

Psychedelika in der Depressions- behandlung: Ist es augmentierte Psychotherapie?



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Donnerstag Fortbildung Triplus Oberwil, Michael Rufer, 22. Januar 2026

Einführung

1. NMDA-antagonism

- Ketamine / Esketamine
- Dextometorphan + Bupropion / Esmethadone
- Laughing gas (N₂O nitrous oxide)

2. 5-HT-agonism

- Psilocybin
- Lysergic acid diethylamide (LSD)
- Ayahuasca / DMT

3. Monoamine reuptake

- MDMA for PTSD

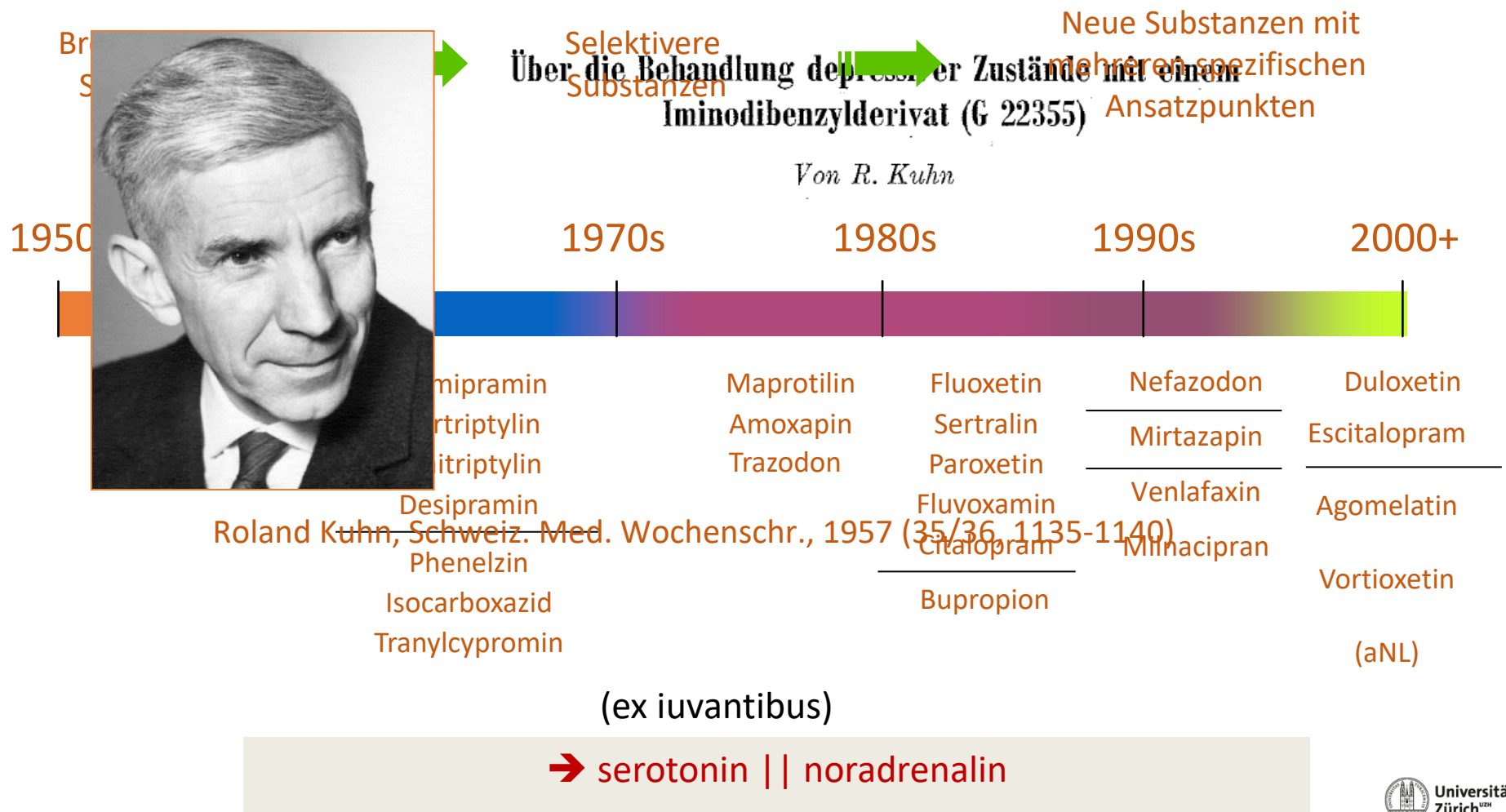
4. Implementation

5. Mechanisms

- Discuss

Monoamine hypothesis of depression

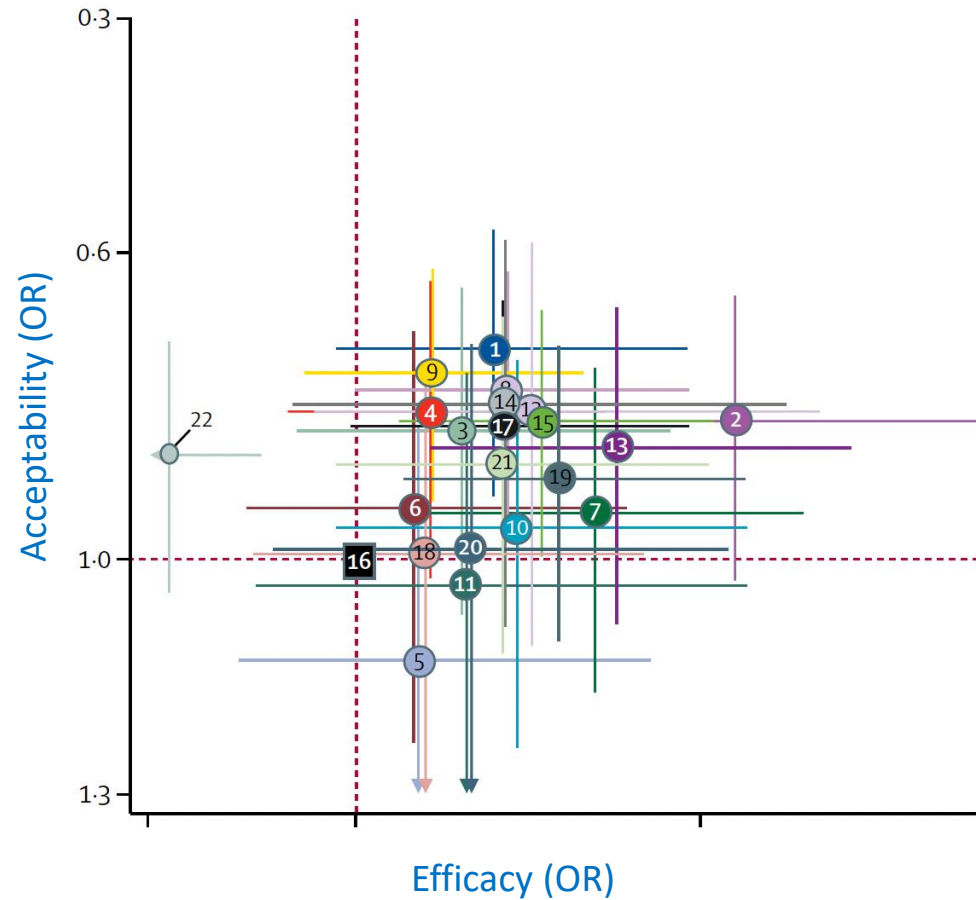
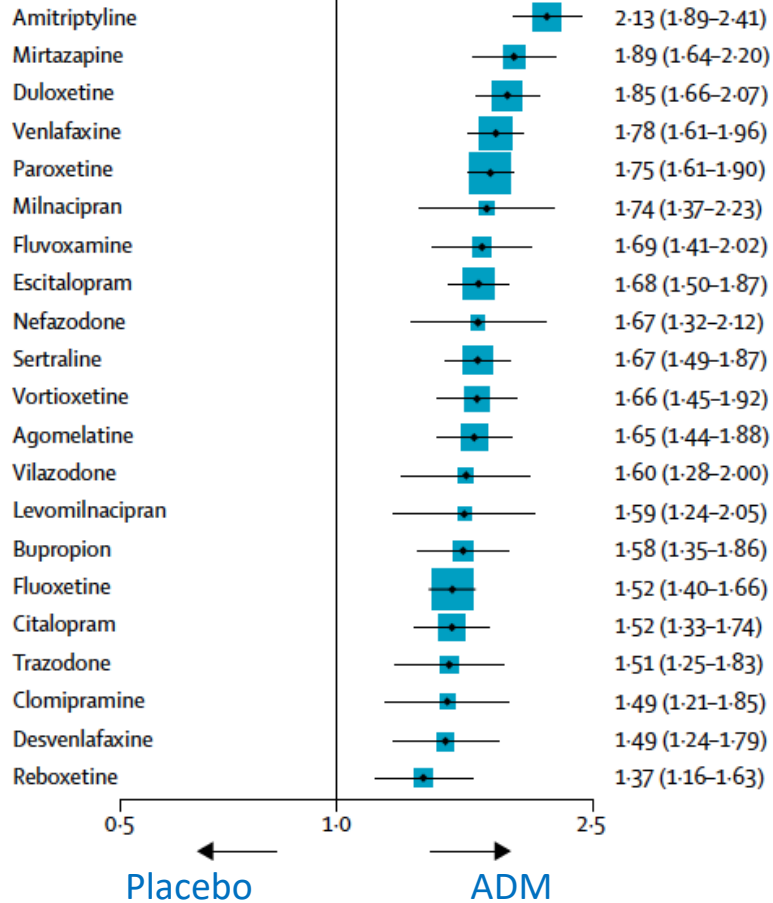
Monoamine hypothesis since >60 years



Antidepressants – metaanalysis

> 522 RCT, 116.477 patients

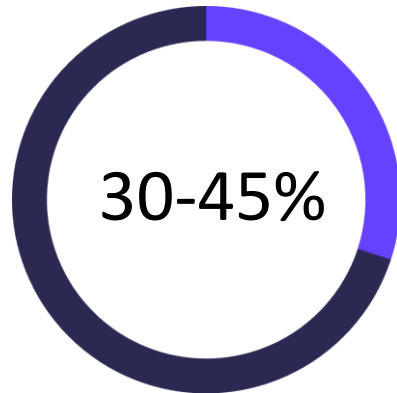
Efficacy (response rate)



Challenge of treatment selection

> Current reality

- The majority of patients with depression do not achieve remission with their first treatment.
- At least 30% don't respond to two consecutive evidence-based treatments and may be classified as TRD.



Remission rate
at 1st treatment

> The problem

- Treatment guidelines emphasize severity as main element for treatment choice, but lack reliable ways to evaluate it.
- Research doesn't support idea that response depends solely on syndrome severity.
- Need to characterize individual patients beyond syndromal diagnosis has been emphasized to personalize treatment.
- However, evidence guiding personalization remains fragmentary
 - treatment selection typically follows a trial-and-error approach based on clinician or patient preference and safety concerns.



Stephen Ross holding a bowl with a psilocybin capsule.



A bottle of psilocybin in Ross's lab is weighed every day to prevent theft.

High hopes

Psychedelic drugs fell from grace in the 1960s. Now, scientists are rediscovering them as potential treatments for a range of illnesses

By Kai Kupferschmidt





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OUTLOOK | 28 September 2022

Research round-up: psychedelic medicine

Predicting bad trips, treating depression without hallucinations, and other highlights from studies of psychedelics.


Michael Eisenstein


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Related Articles

Psychedelic medicine faces the acid test



Taking the tripping out of psychedelic medicine



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- MDMA for PTSD

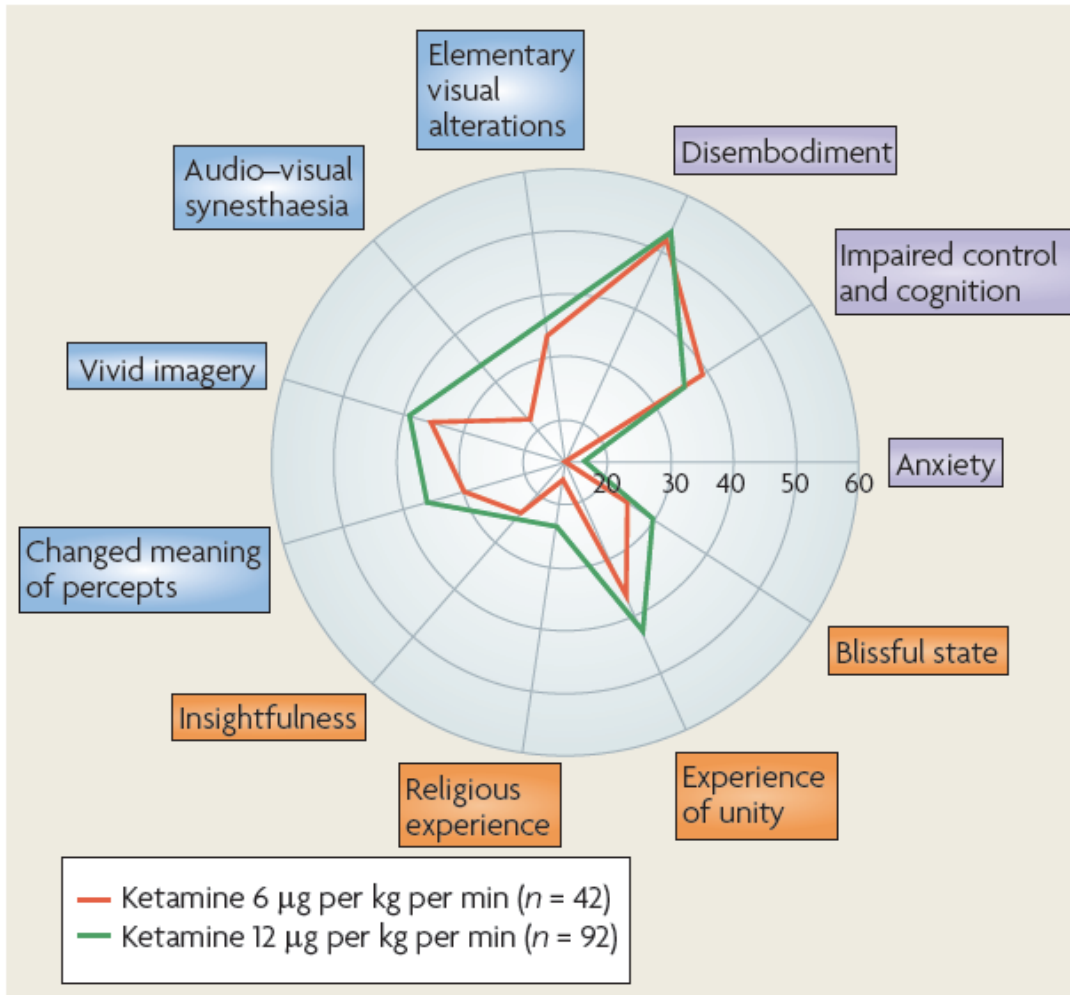
4. Implementation

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- Discuss

Psychologic effects of ketamine

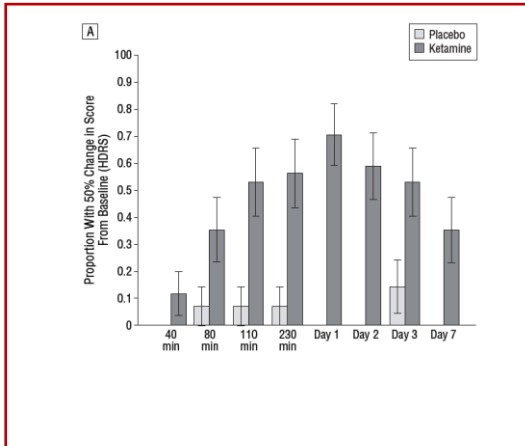
- > Disembodiment
- > Impaired control and cognition
- > Experience of unity
- > Vivid imagery
- > Changed meanings of perceptions



NMDA antagonists

Ketamine

Ketamine i.v.



Zarate et al, Arch Gen Psychiat 2006

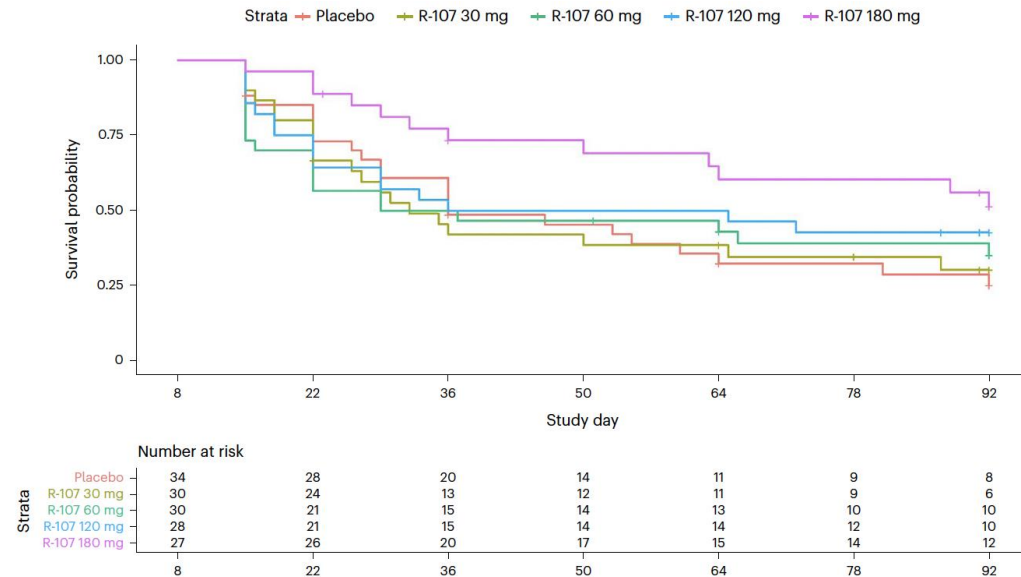
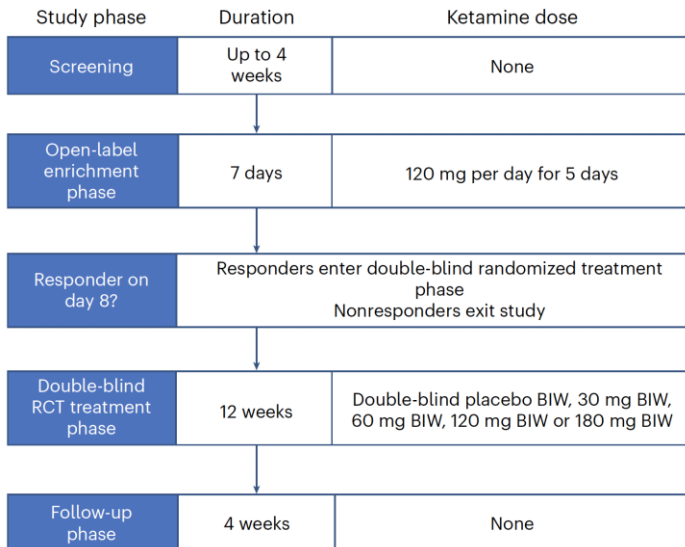
h

erKetamin p.o. in TRD: tx@home

> Oral extended release ketamin in patients with TRD

- randomized, doubleblind, N > 200
- dose-response, placebo

> Tx at home (2 x/wk for 12 wks)

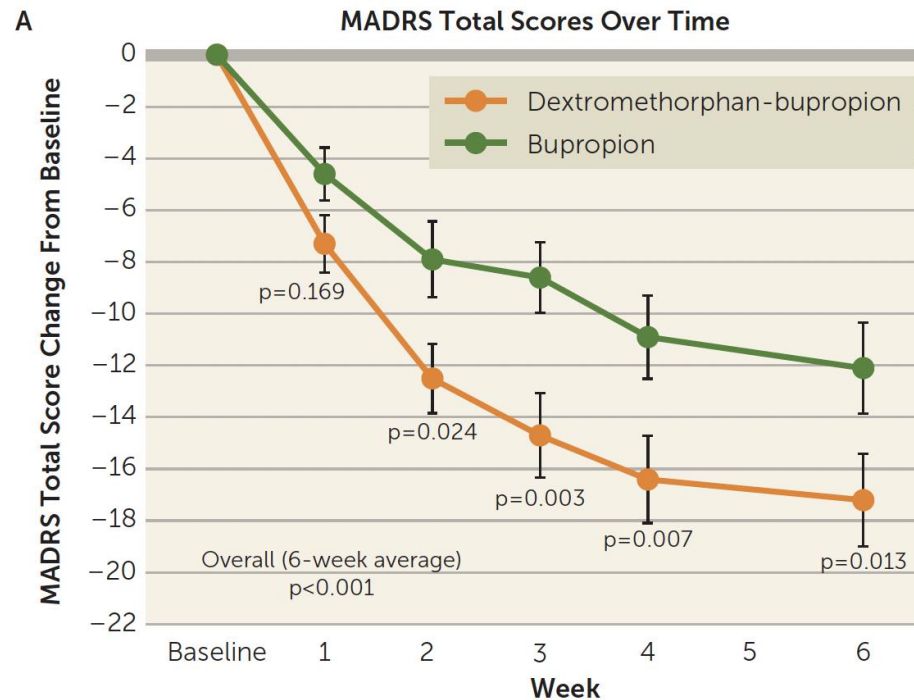


Dextrometorphan + bupropion

- Bupropion: CYP450-2D6 inhibitor
- Dextrometorphan: NMDA antagonist
 - (Auvelity)

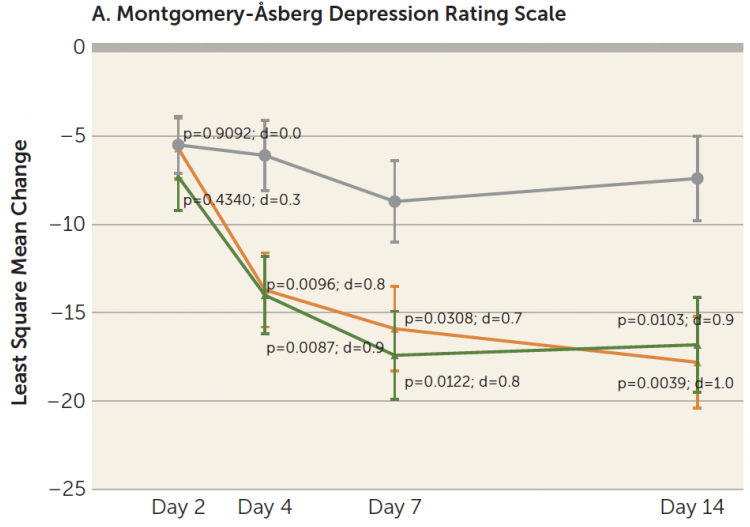
(Auvelity
August 2022 –
FDA breakthrough
rapid acting ADM

- > Phase 2 RCT, 35 vs. 39 pat., MDE, 18-65 J, moderate to severe depression
- > 45 mg/105 mg (dextrometorphan/bupropion) p.o. vs. bupropion 105 mg p.o.
- > 1 x / d for 3 d, then 2 x / d for 6 w
- > Primary endpoint: MADRS



Esmethadone – phase 2 RCT in MDE

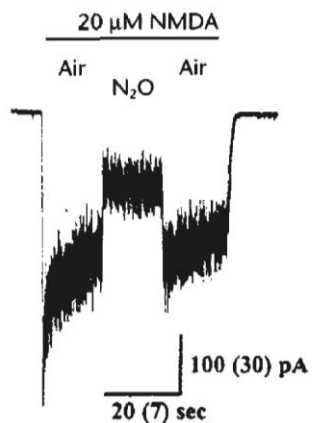
- > Esmethadone = NMDA-R antagonist
 - 7 d phase II study
 - N = 62 (3 x 21) MDE pat., DTD (1-3 treatment attempts)
 - RCT, 25 mg, 50 mg esmethadone, placebo
 - Rapid action after 4 d
 - Persistent until 14th d



Fava et al., REL-1017 (esmethadone) as adjunctive treatment in patients with major depressive disorder: A phase 2a randomized double-blind trial. Am J Psychiatry 2022

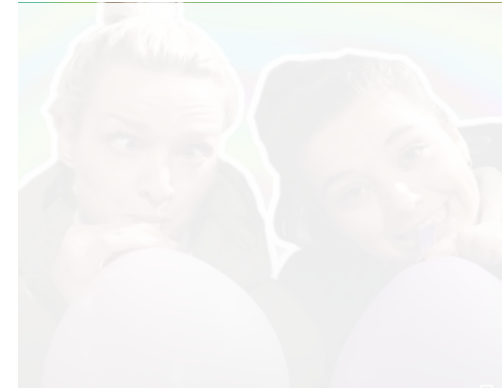
N₂O/nitrous oxide/laughing gas

NMDA-R antagonism



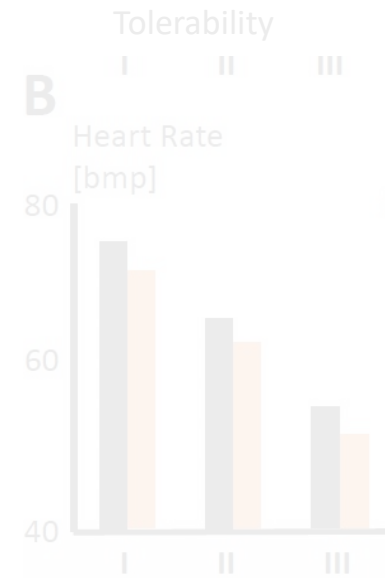
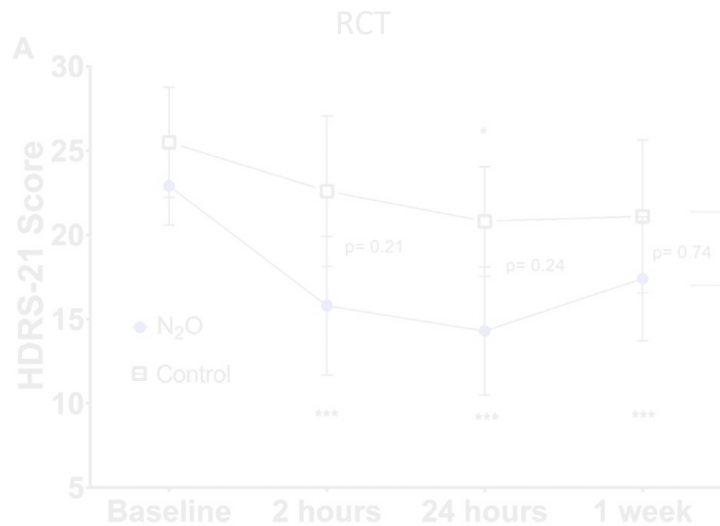
NMDA-R antagonism

Jevtovic-Todorovic V et al. Nat Med 1998



Euphoria, abuse

> 1 hour, 50%



> 20 TRD pat., 1 h: 50% N₂O/O₂ vs. nitrogen/O₂

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5-HT

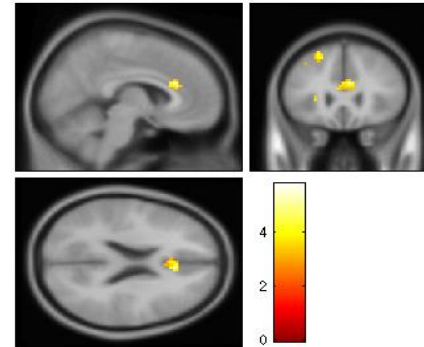
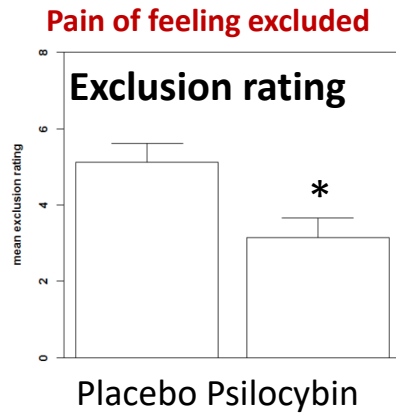
Psilocybin

Magic Mushroom

Psilocybin: emotional pain of social exclusion

> Psilocybin reduced

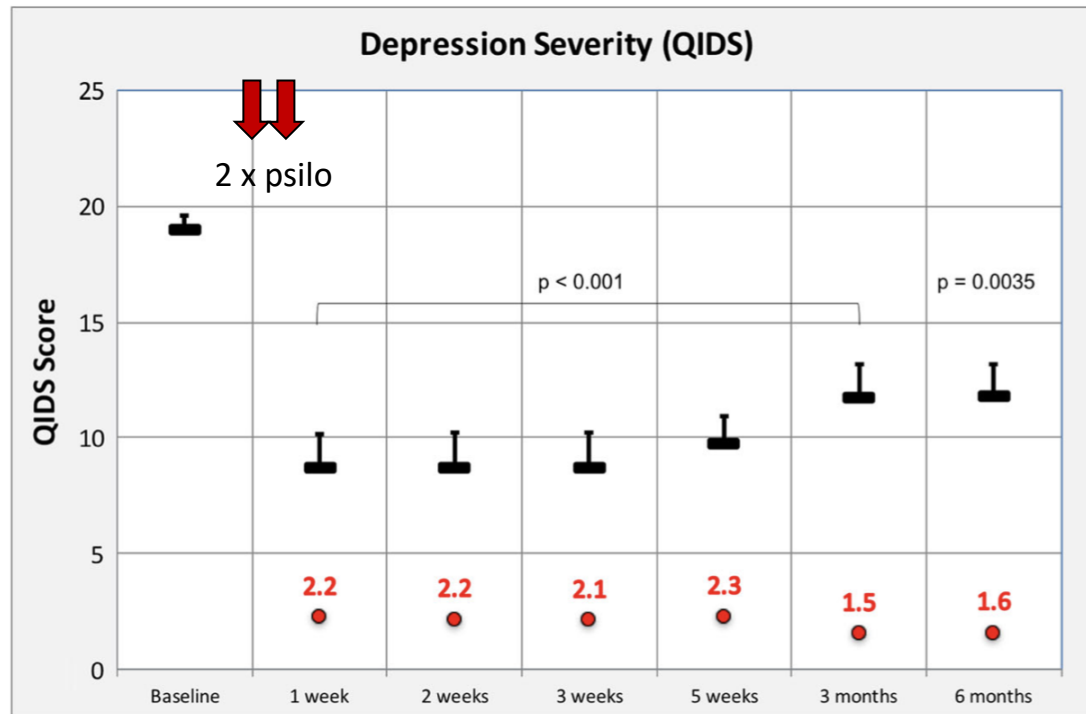
- social pain
- ACC BOLD activity reduced



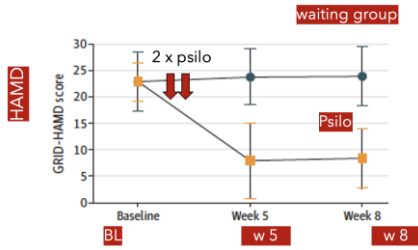
Placebo>Psilocybin
Exclusion>Inclusion

ACC, $p < 0.05$ (FWE),
T = 5.79, N = 21

Psilocybin: in TRD, 6 months effects

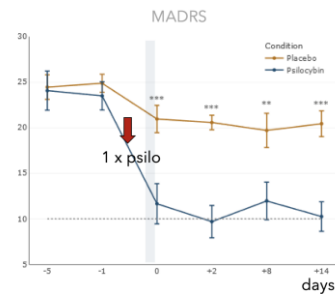


Unmedicated MDE



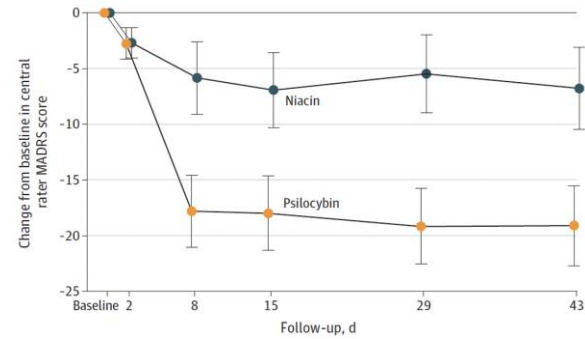
Davis et al 2020

Placebo-controlled



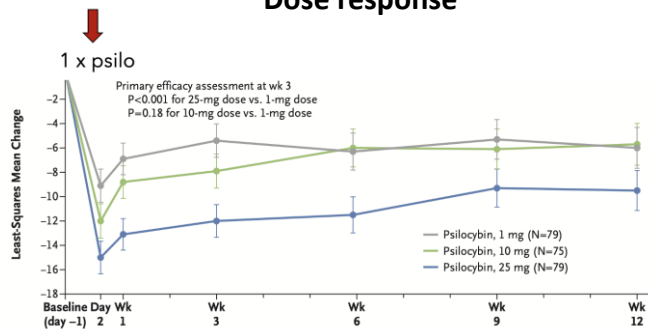
von Rotz et al 2023

Placebo-controlled



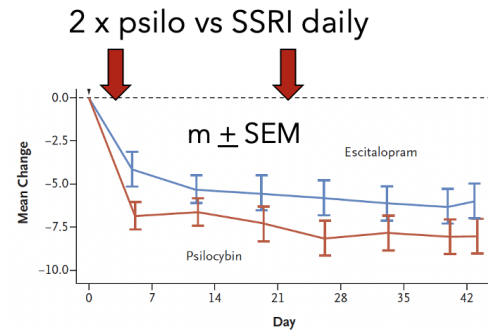
Raison et al 2023

Dose response



Goodwin et al 2022

SSRI-controlled



Carhart-Harris et al 2021

Long way from evidence to approval

Drug Design, Development and Therapy

Dovepress

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ORIGINAL RESEARCH

The Promise of Therapeutic Psilocybin: An Evaluation of the 134 Clinical Trials, 54 Potential Indications, and 0 Marketing Approvals on ClinicalTrials.gov

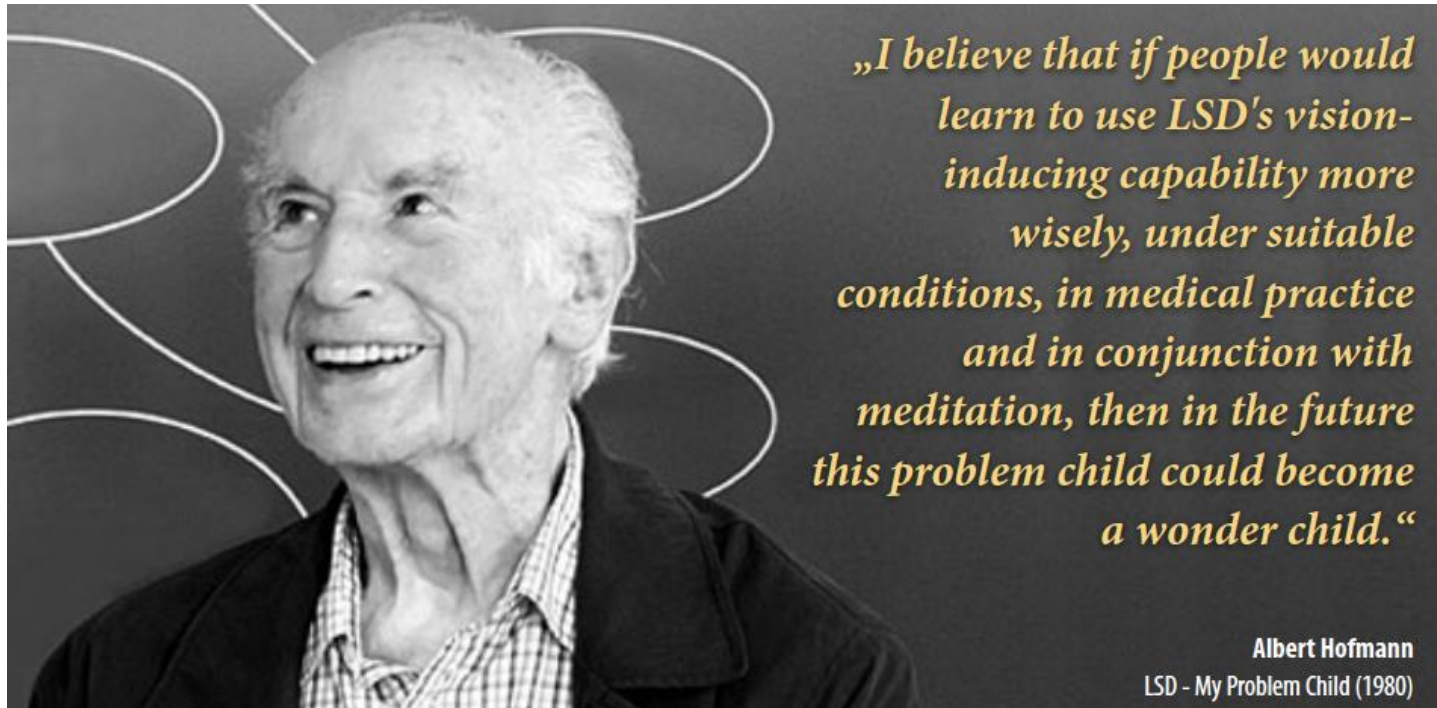
Sarah A Norring*, Michael G Spigarelli*

PsyBio Therapeutics, Inc., Sunrise, FL, USA

*These authors contributed equally to this work

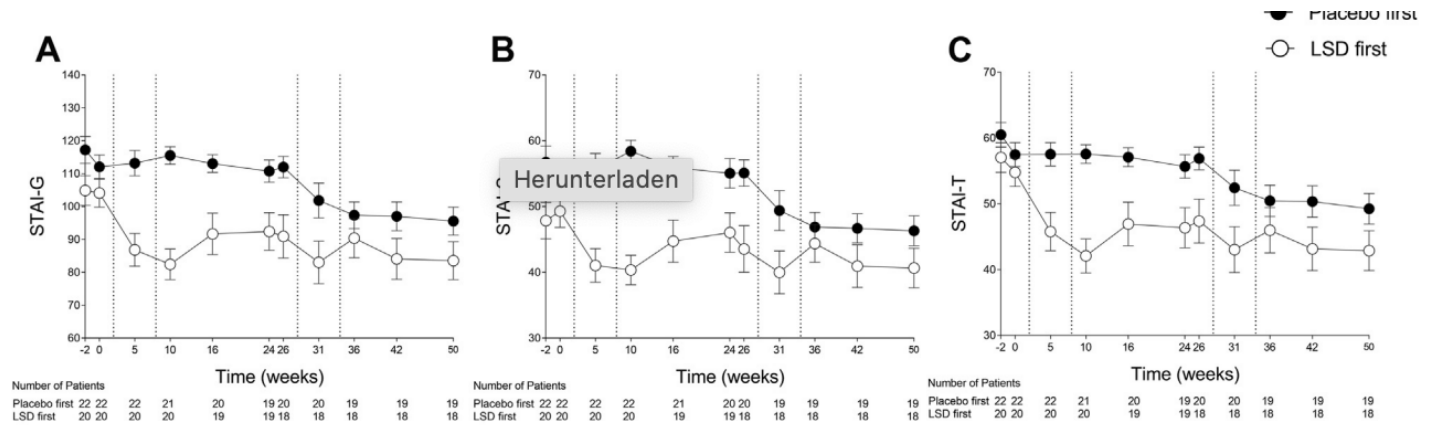
Correspondence: Sarah A Norring, Director of Program Management for PsyBio Therapeutics, Inc., 3130 N Pine Island Road, Sunrise, FL, 33351, USA, Tel +1 813 390 1488, Email sarahanorring@gmail.com

LSD - lysergic acid diethylamide



LSD in GAD and comorbid symptoms of depression

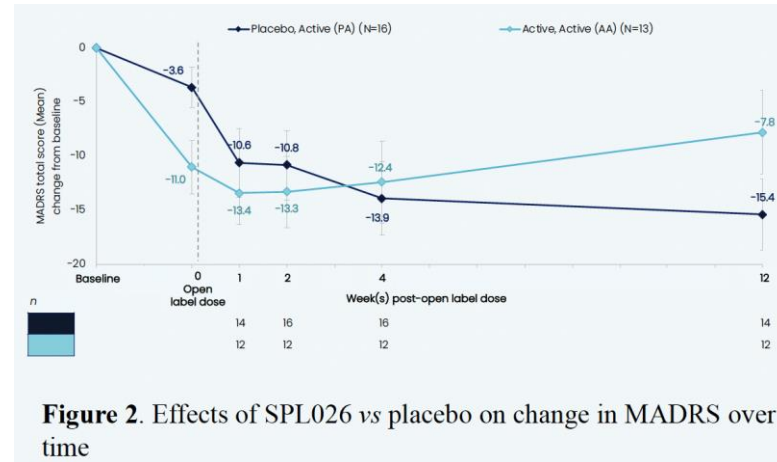
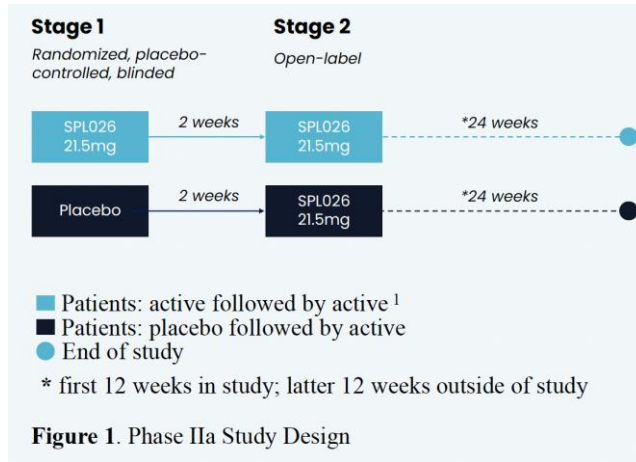
Anxiety ratings STAI





Ayahuasca

DMT in MDE



- > SPL026 was demonstrated to have a very good safety and tolerability profile in patients with MDD; no treatment-related SAEs and all treatment-related AEs were mild to moderate
- > The proof-of-concept Phase IIa study met its primary endpoint with SPL026 demonstrating a rapid and durable antidepressant effect out to 6 months post-dose when compared to placebo as assessed using the MADRS scale
- > No significant difference observed between a 1- and 2-dose regimen, indicating that just one dose of SPL026 with support therapy is sufficient to elicit this durable antidepressant effect

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How ecstasy and psilocybin are shaking up psychiatry

Regulators will soon grapple with how to safely administer powerful psychedelics for treating depression and post-traumatic stress disorder.

MDMA for PTSD

FEBRUARY 1, 2022 | 14 MIN READ

A Psychedelic May Soon Go to the FDA for Approval to Treat Trauma

MDMA, known as Ecstasy in the clubs, gained high marks in a clinical trial for PTSD

BY JENNIFER M. MITCHELL

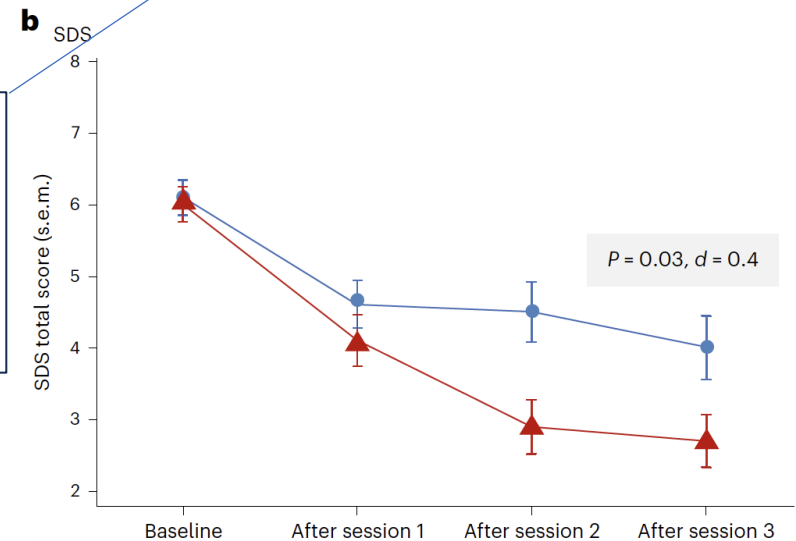
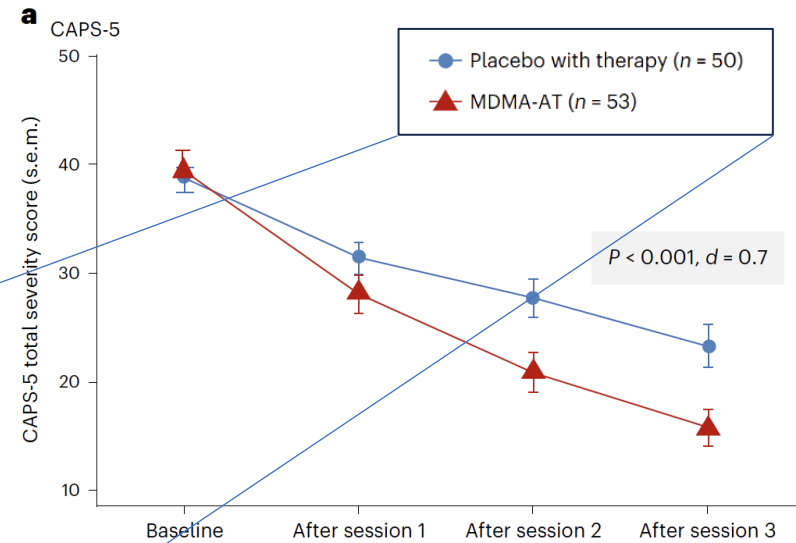


Crystallized MDMA imaged through a polarized light microscope. Maurice Mikkers

MDMA for PTSD

MAPP2 study

- > 3,4-methylenedioxyamphetamine-assisted therapy
- > entactogen that promotes monoamine reuptake inhibition and release (primarily by inducing conformational change of pre-synaptic transporters)



● Placebo with therapy (n = 50)
▲ MDMA-AT (n = 53)

MDMA for PTSD

- > But FDA scientists themselves had a number of concerns about Lykos's studies
 - lacking crucial psychological and physiological safety data

- > Blinding – major concern was the fact that participants — and their therapists —
 - could almost always tell whether they had received MDMA or a placebo

nature

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NEWS | 05 June 2024

MDMA therapy for PTSD rejected by FDA panel

Scientific advisers vote overwhelmingly that the risks of MDMA treatment for post-traumatic stress disorder outweigh the benefits.

By [Sara Reardon](#)



MDMA has been tested as a treatment for post-traumatic stress disorder but has now garnered a vote of no confidence from FDA advisers. Credit: DEA/Science Source/Science Photo Library

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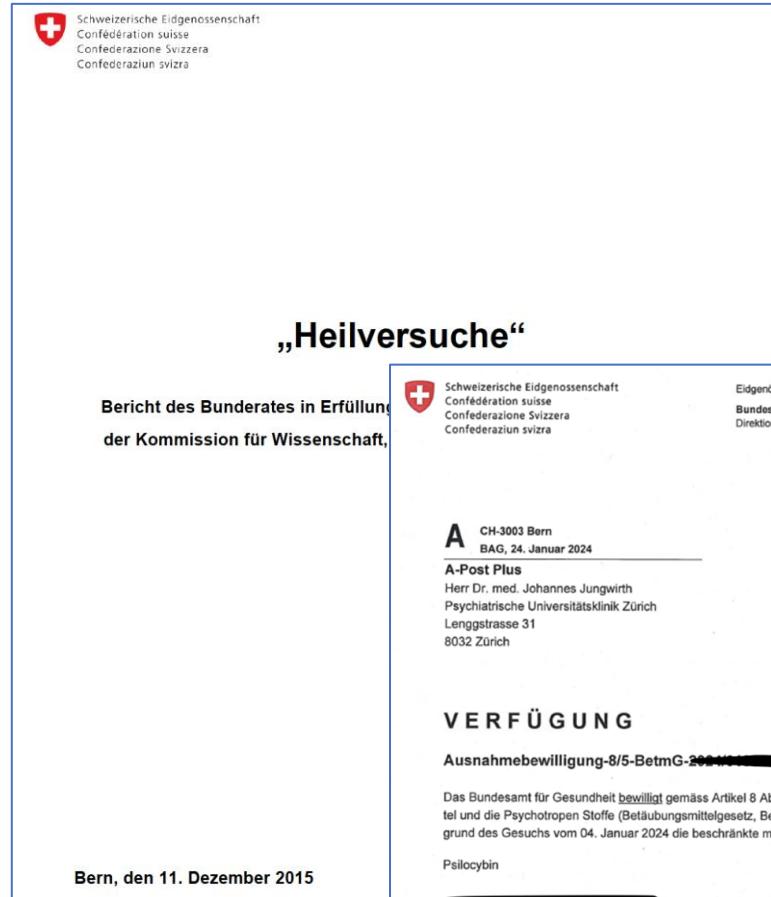
- MDMA for PTSD

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- Discuss

Compassionate use of non-registered compounds in Switzerland



- > Special law in Switzerland 2015
- > Permission for individual cases through Federal Office of Health
- > No clear criteria
- > Currently guidelines developping

2nd opinion clinic for TRD @ PUK



Psychiatrische
Universitätsklinik Zürich

Klinik für Psychiatrie, Psychotherapie und Psychosomatik
Zentrum für Depressionen, Angsterkrankungen und Psychotherapie

Manual zur Behandlung mit Psilocybin innerhalb des «Compassionate Use»

Version: 1.0

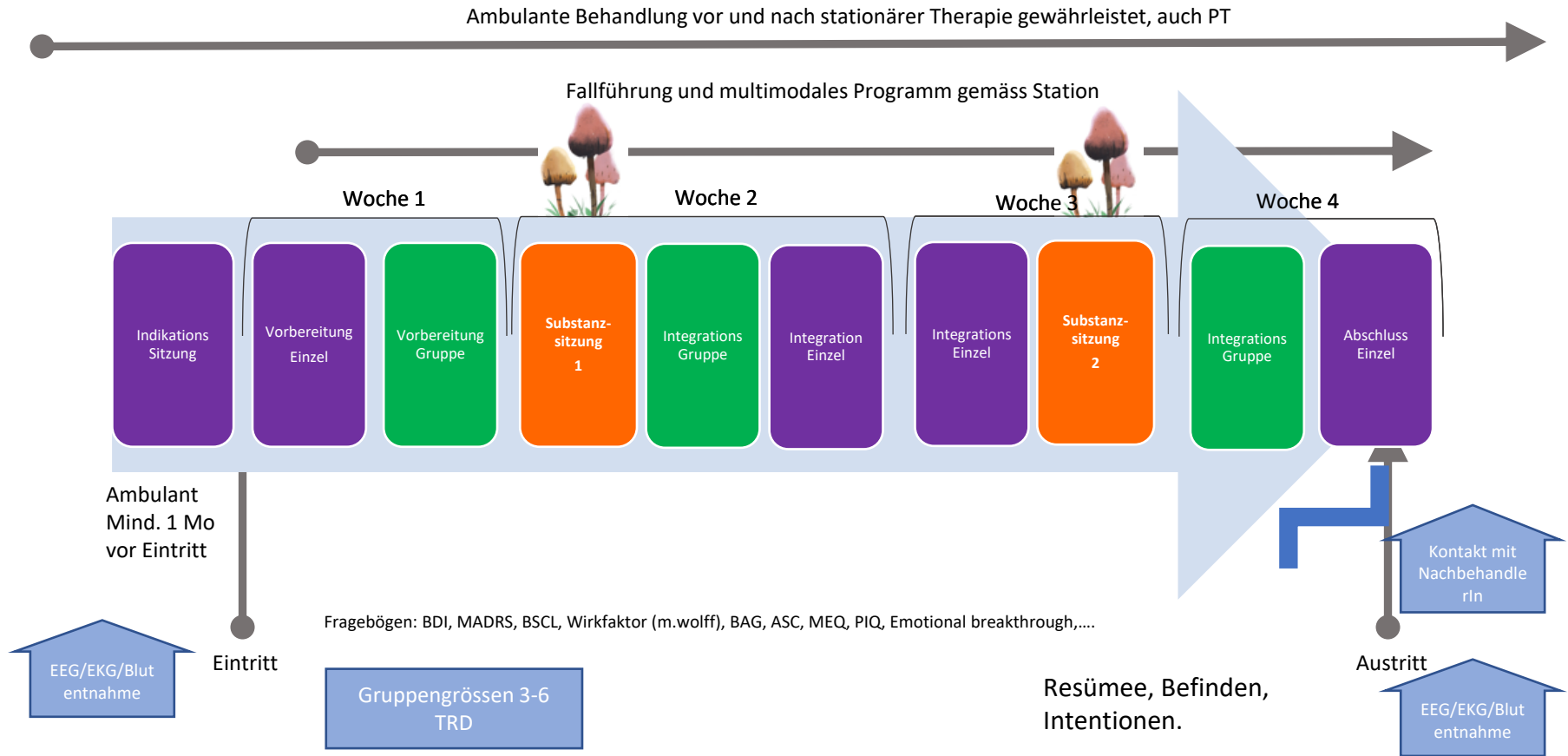
Datum: 15. Juni 2023

Verfasser: Johannes Jungwirth

Psilocybin – clinical implementation



Inpatient psilocybin group therapy





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Mechanisms of action

receptors / circuits / neuroplasticity / psychotherapy

Table1A: Binding Profile of Serotonergic Psychedelics (5-HT receptors)

Receptor	DMT ¹	Psilocin ²	LSD ²	Mescaline ²	5-MeO-DMT ²	
5HT1A	183	62.6	7.3	1841	1.9	
5HT1B	12					
5HT1D	3					
5HT1E	5					
5HT2A	12	D1	271.1*	19.9*	177	>10,000
5HT2B	18	D2	>10,000	>10,000	110.1	>10,000
5HT2C	36	D3	>10,000	101.2	27	>10,000
5HT5A	21	D4	>10,000	>10,000	158.4	>10,000
5HT6	46	D5	>10,000	>10,000	344.4	>10,000
5HT7	20	SERT	6000	>10000	>10000	>10000
		DAT	>10000	6000	>10000	>10000
		SIGMA1	5209	>10000	>10000	>10000
		SIGMA2	>10000	>10000	>10000	>10000
		TAAR1(rat) ³	2200	1400	450	3300
		TAAR1(mouse) ³	3300	1700	>10000	>10000

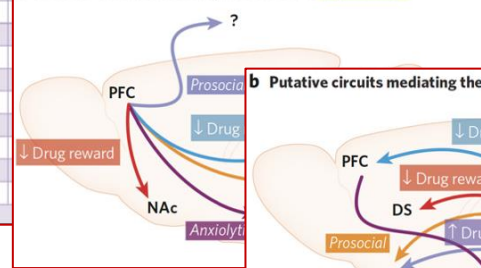
Values in nanomolar [nM]

Table1B: Binding Profile of Serotonergic Psychedelics at other receptors

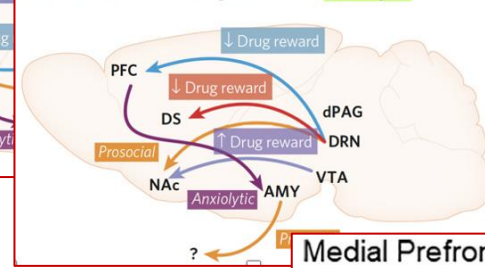
Receptor	DMT ²	Psilocin ²	LSD ²	Mescaline ²	5-MeO-DMT ²
D1	271.1*	19.9*	177	>10,000	79.5
D2	>10,000	>10,000	110.1	>10,000	
D3	>10,000	101.2	27	>10,000	
D4	>10,000	>10,000	158.4	>10,000	
D5	>10,000	>10,000	344.4	>10,000	
SERT	6000	>10000	>10000	>10000	
DAT	>10000	6000	>10000	>10000	
SIGMA1	5209	>10000	>10000	>10000	
SIGMA2	>10000	>10000	>10000	>10000	
TAAR1(rat) ³	2200	1400	450	3300	
TAAR1(mouse) ³	3300	1700	>10000	>10000	

Values in nanomolar [nM]

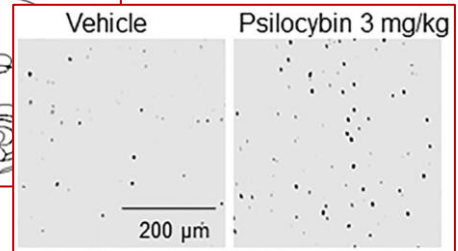
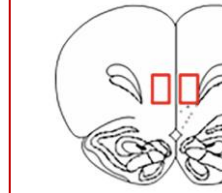
a Putative circuits mediating the effects of psychedelics



b Putative circuits mediating the effects of entactogens



Medial Prefrontal Cortex



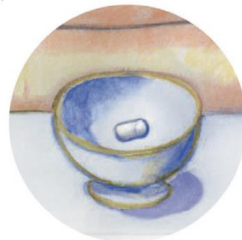
Preparation

Therapeutic outcome depends on initial state



Drug administration

Acute effect defines therapeutic outcome



Integration

Therapeutic outcome depends on dosing experience



Psychotherapy or safety measure?

Must Psilocybin Always “Assist Psychotherapy”?

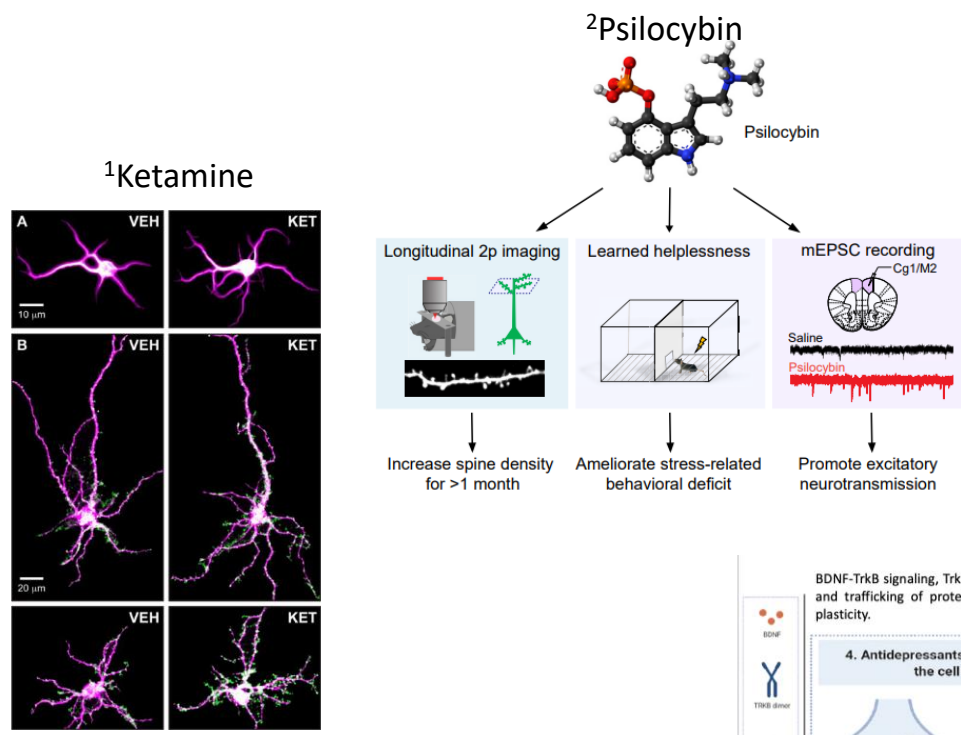
Guy M. Goodwin, F.Med.Sci., Ekaterina Malievskaia, M.D., Gregory A. Fonzo, Ph.D., Charles B. Nemeroff, M.D., Ph.D.

Drugs such as psilocybin and many other serotonergic agents can produce a powerful psychedelic experience. It is now commonplace to hear the expression “psychedelic-

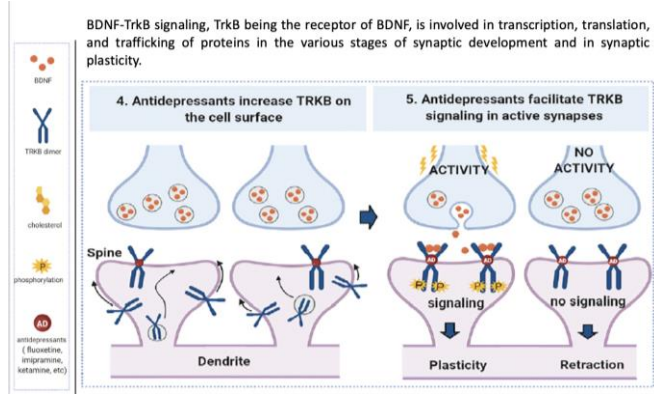
and safety, not psychotherapies. Indeed, the drug effect can only be established unambiguously if psychological support is available largely to ensure safety and is applied in a

- > Psychotherapy-supported psychedelic treatment rather than psychedelic-assisted treatment

Neuroplasticity

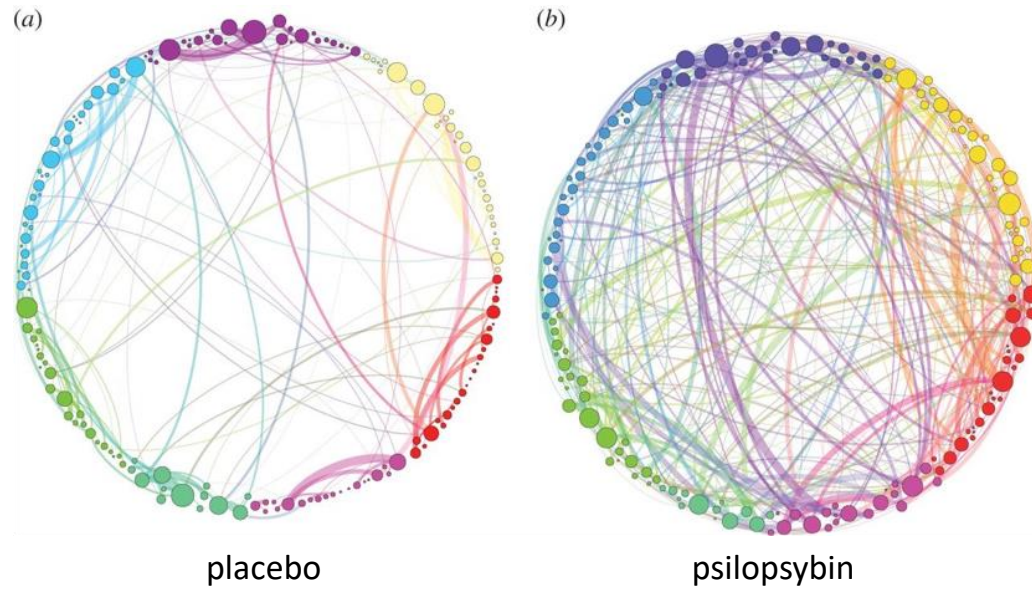


3 Classic ADM



1 Olson. Psychoplastogens: a promising class of plasticity-promoting neurotherapeutics. J Exp Neurosci, 2018
 2. Shao et al, Neuron 2021, 109, 2535 - 2544
 3. Casarotto et al., 2021, Cell 184, 1299 – 1313

15 healthy volunteers after i.v. infusion of placebo and psilocybin



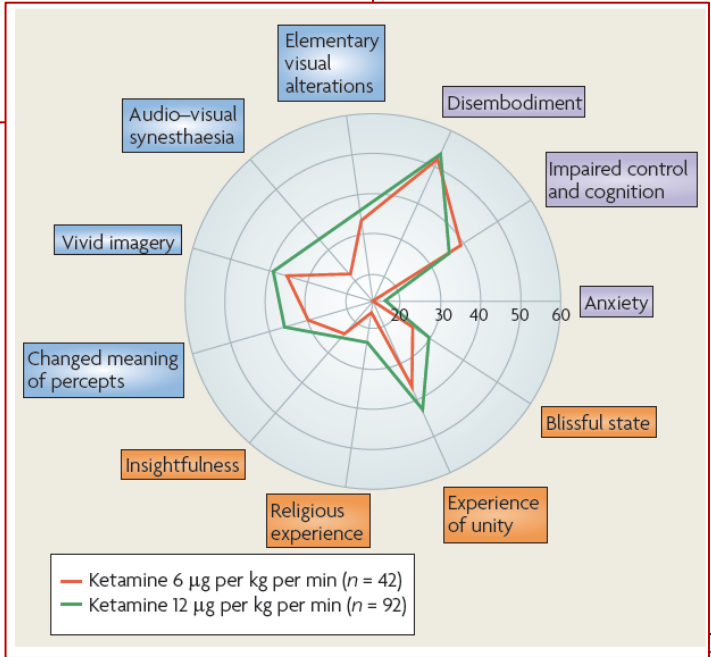
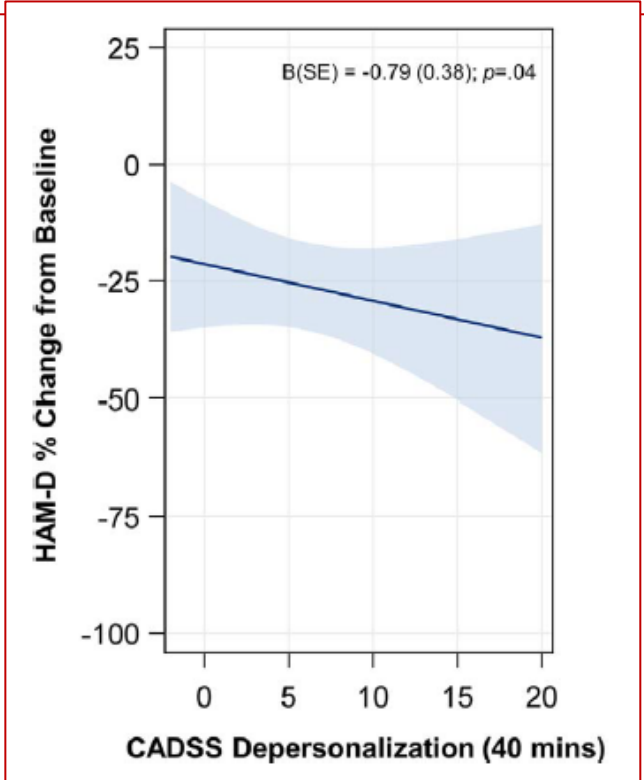
Is psychedelic experience necessary?

European Archives of Psychiatry and Clinical Neuroscience
<https://doi.org/10.1007/s00406-024-01770-7>



Are “mystical experiences” essential for antidepressant actions of ketamine and the classic psychedelics?

Kenji Hashimoto¹



Psychedelic Drugs

Neural Plasticity

≠

Subjective Effects

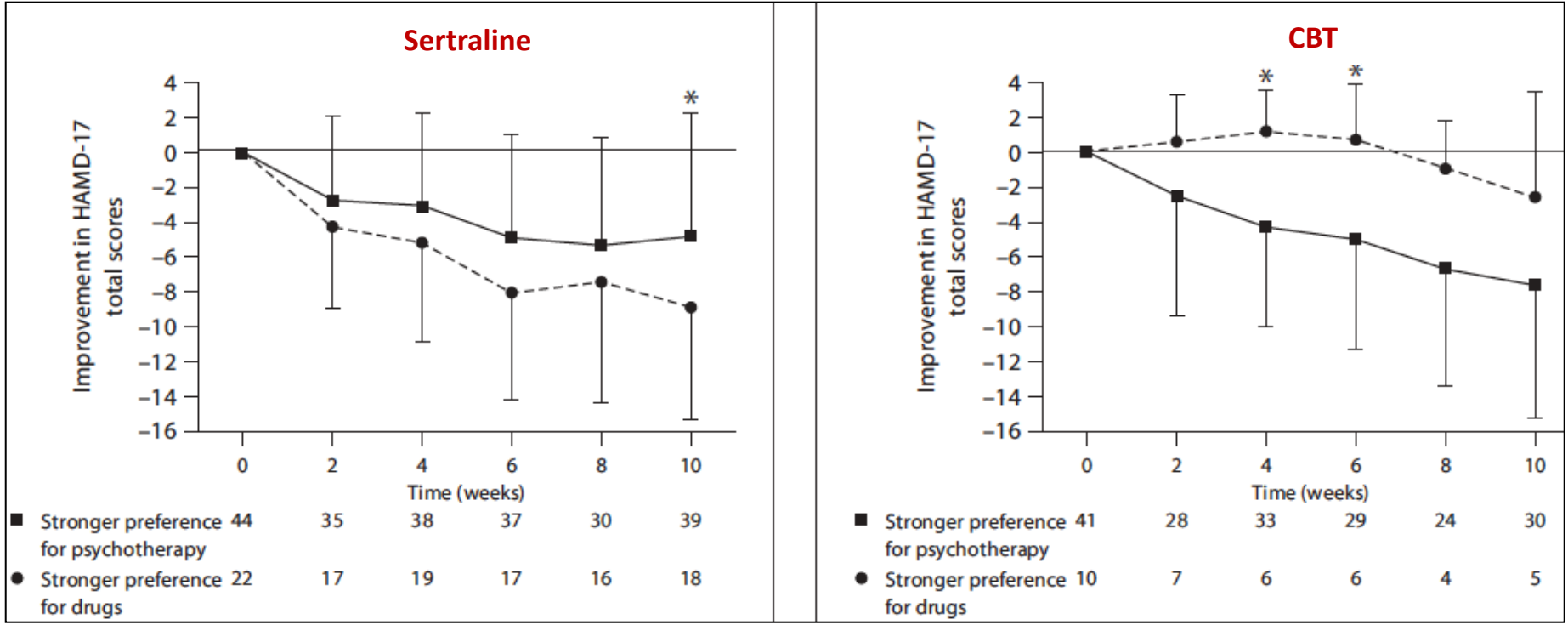
Hashimoto K. Eur Arch Psychiatry Clin Neurosci 2024, doi:10.1007/s00406-024-01770-7
 Vollenweider et al 2010; Olson DE. ACS Pharmacol Transl Sci 2021, 4:2, 563-7, doi:10.1021/acspsci.0c00192
 Kozak Z et al. Expert Opin Investig Drugs 2023, 32:10, 887-900, doi:10.1080/13543784.2023.2273493
 van den Berg M et al. Psychopharmacology (Berl) 2022, 239:6, 1853-79, doi:10.1007/s00213-022-06106-8
 Niciu et al, J Affect Disn2018

Patients' and doctors' expectations



“He cures most successfully in whom the people have the most confidence”

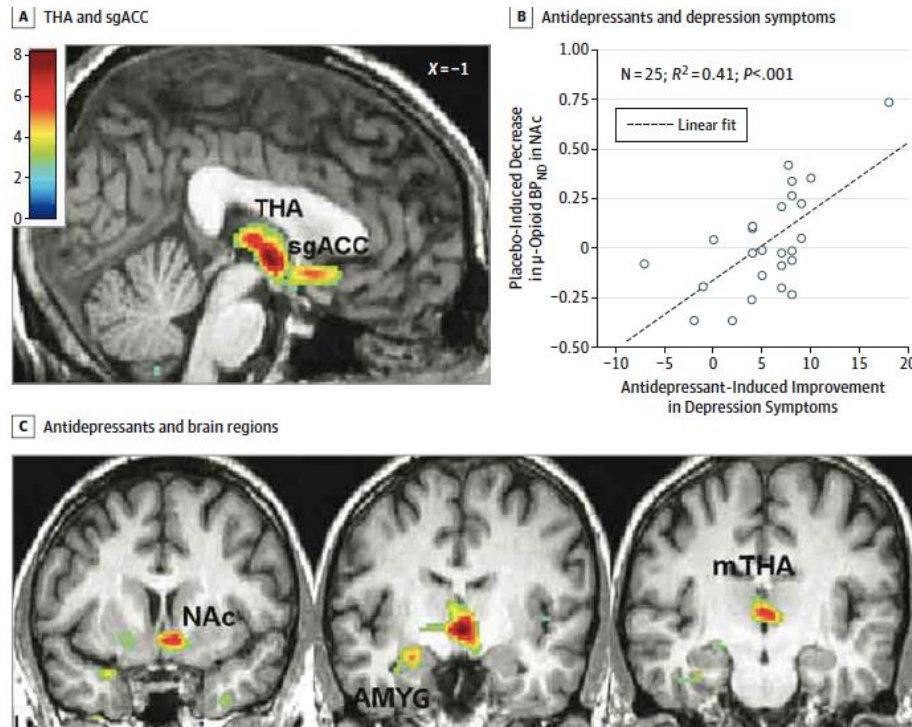
Patients' preference



- ➔ preferred treatment more efficacious
- ➔ non preferred treatment: AMD > PT

Expectation effect and opioid receptor sensitivity in depression tx

Association between PL-induced activation of u-opioid receptor mediated neurotransmission and open label ADM response



Economy

Bloomberg

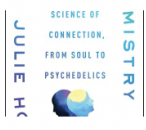
Showing results for "compass psilocybin"



Wealth
Billionaire Took Psychedelics, Got Bitcoin and Is Now Into SPACs
By Devon Pendleton
German investor Christian Angermayer has made a fortune on the risky and faddish. His portfolio includes crypto, weed and space travel.
April 23, 2021



Markets
Psychedelics ETF to Launch After Sector Attracts Thiel's Money
By Michael Bellusci
The world's first exchange-traded fund for psychedelic-drug companies will debut this week in Toronto, as the investment industry tries to capitalize on rising interest in prospective mental health treatments using the drugs.
January 26, 2021



Pursuits
Psychedelic Schools Teach Mental Health Therapists MDMA, Psilocybin
By Michelle Lhoog
For hundreds or thousands of dollars, you can get certified to administer mind-altering—and some say, mind-healing—drugs.
January 18, 2021

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HEALTH ▸ PSYCHOLOGY ▸ MENTAL HEALTH

The FDA is fast-tracking a second psilocybin drug to treat depression

The magic mushroom compound was just given “breakthrough” status for treating depression—again.

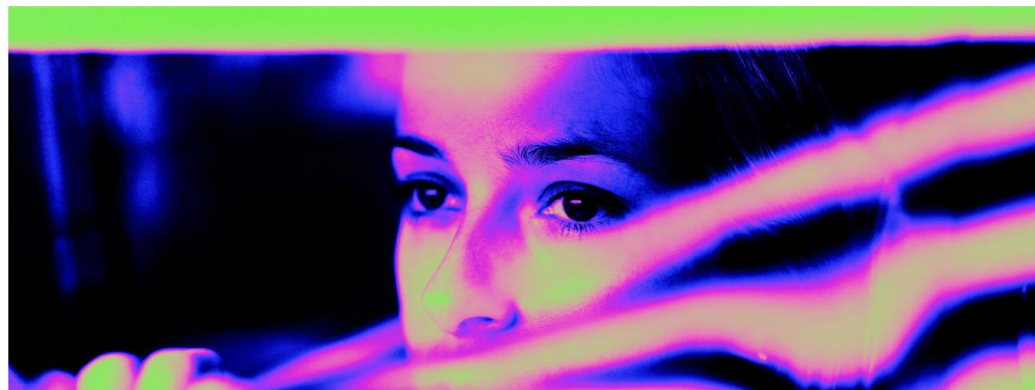
BY [RACHEL FELTMAN](#) POSTED ON NOV 26, 2019 4:07 PM EST 3 MINUTE READ



03-07-2024 | NEWS

Psychedelic news: The government finally fast-tracked LSD as an anxiety treatment

MindMed, the first publicly traded pharmaceutical company focused on psychedelics, said its drug has received a breakthrough designation from the FDA.



Game changers?

> Expert Opinion, Stand 2023

- Psychedelics may represent a new era of treatment in psychiatric disorders.
- Treatment-resistant depression (TRD) is prevalent and associated with a significant burden, highlighting a demand for novel treatments.
- Preliminary evidence suggests that psilocybin is effective and safe in TRD.
- Evidence on the efficacy of LSD, DMT, 5-MeO-DMT, ayahuasca, mescaline, and MDMA in TRD is limited.
- Psychological support is an important component of treatment with psychedelics which serves to maximize benefits and mitigate potential adverse reactions.
- Further research is needed to confirm efficacy and to understand the mechanisms and long-term effects of psychedelics in TRD.

APA Official Actions

Position Statement on the Use of Psychedelic and Empathogenic Agents for Mental Health Conditions

Approved by the Board of Trustees, July 2022
 Approved by the Assembly, May 2022

“Policy documents are approved by the APA Assembly and Board of Trustees. . . These are . . . position statements that define APA official policy on specific subjects. . .” – *APA Operations Manual*

Issue:

Promising preliminary research involving psychedelics for the treatment of serious and disabling conditions such as treatment-resistant depression and posttraumatic stress disorder have stimulated growing interest in the therapeutic potential of these agents. Classical psychedelics, both plant derived and synthetic compounds, include serotonin-2A receptor agonist drugs that have powerful dose-related

Psychedelics pipeline

Compound	Sponsor(s)	Phase	Comments
Psilocybin	COMPASS Pathways, Usona Institute, Eleusis Therapeutics, Cybin IRL Limited, Halucenex Life Sciences, TRYP Therapeutics	III	Most trials use protocols of single- or double-dose paradigms; patients require monitoring for 6–8 h; at least two companies are actively moving toward regulatory approval, with Phase III trials underway; third company is exploring development of psilocybin analog
MDMA	MAPS	III	Positive top-line data from recently completed Phase III trial; this is second positive Phase III trial of MDMA for PTSD, which is expected to lead to regulatory approval in the USA
DMT	GH Research, Small Pharma, Beckley Psytech Limited	II	Small Phase II trials showed promising results in MDD; at least two companies are exploring developing DMT-like compounds at least one company is exploring the commercial development of LSD
LSD	MindMed, MAPS	II	Small Phase II trials showed promising results in MDD and anxiety disorders; at least one company is exploring the development of XXX

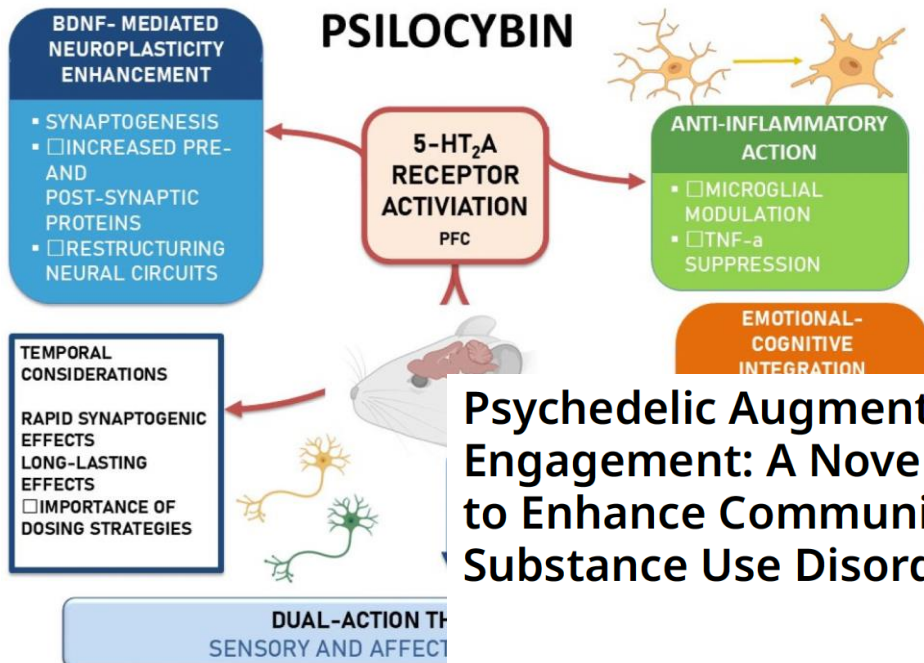
TABLE 2 Phase III trials of psychedelic compounds in development for the treatment of psychiatric disorders.^{1,2}

Phase III	Compound	Condition	Trial design	Intervention	Primary outcome measure	Phase III completion date	Projected/actual enrollment	Primary outcome measure and results if reported	Current status	Sponsor
Phase III	Psilocybin	MDD	RCT, two-arm, parallel, double-blind, placebo-controlled	Psilocybin 5 or 25 mg	Remission rate 6 weeks after first dose	01/05/2023	144	8	Remission rate 6 weeks after first dose (80% improvement as measured by HDRS)	Academic
	Psilocybin	TBD	Open-label II	Psilocybin 5 or 25 mg	Remission rate 6 weeks after first dose	01/05/2023	144	8	Remission rate 6 weeks after first dose (80% improvement as measured by HDRS)	Academic
	MDMA	PTSD	Open-label II	MDMA 120 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	DMT	MDD	Open-label II	DMT 10 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	LSD	MDD	Open-label II	LSD 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	Psilocybin	MDD	Open-label II	Psilocybin 5 or 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	DMT	MDD	Open-label II	DMT 10 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	LSD	MDD	Open-label II	LSD 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	Psilocybin	MDD	Open-label II	Psilocybin 5 or 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	DMT	MDD	Open-label II	DMT 10 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS

TABLE 2 (CONTINUED)

Phase III	Compound	Condition	Trial design	Intervention	Primary outcome measure	Phase III completion date	Projected/actual enrollment	Primary outcome measure and results if reported	Current status	Sponsor
Phase III	Psilocybin	MDD	Open-label II	Psilocybin 5 or 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	DMT	MDD	Open-label II	DMT 10 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	LSD	MDD	Open-label II	LSD 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
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	LSD	MDD	Open-label II	LSD 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS
	Psilocybin	MDD	Open-label II	Psilocybin 5 or 25 mg	Change in depression severity	01/05/2023	104	8	Change in depression severity	MAPS

Weitere Indikationen....



Psychedelic Augmentation of 12-Step Engagement: A Novel, Accessible Approach to Enhance Community-Based Recovery from Substance Use Disorders

Nicky J. Mehtani, Maha N. Mian, Gabrielle Agin-Liebes, Allison R. Coker, Christopher Huebner, Brian T. Anderson & Jennifer M. Mitchell

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To link to this article: <https://doi.org/>

Premorbid	Presymptomatic	Symptomatic	Chronic
Occasional social and recreational use Acute reward and euphoria	Increased frequency of use due to rewarding effects	Compulsive consumption due to increased setting salience Shift to habitual drug use	Drug craving Drug relapse
Increased dopamine in NAc	Increased dopamine in NAc	Decreased dopamine in NAc and increased in CPu	Decreased dopamine and increased glutamate in NAc?

Dopaminergic transmission adaptations¹

Natoli S, et al. Med Sci (Basel). 2025;13
Mehtani NJ, et al. J Psychoactive Drugs. 2025;1-10
Wittenkeller L, et al. Br J Pharmacol. 2025

... perspectives for the future ...

... the future of psychedelic therapy lies not in simplifying its complexity, but in embracing it.

1. NMDA-antagonism

- Ketamine / Esketamine
- Dextometorphan + Bupropion / Esmethadone
- Laughing gas (N_2O nitrous oxide)

2. 5-HT-agonism

- Psilocybin
- Lysergic acid diethylamide (LSD)
- Ayahuasca / DMT

3. Monoamine reuptake

- MDMA for PTSD

4. Implementation

5. Mechanisms

- Discuss

Danke

