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Onderzoek naar psychedelica voor hardnekkige depressie; *laveren* *tussen hoop en hype*

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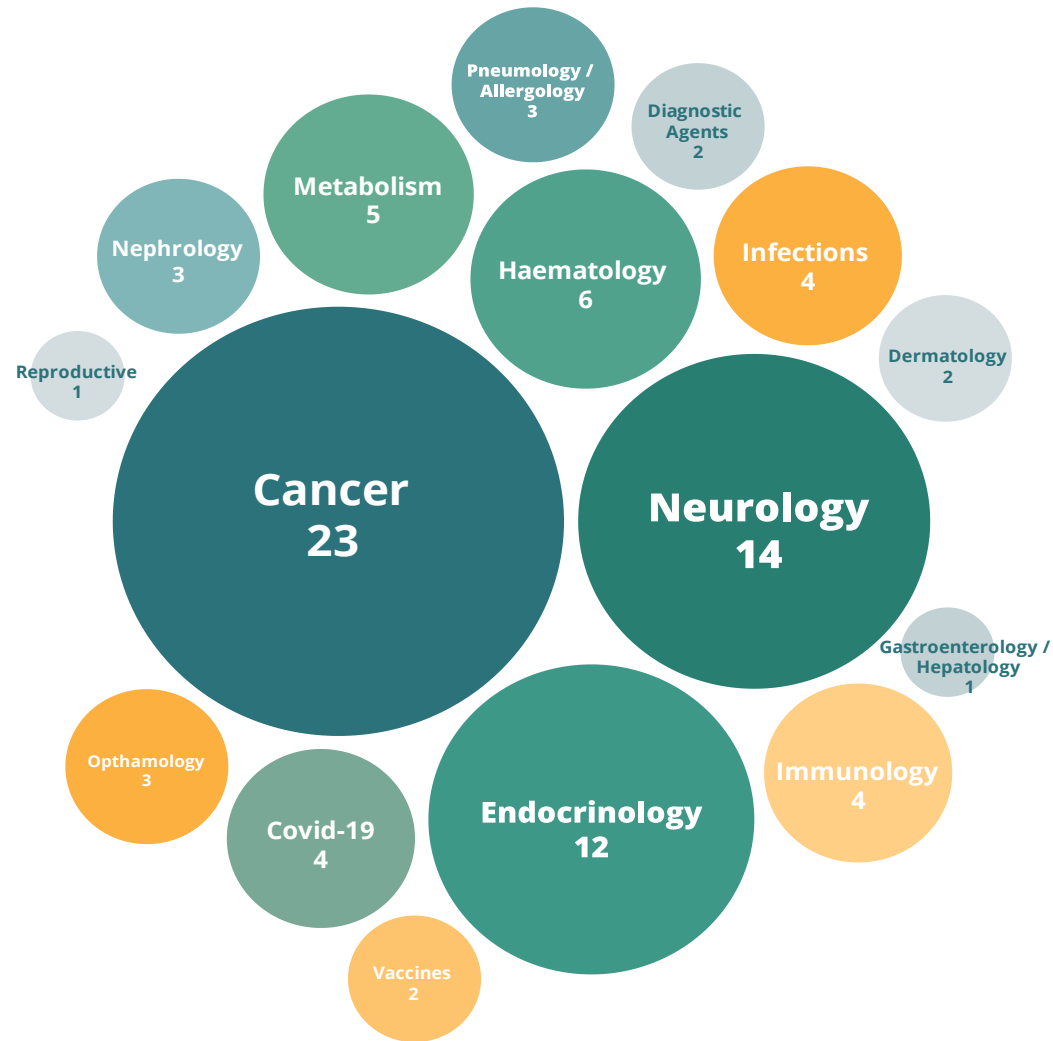
Conflict of interest

Research funding (Public)	Netherlands Organisation Health Research & Development, Netherlands Care Institute, EU Horizon 2020, 2023, NIMH and others
Public-Private research projects	J&J, Novartis, Compass Pathways (Health Holland)
Speakers fee	Janssen Pharmaceuticals
Scientific advisory	Clexio Biosciences
Clinical trials	GH research, Compass, Novartis, Beckley Psytech, Avextra
Shareholder	None
Other	None

Mental disorders;
Impressive disease burden *and* treatment resistance

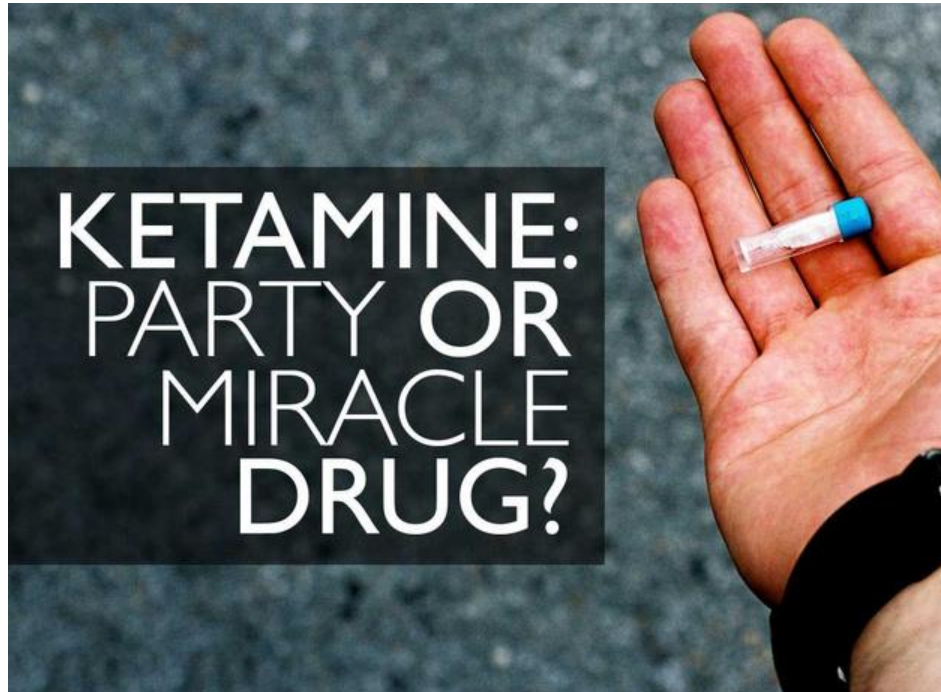


Stagnant
innovation



0/89

New medicines
for **mental disorders**
approved by EMA in 2022



How a new generation of
drugs could change the
way depression is treated

SNIFFING AT A NEW SOLUTION
Novel drugs for depression

E

Dutch history

Professor Jan Bastiaans (1917-1997)

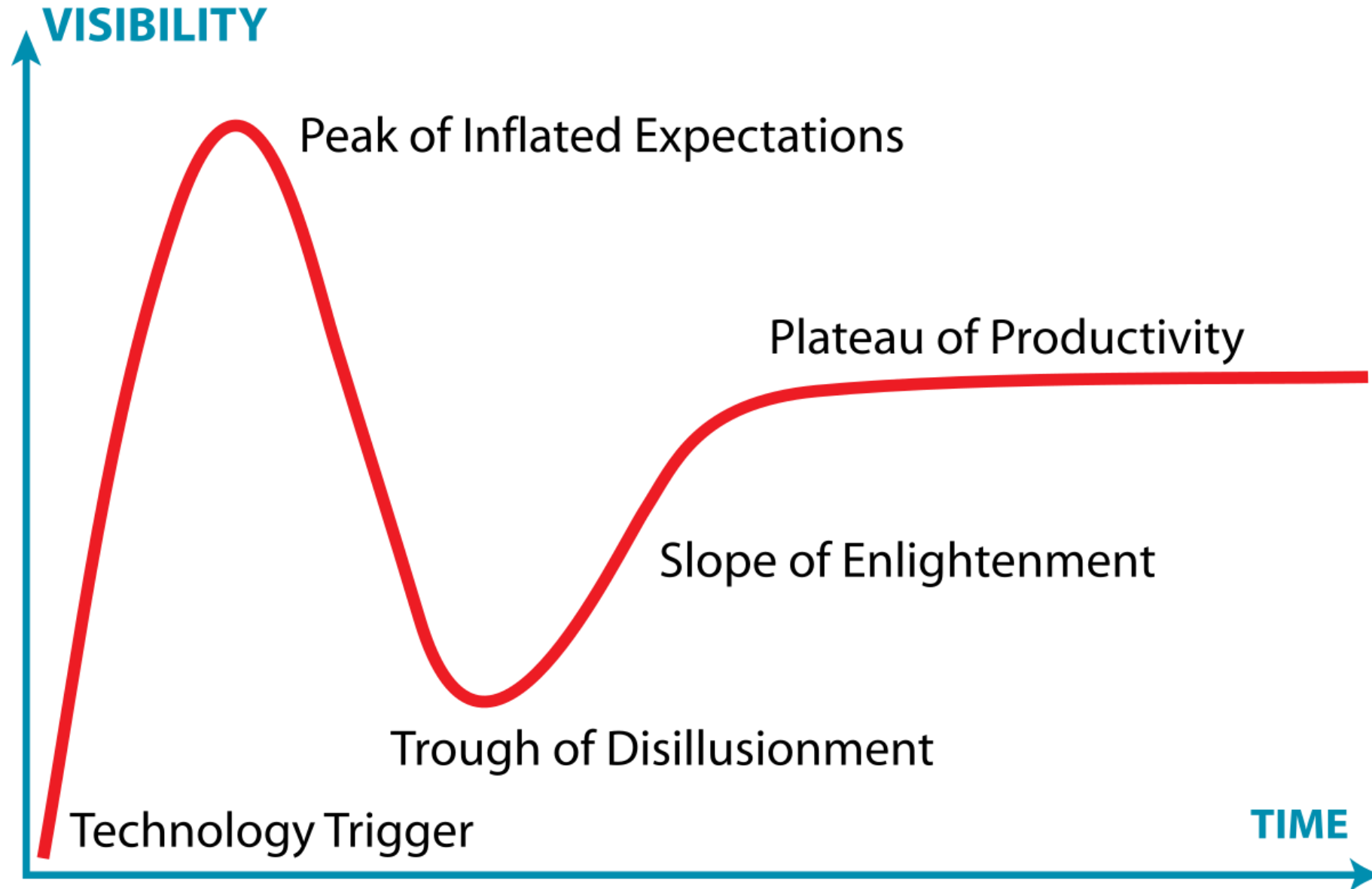


- One of the founders of Center '45 in 1973
- LSD/pentothal - Concentration Camp Survivors
- Directive and confrontational therapy approach
- Continued LSD therapy till 1988 (legally)
- Controversy about his attitude and scientific methods led to parliamentary questions

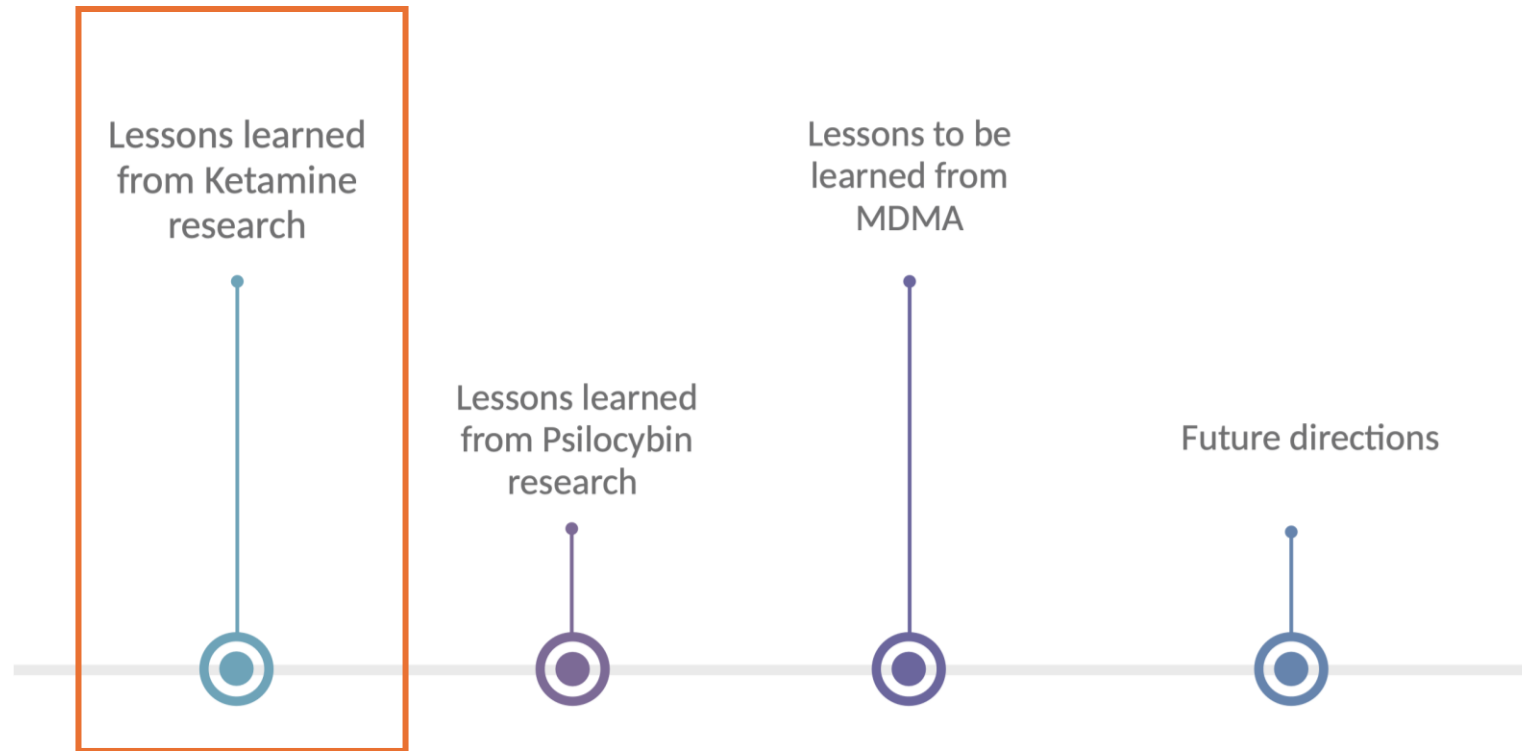
Jan Bastiaans – snapshots of LSD sessions 'Now Do You Get It?'-1969



Psychedelics & the hype cycle



Bringing psychedelics to patients



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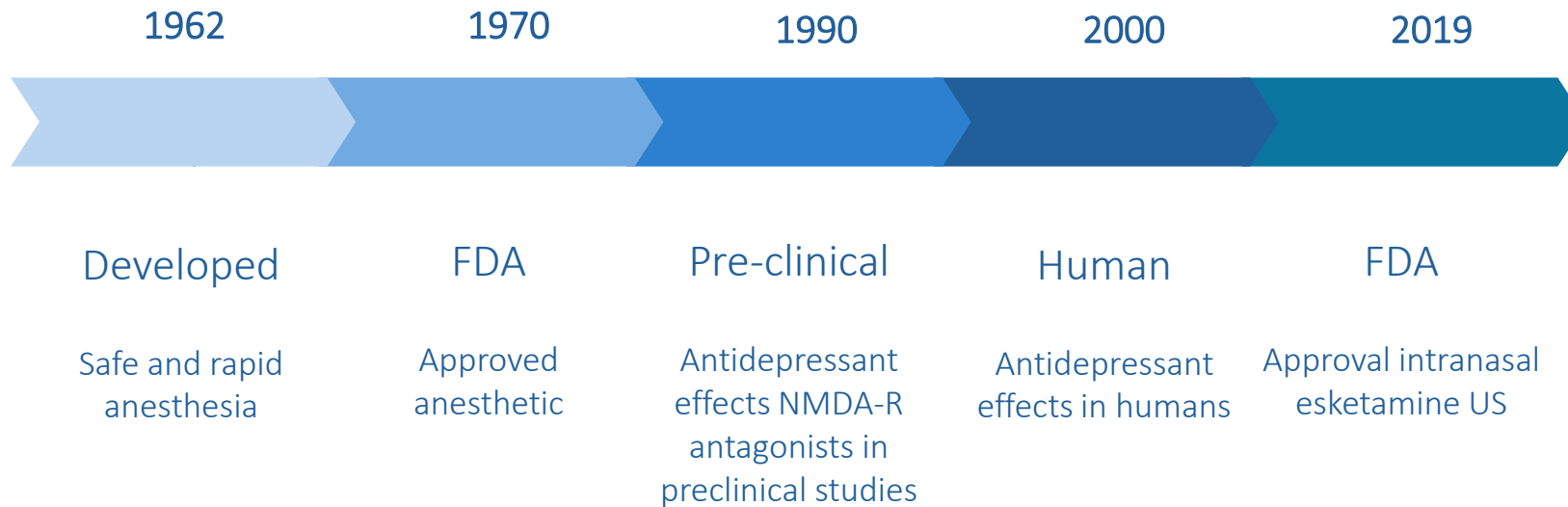
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Ketamine

Glutamatergic action
WHO's *Essential Drugs List*

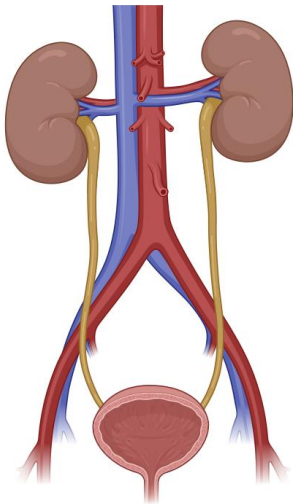
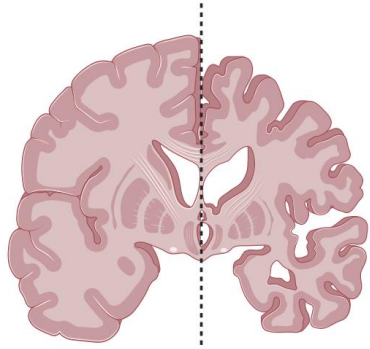
Lessons learned
from Ketamine
research



Side effects of long-term use

Systematic review of studies in chronic recreational users

Lessons learned
from Ketamine
research



- Lower gray matter volume
- less white matter integrity
- lower functional thalamocortical and corticocortical connectivity
- May explain long-term cognitive and psychiatric side effects; memory impairment & executive functioning

Development of side effect questionnaire

Lessons learned from Ketamine research

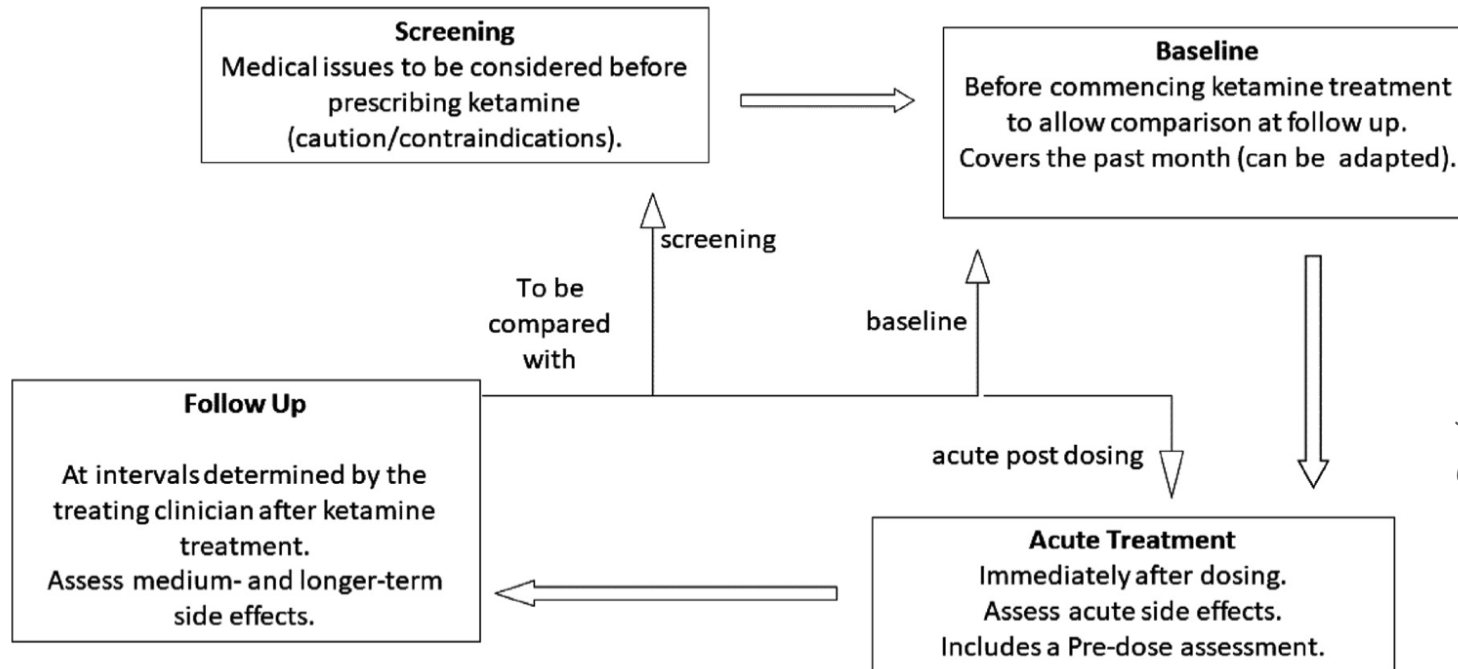


Fig. 1 KSET forms, time points and aims

Short et al. (2020). *Journal of Affective Disorders*. (266).

Can we combine ketamine with other medications?

Systematic reviews and Case series

- **Benzodiazepines** and **probably lamotrigine** **reduce** ketamine's **treatment outcome**.
- Evidence for **an interaction** between **ketamine** and **clozapine, haloperidol, and risperidone**.
Veraart et al. (2021). *International Journal of Neuropsychopharmacology*.
- **Combined** use of **MAOI** and **esketamine** is **less prone to side effects** than presumed.
Veraart et al. (2022). *Journal of Clinical Psychiatry*. 83(6).

Can we prescribe for patients with psychosis vulnerability?

Systematic review

- Ketamine does not exacerbate psychotic symptoms in predisposed patients.
Veraart et al. (2021). *Journal of Clinical Psychiatry*. 82(4).

Patient experiences in a 'medication study'

Qualitative interviews ($N=17$) from off-label oral esketamine

Lessons learned
from Ketamine
research



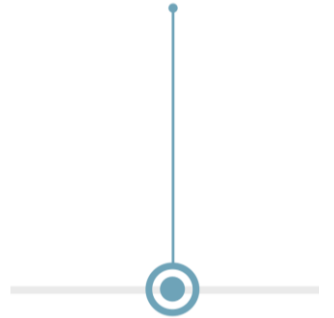
Ketamine treatment room

Patient experiences

*“At a certain moment in the clinic (...) I thought, I don’t know what is happening anymore (. . .)
I had the feeling I was losing myself” (P14)*

- Battle between surrender and holding on to reality
- Loss of control - either scary or meaningful
- Music can work as anchor
- Patients develop strategies to manage (side) effects

Lessons learned
from Ketamine
research



Therapeutic potential of ketamine experiences

Phenomenological study

Lessons learned
from Ketamine
research

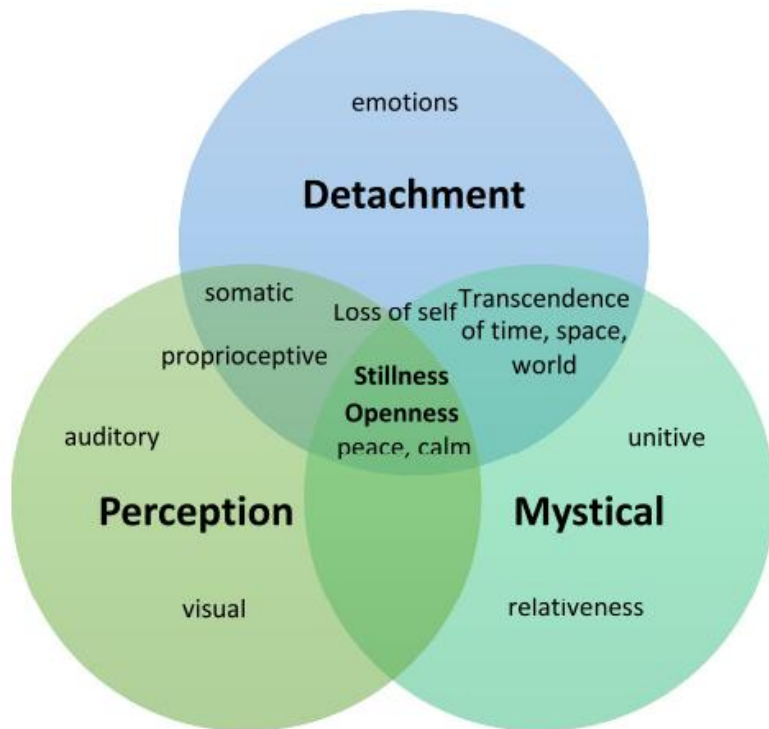
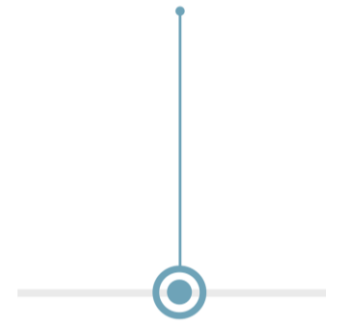


Fig. 1 Overlapping phenomena described by patients during the acute phase of oral esketamine sessions

- Patients reported various effects that suggest a therapeutic potential for depression treatment
- Ongoing psychological support in all stages of esketamine treatment:
 - Increased openness
 - Detachment
 - Interruption of negativity
 - Mystical-type experiences
- Optimize treatment setting

Development of ketamine support module

Lessons learned
from Ketamine
research

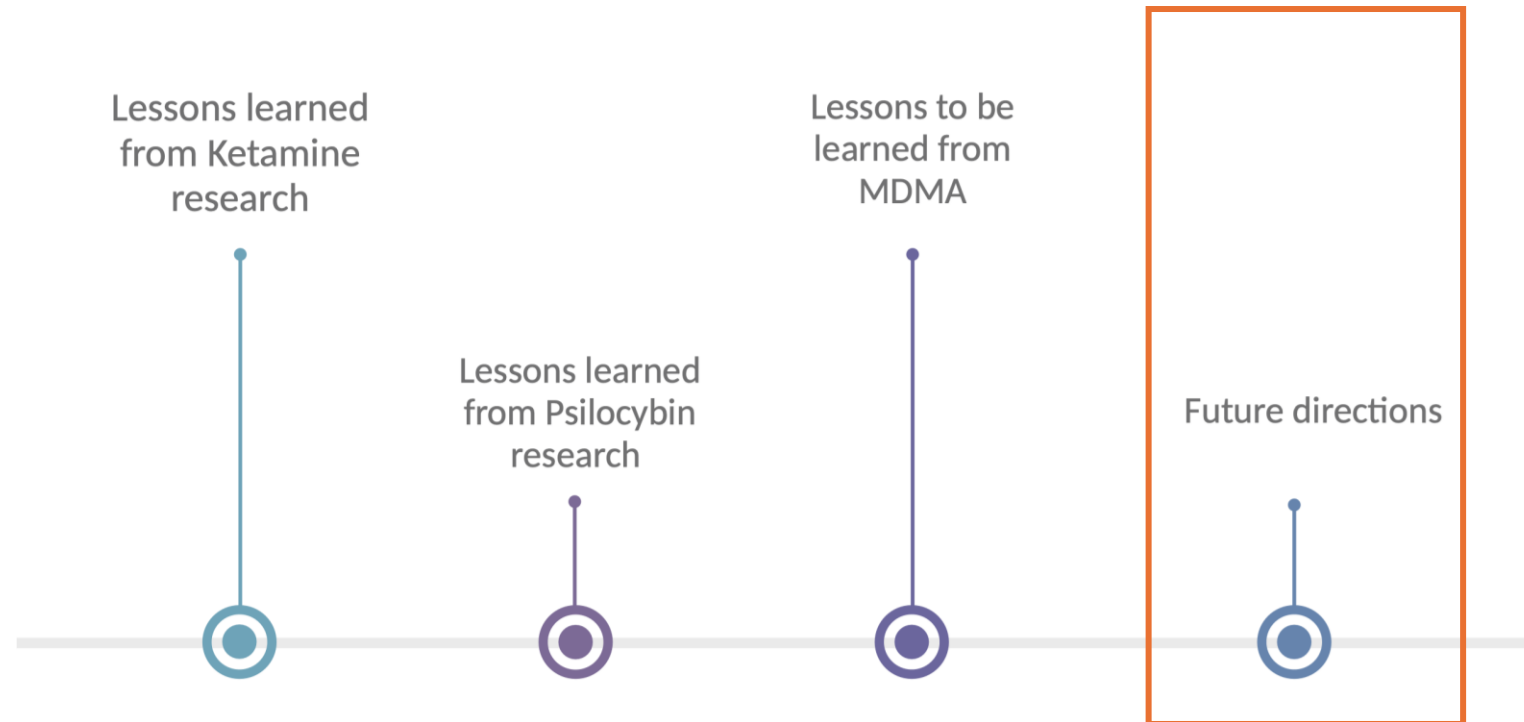


To navigate anxiety and psychedelic experiences for safety and trust

- Attention to Set & Setting
- Preparation, esketamine sessions, integration
- Attitude: supportive, following, open & curious
- Based on Acceptance and Commitment Therapy



Bringing psychedelics to patients



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Upcoming pilot studies oral esketamine

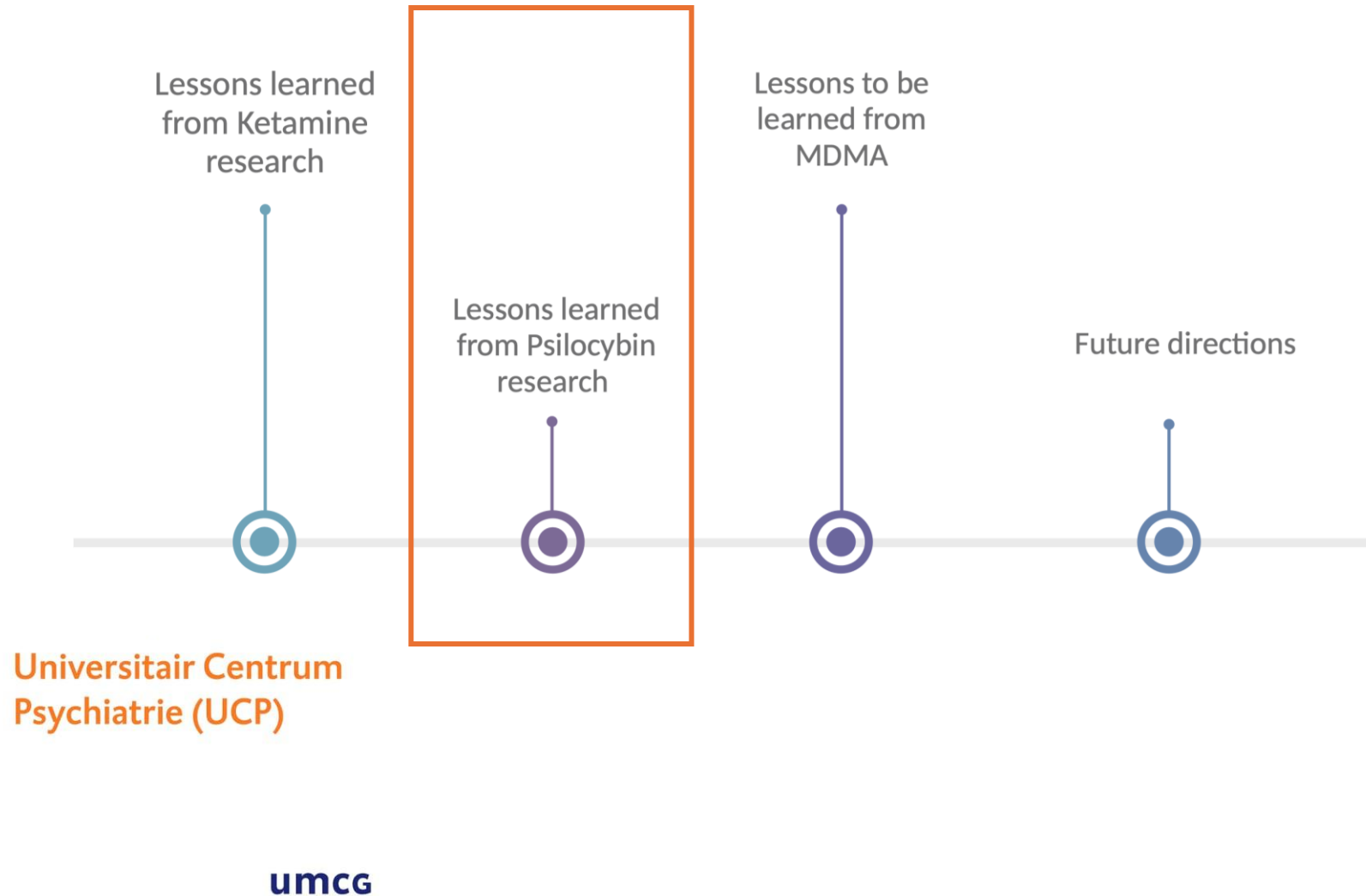
Future directions



- Bipolar depression
- Eating disorders
- Obsessive Compulsive Disorder
- End of life distress



Bringing psychedelics to patients



Some psychedelics & their origins



Psilocybin

- Origin: Mexico, Central America
- Historical use: Religious rituals

5-MeO DMT

- Origin: Mexico, Amazon, Caribbean
- Historical use: Ceremonial practices



MDMA

- Origin: Germany, Merck Pharmaceuticals
- Historical use: Psychotherapy enhancer



Psychedelic Assisted Therapies



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 eyeshades on.

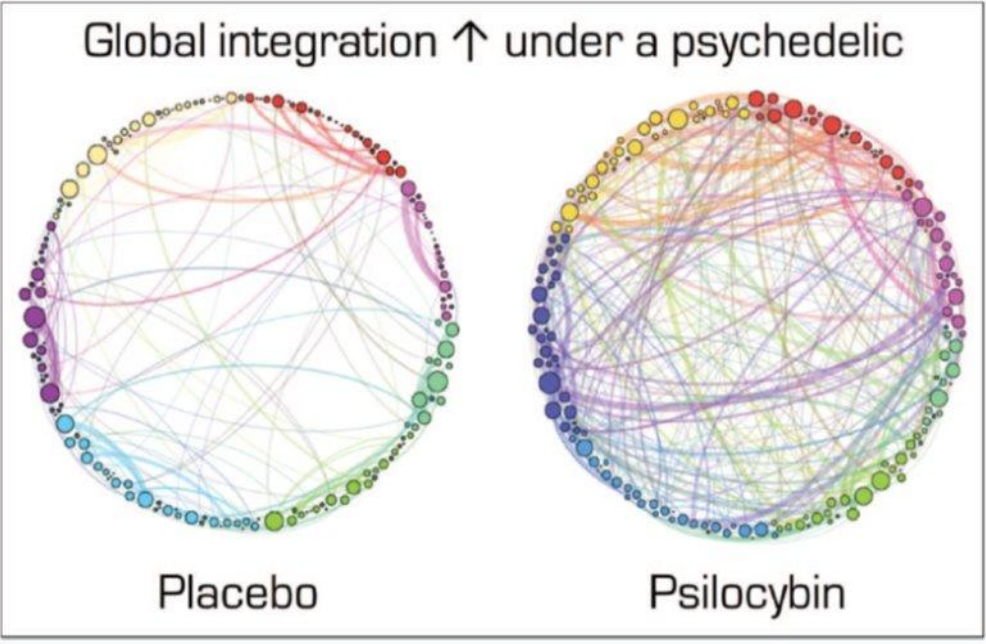
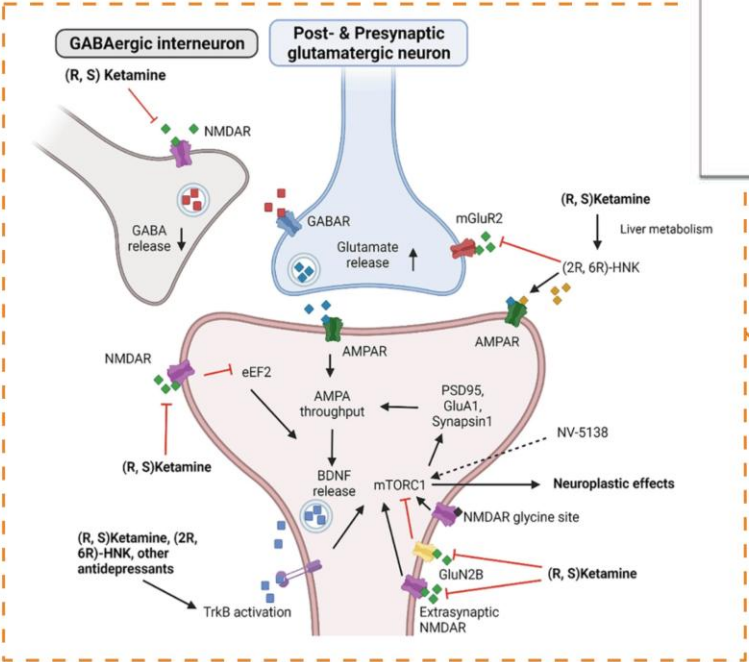


Integration

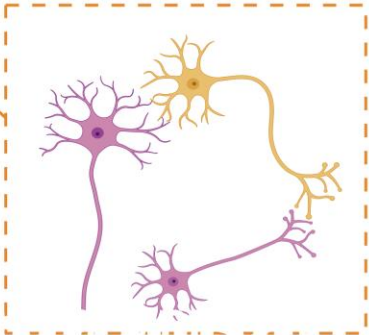
In the weeks following dosing, the participant meets with the clinician(s) to make meaning of their experience and incorporate any insights into their life going forward.

Psychedelics target underlying disease mechanisms

Neuroplasticity



Functional connectivity



Cognitive (in)flexibility

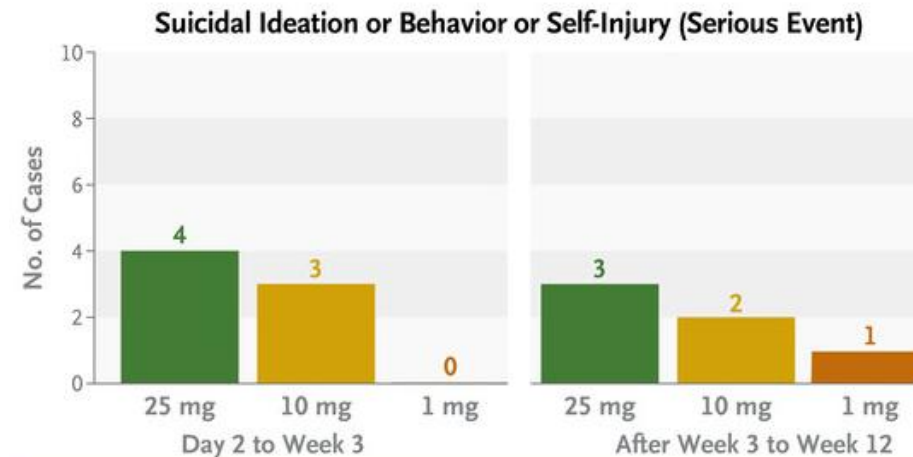
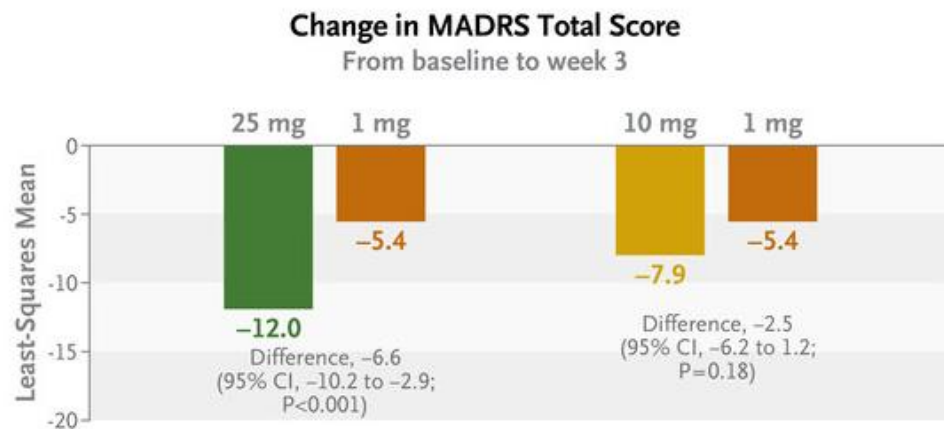
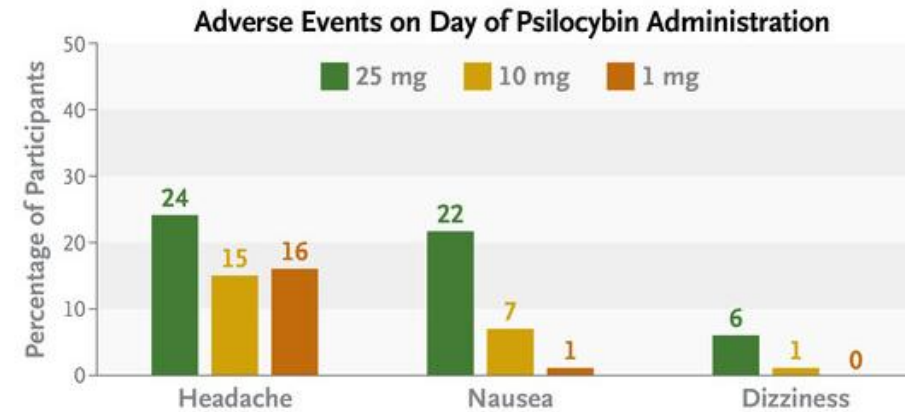


Lessons learned
from Psilocybin
research



Psilocybin therapy

Lessons learned
from Psilocybin
research





What is optimal support?

Patient perspectives: A qualitative study in psilocybin trial

Theme I:

- Distrust in mental healthcare
- Trust in study therapists
- Limited time for preparation
- Managing expectations.

Theme II:

- Trusting to surrender
- Profound and overwhelming experience.
- Music as a guide.

Theme III:

- Desire for multiple psilocybin sessions
- Challenges with sensemaking.

“Patients’ perspectives provided important insights into potential optimization of psilocybin treatment of TRD.”



Adverse effects (AEs) of classic psychedelics

Mixed methods systematic review ($N=598$)

Immediate AEs: Nausea, headaches, and anxiety

Late AEs; headaches, fatigue, low mood, and anxiety

1 serious AE; increased premature ventricular contractions requiring brief hospitalization (MDMA)

Conclusions:

- (1) AEs poorly defined in the context of psychedelic treatments and likely underreported
- (2) Acute challenging experiences may be therapeutically meaningful

Who
participated in
these studies?

Lessons learned
from Psilocybin
research





Do psychedelics really have similar effects across compounds & diagnoses?

Therapeutic processes

- Insight (e.g. illness, causes)
- Changing perspectives of self
- Connectedness
- Transcendent experiences
- More access to emotions

Patient outcomes

- Symptom decrease
- Self-image change
- Connectedness
- Larger emotional repertoire
- Quality of life



What form of psychotherapy works best?

Systematic review Psychedelic Assisted Psychotherapies

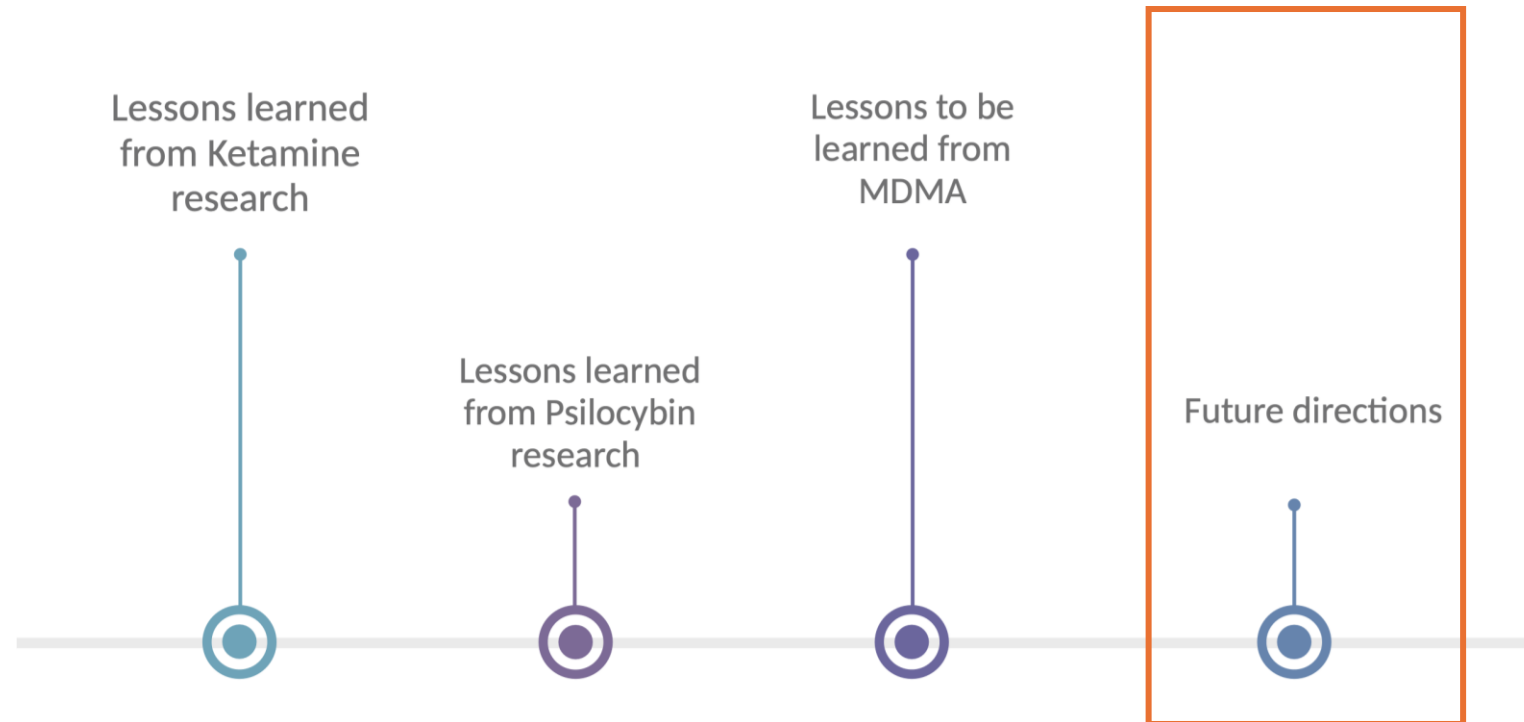
- Wide range of psychotherapeutic approaches have been used
- Studies of varied methodological quality
- Information on interventions mostly incomplete
- MDMA treatment descriptions more homogeneous and elaborate
- Improved reporting needed for replicability, generalisability

Lancet Psychiatry 2024

Quality of reporting on psychological interventions in psychedelic treatments: a systematic review

Carolina Seybert*, Nina Schimmers*, Lucio Silva, Joost J Brecksema, Jolien Veraart, Bárbara S Bessa, Dora d'Orsi, Robert A Schoevers†, Albino J Oliveira-Maia†

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Psilocybin therapy for psychological distress in palliative care patients

Future directions



PRESS RELEASE

European Union funds groundbreaking research into psychedelic therapy

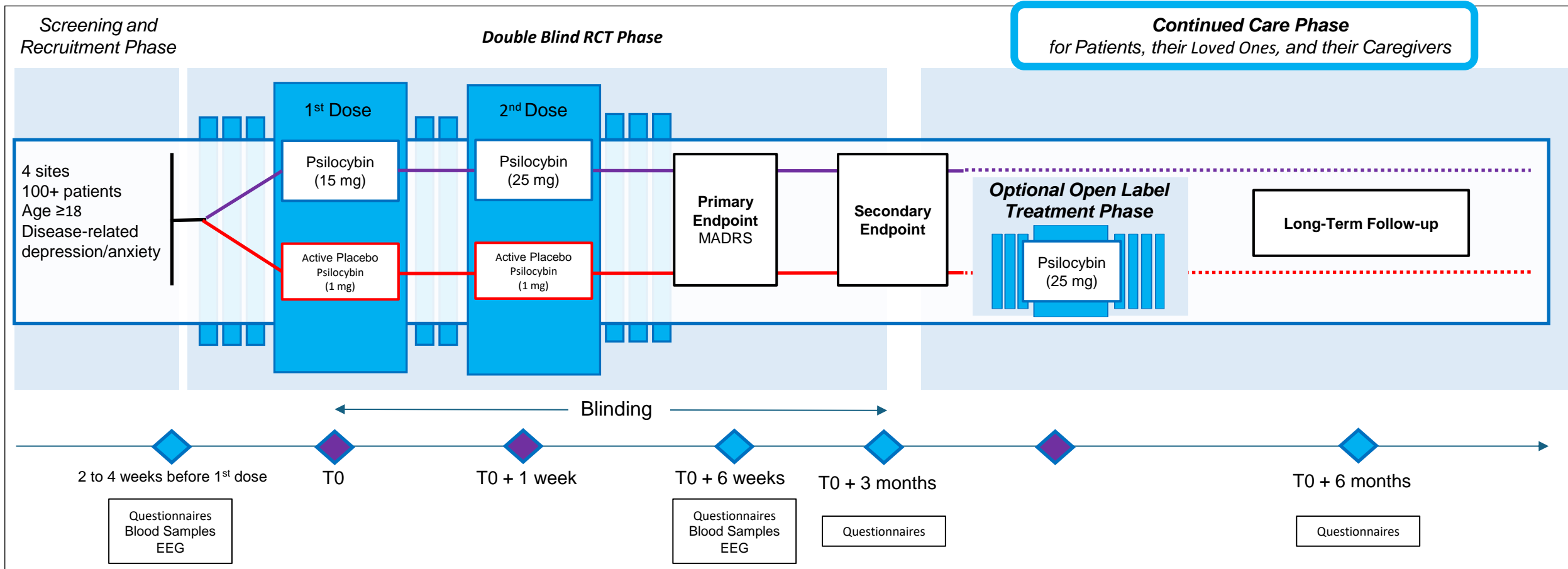


Funded by the
European Union

A European consortium of 19 partners has been awarded over €6.5M by the European Union to study psilocybin to treat psychological distress in people with progressive incurable illnesses requiring palliative care. This is the first time the EU has funded a multi-site clinical study into psychedelic-assisted therapy.



Summary overview of PsyPal



PsyPal key elements

Future directions



Ascending dose (x2)

All participants receive
psilocybin

Therapy manual &
Standardized training

Ethical work package
To address previously
encountered issues



Combination with other
medications

Different chronic medical
conditions

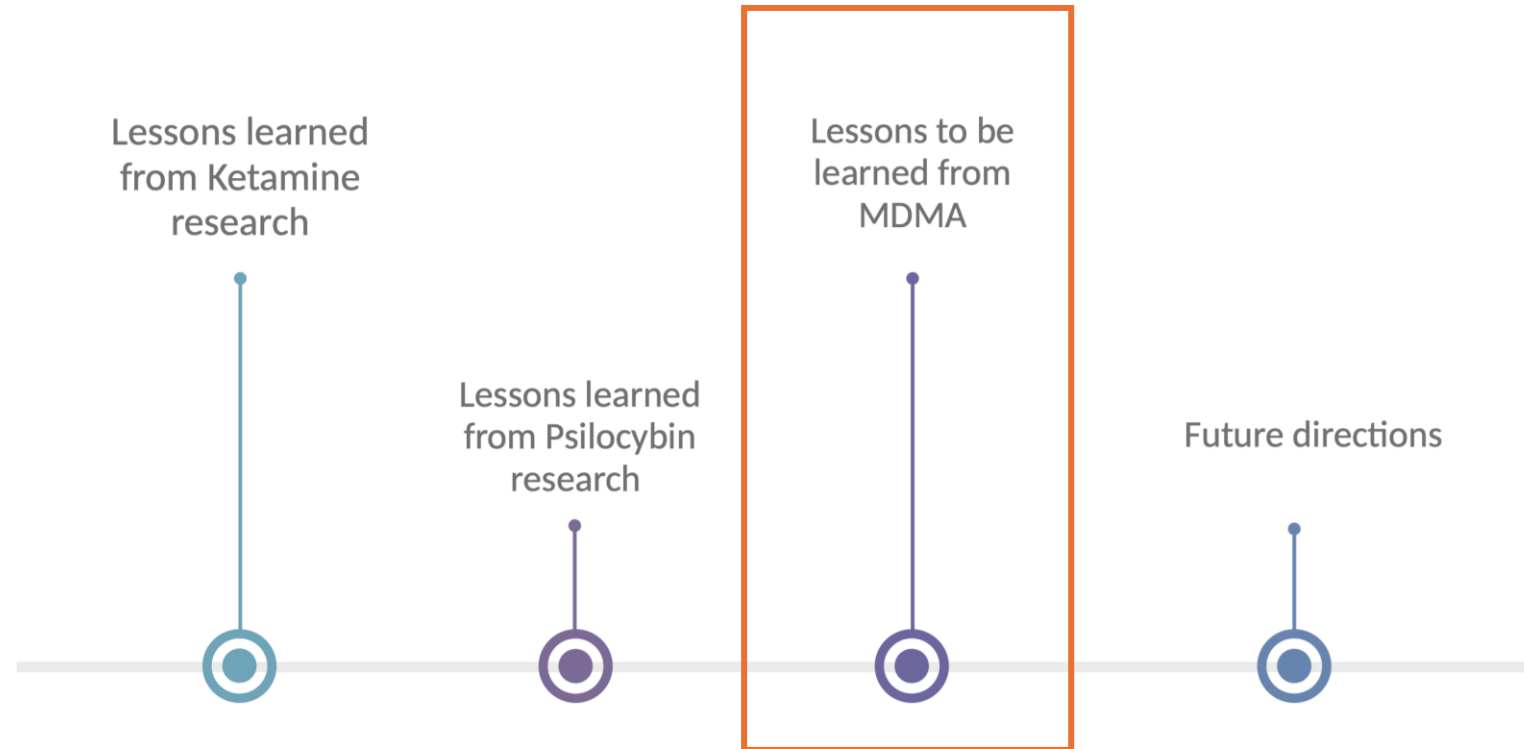
Continued care, Peer
support network & Digital
care platform

Mixed methods
(spiritual..)



Funded by
the European Union

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(in)famous case; boundary violations

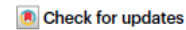
Lessons learned
from Psilocybin
research



- Private practice
- Unlicensed therapist/sitter
- Involvement with client outside of sessions
- More cases are appearing.....

Psychedelic treatments for mental health conditions pose challenges for informed consent

Carolina Seybert, Gonalo Cotovio, Lu s Madeira, Miguel Ricou, Ana Matos Pires & Albino J. Oliveira-Maia



Lessons learned
from Psilocybin
research



Boundary violations position paper (in prep)

- Sexual Boundary Violations exacerbated by the altered states of consciousness, increasing patient vulnerability and suggestibility
- Therapist characteristics and setting may contribute to risk
- Necessity for strict adherence to professional standards, plus specific training
- Implementation of additional safeguards:
 - informed consent procedures
 - non-touch policies
 - rigorous supervision
 - transparent oversight mechanisms
- Future directions call for systematic measurement of adverse effects and the development of ethical standards tailored to PAT

Don't forget the basics

- All of us are potentially vulnerable to violations
- The teaching of ethics must include:
 - Discussions of transference & countertransference
 - The use of third parties, such as supervisors or consultants, to assist the therapist in the monitoring of professional boundaries

Lessons learned
from Psilocybin
research

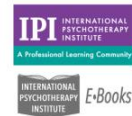


Glen Gabbard



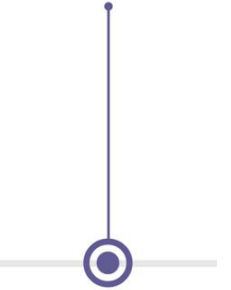
The Recurrent Problem of Boundary Violations in Psychoanalytic and Psychotherapeutic Treatments

**Feb 16
9am-11am ET**



Key Considerations in FDA evaluation MDMA for PTSD

Lessons to be
learned from
MDMA



nature

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NEWS | 05 June 2024

MDMA therapy for PTSD rejected by FDA panel

Scientific advisers to the US Food and Drug Administration vote overwhelmingly that the risks of MDMA treatment for post-traumatic stress disorder outweigh the benefits.

By [Sara Reardon](#)

Functional Unblinding: Most participants could guess their treatment, introducing **bias** that complicates efficacy assessment

Psychotherapy's Role: MDMA was always combined with therapy, so the **specific contribution** of the drug alone is unclear

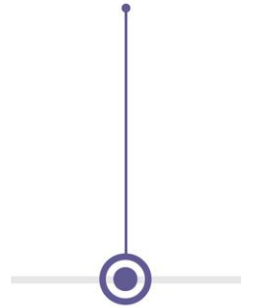
Durability of Effect: Long-term benefit was observed, but high dropout rates and other therapies during follow-up limit data reliability

Report Netherlands State Commission on MDMA

“MDMA Beyond Ecstasy”

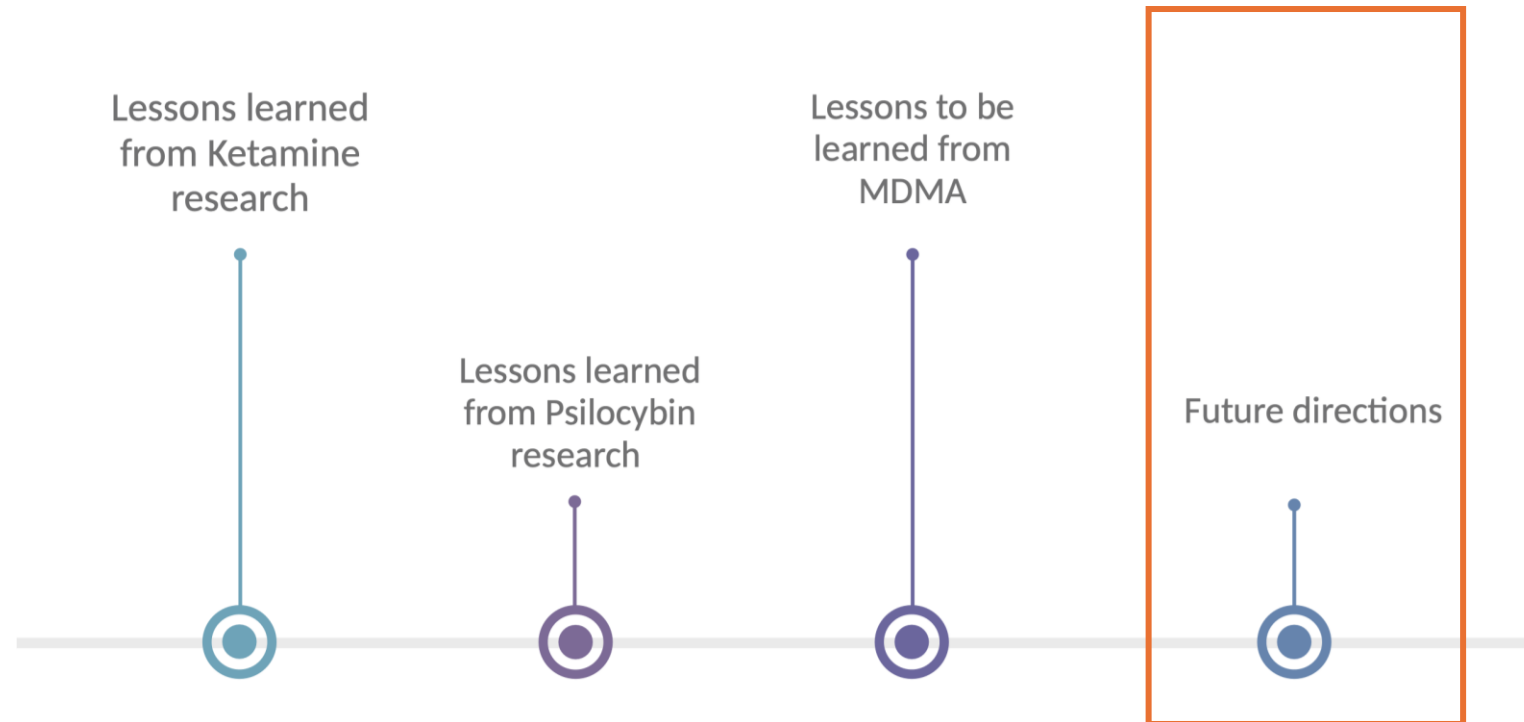
- National drug policy should remain primarily directed at harm reduction & prevention and not blame/stigmatize the user
- MDMA is less harmful than originally thought
Could be moved from List I to List II - but there is a fight against organised crime
- There is a medical need for chronic PTSD-patients;
MDMA-AT should be made available ASAP
- Until MDMA-AT is registered in Europe/NL, the best way to provide state-of-the-art MDMA-AT is through a large naturalistic pre-post study
- Pro-active action is needed to prevent harm due to illegal MDMA-Tx providers

Lessons to be
learned from
MDMA



Full text

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New models of care?



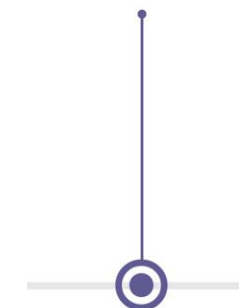
- Attention to Set & Setting
- Training & certification
- Payment models
- Ongoing (hybrid) support

Report for Health Ministry

“Therapeutic Applications of Psychedelics”



Lessons to be
learned from
MDMA



Full text (Dutch)

Report for Health Ministry

“Therapeutic Applications of Psychedelics”

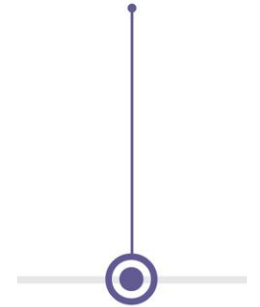
Knowledge Gaps & Research Needs:

- More studies needed on safety, efficacy, and cost-effectiveness
- Infrastructure for large-scale studies and training of therapists must be developed

Risks and Concerns:

- Risks such as anxiety, paranoia, and long-lasting negative effects
- Testing needed in real world patients
- Media hype creates unrealistic expectations among patients.

Lessons to be
learned from
MDMA



Call for National Research Program

Focus areas: high-quality research, gradual treatment rollout, monitoring, accessibility, and training.



SYNAPSE

research. innovate. implement

Innovation
Network for
Mental Health

SYNAPSE

research. innovate. implement



Future directions



OVERVIEW

Improve the health and well-being of patients suffering from **mental disorders** by establishing a country-wide research and implementation infrastructure



25% of the general population faces a mental health problem

€ 22 billion economic costs per year in the Netherlands alone



highest population disease burden and cause the greatest loss of productivity

30%

of patients develop a serious 'treatment-resistant' mental disorder

existential distress

addiction

OCD

depression

post-traumatic stress disorder

chronic pain

eating disorders



1

Nationwide coordination and collaboration of R&D&I efforts.

Patient-centred approach

Follow-up care to monitor long-term effects

2

Large-scale research answering the gaps

Controlled, sustainable, ethical, safe

3

Translation to clinical practice

Development of specific therapeutic skills

4

High-quality training and certification for health care professionals

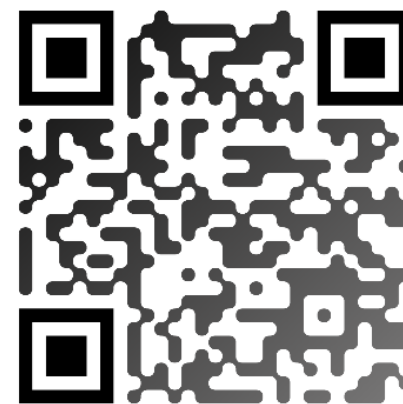
Creating clear guidelines

European Psychedelic Research Network





Thank you for your
attention!



Check out our research website!



Contact: r.a.schoevers@umcg.nl