures: Double-blind comparison of two sedation regimes

Jiri HORACEK [1,2], Tomas PALENICEK [1,2], Jiri MALEK [2], Vladimir SCIGEL [4], Alice KURZOVA [2], Ladislav HESS [3]

1 Prague Psychiatric Centre, Prague, Czech Republic
2 3rd Medical Faculty of Charles University, Prague, Czech Republic
3 Institute for Clinical and Experimental Medicine, Laboratory of Experimental Anaesthesiology, Prague, Czech Republic
4 Institute of Clinical and Experimental Dental Medicine, First Faculty of Medicine, Charles University, Prague, Czech Republic

Correspondence to: Prof. Dr. Jiri Horacek, PhD.
Prague Psychiatric Centre,
Ústavní 91, CZ–181 03 Praha 8, Czech Republic.
TEL: +420 266 003 370; FAX: +420 266 003 366; E-MAIL: horacek@pcp.lf3.cuni.cz

Submitted: 2012-06-12 *Accepted: 2012-06-19* *Published online: 2012-00-00*

Key words: **intellectually disabled patients; mental retardation; dental procedures; oral analgesic sedation; premedication; anesthesia; ketamine; clonidine; midazolam**

Neuroendocrinol Lett 2012; 33(4):101–105 **PMID:** ----- NEL330412AXX

Abstract

BACKGROUND: Dental procedures on intellectually disabled patients represent a clinical challenge. The oral administration of sedating drugs can remediate the problems with cooperation and enable the medical procedures to take place. Standard guidelines are lacking for oral sedation of the intellectually disabled.
OBJECTIVE: To compare two oral combinations of sedating drugs in terms of time to the onset and achievement of full sedation, vital signs, behavioral measures and

Psilocybin in healthy volunteers

Trials with a EudraCT protocol (1) | Paediatric studies in scope of Art45 of t

1 result(s) found for: 2012-004579-37. Displaying page 1 of 1.

EudraCT Number: 2012-004579-37	**Sponsor Protocol Number:** MZ12-PCP-PalenicekTomas-A	**Start Date*:** 2014-06-18
Sponsor Name: National Institute of Mental Health		
Full Title: Animal and human serotonergic model of schizophrenia: validity evaluated by qEEG and fMRI		
Medical condition: Inclusion criteria: a) Men and women at age between 28 and 65 years b) healthy volunteers with negative psychiatric history (severe mental illnesses that meet the criteria of ICD 10 F0.X - F99.X) ...		
Disease:		
Population Age: Adults		**Gender:** Male, Female
Trial protocol: CZ *(Ongoing)*		
Trial results: *(No results available)*		

Psychopharmacology
https://doi.org/10.1007/s00213-017-4807-2

ORIGINAL INVESTIGATION

Psilocybin disrupts sensory and higher order cognitive processing but not pre-attentive cognitive processing—study on P300 and mismatch negativity in healthy volunteers

Anna Bravermanová[1,2] · Michaela Viktorinová[1,3] · Filip Tylš[1,3] · Tomáš Novák[1,3] · Renáta Androvičová[1,3] · Jakub Korčák[1,3] · Jiří Horáček[1,3] · Marie Balíková[2] · Inga Griškova-Bulanova[4] · Dominika Danielová[1,3] · Přemysl Vlček[1,3] · Pavel Mohr[1,3] · Martin Brunovský[1,3] · Vlastimil Koudelka[1] · Tomáš Páleníček[1,3]

Received: 12 May 2017 / Accepted: 29 November 2017

Abstract

Rationale Disruption of auditory event-related evoked potentials (ERPs) P300 and mismatch negativity (MMN), electrophysiological markers of attentive and pre-attentive cognitive processing, is repeatedly described in psychosis and schizophrenia. Similar findings were observed in a glutamatergic model of psychosis, but the role of serotonergic 5-HT_{2A} receptors in information processing is less clear.

Objectives We studied ERPs in a serotonergic model of psychosis, induced by psilocybin, a psychedelic with 5-$HT_{2A/C}$ agonistic properties, in healthy volunteers.

Methods Twenty subjects (10M/10F) were given 0.26 mg/kg of psilocybin orally in a placebo-controlled, double-blind, cross-over design. ERPs (P300, MMN) were registered during the peak of intoxication. Correlations between measured electrophysiological variables and psilocin serum levels and neuropsychological effects were also analyzed.

Results Psilocybin induced robust psychedelic effects and psychotic-like symptoms, decreased P300 amplitude ($p = 0.009$) but did not affect the MMN. Psilocybin's disruptive effect on P300 correlated with the intensity of the psychedelic state, which was dependent on the psilocin serum levels. We also observed a decrease in N100 amplitude ($p = 0.039$) in the P300 paradigm and a negative correlation between P300 and MMN amplitude ($p = 0.014$).

Conclusions Even though pre-attentive cognition (MMN) was not affected, processing at the early perceptual level (N100) and in higher-order cognition (P300) was significantly disrupted by psilocybin. Our results have implications for the role of 5-HT_{2A} receptors in altered information processing in psychosis and schizophrenia.

Keywords Psilocybin · Model of psychosis · Human · ERP · MMN · P300

PI – MUDr. Tomáš Páleníček, PhD.

Ketamine in depression (NIMH)

- **PI:** Prof. MUDr. Jiří Horáček, PhD., **co-PI:** MUDr. Veronika Andrashko
- **Open label**
- **No. of participants:** 40 patients with MDD of moderate to severe intensity without psychotic features.
- **Study objectives:**

one-week, open-label clinical trial, evaluating the predictors of antidepressant effect of single ketamine infusion by a complex battery of candidate clinical and neurobiological parameters in patients with non-psychotic depression, with a two-week open follow-up period

Trials with a EudraCT protocol (1) | Paediatric studies in scope of Art45 of the

1 result(s) found for: ketamine and depression and národní. Displaying page 1 of 1.

EudraCT Number: 2018-001539-39	**Sponsor Protocol Number:** NV18-04-00260	**Start Date*:** Information not available in EudraCT
Sponsor Name: Národní ústav duševního zdraví		
Full Title: Clinical and neurobiological predictors of response to ketamine: towards personalized treatment of depression		
Medical condition: Moderate to severe depression without psychotic symptoms		
Disease:		
Population Age: Adults		**Gender:** Male, Female
Trial protocol: CZ *(Ongoing)*		
Trial results: *(No results available)*		

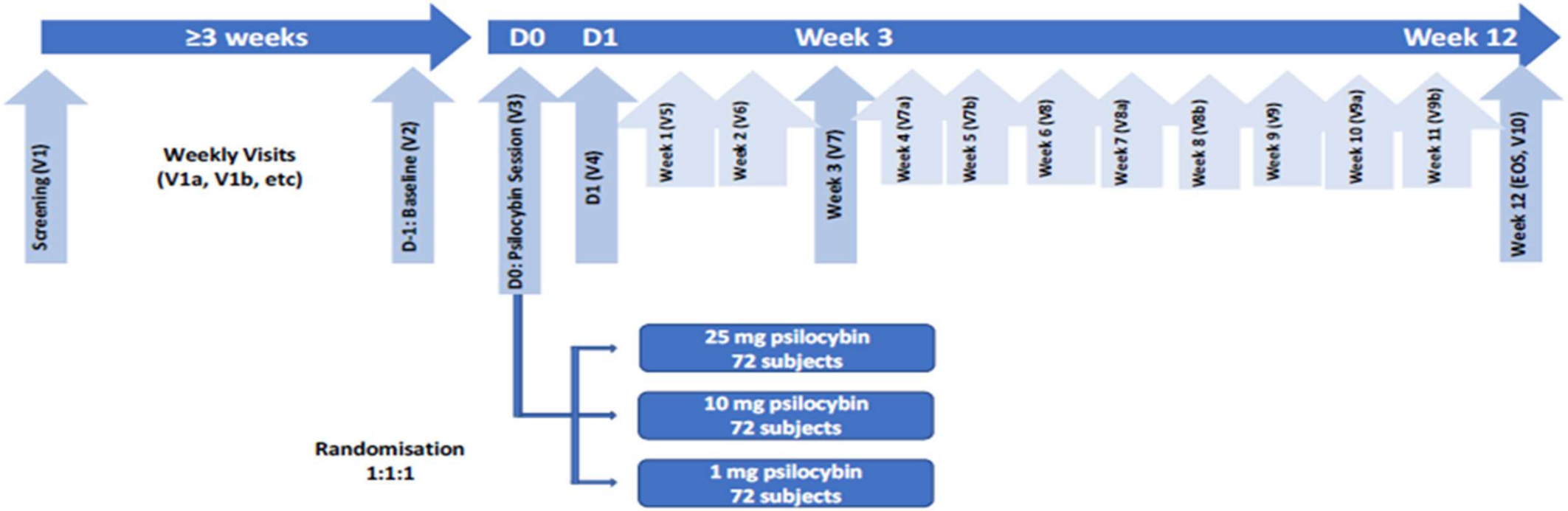
Psilocybin in TRD - Compass Pathways

The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)

EudraCT Number: 2017-003288-36/
Study Number: COMP001
Clinical Phase: 2
Target Population: TRD
Number of Participants: 216 participants

Objectives: The main purpose of this study is to allow COMPASS to determine the optimal candidate dose of psilocybin, either 10 mg or 25 mg. The intent of the primary efficacy analysis is to demonstrate superiority of at least one optimal candidate dose (10 mg or 25 mg) of psilocybin versus the 1 mg psilocybin via the following objectives.
The primary objective of this study is to evaluate the efficacy of psilocybin (25 mg or 10 mg) compared to 1 mg, administered under supportive conditions to adult participants with TRD, in improving depressive symptoms, as assessed by the change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from Baseline. Baseline is defined as the assessment score obtained on Day -1. The primary timepoint is Week 3; this variable will be analysed for the change from Baseline to Day 1, and Weeks 1, 3, 6, 9, and 12.

Psilocybin in TRD - Compass Pathways



Psilocybin vs ketamine in TRD (NIMH)

Psilocybin versus ketamin **eatment-resistant depression**

- **PI:** MUDr. Tomáš Páleníč UDr. Jiří Horáček. PhD.
- **Protocol Number**: PSIKET_001
- **Phase:** II
- **EUDRACT NUMBER:** 2018-004
- **Study objectives:**
  - The primary objective of the ocybin 20 mg compared to ketamine 200 mg using the M edication. We assume that after 24 hours psilocybin 20 mg and k ct (decrease in depressive symptoms according to the M bstances will be more pronounced compared to antidepressant
  - A key secondary objective wi nt effect in the first two weeks (days 3, 7 and 14) after psiloc lly does not exceed one week after a single dose) using the MAD essant effect of psilocybin will be more significant compared to unced after 2 weeks from a single application.

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ADRESA PRO DORUČENÍ: Národní ústav duševního zdraví, MUDr. Tomáš Páleníček PhD., Topolová 748, 250 67 Klecany, Česká republika

Sp. zn. sukls131878/2020
Vyřizuje/linka: Trunečková / 208
Datum: 14. 7. 2020

SDĚLENÍ O POVOLENÍ OHLÁŠENÉHO KLINICKÉHO HODNOCENÍ

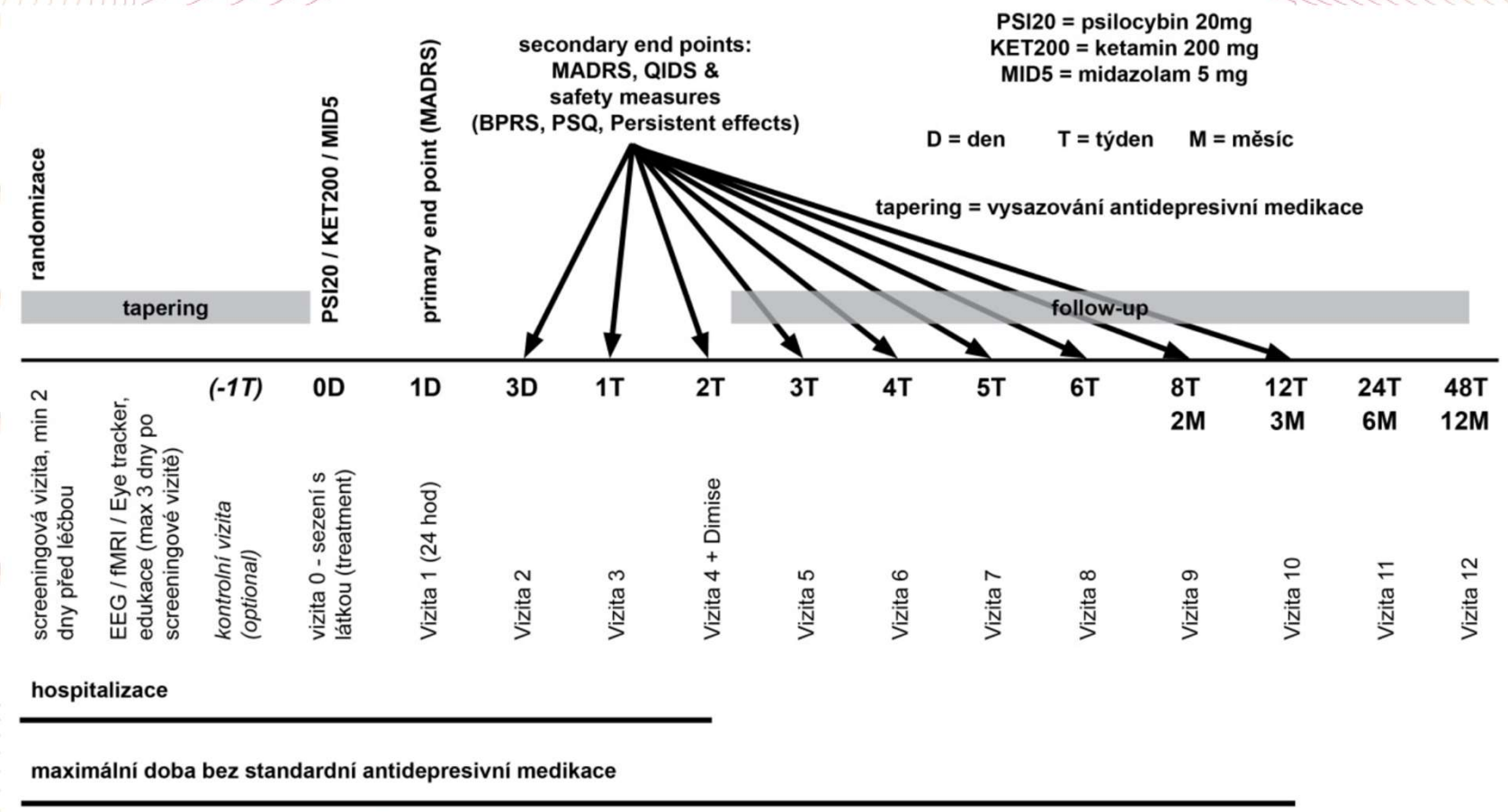
Státní ústav pro kontrolu léčiv, se sídlem Šrobárova 48, 100 41 Praha 10 (dále jen „Ústav"), je správním orgánem příslušným dle § 13 odst. 2 písm. b) zákona č. 378/2007 Sb., o léčivech a změnách některých souvisejících zákonů (zákon o léčivech), ve znění pozdějších předpisů (dále jen „zákon o léčivech") k povolení ohlášeného klinického hodnocení léčivých přípravků.

Dne 26. 5. 2020 obdržel Ústav žádost o povolení ohlášeného klinického hodnocení léčivého přípravku Psilocybin, číslo protokolu: PSIKET_001CZE, EudraCT number: 2018-004480-31, společnosti Národní ústav duševního zdraví, IČ: ---, se sídlem Topolová 748, 250 67 Klecany, Česká republika, zastoupené společnosti Národní ústav duševního zdraví, IČ: 00023752, se sídlem Topolová 748, 250 67, Klecany, Česká republika (dále jen „účastník řízení").

Doručením žádosti Ústavu bylo zahájeno správní řízení vedené pod sp. zn. sukls131878/2020.

Ústav podanou žádost dle § 55 odst. 2 zákona o léčivech a současně dle § 37 správního řádu posoudil z hlediska její úplnosti a shledal ji neúplnou. Tuto skutečnost sdělil účastníku řízení dopisem ze dne 29. 5. 2020, ve kterém ho vyzval k odstranění nedostatků žádosti a usnesením správní řízení přerušil na 90 dnů ode dne doručení výzvy k doplnění žádosti.

Psilocybin vs ketamine in TRD (NIMH)



Psilocybin vs ketamine in paliative care

Psilocybin versus ketamine – fast acting antidepressant strategies in depression co-morbid with oncological diagnosis

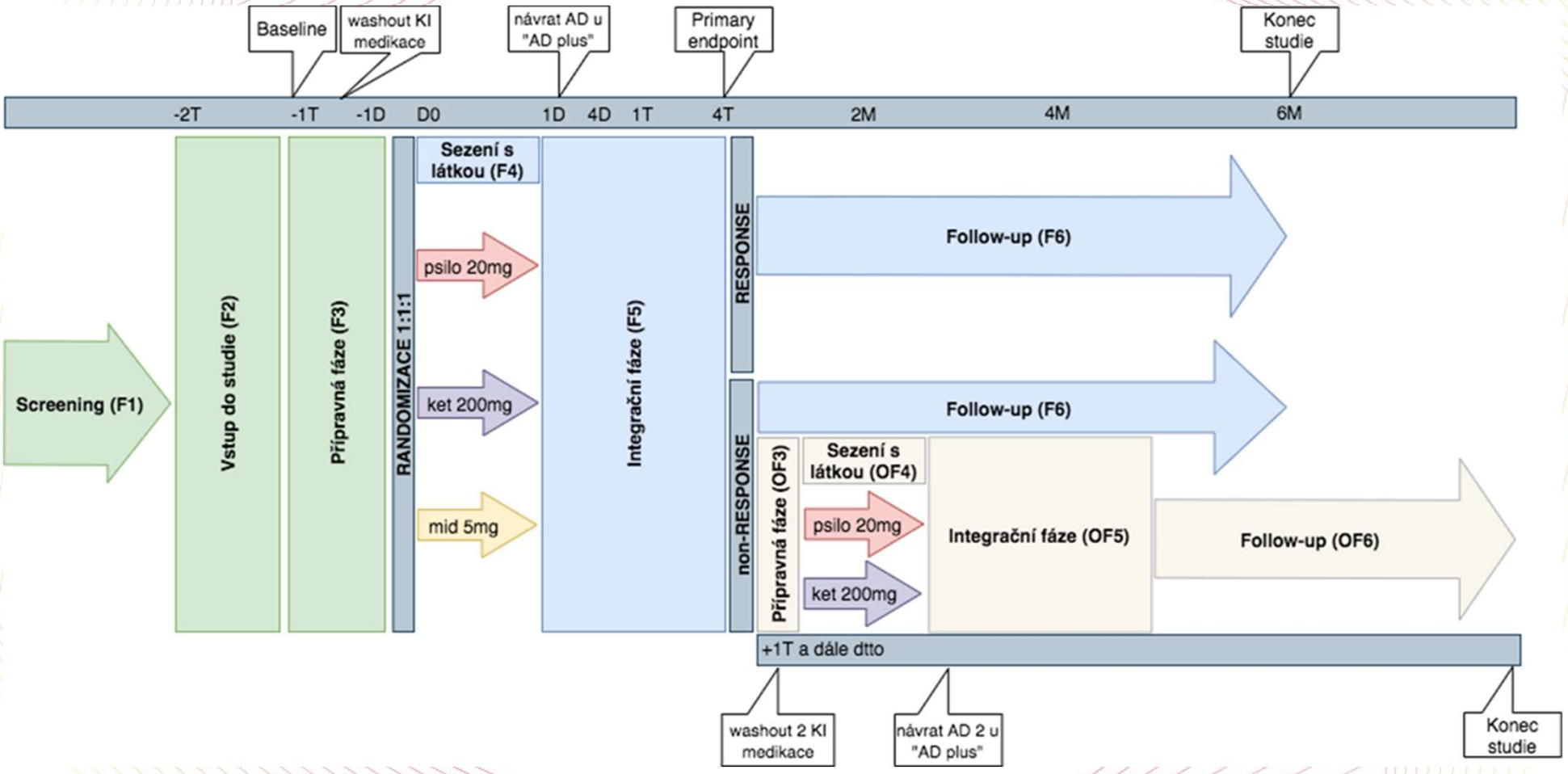
- **PI:** Prof. MUDr. Jiří Horáček, PhD., **co-PI:** MUDR. Anna Bravermanová, PhD
- **Protocol Number**: PSIKET_002CZE
- **Phase:** II
- **EUDRACT NUMBER:**
- Study subjects: 60

The purpose of this clinical trial is therefore to verify the efficacy and safety of psilocybin 20 mg in the treatment of depression in adult cancer patients in a randomized clinical trial with active comparator ketamine 200 mg (rapid antidepressant) and negative control midazolam 5 mg (non-antidepressant).

Study objectives:

- **Primary:** evaluation of the efficacy of psilocybin in the treatment of depression comorbid to cancer 4 weeks (day 28) after its administration
- **Secondary:** evaluation of the onset and duration of the antidepressant effect of psilocybin and ketamine

Psilocybin vs ketamine in paliative care



MDMA in PTSD (MAPS)

An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with Posttraumatic Stress Disorder

PI: MUDr. Tomáš Páleníček, PhD., **co-PI:** Mgr. Michaela Viktorinová

- **Protocol Number**: MP18
- **Phase:** II
- **EUDRACT NUMBER:** 2018-001718-13
- **Study population:** 40 participants with a confirmed diagnosis of at least severe PTSD
- **Study objectives:**
  - The primary objective of this study is to evaluate the effectiveness of MDMA-assisted psychotherapy for treatment of PTSD, as measured by the estimate of change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).
  - The secondary objective is to evaluate the effectiveness of MDMA-assisted psychotherapy for PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS) item scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline).

THANK YOU

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