Psychedelika-assistierte Therapie mit Ayahuasca und DMT

Potenziale und Herausforderungen

Psychiatrisches Kolloquium PUK | Freitag, 5. April 2024

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Psychedelika - Potential für Psychiatrie

**Psychedelic**
- Serotonin receptors
  - $5\text{-HT}_{2A}$, $5\text{-HT}_{2C}$, $5\text{-HT}_{1A}$, …
- Signal transduction pathways

**Molecular**
- Neural plasticity
  - (structural remodeling, gene expression, …)
  - Spiking activity dynamics

**Cellular and circuit**
- Regional suppression
  - (default mode network)
- Functional connectivity

**Network**

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Kelmendi et al.  
*Current Biology, 2022*
Psychedelics Research

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
Psychedelics Research

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 Kiepfereschmidt

Psychedelika - Potential für Psychiatrie
Psychedelika - Wirksamkeitsstudien

US could soon approve MDMA therapy – opening an era of psychedelic medicine

Perceptions have shifted dramatically in the past few years on the therapeutic value of illicit drugs such as ecstasy. But questions still linger about what FDA approval might look like.

Sara Reardon

Illustration by Adrià Volità

Mitchell et al.
Nature Med, 2021
Psychedelika - Wirksamkeitsstudien

The NEW ENGLAND JOURNAL of MEDICINE

Established in 1812
November 3, 2022
Vol. 387 No. 18

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

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. Error bars represent standard errors.

Goodwin et al. NEJM, 2022
Some meta-analyses suggest that psychedelics might actually be more effective in reducing symptoms of depression and anxiety compared to conventional antidepressants in terms of their effect size.

It is plausible that the reported effectiveness of psychedelics in clinical trials might undergo revisions as more comprehensive, diverse, and long-term studies in larger sample sizes are conducted.

Galvão-Coelho et al.  
*Psychopharmacology, 2021*
Psychedelika - Wirkstoffklassen

**Tryptamines**
- Psilocybin
- Psilocin
- 5-MeO-DMT

**Ergolines**
- LSD
- DMT

**Phenethylamines**
- DOI
- DOM
- 2C-B
- 25I-NBOMe
- Mescaline
- MDMA

**Dissociatives and delirants**
- Ketamine
- Ibogaine
- Muscimol

Naturally produced
Synthetic

Kelmendi et al.
Current Biology, 2022
Ayahuasca, used for centuries in South American jungles, is booming in the U.S.

Illustration by Bjørn Lie
Ayahuasca - Ethnobotanik

Hallucinogens of Plant Origin

Interdisciplinary studies of plants sacred in primitive cultures yield results of academic and practical interest.

Richard Evans Schultes

Fig. 5. A witch doctor of the Noanama tribe holding trunk and leaves of the dimá plant (*Banisteriopsis* sp.) from which an hallucinogenic drink is prepared. Near mouth of Calima River, San Juan drainage area, Pacific Coast, Colombia. [Photograph by G. Reichel-Dolmatoff]
Ayahuasca - Ethnobotanik

Hallucinogens of Plant Origin

Interdisciplinary studies of plants sacred in primitive cultures yield results of academic and practical interest.

Richard Evans Schultes

Fig. 1. Main hallucinating constituents of psychotomimetic plants.
Ayahuasca - Ethnobotanik

**Beta-Carboline (z.B. Harmin, Harmalin, THH, etc.)**
- MAO-A Hemmer (reversibel)
- hemmen Abbau von N,N-DMT sowie 5-HT und NA

**N,N-Dimethyltryptamin (N,N-DMT)**
- oral inaktiv (Abbau durch GI-MAO-A)
- oral aktiv in Kombination mit MAO-A Hemmern
- Affinität an 5-HT1A/2A/2C, D1-3, alpha1A/2A, TAAR1, H1, SERT, DAT, NET

Carbonaro et al. 
*Brain Res Bull, 2016*
Chemical evidence for the use of multiple psychotropic plants in a 1,000-year-old ritual bundle from South America

Melanie J. Miller\textsuperscript{a,b,1}, Juan Albarracin-Jordan\textsuperscript{c}, Christine Moore\textsuperscript{d}, and José M. Capriles\textsuperscript{e,1}

\textsuperscript{a}Department of Anatomy, University of Otago, Dunedin 9016, New Zealand; \textsuperscript{b}Archaeological Research Facility, University of California, Berkeley, CA 94720; \textsuperscript{c}Instituto de Investigaciones Antropológicas y Arqueológicas, Universidad Mayor de San Andrés, La Paz, Bolivia; \textsuperscript{d}Immunalysis Corporation, Pomona, CA 91767; and \textsuperscript{e}Department of Anthropology, The Pennsylvania State University, University Park, PA 16802

Edited by Linda R. Manzanilla, Universidad Nacional Autónoma de México, Mexico, D.F., Mexico, and approved April 9, 2019 (received for review February 6, 2019)

Fig. 1. The study area is located in the south-central Andes (A), in the Lípez highlands of southwestern Bolivia (B). An aerial view of the Sora River Valley (C) shows Cueva del Chileno on its eastern side (c/o GeoEye Foundation), and a photograph (D) of the exterior of the rock shelter during excavation.

Fig. 2. The Cueva del Chileno ritual bundle consisting of: outer leather bag (A), expertly carved and decorated wooden snuffing tablets with anthropomorphic figurines (B and C), intricate anthropomorphic snuffing tube with two human hair braids attached to it (D), animal-skin pouch constructed of three fox snouts (L. culpaeus) stitched together (F), two camelid (L. glama) bone spatulas (F), two small pieces of dried plant material attached to wool and fiber strings (G), and a polychrome woven textile headband (H). Artifacts (E, F, and G) were tested using LC-MS/MS analysis.
Chemical evidence for the use of multiple psychotropic plants in a 1,000-year-old ritual bundle from South America

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Edited by Linda R. Manzanilla, Universidad Nacional Autónoma de México, Mexico, D.F., Mexico, and approved April 9, 2019 (received for review February 6, 2019)

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Fig. 3. LC-MSMS results from the fox-snor pouch indicating the presence of cocaine, BZE, harmine, bufotenine, DMT, and peak potentially corresponding to psilocin.
Ayahuasca - Religiöser Gebrauch

projeto
A Igreja da Floresta

Vila Céu do Mapia, Floresta Nacional do Purus, Amazonas

Santo Daime
Ceu do Mapia, Brazil
Ayahuasca - Trendmedizin des Westens

The New York Times

Ayahuasca: A Strong Cup of Tea

Ayahuasca, used for centuries in South American jungles, is booming in the U.S.

Illustration by Bjørn Lie
Only 10% of these four million people belong to Indigenous groups where ayahuasca has traditionally been an integral part of their knowledge systems, which highlights the significant impact of the globalization of this plant medicine.
Insights and subsequent life and lifestyle changes appear to have a central role in the transformative effects reported by individuals consuming ayahuasca, with these occurring across contexts of use and demographic groups.
International cross-sectional study of ayahuasca drinkers in a variety of settings (n = 8907)

Perkins et al.
Psychoactives, 2023
Ayahuasca - Subjektive Wirkung

A journey into the depths of the human soul at the Musée du quai Branly

‘Shamanic Visions’ explores the effects of ayahuasca, the hallucinogenic Amazonian plant, on the arts.
Ayahuasca - Subjektive Wirkung

The mental effects of ayahuasca are described as comparably more sober and clear-headed in style (compared to other psychedelics such as LSD or psilocybin):

- **Psychological Insights & Meaning Enhancement**
  - existential self-realization through perceived exposure to inner mechanics of consciousness (e.g. behaviors, motivations, decision-making, character traits, beliefs, etc.)

- **Mindfulness & Embodied Presence**
  - increased recognition of external and mental events with curiosity, openness, and acceptance

- **Empathy, Affection, and Sociability Enhancement**
  - feelings of positive mood, compassion, and connection with others

- **Language Suppression**
  - pre-verbal, intuitive, pre-reflective, symbolic experiences

- **Personality Regression**
  - autobiographical memory enhancement, insights into life trajectory, trauma processing

- **Regenerative & Afterglow Phenomena**
  - mental clarity, emotional stability, calmness, increased focus, cognitive refreshment
Ayahuasca - Therapeutisches Potenzial

Scientific Evidence
- antidepressant effect in treatment-resistant depression
- decrease in suicidal ideation
- positive outcomes in substance use, eating disorders, PTSD, grief therapy

Health Benefits
- promotes mindfulness, decentering, and cognitive flexibility
- confronting difficult emotions or psychological content can be experienced as therapeutic

Brain Health
- activates brain areas related to episodic memory and the awareness of emotions and internal sensations
- DMT promotes neurogenesis and neuroprotection (in vitro and in vivo)
- Harmala alkaloids stimulate adult neurogenesis (in vitro)

Mental Health
- used to support psychological well-being, personal development, social cohesion, and spiritual experiences
- most people who take ayahuasca are well-adapted and integrated in their social, working, and family environments

Online: https://www.iceers.org/ayahuasca-technical-report/the-therapeutic-potential-of-ayahuasca/
Ayahuasca - Risiken & Nebenwirkungen

Adverse Effects

- **nausea, vomiting, and diarrhea** are the main physical adverse effects
- „la purga“ (purging ritual) in traditional Amazonian medicine is an intended therapeutic effect

Adverse Reactions

- Psychedelic effects can be transiently very intense and challenging
- Difficult **psychological adverse reactions** are the primary risk
- With appropriate support, also challenging experiences can have positive, long-lasting effects

Risk Factors

- Risks could be related to **unknown source or composition** of the brew
- Beta-carbolines (MAOI) can interact with tyramine-rich foods
- Combination of MAOIs with SSRIs or similar drugs is **counterindicated** (risk of serotonin syndrome)

Toxicity & Abuse

- **No signs of toxicity** in the body or brain after chronic use
- Low risk of abuse and no signs of physical dependence
- Protective antiaddictive effect regarding harmful drugs and alcohol consumption

Ayahuasca vs. DMT

- Ayahuasca is a natural decoction with about **2,000 plant components**
- The amounts of **DMT vary depending on the batch**, in clinical trials between 0.5-1mg/kg of DMT
- 45-60 minutes to onset and **2-6 hours duration**, usually **repeated servings** per session
- Regulations are different by country, the **DMT-containing plants are not regulated** in most places.
- The **ritual use of ayahuasca** is rooted in Indigenous cosmologies and syncretic religious beliefs.
- **Modern ayahuasca practices** and ceremonial designs are adapted for Western participants.

- DMT (N,N-dimethyltryptamine) is a **ubiquitous tryptamine** found in some plants, animal species, and human body fluids.
- The acute effects of DMT are **more intense and last for 10-20 mins** when inhaled or injected.
- Synthetic or extracted DMT is listed in **Schedule 1**, in the 1971 Convention on Psychotropic Substances, and is **illegal in most jurisdictions**.
- **Amazonian tribes** also use **DMT-containing snuffs** such as Yopo (Anadenanthera peregrina)
- **Western recreational use** of DMT is rooted in the cultural history of the psychedelic movement.

Online: [https://www.iceers.org/ayahuasca-technical-report/ayahuasca-pharmacology/](https://www.iceers.org/ayahuasca-technical-report/ayahuasca-pharmacology/)
Ayahuasca - Wirkmechanismen

Neuroendocrine Effects
- Hypothalamus
- Pituitary Gland
- Adrenal Glands
  - HPA axis → Function normalization
  - ↑ Stress adaptation
  - ↑ Cortisol levels
- Other Hormones
  - ↑ Prolactin
  - ↑ Growth hormone

Dopaminergic Effects
- D1 & D2 → Augmented activation (Mainly MAO-A inhibition by β-carbolines)
  - ↑ Motivation
  - ↓ Anhedonia

Glutamatergic Effects
- AMPA → Augmented activation (DMT via 5-HT2A)
  - ↑ BDNF
- mGluR2/3 & NMDA → Modulation of psychoactive effects (DMT)

Neurotransmitter Transport
- SERT & VMAT2 → Transporter substrate (DMT)
  - ↑ Intraneuron DMT accumulation
  - ↑ Sigma-1 activation
  - ↑ TAAR-1 activation

Neurotrophic Factors
- BDNF & VEGF → Induce expression (via various receptors)
  - ↑ Neuroplasticity
  - ↑ Neuroprotection

Serotonergic Effects
- 5-HT1A,2A,2C → Agonist (Mainly DMT)
  - ↑ Antidepressant effects
  - ↑ Stress adaptation
  - ↑ Neuroprotection
  - ↓ DMN
- MAO-A inhibition and SSRI effect → Augmented serotonin levels (β-carbolines)
  - ↑ BDNF & VEGF
  - ↑ Antidepressant effects
  - ↑ Stress adaptation
  - ↑ Improved HPA function

Cannabinoid Effects
- AEA & 2-AG → Secretion modulation
  - ↓ Inflammatory response (?)

Sigma-1 Effects
- Sigma-1 → Agonist (DMT)
  - ↑ Cell survival and proliferation
  - ↑ Neuroplasticity
  - ↑ Neuroprotection

Ayahuasca's Substances
- DMT
- Harmine
- THH
- Harmaline
Activation of 5-HT2A by DMT can potentiate the expression of genes encoding transcription factors known to be associated with synaptic plasticity, memory, and attention. The 5-HT2A receptor is found widespread in the mammalian brain throughout the cortex, striatum, hippocampus, and amygdala. Transcription modulation may underlie the known antidepressant effects of serotonergic psychedelics.

The β-carbolines harmine and harmaline act as selective and reversible MAO-AI, while THH acts as an inhibitor of the 5-HT reuptake. Harmine seems to cause increased DA release and inhibition of the DA transporter (DAT), resulting in tonic elevations of DA in the synaptic cleft.

Brito-da-Costa et al. Pharmaceuticals, 2020
Psychedelika steigern die Neuroplastizität

McClure-Begley & Roth
Nat Rev Drug Discovery, 2022

Ly et al.
Cell Rep, 2018

Upregulation IEGs
Upregulation BDNF mRNA
Upregulation other plasticity genes
Increased BDNF protein
Rate of dendritogenesis, synaptogenesis, spinogenesis
Density of synapses, dendrites, dendritic spines

Calder & Hasler
Neuropsychopharmacology, 2022

VEH, DOI, DMT, LSD

Significant increase
Increase observed in this time period
No change
Human study

<1h 2h 4h 6h 1d 2d 3d 5d 7d >30d
Human brain effects of DMT assessed via EEG-fMRI

Christopher Timmermann1, Leor Roseman1, Sharad Haridas2, Fernando E. Rosas1,2,3, Lisa Luan1, Hannes Kettner4, Jonny Martell3, David Erritzoe2, Enzo Tagliazucchi5, Carla Pallavicini1, Manesh Girn6, Andrea Alamia7, Robert Leech1, David J. Nutt8, and Robin L. Carhart-Harris1

Edited by Marcus Raichle, Washington University in St Louis School of Medicine, St. Louis, MO; received November 12, 2022; accepted December 14, 2022.

DMT vs PCB

GFC

PCB

DMT
Psychedelika steigern die neuronale Flexibilität
Psychoplastogens are compounds that can induce changes in perception, mood, and cognitive processes without causing hallucinogenic effects. These substances potentially offer the benefits of psychedelics without the trip, making them suitable for use in a wider range of therapeutic contexts.

Olson
ACS Pharmacol. Transl. Sci. 2020
Die Integration von Ayahuasca in westliche Gesundheitssysteme setzt interkulturellen Respekt und Bereitschaft für Dialog voraus.

Die biomedizinische Forschung mit Ayahuasca-Wirkstoffen wirft Fragen der kulturellen Aneignung auf, die es zu reflektieren gilt.

Die Nutzung synthetisierter Moleküle könnte eine ökologisch nachhaltige Lösung für die steigende Nachfrage nach Ayahuasca im Westen sein.

Im Westen existieren polarisierende Ansichten über den Gebrauch von Ayahuasca, während die indigenen Traditionen sich durch Globalisierung stetig wandeln.

Es sollte ein transkulturelles ethisches Anliegen sein, sichere Erfahrungsräume zu ermöglichen, die auf die jeweilige Kultur abgestimmt sind.
We promote well being in the world by supporting scientific research of consciousness and indigenous stewardship of ecosystems and biodiversity.
Klinische Forschung mit Ayahuasca- und DMT-Präparaten


1931: DMT-Synthese (Richard Manske)

1956: Entdeckung der psychotropen Effekte von DMT (Stephen Szára)

1976: Erste DMT-Studien an der PUK Zürich (Dittrich, Angst, Scharfetter)


1984 - 2003: Pharmakokinetik & -dynamik von Ayahuasca (McKenna, Callaway, Riba)

2015 - 2018: Erste klinische Studien mit Ayahuasca in MDD (Osorio, Palhano-Fontes)

2018 - heute: Entwicklung von DMT-Präparaten für Psychiatrie (Reconnect Labs, Small Pharma, ATAI, MindMed)

Vergleich veränderter Bewusstseinszustände unter den Halluzinogenen (—)-Δ⁹-trans-Tetrahydrocannabinol (Δ⁹-THC) und N,N-Dimethyltryptamin (DMT)

A. Dittrich, P. Bickel, J. Schöpf und D. Zimmer
Psychiatrische Universitätsklinik Burghölzli, Forschungsdirektion, Postfach 68, CH-8029 Zürich, Schweiz

Dr Richard Manske  Dr Stephen Szára  Dr Rick Strassman
Table 1. Chemical composition and alkaloid content of ayahuasca preparations.

<table>
<thead>
<tr>
<th>Ayahuasca Preparations</th>
<th>DMT (mg/mL)</th>
<th>Harmane (mg/mL)</th>
<th>Harmaline (mg/mL)</th>
<th>THH (mg/mL)</th>
<th>Total Alkaloids (mg/mL)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rio Purús¹</td>
<td>0.13</td>
<td>0.15</td>
<td>n.a.</td>
<td>0.05</td>
<td>0.33</td>
<td>[26]</td>
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<tr>
<td>UDV</td>
<td>0.24</td>
<td>1.70</td>
<td>0.20</td>
<td>1.07</td>
<td>3.21</td>
<td>[13]</td>
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<tr>
<td>Pucallpa²</td>
<td>0.60</td>
<td>4.67</td>
<td>0.41</td>
<td>1.60</td>
<td>7.28</td>
<td>[16]</td>
</tr>
</tbody>
</table>

¹ A river that flows through the countries of Brazil and Peru. ² A city from Peru. DMT: N,N-Dimethyltryptamine; THH: Tetrahydroharmine; UDV: União do Vegetal; n.a.: Information not available.

MONOAMINE OXIDASE INHIBITORS IN SOUTH AMERICAN HALLUCINOGENIC PLANTS: TRYPTAMINE AND β-CARBOLINE CONSTITUENTS OF AYAHUASCA

DENNIS J. MCKENNA⁶, G.H.N. TOWERS⁶ and F. ABBOTT⁷

⁶Department of Botany and ⁷Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, B.C. (Canada)

(Accepted November 28, 1983)

PERUVIAN AYAHUASCA — HPLC QUANTITATION OF UNDILUTED SAMPLES

<table>
<thead>
<tr>
<th>Name of sample</th>
<th>Alkaloid concentration (mg/ml)⁸</th>
<th>Harmine %</th>
<th>Harmane %</th>
<th>THH %</th>
<th>Harmaline %</th>
<th>DMT %</th>
<th>Total %</th>
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<tbody>
<tr>
<td>Don Fidel no. 1</td>
<td>tr</td>
<td></td>
<td>66</td>
<td>3.85</td>
<td></td>
<td></td>
<td>10</td>
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<td></td>
<td></td>
<td>(0.01)</td>
<td>(0.05)</td>
<td>(0.1)</td>
<td></td>
<td>(0.01)</td>
<td>(0.19)</td>
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<td>Don Fidel no. 2</td>
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<td>62</td>
<td>4.64</td>
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<td>(0.3)</td>
<td>(0.1)</td>
<td>(0.1)</td>
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<td></td>
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<td>(0.2)</td>
<td>(0.06)</td>
<td>(0.2)</td>
<td></td>
<td>(0.2)</td>
<td>(0.1)</td>
</tr>
<tr>
<td>Don Juan no. 1</td>
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<td>66</td>
<td>5.3</td>
<td></td>
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<td>6</td>
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<td></td>
<td></td>
<td>(0.36)</td>
<td>(0.1)</td>
<td>(0.1)</td>
<td></td>
<td>(0.16)</td>
<td>(0.36)</td>
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<tr>
<td>Don Juan no. 2</td>
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<td>67</td>
<td>5.5</td>
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<td></td>
<td></td>
<td>(0.26)</td>
<td>(0.07)</td>
<td>(0.14)</td>
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<td>(0.2)</td>
<td>(0.28)</td>
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<tr>
<td>Average alkaloid content⁹</td>
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<td>65</td>
<td>4.67</td>
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<td>8</td>
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<tr>
<td></td>
<td></td>
<td>(0.2)</td>
<td>(0.08)</td>
<td>(0.06)</td>
<td></td>
<td>(0.06)</td>
<td>(0.23)</td>
</tr>
</tbody>
</table>

⁸Figures given are mg alkaloid/ml of undiluted sample, ± S.E., shown in parentheses; percentages are % total alkaloid.

⁹Average based on n = 18 replicate injections.

- large PKPD variability
- challenge for standardization

Fig. 3. In vitro inhibition of rat-liver MAO by ayahuasca samples. See text for details.
Human Pharmacology of Ayahuasca: Subjective and Cardiovascular Effects, Monoamine Metabolite Excretion, and Pharmacokinetics

JORDI RIBA, MARTA VALLE, GLORIA URBANO, MERCEDES YRITIA, ADELAIDA MORTE, and MANEL J. BARBANOJ

Fig. 2. Time curves of scores on the seven VAS items (means from 18 volunteers) after administration of placebo (circle), 0.6 mg of DMT/kg of body weight ayahuasca (square), and 0.85 mg of DMT/kg of body weight ayahuasca (triangle). Filled symbols indicate a significant difference from placebo.
Dose-Response Study of N,N-Dimethyltryptamine in Humans

I. Neuroendocrine, Autonomic, and Cardiovascular Effects

Rick J. Strassman, MD, Clifford R. Qualls, PhD

Figure 1. Mean dimethyltryptamine (free base) values in 10 subjects after four doses of intravenous dimethyltryptamine fumarate (0.05 mg/kg [squares], 0.1 mg/kg [triangles], 0.2 mg/kg [diamonds], and 0.4 mg/kg [closed circles]) and saline placebo (open circles).
Phase 2a safety and efficacy for SPL026 (IV DMT) in 34 participants with MDD, demonstrating a clinically relevant and statistically significant reduction in depression symptoms at two weeks after dosing (-7.4 point difference in MADRS between SPL026 and placebo).

https://cybin.com/development-pipeline/
Translationale Arzneimittelentwicklung von DMT-Präparaten

Figure 1 | The approval process. Drug approval involves passing a number of steps, including preclinical and clinical studies, and later, post-marketing research. FDA, Food and Drug Administration; IND, Investigational New Drug application; NDA, New Drug Application.
Später Schauen

Psychodelika in der Therapie – Die Forschung holt auf


Sie wurden verteufelt, verbannt und verboten: Psychedelische Substanzen wurden lange Zeit als Drogen abgetan. Zu schnell gerieten Psychedelika in den 1960er-Jahren unkontrolliert aus dem Labor in den Massenkonsum und wurden daraufhin weltweit verboten. Das psychotherapeutische Potenzial der Substanz... **MEHR INFOS**
Entwicklung eines DMT-Kombinationspräparats

**Dose-finding pilot trial**
PKPD & Safety/Tolerability
- n=10 healthy participants
- 30-90 mg DMT
- 150-250 mg Harmine
  (oral vs. parenteral routes of administration)

**Randomized, double-blind, placebo-controlled trial**
- n=31 healthy participants
- 100 mg DMT
- 100 mg Harmine
- Placebo

**Phase 1 Study**
PKPD & Safety/Tolerability
- n=16 healthy participants
- different dose ratios of DMT and Harmine

**Phase 2a Study (2024)**
PoC in Substance Use Disorders

**References**
- Dornbierer et al.
  *Frontiers Pharmacology, 2023*
- Müller & Aicher & Dornbierer et al.
  under review
- Aicher & Müller et al.
  *Frontiers Psychiatry, 2024*
- Egger & Jareño et al.
  in preparation
Isolation von N,N-DMT aus der Wurzelrinde von Mimosa hostilis (Incubator Lab, IREM UZH)
Entwicklung eines DMT-Kombinationspräparats

Rationale
- precise
- individualized
- patient-oriented dosing
- circumvention of the gastrointestinal tract

Advantages
- better tolerability (less undesired effects)
- low PKPD-variability
- improved controllability
- empathogenic effects

Dornbierer et al.
Frontiers Pharmacology, 2023
Overcoming the clinical challenges of traditional ayahuasca: a first-in-human trial exploring novel routes of administration of N,N-Dimethyltryptamine and harmine


open-label, within-subject, dose-escalation study

10 healthy male participants (30.7 ± 5.4 y; BMI 18.5–25)

Harmine: 150-250 mg (oral vs. buccal)
DMT: 30-90 mg (oral vs. intranasal)

Dornbierer et al.
Frontiers Pharmacology, 2023
Studiensetting (RCT)

Psychedelic Lab Space @ University of Zurich
Studiendesign (RCT)

Psychedelic Lab Space @ University of Zurich

- double-blind, randomized, placebo-controlled, within-subject study
- 31 healthy male participants (25 ± 4 years | BMI 18.5–25)
- 100 mg Harmine (buccal) + 100 mg DMT (intranasal)
- 100 mg Harmine (buccal) + Placebo (intranasal)
- Placebo (intranasal) + Placebo (intranasal)

Müller & Aicher & Dornbierer et al. in review
Retrospective assessment of the subjective experience of the three drug conditions: DMT & harmine, harmine, placebo. Psychological insights (avoidance and maladaptive patterns, goals and adaptive patterns, global score); emotional breakthrough; connectedness (to self, others, and nature, and global score); challenging experience (fear, grief, physical distress, insanity, isolation, death, paranoia, global score).
DMT & Harmin - Psychologische Effekte

Pre- vs. Post-Session Ratings | Ecological Momentary Assessments (EMA)

- **shift from negative to positive emotions** after DMT/harmine
- **increase in emotional acceptance, empathy, connection and optimism** after DMT/harmine
- **decrease in self-criticism, fear of failure, dissociation and pessimism** in high sensitivity subgroup

The subjective experience (11D-ASC, PIQ, EBI) **strongly correlated** with positive persisting effects and significance measures.

Aicher & Müller et al.  
*Frontiers Psychiatry, 2024*
Ablauf einer Psychedelischen Therapie

**Preparation**

The participant meets with the study clinician(s) to build rapport, discuss what to expect during the dosing session, and set intentions for their experience.

**Dosing**

After receiving the drug, the participant is monitored by clinician(s) in a comfortable environment. The participant typically listens to music with eye-shades on.

**Integration**

In the weeks following dosing, the participant meets with the clinician(s) to make meaning of their experience and incorporate any insights into their life going forward.

Aday et al.  
*Psychopharmacology, 2022*
Einfluss von Set und Setting

States and Traits
Predicting Psychedelic Effects

Intensity of acute effects
Mystical Effects
Adverse Effects

Absorption
Openness
Acceptance
Surrender
Preoccupation
Apprehension
Confusion

Aday et al.
ACS Pharmacol Transl Sci 2021
Deconstructed, parsed, and diagnosed. A hypothetical example illustrates how precision medicine might deconstruct traditional symptom-based categories. Patients with a range of mood disorders are studied across several analytical platforms to parse current heterogeneous syndromes into homogeneous clusters.

Symptom-based categories
- Major depressive disorder
- Mild depression (dysthymia)
- Bipolar depression

Integrated data
- Genetic risk
- Polygenic risk score
- Brain activity
- Insula cortex
- Physiology
- Inflammatory markers
- Behavioral process
- Affective bias
- Life experience
- Social, cultural, and environmental factors

Data-driven categories
- Cluster 1
- Cluster 2
- Cluster 3
- Cluster 4

Behavioral Rigidity
Social Disconnection
Anhedonia
Negative Mood

Fig. adapted from Insel & Cuthbert
Science, 2015
Psychedelika - Transdiagnostische Wirkfaktoren

**NEGATIVE VALENCE**
- Acute Threat “Fear”
- Potential Threat “Anxiety”
- Sustained Threat
- Loss
- Frustrative Non-Reward

**POSITIVE VALENCE**
- Approach Motivation
  - Reward Valuation
  - Effort Valuation
  - Expectancy
  - Action Selection
- Initial Responsiveness to Reward
- Sustained Responsiveness to Reward
- Reward Learning
- Habit

**COGNITIVE**
- Attention
- Perception
  - Visual
  - Auditory
  - Olfactory
- Declarative Memory
- Language Behaviour
- Cognitive Control
  - Goal Selection, Updating, Representation & Maintenance
  - Response Selection
  - Inhibition
  - Performance Monitoring
- Working Memory
  - Active Maintenance
  - Flexible Updating
  - Limited Capacity
  - Interference Control

**SOCIAL**
- Affiliation & Attachment
- Social Communication
  - Reception of Facial Communication
  - Production of Facial Communication
  - Reception of Non-Facial Communication
  - Production of Non-Facial Communication
- Perception & Self
  - Agency
  - Self-Knowledge
- Perception & Others
  - Animacy Perception
  - Action Perception
  - Understanding of Mental States

**AROUSAL & REGULATION**
- Arousal
- Circadian Rhythms
- Sleep & Wakefulness

Fig. adapted from Yücel et al. *Addiction, 2018*
Psychedelika - Verstärker der Theory of Mind

**Emotional processing**
- Reduction of processing of negative stimuli
- Alterations in amygdala activity and connectivity

**Potential therapeutic effect**
- Normalization of negative bias
- Reduction of rumination
- Improvement of patient–therapist relationship
- Reduced social withdrawal
- Reinstatement of reward processing

**Self-processing**
- Decreased self–other differentiation
- Positive self-dissolution
- Unity

**Social processing**
- Increased empathy
- Reduced rejection sensitivity

Vollenweider & Preller
*Nat Rev Neurosci, 2020*
• Psychedelika erfahren ein wissenschaftliches Revival, das neue Möglichkeiten für die Behandlung von psychischen Störungen bietet, insbesondere für Depressionen, Angststörungen, Abhängigkeitserkrankungen, und Traumafolgestörungen.

• Aufgrund ihrer psychoplastogenen Wirkung dienen Psychedelika vorwiegend als Verstärker der neuronalen Plastizität, auf deren Grundlage sich salutogenetische Veränderungsprozesse anbahnen können.

• Durch Emotionsaktivierung und Flexibilisierung des Denkens werden psychedelicische Erfahrungen auch als transdiagnostische Verstärker zur Vertiefung von psychotherapeutischen Interventionen genutzt.

• Psychedelika zeigen in einem kontrollierten Setting ein relativ gutes Sicherheitsprofil und eine gute Verträglichkeit, es braucht noch größere Vergleichsstudien zu Langzeitwirkungen und -verträglichkeit im Rahmen von klinischen Anwendungen.

• Aufgrund der kürzeren Wirkdauer und besseren Steuerbarkeit könnten innovative DMT-Präparate eine Alternative zu klassischen Psychedelika wie LSD, Psilocybin oder Meskaline darstellen, es sind jedoch weitere klinische Studien notwendig.

Take Home Messages
Vielen Dank für Ihre Aufmerksamkeit

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