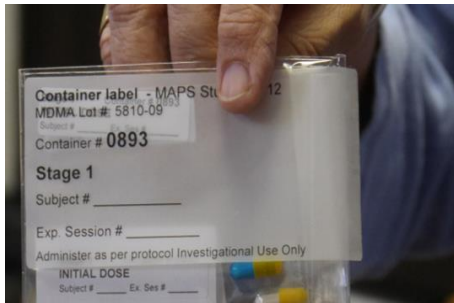


"Update on the status of 'new wave' psychotherapy, the case of MDMA-AT for PTSD"

Leuven, UPC Kortenberg, November 6, 2024



Prof dr Col ret'd Eric Vermetten, MD, PhD – Leiden University Medical Center, Dept Psychiatry

So where to start?

Psychedelic Clinical Trials 2010-2024 (excluding ketamine)

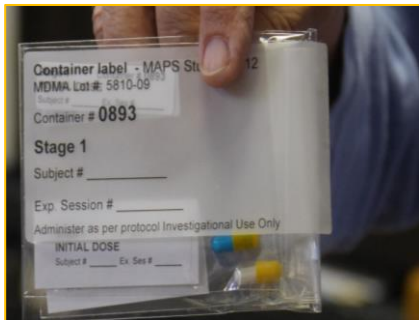
nature > news feature > article

NEWS FEATURE • 27 JANUARY 2021

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.

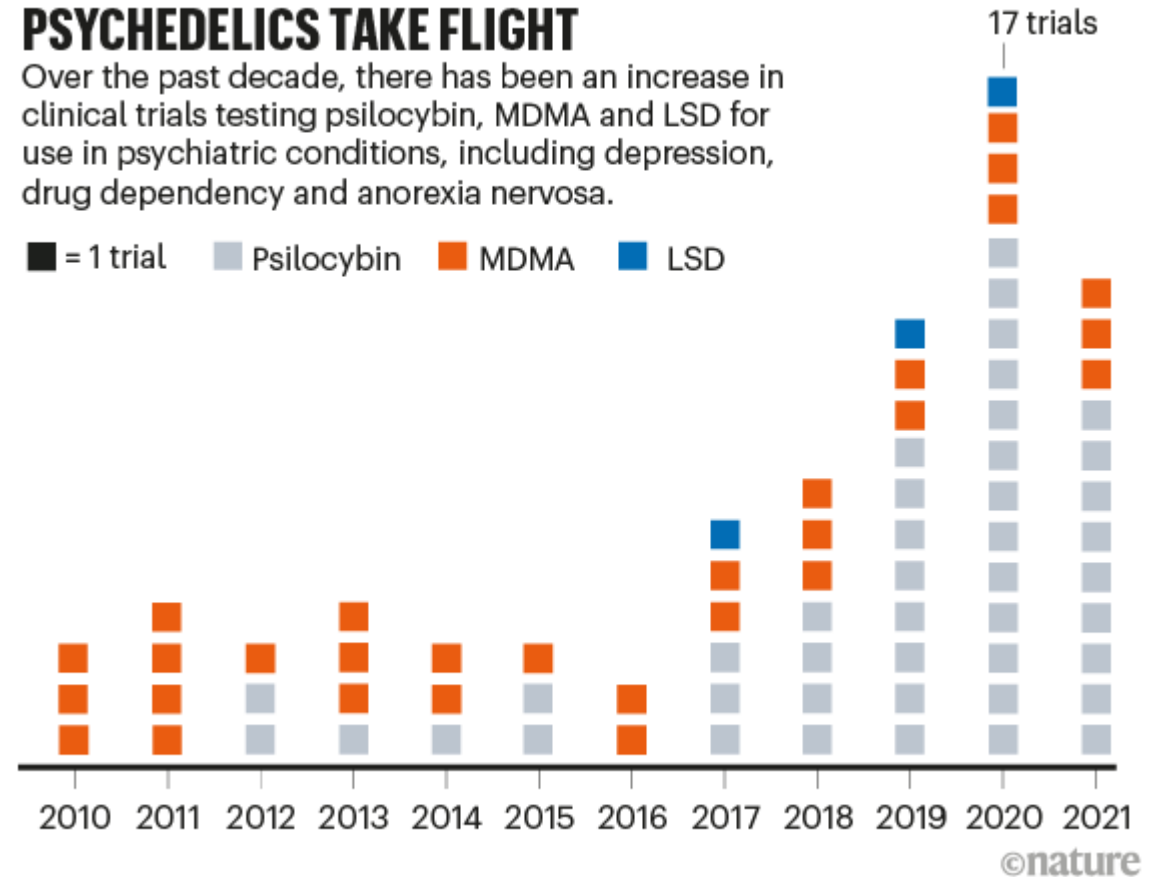
[Paul Tullis](#)



PSYCHEDELICS TAKE FLIGHT

Over the past decade, there has been an increase in clinical trials testing psilocybin, MDMA and LSD for use in psychiatric conditions, including depression, drug dependency and anorexia nervosa.

■ = 1 trial ■ Psilocybin ■ MDMA ■ LSD



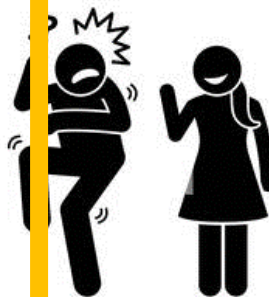
05/11/2024: 60 studies on psychedelics and PTSD, 37 with MDMA, of which 16 completed, 12 with psilocybin of which 2 completed, 1 safety study



Avoiding thinking of the trauma



Avoiding talking about the trauma



Easily triggered



Negative mood



Negative thinking



Always on guard



Avoiding places



Avoiding activities



Flashbacks



Difficulty concentrating



Aggressive behavior



Loss of interest



Feeling guilt or shame



Substance abuse



Sleeping difficulties



Bad dreams

New realities in psychotrauma

Challenges to Mental Health in 2024 and beyond

Challenge	Description	Impact (Estimated Number of People Affected)	Cost (Estimated Annual Economic Cost in EUR)
Impact of the COVID-19 Pandemic	Significantly increased prevalence of mental health issues, including anxiety, depression, and stress-related disorders.	50 million	150 billion
Stigma and Discrimination	Persistent stigma and discrimination against individuals with mental health problems, leading to social exclusion and reduced help-seeking.	20 million	50 billion
Workplace Mental Health	High levels of stress and burnout among workers, necessitating legislative measures to protect mental health in the workplace.	30 million	70 billion
Variability in Access to Mental Health Services	Significant variability in the accessibility and quality of mental health services across Europe, particularly in Eastern Europe and rural areas.	Varies by region	N/A
Impact of Geopolitical Events	Increased incidence of PTSD and other mental health disorders due to recent geopolitical events, such as the conflict in Ukraine, Israel/Gaza/other hot spots.	10 million	30 billion
Financial Constraints and Resource Allocation	Inadequate funding for mental health services, leading to overburdened systems struggling to meet demand.	All regions	80 billion
Integration and Coordination of Services	Lack of integration and coordination within mental health care systems, resulting in fragmented services that are difficult to navigate.	All regions	N/A

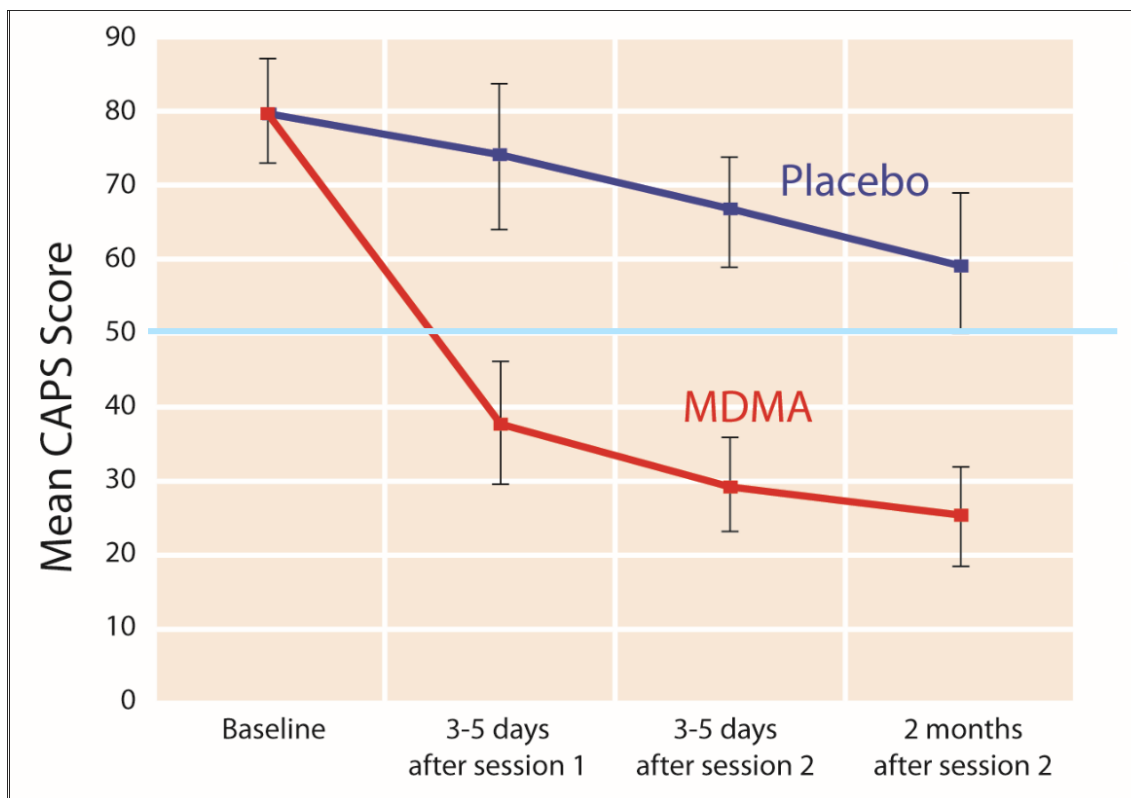


Innovations in New Drug Targets in Medicine last 10 years, Psychiatry is lagging behind!

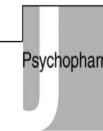
Aspect	Psychiatry (Mental Health)	Neurology
Focus Areas	Neurotransmitter modulation, neuroplasticity enhancers, psychostimulants	Neuroprotection, ion channel modulation, immunomodulation
Mechanisms of Action	Receptor agonists/antagonists, reuptake inhibitors, NMDA receptor antagonists	Enzyme inhibitors, channel modulators, anti-inflammatory agents
Development Trends	Slow pipeline, recent interest in psychedelics	Rapid advances, focus on biologics and gene therapies
Regulatory Dynamics	High demand, high regulatory scrutiny	Orphan drugs incentives, complex trials
Therapeutic Outcomes	Symptom management, variable efficacy	Disease modification, functional restoration
New Compounds Developed	Approximately 20 new compounds, of which 2 in PTSD	Approximately 120 new compounds

Landmark study

Mean CAPS-4 Scores TR - PTSD



Original Paper



Journal of Psychopharmacology
0(0) 1-14
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DOI: 10.1177/0269881110376371
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The safety and efficacy of
±3,4-methylenedioxymethamphetamine-
assisted psychotherapy in subjects with
chronic, treatment-resistant posttraumatic
stress disorder: the first randomized
controlled pilot study

Michael C Mithoefer¹, Mark T Wagner², Ann T Mithoefer¹,
Lisa Jerome³ and Rick Doblin³

Abstract

Case reports indicate that psychiatrists administered ±3,4-methylenedioxymethamphetamine (MDMA) as a catalyst to psychotherapy before recreational use of MDMA as 'Ecstasy' resulted in its criminalization in 1985. Over two decades later, this study is the first completed clinical trial evaluating MDMA as a therapeutic adjunct. Twenty patients with chronic posttraumatic stress disorder, refractory to both psychotherapy and psychopharmacology, were randomly assigned to psychotherapy with concomitant active drug (n=12) or inactive placebo (n=8) administered during two 8-h experimental psychotherapy sessions. Both groups received preparatory and follow-up non-drug psychotherapy. The primary outcome measure was the Clinician-Administered PTSD Scale, administered at baseline, 4 days after each experimental session, and 2 months after the second session. Neurocognitive testing, blood pressure, and temperature monitoring were performed. After 2-month follow-up, placebo subjects were offered the option to re-enroll in the experimental procedure with open-label MDMA. Decrease in Clinician-Administered PTSD Scale scores from baseline was significantly greater for the group that received MDMA than for the placebo group at all three time points after baseline. The rate of clinical response was 10/12 (83%) in the active treatment group versus 2/8 (25%) in the placebo group. There were no drug-related serious adverse events, adverse neurocognitive effects or clinically significant blood pressure increases. MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm, and it may be useful in patients refractory to other treatments.

- 550 citations
- Safety studies, tolerability
- 6 RCTs – large effect size, Cohen 0.8

Psychedelic Substances in Treatment of PTSD



International Journal of Neuropsychopharmacology (2020) XX(XX): 1–16

doi:10.1093/ijnp/pyaa018
Advance Access Publication: 14 March 2020
Review

REVIEW

Reviewing the Potential of Psychedelics for the Treatment of PTSD

Erwin Krediet, Tijmen Bostoen, Joost Brecksema, Annette van Schagen, Torsten Passie, Eric Vermetten

Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands (Mr Krediet, Dr Bostoen, Mr Brecksema and Dr Vermetten); ARQ National Psychotrauma Center, Diemen, The Netherlands (Mr Krediet, Drs Bostoen, van Schagen, and Vermetten); Department of Psychiatry, University Medical Center Groningen, Groningen, The Netherlands (Mr Brecksema); Military Mental Health Care, Utrecht, The Netherlands (Dr Vermetten); Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany (Dr Passie); Dr. Senckenberg Institute for the History and Ethics in Medicine, Goethe University Frankfurt/Main, Frankfurt am Main, Germany (Dr Passie).

Correspondence: Eric Vermetten, MD, PhD, Department of Psychiatry, Leiden University Medical Center, Leiden, Albinusdreef 2, 2333 ZA Leiden, The Netherlands (e.vermetten@lumc.nl).



Substance	Therapeutic rationale ^a	Administration	Setting	Evidence
MDMA	- Increases release of serotonin, dopamine, norepinephrine, oxytocin, prolactin, vasopressin, and cortisol. - Serves as a catalyst to psychotherapy. - Increases fear extinction. - Reduces amygdala activity. - Reopens critical period for social reward learning. - Reduces fear response and shame. - Increases openness and interpersonal trust. - Increases emotional empathy. - Improves processing traumatic memories.	- Route of administration: oral. - Dose: 75–125 mg. - Duration of action: 4–8 h. - Administration at start of therapy session. - Multiple administrations (typically 3 sessions) spaced 1 mo apart.	- Clinical but aesthetically pleasant room. - Presence of 2 therapists. - Use of music to deepen and support therapeutic process. - Embedded within psychotherapeutic treatment (nondirective). - Multiple nondrug preparation and integrative sessions.	- Sustained reduction of PTSD symptoms. - Phase 2 RCT (n = 105) completed in 2016. - Phase 3 RCT expected to be completed in 2021. - Other indications: alcohol use disorder and social anxiety (in autistic adults).
Ketamine	- NMDA receptor antagonist. - Rapid (temporary) symptom reduction. - May serve as a catalyst to psychotherapy. - Increases synaptic plasticity. - Facilitates fear extinction and blocks memory reconsolidation. - May increase receptivity to therapeutic interventions. - May improve ability to process traumatic memories.	- Route of administration: i.v., i.m., intranasal, oral. - Dose: typically 0.50 mg/kg over 40 min. - Duration of action: 40–70 min. - Administration at start of treatment, beginning of therapy session, after memory retrieval, or without psychotherapy (depending on rationale). - Single or multiple administrations spaced days to weeks apart.	- Clinical room with no to minimal attention to aesthetics. - Psychological support varies from minimal support from nurse/psychiatrist to extensive support from psychotherapist. - Virtually no use of music. - Currently not embedded within psychotherapeutic framework. - No nondrug preparation and integrative sessions.	- Rapid (temporary) reduction of PTSD and depressive symptoms. 1 RCT (n = 41) completed in 2014. - Multiple RCTs ongoing. - Increasing evidence for treatment of depression. - Other indications: anesthesia, depression, suicidality, alcohol and opiate addiction.
Classical psychedelics	5-HT_{2A} receptor agonists. - Serve as a catalyst to psychotherapy. - Increase synaptic plasticity. - Can reduce amygdala reactivity during emotional processing. - Increase insightfulness and introspection. - Increase divergent thinking and mindfulness-related capacities. - May reduce avoidance. - Can increase emotional empathy. - Can induce emotional breakthrough experiences. - May resolve existential distress. - May increase access to traumatic memories.	- Route of administration: oral. - Dose: 10–25 mg (psilocybin), 50–200 µg (LSD). - Duration of action: 4–12 h. - Administration at beginning of therapy session. - Single or multiple administrations (typically not more than 3) spaced weeks to months apart.	- Clinical but aesthetically pleasant room. - Presence of 2 therapists/guides. - Use of music to deepen and support therapeutic process. - Often embedded within psychotherapeutic treatment (nondirective). - Multiple nondrug preparation and integrative sessions.	- No RCTs in PTSD. - Extensive psychotherapeutic use of LSD and psilocybin during first wave (1950–1970) of research with psychedelics. - Used in treatment of concentration camp syndrome in 1960s and 1970s. - Recent evidence from studies in other indications with high effect sizes. - Other indications: depression, substance use disorders, end of life anxiety, and obsessive-compulsive disorder.
Cannabinoids	- Target the endocannabinoid system (e.g., CB1 and CB2 receptors). - Symptom management (insomnia and nightmares). - May serve as a catalyst to psychotherapy. - May increase fear extinction (decreased fear extinction with chronic use). - May improve ability to process traumatic memories.	- Route of administration: oral, sublingual, or inhaled (vaporized or smoked). - Dose: varying dosages and different ratios of THC/CBD. - Duration of action: 3–8 hours. - Daily administration in case of symptom management.	- Take-home prescription. As such, used in a variety of settings. - Depending on symptoms, used throughout the day or just before sleep.	1 small RCT (n = 10) with nabilone completed in 2015. - Multiple RCTs with medical cannabis ongoing. - Other indications: symptom management for multiple nonpsychiatric indications, e.g., multiple sclerosis and oncology (pain, cachexia, and nausea).

Abbreviations: CB1 and CB2, cannabinoid 1 and 2 receptors; CBD, cannabidiol; 5-HT_{2A}, serotonin 2A receptor; LSD, lysergic acid diethylamide; MDMA, 3,4-Methylenedioxymethamphetamine; NMDA, N-methyl-D-aspartate; PTSD, posttraumatic stress disorder; RCT, randomized controlled trial; THC, tetrahydrocannabinol.
^aTherapeutic rationale based on both (pre)clinical research and clinical observations.

2001- 2021

*Head of Research Military Mental Health
Department Defense, Netherlands*

2013 - current

*Professor Psychiatry
Leiden University Medical Center*

2013 – current

*Adjunct Professor
New York University School of Medicine*

2021- current

*Consultant Mental Health
United Nations*



Pioneers in Psychedelic Research



Rick Doblin



Amanda Felding



Eric Vermetten



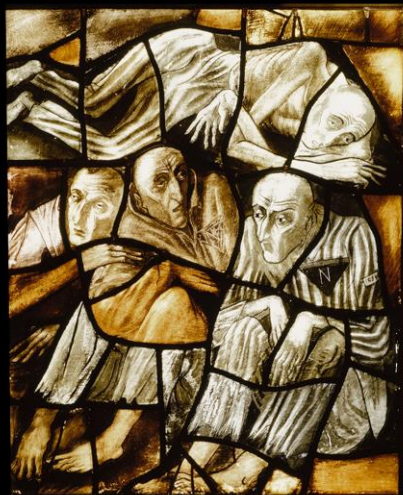
With
Rick Doblin, Amanda Felding
& Eric Vermetten



The Dutch Psychiatrist Who Treated Traumatized Holocaust Survivors With LSD

In the '60s, Jan Bastiaans, using breakthrough experimental treatment with LSD, freed Holocaust survivors from their traumas. He became a national hero but was later shunted aside and treated patients in the underground. Is his legacy still worthy?

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Dutch Newspapers on War Victims and Their LSD-treatment by Jan Bastiaans

From KZ-syndrome to PTSD

Leo van Bergen





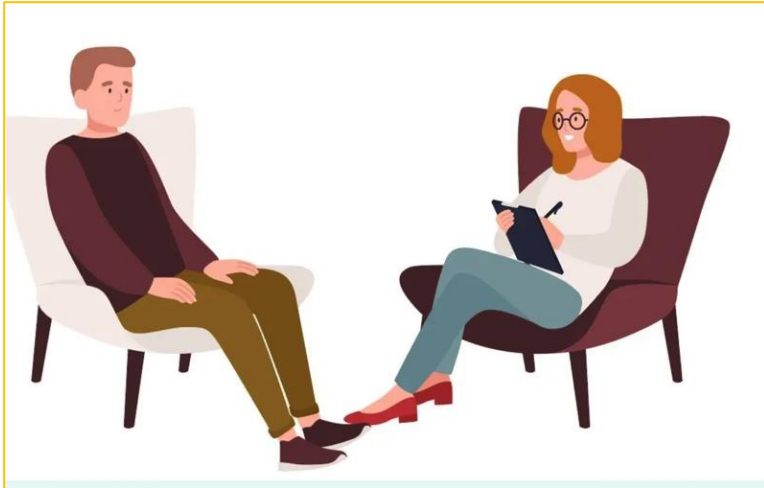


"Begrijpt u nu waarom ik huil?"

Louis van Gasteren

Current Treatments for PTSD and trauma disorders

Psychotherapy



*Prolonged Exposure (PE)
Cognitive Processing Therapy
(CPT)
Based on models of fear
extinction
Talk about trauma in a highly
directed way – desensitization*

Pharmacotherapy



*Dampen distressing
symptoms, mostly
hyperarousal symptoms
Chronic use, side effects,
too numbing*

First wave

Behavior therapy:
*Behavioral modifications
based on fear
conditioning*

Second wave

Cognitive therapy and
CBT:
*Identify and challenge
dysfunctional cognitions*

Third wave

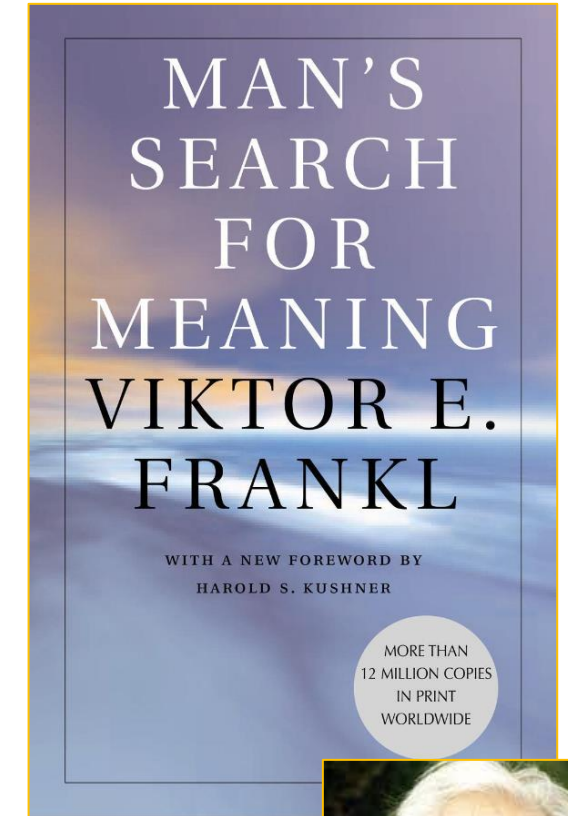
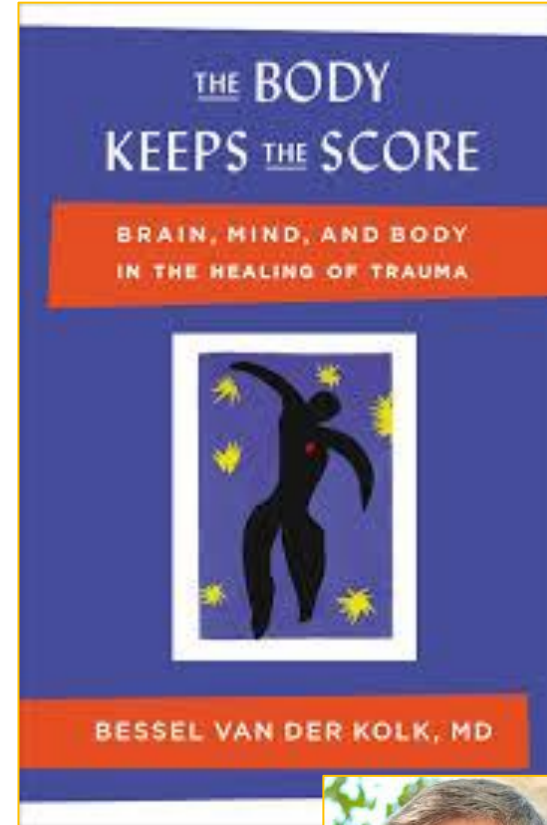
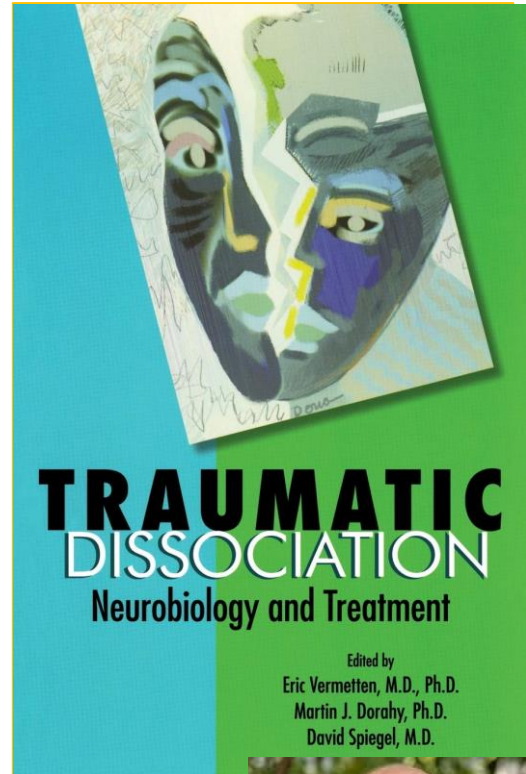
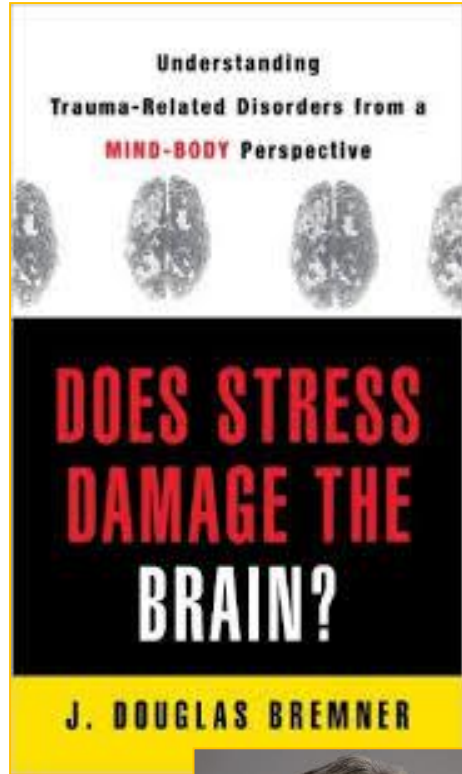
Emerging:
*Metacognitive shifts,
experiential change
strategies*

Reappraisal of Value of Transformative Experiences

Stan Grof, Jan Bastiaans



Changing visions on Trauma, Stress, Dissociation and PTSD



Why MDMA?

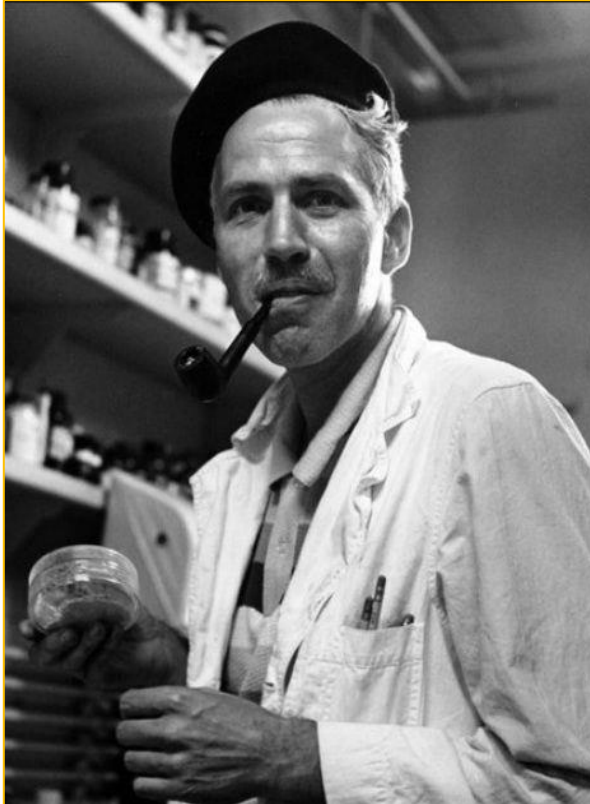
- Rapid and Effective Symptom Reduction +++++
- Treatment-Resistant Conditions +++++
- Long-Term Benefits ++
- Enhanced Therapeutic Experience +++++
- Improved Emotional Processing +++++
- Potential for Long-Lasting Effects +++
- Innovation in Mental Health Treatment +++
- Neurobiological Effects +++
- Safety and Tolerability +++
- High Burden of Mental Health Disorders +++
- Growing Body of Research +++++



‘Second Generation Psychopharmacotherapy’

Alexander Shulgin (1925-2014)

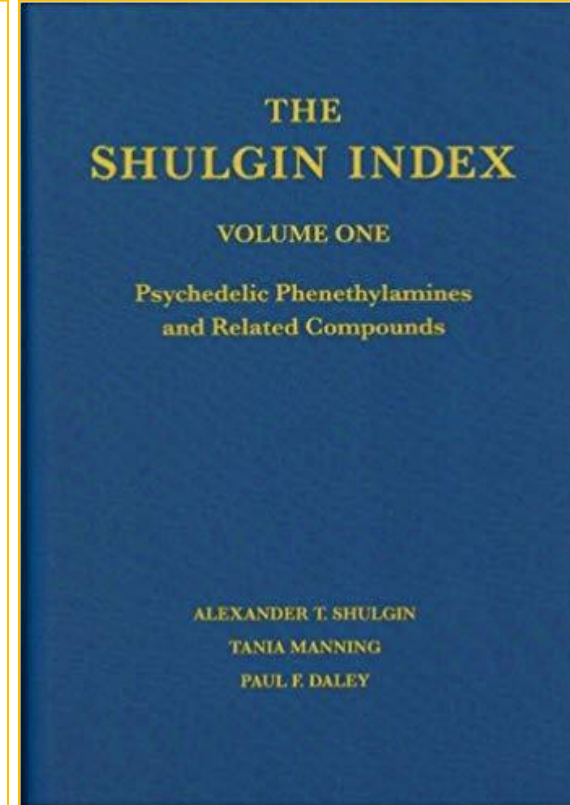
Credited for introducing MDMA to psychology

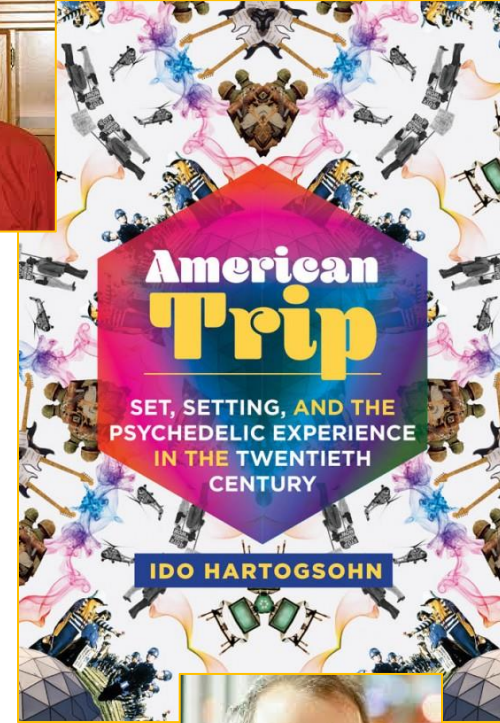
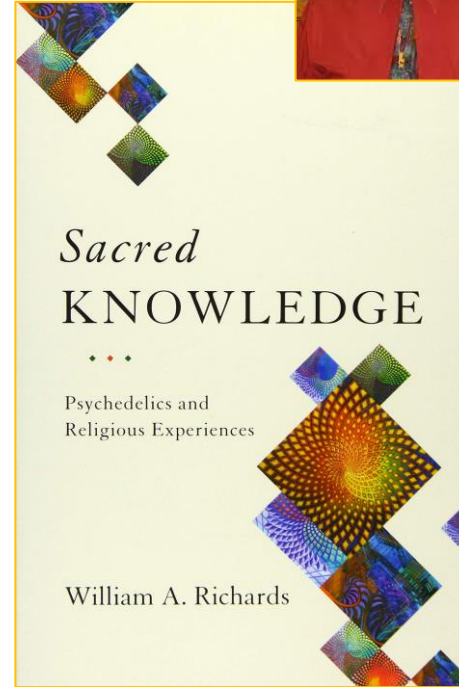
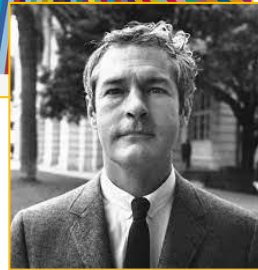
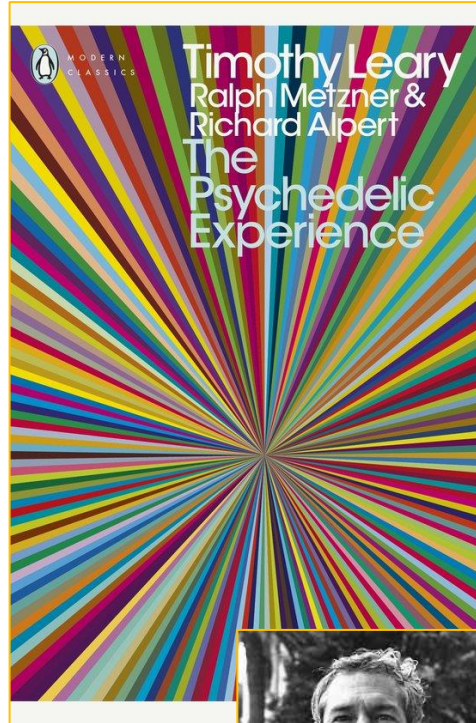
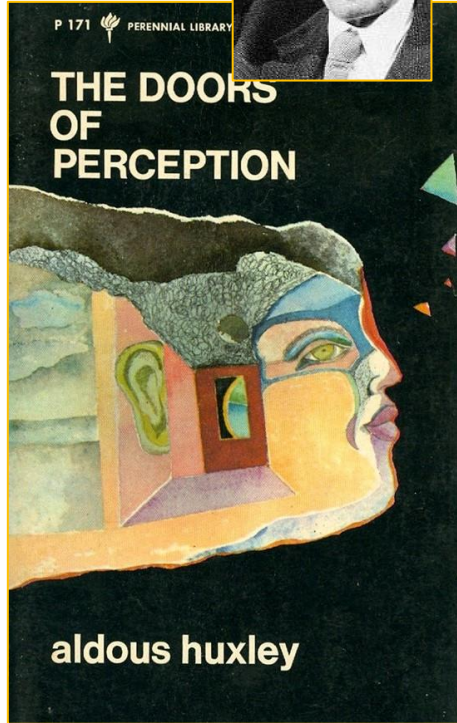
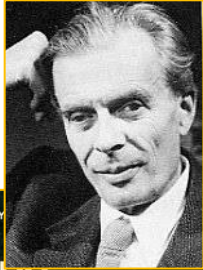
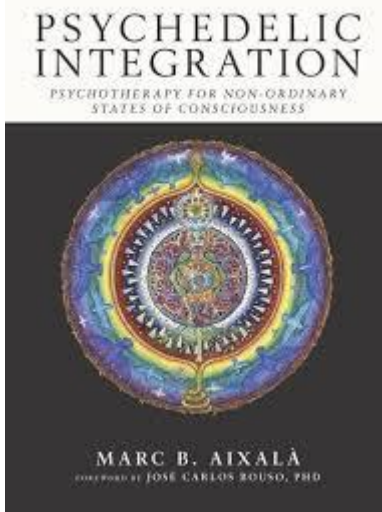
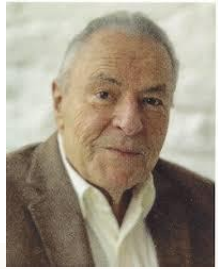


Before taking MDMA, clients should be prepared that they may encounter aspects of this darker side of themselves. She recommends that these issues should be discussed before starting a session, in relation to the patient's biography and current issues.

One of the problems that most humans beings suffer from is the suspicion that the core essence of who they are deep down is a monster. There is terrible fear . . . when you get down to it. . . . MDMA removes that fear. . . . During psychedelic therapy, . . . what we do is we go into it and look through its eyes, so that we become it. But we're all afraid that we got stuck with the demon. . . . Once you get inside the demon, the first thing you experience is a lack of fear, and then you begin to recognize that this is also the survivor aspect of yourself. There's a part that takes care of you. Then it begins to transform, and you recognize its quality of total selfishness—it's going to take care of you and nobody else, right? —but it's your ally. And then you begin to recognize its positive aspects. (Shulgin and Shulgin, 1995: 131, 135–136)

In the end, the shadow aspects of the psyche can be integrated and the shadow will take its place as a devoted ally and protector. To confront and learn to know the shadow can take more than one session, but the transformative power of this encounter is claimed to be enormous. Ann Shulgin's Jungian interpretation of MDMA psychotherapy was inspired by her first husband, John Perry, a psychiatrist trained by Jung (Perry, 1974).



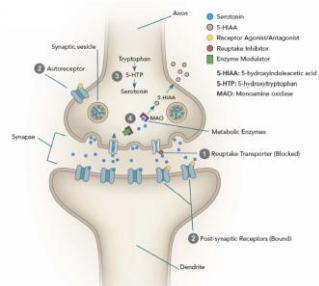
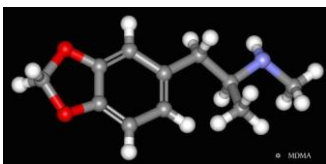


Closer look at MDMA

Increases release of: serotonin (5-HT), norepinephrine (NE), dopamine (DA)

Enhances release of hormones: oxytocin, prolactin, vasopressin, cortisol

Ring-substituted phenylisopropylamine derivative
Patented in 1914 by Merck
now off-patent



- Psychophysical relaxation
- Intensified feelings - euphoria
- Decreased anxiety
- Increased openness and communication
- Enhanced closed-eyes imagery
- Intensified body experience

Activation of emotions

Enhanced imagery

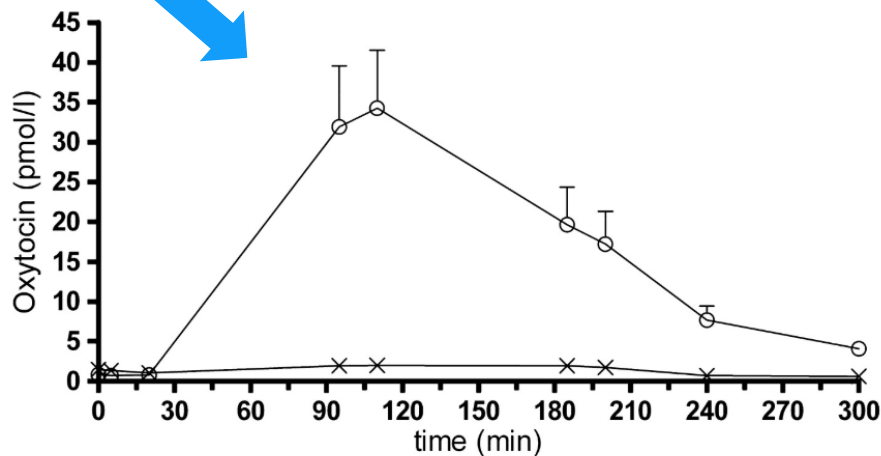
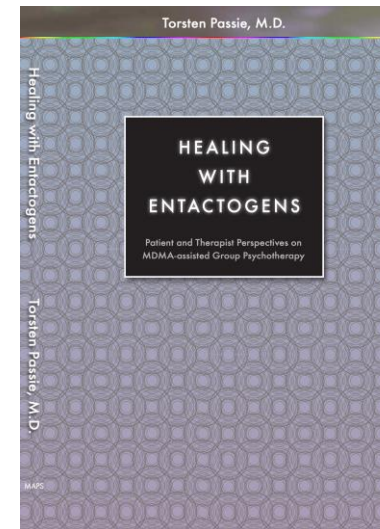
Speeding up of intrapsychological processes

Reprocessing of traumatic events

Catharsis

• “Entactogen”

- Insightfulness
- Less perceived loss of control than classical psychedelics
- Closeness to others
- Empathy
- Well-being



Rwanda UNAMIR II, 1993



Affected family

Push back

Triggers

Stigma

Smells

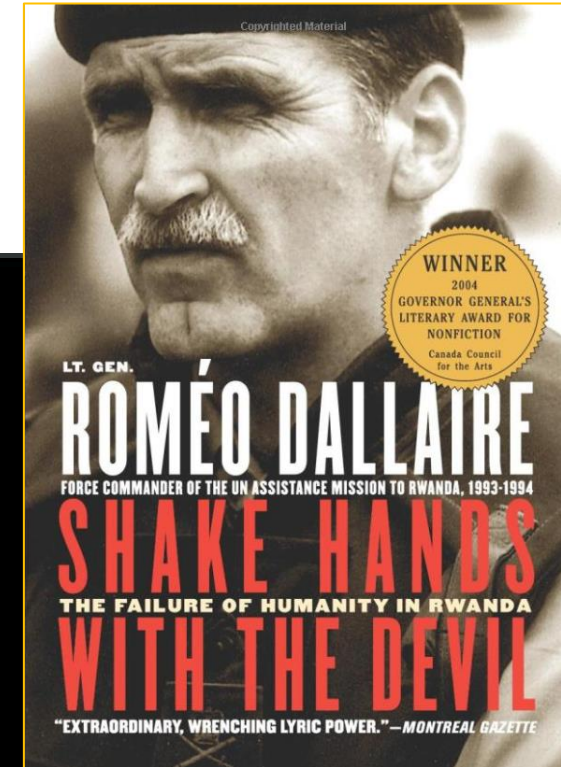
Food

Rusted vehicles

Little kids

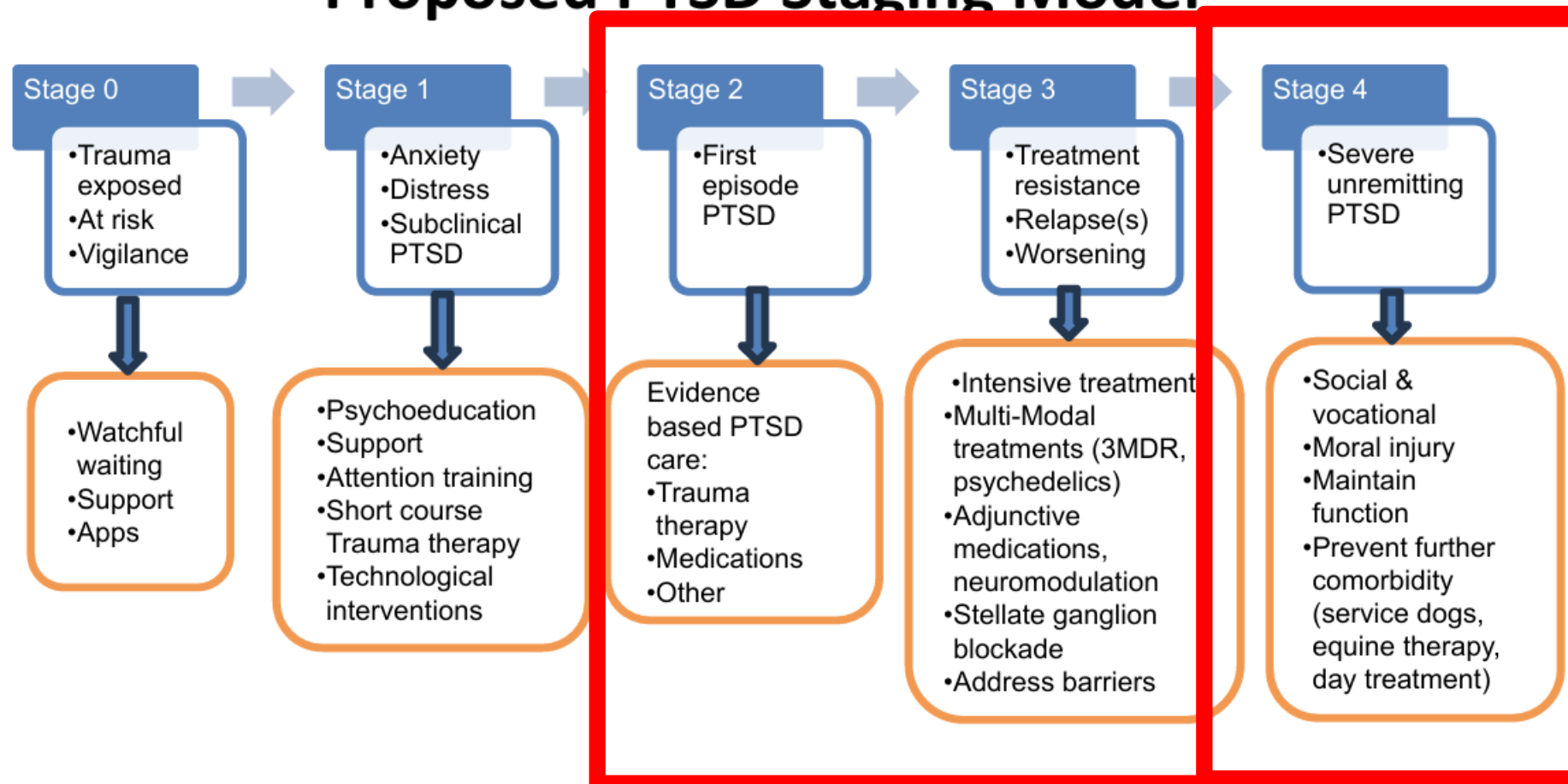
Therapy

*Loudness of
silence*





Proposed PTSD Staging Model



Mithoeffer model

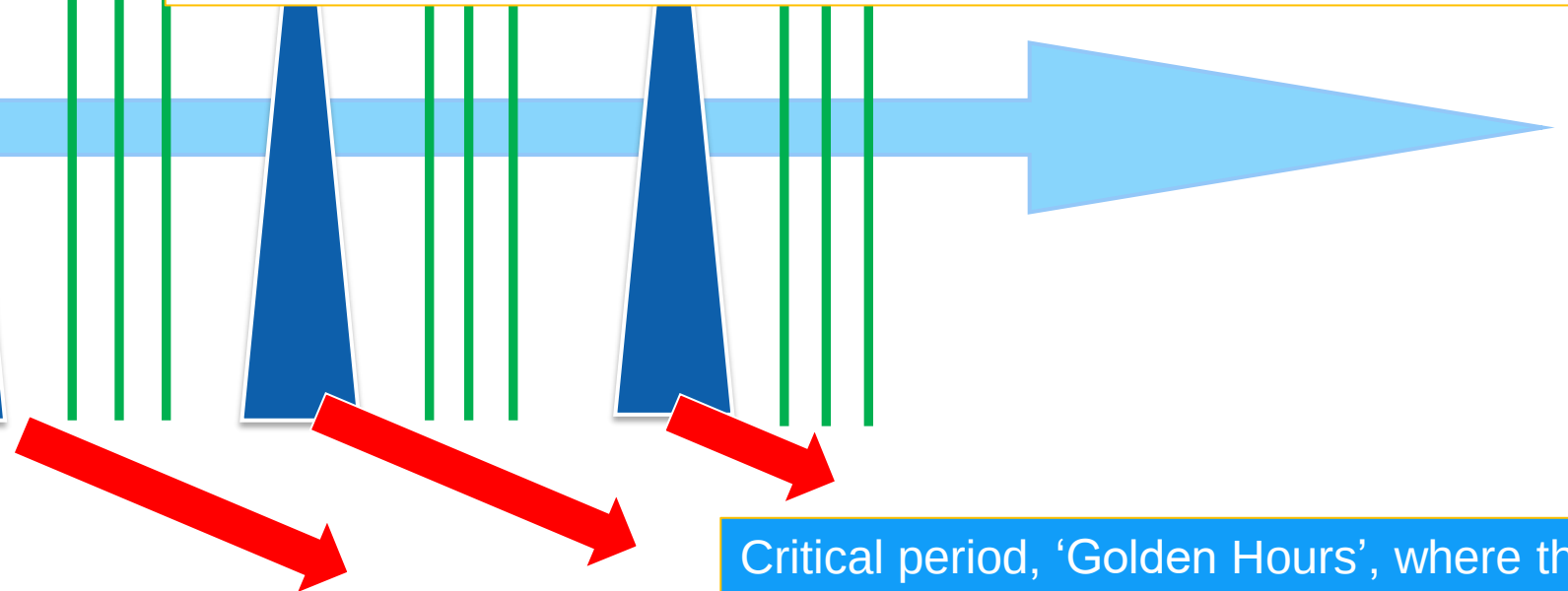
> Nature. 2019 May;569(7754):116-120. doi: 10.1038/s41586-019-1075-9. Epub 2019 Apr 3.

Oxytocin-dependent reopening of a social reward learning critical period with MDMA

Romain Nardou^{1 2 3}, Eastman M Lewis^{1 2 3}, Rebecca Rothhaas^{1 2 3}, Ran Xu^{4 5}, Aimei Yang^{4 5 6}, Edward Boyden^{4 5 6}, Gül Dölen^{7 8 9}

Affiliations + expand

PMID: 30944474 DOI: 10.1038/s41586-019-1075-9



Critical period, 'Golden Hours', where the brain is sensitive to reward value of (pro)social behaviors (Nardou, Nature, 2019)

MDMA assisted psychotherapy (courtesy Michael and Annie Mithoefer)

Marine Veteran
2 tours in Iraq as Humvee turret gunner
Middle of first MDMA session
75mg + 37.5mg



... peaceful about the fact that that's my journey



In subsequent sessions
he went on to process many more painful aspects
of fighting in Iraq



General factors

- Therapeutic alliance
- Empathy
- Goal consensus
- Positive intention
- ‘Mastery’
- Congruence/’genuineness’
- Mentalisation
- Emotional experience

Psychedelic specific factors

- Relational attachment
- Emotional range expanded
- Embodiment
- Revised life priorities
- Exaltic feeling of joy, bliss or love
- Ineffability
- Alteration to identity during experience
- *Bad trip experiences of transient psychological distress*

Several therapeutic orientations to MDMA assisted therapy

- | | |
|--|--|
| • Inner-directed psychotherapy | <i>MAPS, Mitthoefer</i> |
| • Internal Family Systems (IFS) | <i>Schwartz</i> |
| • Relational/psychodynamic | <i>Guss, Bennett and Vald</i> |
| • CBT | <i>Johnson</i> |
| • PE/EMDR | <i>Rothbaum, Foa</i> |
| • Motivational interviewing | <i>Meta Model - Bogenschutz</i> |
| • Acceptance and commitment therapy (ACT) | <i>Hexaflex Model - Sloshower and Guss</i> |
| • Psychomotor therapy | <i>Van der Kolk, Levine</i> |
| • Couples Therapy | <i>Wagner</i> |
| • Family Therapy | <i>Lalla</i> |
| • Transtheoretical Psychedelic Support | <i>Goldman and Nielson</i> |
| • Multi-theoretical Psychedelic Assisted Psychotherapy | <i>Belser and Brennan</i> |

Check for updates

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Perceived key change phenomena
of MDMA-assisted psychotherapy
for the treatment of severe PTSD:
an interpretative
phenomenological analysis of
clinical integration sessions

Macha Godes^{1*}, Jasper Lucas² and Eric Vermetten³

¹Institute of Psychology, Social Science Department, University of Amsterdam, Amsterdam,
Netherlands, ²Institute of Psychology, Social Science Department, Leiden University, Leiden,
Netherlands, ³Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands



Fictive name	Gender	Age	Ethnicity	Cause of PTSD	CAPS-5 baseline	CAPS-5 termination
Sophie	Female	25	White	Developmental trauma/multiple trauma	43	23
Isa	Female	43	White	Developmental trauma/multiple trauma	47	5
Rose	Female	23	White	Developmental trauma/multiple trauma	55	14
Jacky	Female	40	White	Developmental trauma/multiple trauma	38	5
Nick	Male	50	White	Veteran/combat exposure	41	13
Rico	Male	32	Asian	Veteran/combat exposure	53	13
Harry	Male	41	White	Developmental trauma	47	10

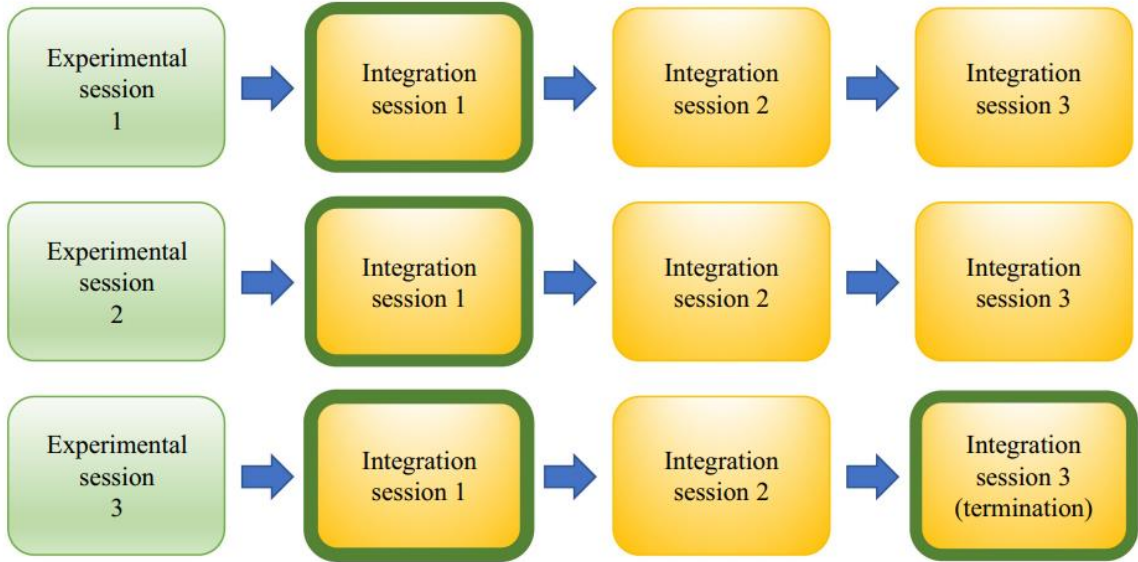


FIGURE 3
Selected integration sessions per participant for qualitative analysis (shown with green border).

Key change phenomena of MDMA-Assisted Psychotherapy for the treatment of severe PTSD



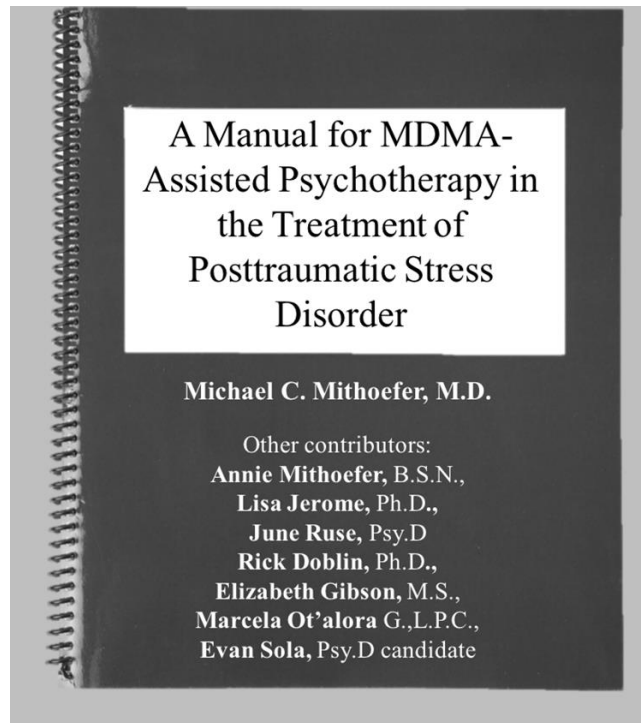
Interpretative Phenomenological Analysis - 2240 minutes of **videotaped integration sessions** - coded and analyzed (n=7).

All participants reported experiencing a range of benefits during the course and at the end of the treatment.

- 1. Tolerance of conflict:** staying with what 'is'
- 2. Processing trauma:** insight, reflecting, mental clarity, recovery of traumatic memories, disentangling trauma from self, reuniting lost parts
- 3. Positive emotions:** self-acceptance; joy, happiness, gratitude; hope and empowerment; relaxation, calmness, peace;
- 4. Interpersonal reflections:** comfort; gratitude, compassion, empathy
- 5. Felt Connection:** union, wider perspective; *inner healer intelligence*; accessibility to emotions, in contact with feelings; mind-body connection

When you say, 'the inner healer' I think that the medicine (MDMA) allows something within you to find that awaiting ability to express it, whatever that something is. So, there's definitely a almost esoteric sense to it, for lack of a better term, there's some kind of magic to that, of you getting in that spot and be like, "hey, remember this?" And it's not always a good thing. But it's there. It's being brought up for a reason. And that to me is like, whoa. Yeah, truly It really is. It's like a moment of like, Oh, yeah, there's this memory. That's there for a reason. What is it bringing me? What is it teaching me and why is it still prevalent? What does it mean?"

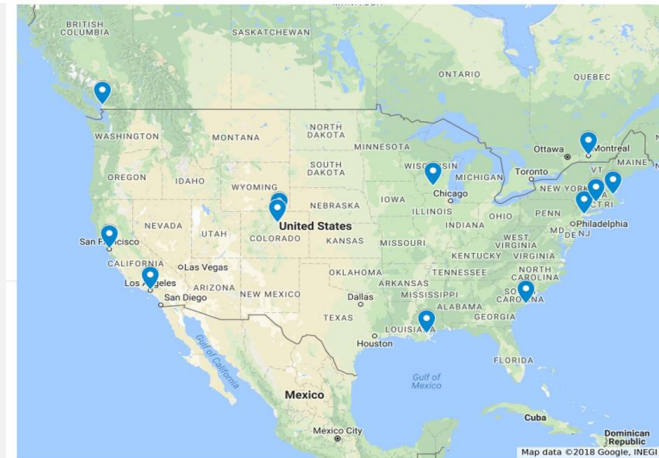
Adaptation of the foundation by Stanislav Grof, MD and others



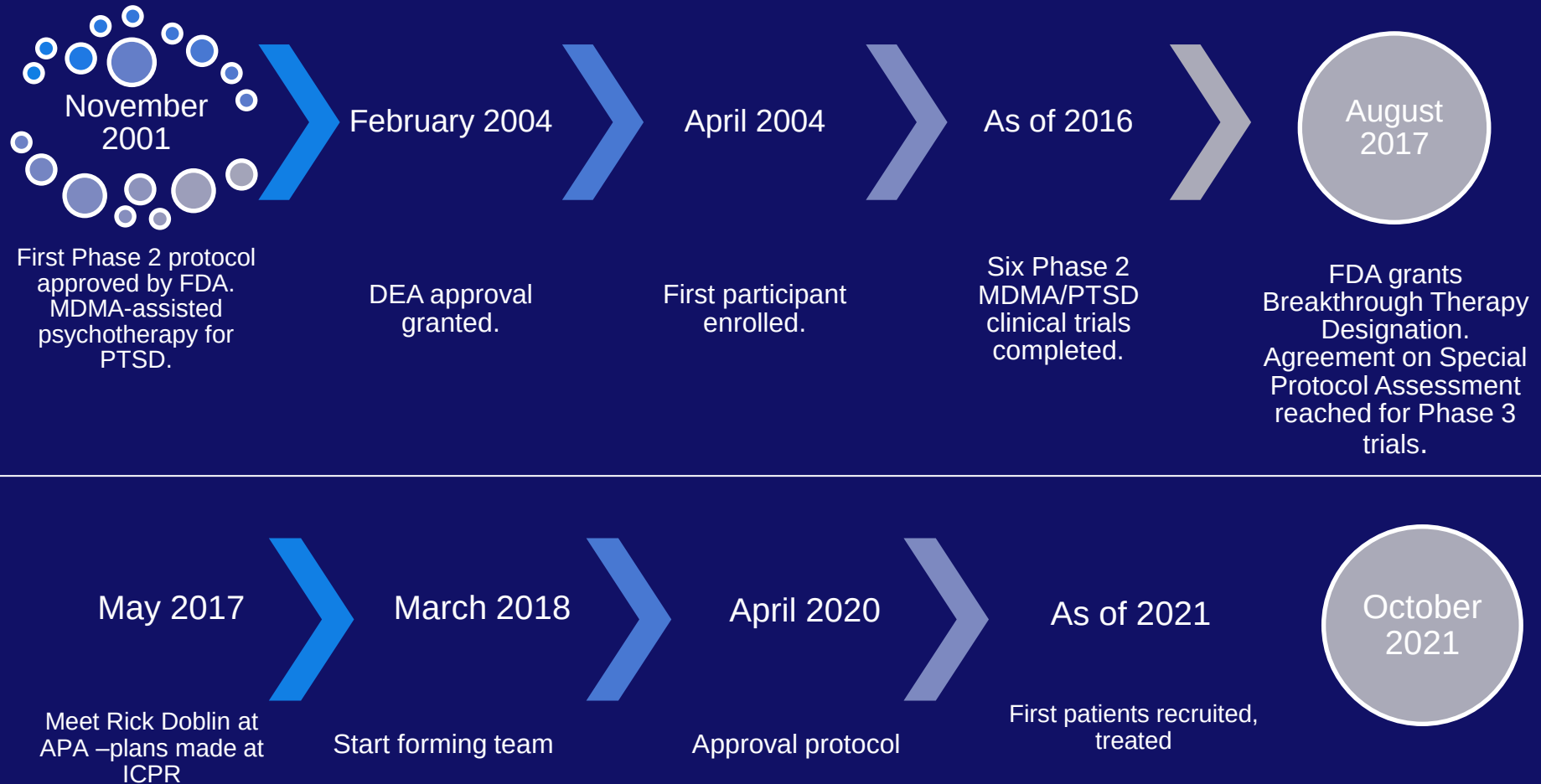
16 active sites in
North America

2 sites in Israel

Studies planned
in 7 European
Countries



MAPS and the Revival of Clinical Research to MDMA Assisted Psychotherapy in PTSD (2022)



LMC June 12, 2018 Scientific Advisory Board meeting: EMA in London



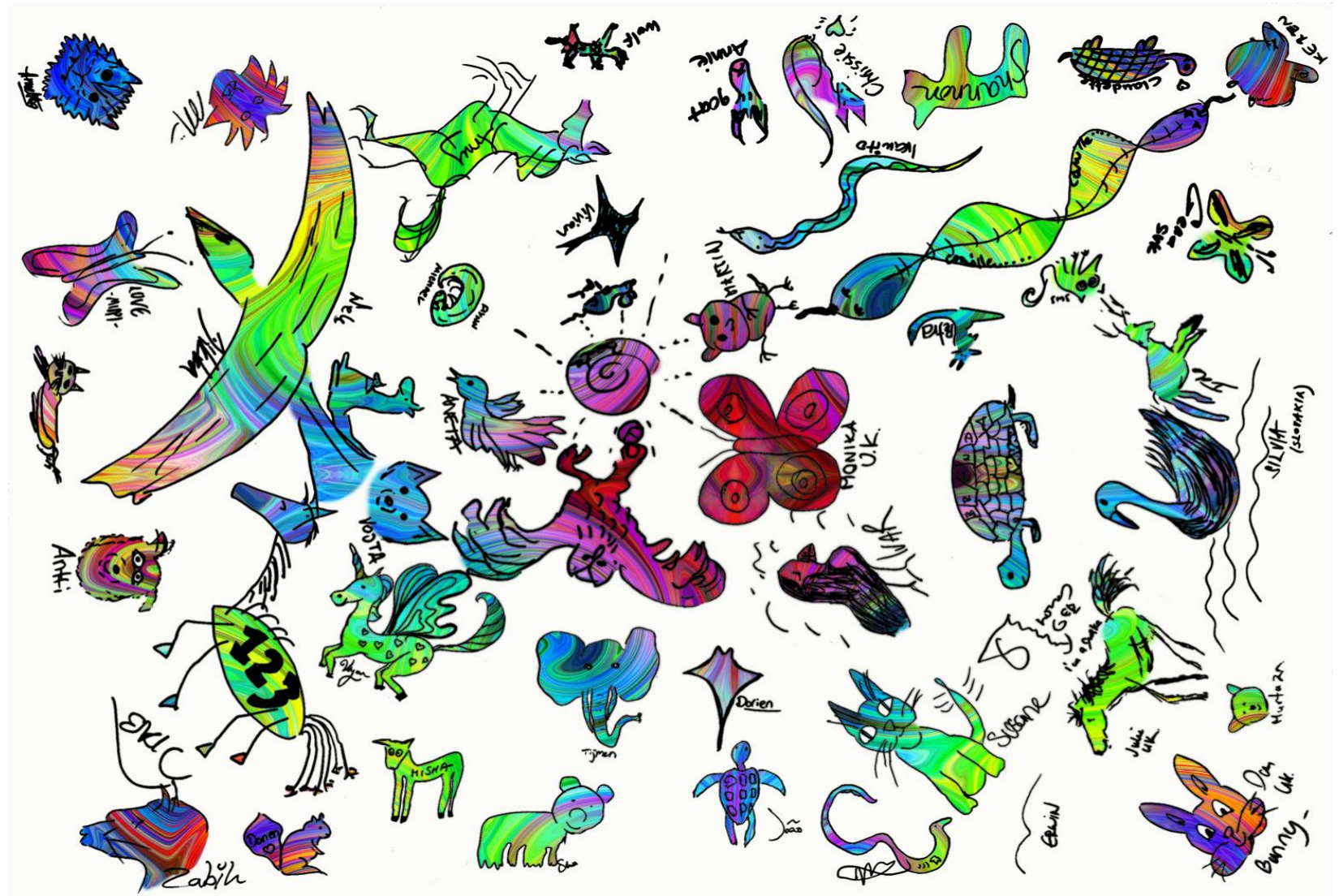
EMA agreed to accept
FDA data.

Required 1 pivotal 70-
person Phase 3 study.

Request we enroll
some refugees and
migrants.

MDMA assisted psychotherapy training, The European teams





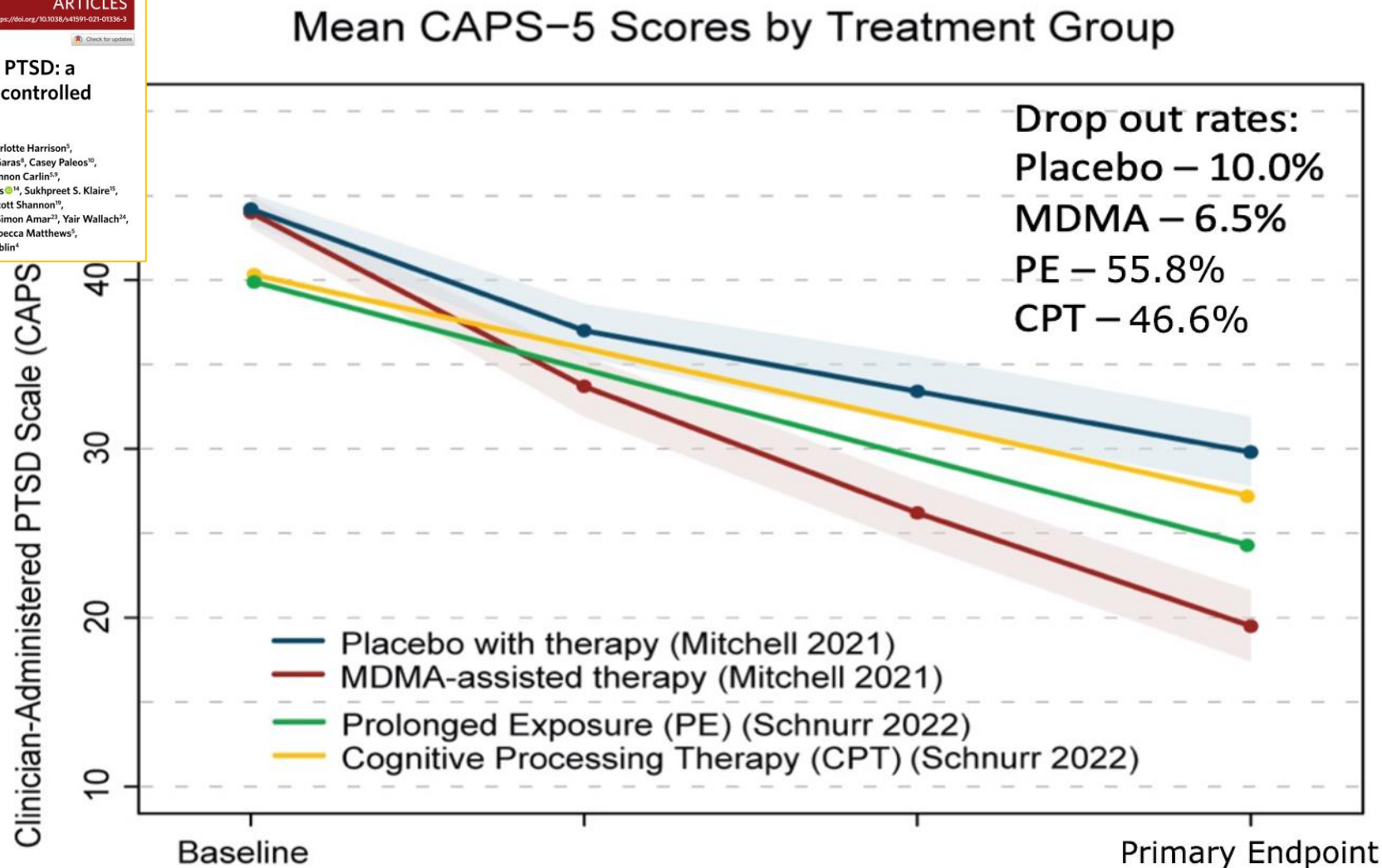
Results of first Phase 3 trial of MDMA-assisted therapy compared to a separate VA study of PE vs CPT

nature
medicine

ARTICLES
<https://doi.org/10.1038/s41591-021-01336-3>

OPEN
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell^{1,2,3,4}, Michael Bogenschutz², Alia Lilienstein⁴, Charlotte Harrison⁵, Sarah Kleiman⁶, Kelly Parker-Guilbert⁷, Marcela Ot'alora G.^{8,9}, Wael Garas⁸, Casey Paleos¹⁰, Ingmar Gorman¹¹, Christopher Nicholas¹², Michael Mithoefer^{5,13}, Shannon Carlin¹³, Bruce Poulter¹⁴, Ann Mithoefer⁵, Sylvestre Quevedo^{2,14}, Gregory Wells¹⁴, Sukhpreet S. Klaire¹⁵, Bessel van der Kolk¹⁶, Keren Tzarfaty⁵, Revital Amiaz¹⁷, Ray Worthy¹⁸, Scott Shannon¹⁹, Joshua D. Woolley², Cole Marta²⁰, Yevgeniy Gelfand²¹, Emma Hapke²², Simon Amar²³, Yair Wallach²⁴, Randall Brown¹³, Scott Hamilton²⁵, Julie B. Wang⁵, Allison Coker¹⁵, Rebecca Matthews⁵, Alberdina de Boer⁵, Berra Yazar-Klosinski⁴, Amy Emerson⁴ and Rick Doblin⁴

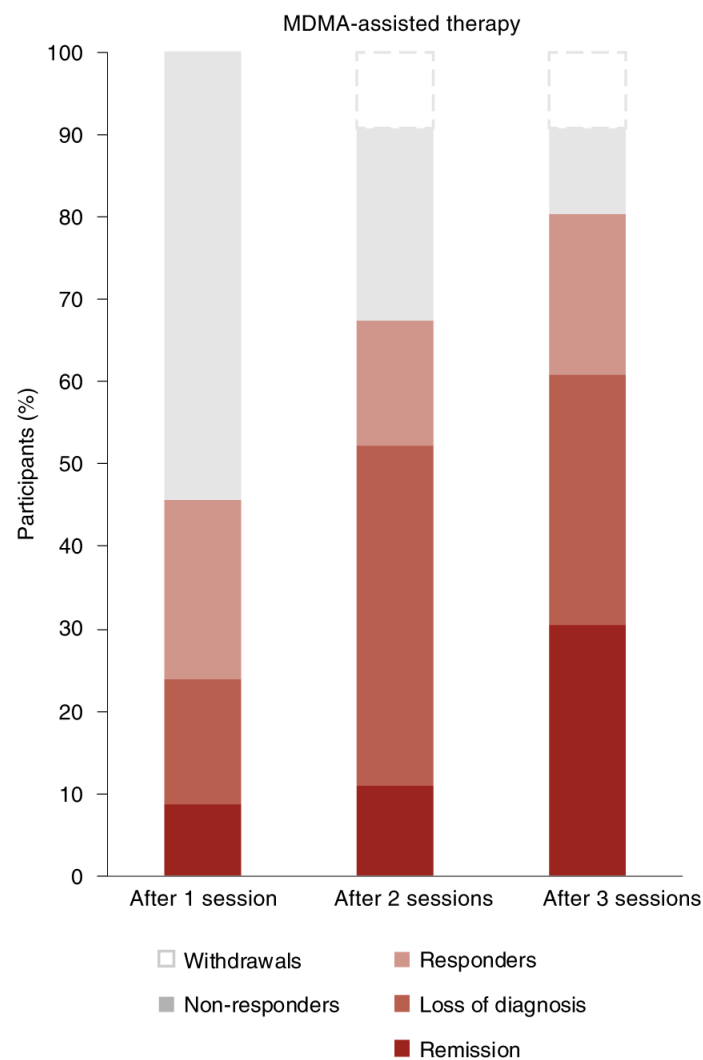
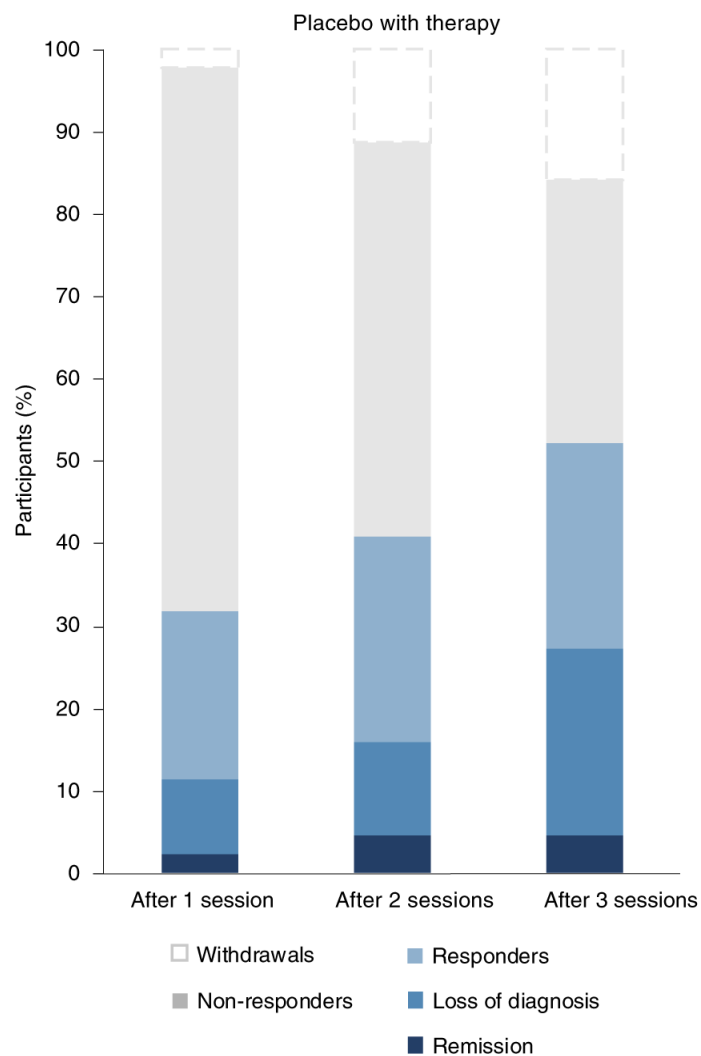


Mitchell JM, et al. *Nat Med*. 2021. 27(6):1025–1033.

Schnurr PP, et al. *JAMA Netw Open*. 2022. 5(1):e2136921

The above graph does not represent a head-to-head comparison of MDMA-assisted therapy to PE or CPT alone.

Treatment Response in Phase 3 Trial



Over 60% of patients in MDMA group had no diagnosis of van PTSD after treatment, compared to 35% in the placebo group, on primary end point.

MDMA was equally effective in patients with comorbid disorders

No effect of dissociative subtype

Consistent effect across 15 study sites

To date 33 studies have been published, showing very good outcome and high effect sizes

Primary Study	Type source/phase	Outcome ^{1°}	Clinical Resp (+/- %)	Loss of Diagn (+/- %)	Remission (+/- %)	Relapse (+/- %)	Change Scores (MDMA-Plac)	SMD, <i>d</i> or Hedges' <i>g</i>	Sample (n=)
Kisely et al., 2023	Meta-analysis ^{2, 3}	CAPS	-	-	-	-	-	-0.86 ^{*****}	82:54
Smith et al., 2022	Meta-analysis ^{2, 3}	CAPS	3.65 (RR)	2.10 (RR)	-	-	-22.03 ^{**}		101:62
Mitchell et al., 2021	RCT ³	CAPS	-	67 vs 32	33 vs 5	-	-11.9 ^{****}	0.91 ^{****}	46:43
Mithoefer et al., 2019	P-DS ^{RCT2}	CAPS	-	54 vs 23	-	-	-22.0 ^{****}	0.8 ^{****}	72:31
Jerome et al., 2020	P-DS LTFU ^{RCT2}	CAPS	82 ^{TE} vsB, 26 ^{LTFU} vsTE	56 ^{TE} , 67 ^{LTFU}	-	12	-50.6 ^{****B} , -5.2 ^{*TE}	0.23 ^{*LTFU} vsTE	91
Ot'alora et al., 2018	RCT ²	CAPS	50, 56 vs 17 ^{ITT}	42, 44 vs 33	-	-	-33.0 [*] , -20.4 ^{PP}	1.12 [*] , 0.73	9:9:5
Mithoefer et al., 2018	RCT ²	CAPS	67, 100 vs 29	58, 86 vs 29	-	-	-32.9 ^{**} , -46.9 ^{***}	1.1 ^{**} , 2.8 ^{***}	12:7:7
Oehen et al., 2013	RCT ²	CAPS	50 vs 0, 100 ^{OLC}	0 vs 0, 50 ^{OLC}	-	-	-18.8		8:4
Mithoefer et al., 2011	RCT ^{p2}	CAPS	83 vs 25; 100 ^{OLC}	83 vs 25	-	-	-33.2 [*]	1.24 ^{??*}	12:8
Mithoefer et al., 2013	LTFU ^{RCT2}	CAPS	74 ^{ITT}	-	-	13 ^{COMPL}	-0.9 ^{LTFU} vsTE		16
Bouso et al., 2008	RCT ^p	SSSPTSD	-	-	-	-	-11.5, -4.5		1:3:2
Wang et al., 2021	P-DS ^{SGA2}	CAPS	92 ^{****}	76 ^{***}	-	-	-29.89 ^{****}	2.2 ^{****}	36
NCT01458327	SGA	CAPS	-	-	-	-	-62.0 ^{2m} , -40.7 ^{LTFU}		3
Monson et al., 2020	SGA ^{p1,2}	CAPS	-	83	-	-	-4.64 ^{Beta} ***	1.88-2.25 ^{****}	6 ^{pat}
Jardim et al., 2021	SGA ^p	CAPS	100	-	-	-	-48	0.92 ^r	3
Ancillary Quant									(n=)
Lewis et al., 2023	RCT3	METHYL	-	-	-	-	41.88 ^{Beta} **	-	16:7
V. d. Kolk et al., 2023	RCT3	S-EXP ^{batt}	-	-	-	-	various ^{****}	-	42:40
Nicholas et al., 2022	RCT3	AUDIT	-	-	-	-	-1.42 ^{*n.s.} afterBadj	0.45 ^{*n.s.} afterBadj	42:40
Brewerton et al., 2022	RCT3	EAT-26	-	-	-	-	-2.36	0.33 [*]	42:40
Ching et al., 2022	P-DS ^{mixed2,3}	CAPS	-	65, 71 vs 29, 26	-	-	-13.93 ^{***Madj} ,subgr	1.08 ^{***adj} ,subgr	83:44
Feduccia et al., 2021	P-DS ^{RCT2}	CAPS	-	64 ^{n-taper} vs 25 ^{taper*}	-	-	-18.5	-	33:16
Feduccia et al., 2019	P-DS ^{RCT2}	CAPS	-	53 vs -	-	-	-19.1 ^{par} , -19.1 ^{sertr}	-	38:14
Ponte et al., 2021	P-DS ^{RCT2}	PSQI	53 vs 13 ^{**}	-	-	-	-4.09 ^{**}	-	45:16
Gorman et al., 2020	P-DS ^{RCT2}	PTGI	-	-	-	-	26.2 ^{***}	1.14 ^{***}	41:14
Singleton et al., 2023	RCT2	fMRI	-	-	-	-	+RSFC ^{amy-hipp} *unc	-	9
Wagner et al., 2017	RCT2	NEO-PI-R	-	-	-	-	6.29 ^{Openness}	-	12:8
Christie et al., 2022	SGA2	CPGS	-	-	-	-	-GPGS ^{*High} subgr	-	32
Wagner et al., 2021	SGAp1,2	GR, RE ^{batt}	-	-	-	-	various ^{***}	see publication	6 ^{pat} :6 ^{part}
Ancillary Qual									(n=)
Barone et al., 2019	RCT2	M-Case	IPA						19
Godes et al., 2023	P-DS ^{SGA2}	M-Case	IPA						7
Wagner et al., 2019	SGAp1,2	Case	Narrative						2
Ching et al., 2022	SGA2	Case	IPA						1
Brewerton et al., 2021	RCT2	Vignette	Narrative						1

Table 2. Included studies (n=33) using MDMA for PTSD. Means at primary endpoint unless stated otherwise. * = $p < .05$; ** = $p < .01$; *** = $p < .001$; **** = $p < .0001$; ***** = $p < .00001$. n = MDMA:control. P-DS = Pooled-data study; SGA = Single group assignment; B = Baseline; TE = Treatment Exit; PE = Primary endpoint; OLC = Open-label crossover; ITT = Intent-to-treat set; PP = Per Protocol set; COMPL = Completers. Long-term follow-up uncontrolled due to cross-over design. Gray shading = Number(s) not explicitly stated in the original publication, but calculated with numbers that were reported. The reader is recommended to only copy numbers from the original publications.

Dutch State Committee on MDMA and Health



Prof dr mr Brigit Toebes, chair
Prof dr em Wim van den Brink
Vice chair

Members:
Dr Emile Kolhoff
Femke Gresnigt
Martha de Jonge
Prof dr Eric Vermetten

Secretary:
Ward de Cock
Philippus Zandstra

And students!

June 6, 2024 State Committee Report handed to Minister of Health – the Netherlands

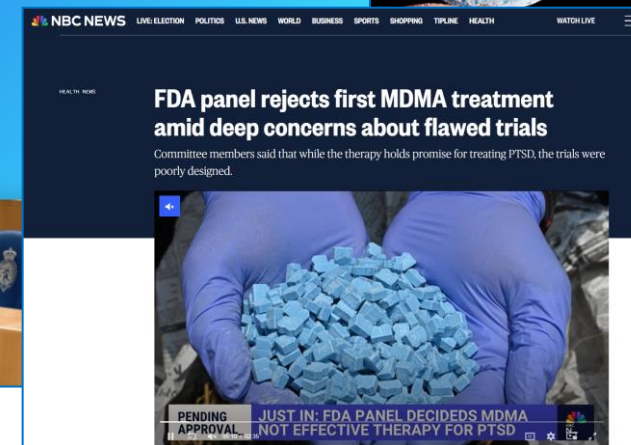
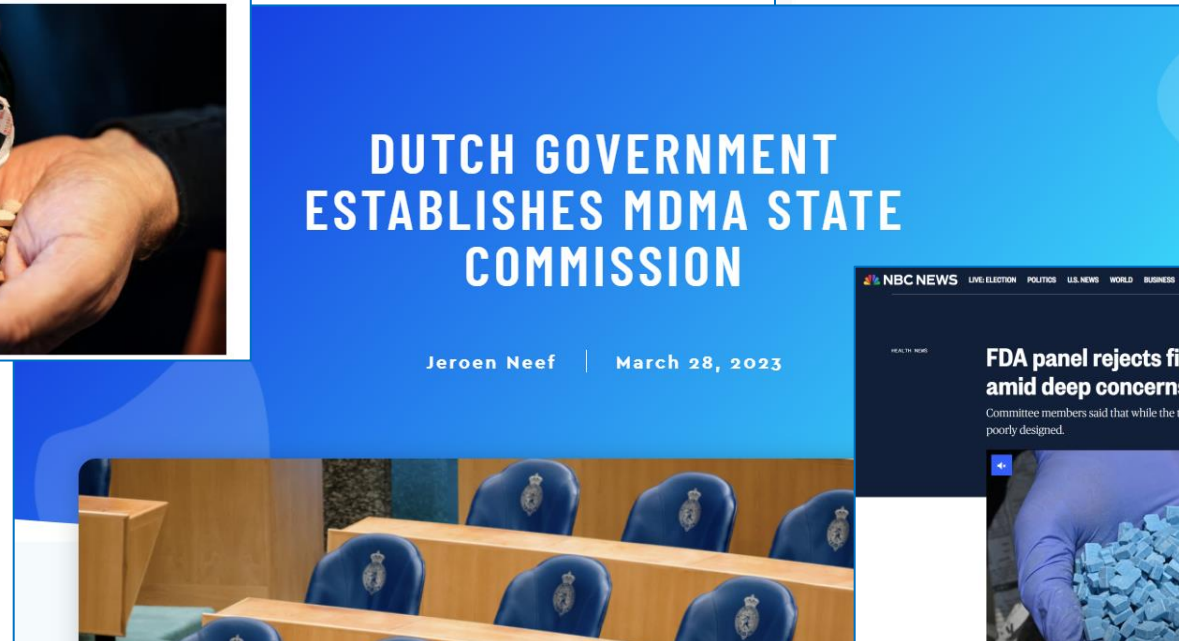
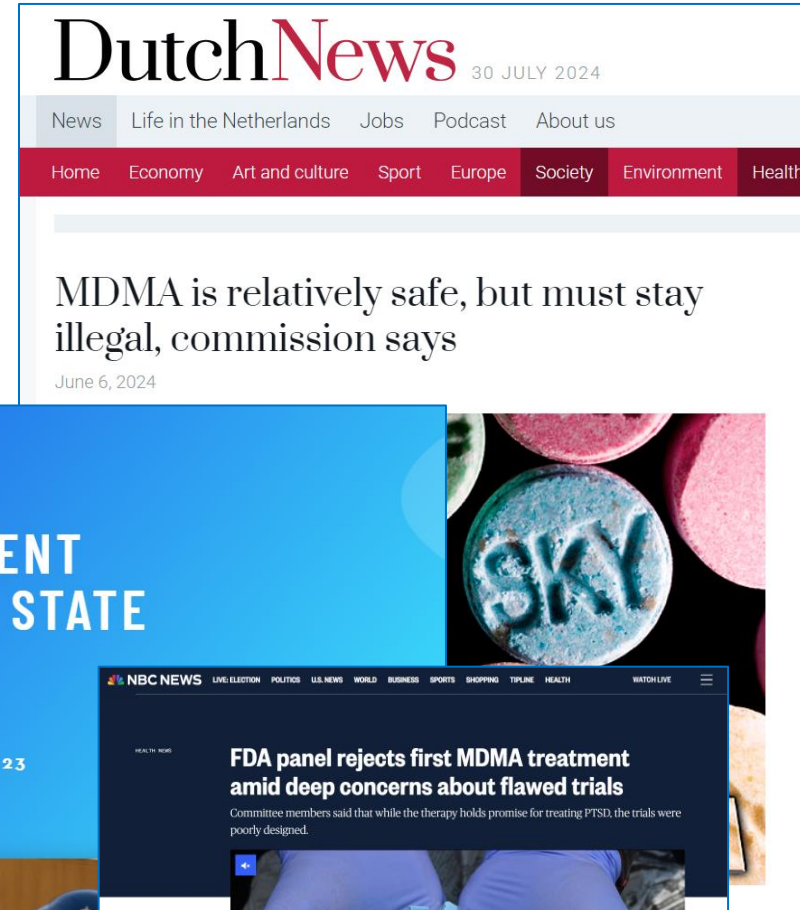


Make MDMA-AT for PTSD
possible ASAP

Naturalistic research –
preferably with EU
partners

Negotiation with national
IRBs/EMA on enrollment
and *real world* data

June 4 and June 6



Regarding the clinical use of MDMA, the committee concluded that:

1. MDMA-Assisted Therapy (MDMA-AT) seems to be an effective and safe treatment for chronic and treatment-resistant patients with PTSD.
2. There is not sufficient evidence for conclusions about efficacy of MDMA-AT in other psychiatric or neurological disorders, but the committee is aware that with time, a wider application of MDMA-AT might become relevant.
3. With approximately 400.000 people suffering from PTSD and less than 25% of them receiving evidence-based trauma-treatment, there is a serious unmet need for PTSD treatment. The Dutch government should facilitate the introduction and use of MDMA-AT for these people as soon as possible.
4. It is unlikely that a registration dossier for MDMA-AT will be submitted (any time soon) to the European Medicines Agency (EMA) or the Netherlands Medicines Evaluation Board (MEB) to obtain marketing authorisation in the EU or the Netherlands.
5. Potential alternatives such as off-label use, compassionate use, and extended access to MDMA-AT are not possible or not feasible. Therefore, the committee proposes to start a large naturalistic study that prospectively monitors PTSD patients receiving MDMA-AT as soon as possible.
6. MDMA-AT should only be provided by qualified therapists working in specialized treatment settings.
7. Initially there will be a shortage of trained therapists and specialized treatment settings. The committee is concerned that this may cause registered therapists to help patients outside the context of these specialized settings and that commercial providers may offer MDMA as a quick solution for mental trauma-related distress. To prevent unnecessary damage, professional organizations of psychiatrists and psychologist should provide clear ethical and judicial guidance to their members and a hotline/helpline should be installed to assisted people with negative experiences outside the regular specialized treatment settings.
8. The Ministry of Health, professional organizations and treatment providers should be realistic in their communication to the public and the patients about the successes and potential adverse effects of MDMA-AT in PTSD.



A second chance to psychedelics



European Medicines Agency

The mission of EMA is to foster scientific excellence in the evaluation and supervision of medicines in the EU.

Published Mar 16, 2023

+ Follow

There is a lot of stigma around psychedelics like LSD, MDMA (as in ecstasy) and psilocybin (a naturally occurring compound found in "magic mushrooms"), as they are often associated to harmful behaviour and abuse. Their use was restricted in 1971, when they were added to the United Nation's Convention of Psychotropic Substances **as drugs claimed to create a serious risk to public health**, with no

Others also viewed



Community is needed to prevent suicide

Shaun Foley · 11mo



Treating youth with drug use disorders: can you know how it's going to go?

Morten Hesse · 2w



URL Masking with IP Obfuscation

Daniel Jordão · 2y



ATMP workshop at EU Parliament planned for 22Mar23

Pierre Mermet-Bouvier · 3d



Silicon Valley lessons for investors

Tatiana Indina · 2d



Our 2022 results: looking back on a remarkable year

Flemming Ornskov, MD, MPH · 6d



10 Most Popular Tech Scouting Questions Answered

Ludwig Melik · 6mo



Welcome to our very first newsletter!

NDA Group AB · 3d

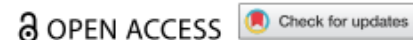


Poster by David Parker

**MDMA is GOLD,
but not a magic bullet**



SHORT COMMUNICATION



Expert opinions on implementation of MDMA-assisted therapy in Europe: critical appraisal towards training, clinical practice, and regulation

Jerome Herpers ^{a,b}, Natalie Maximets ^c, Noah N. N. van Dongen ^d, Josjan Zijlmans ^{e,f} and Eric Vermetten ^g

^aGGZ Oost Brabant, Boekel, The Netherlands; ^bUw Psychiater, Zwolle, The Netherlands; ^cDepartment of Clinical, Neuro- and Developmental Psychology, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ^dDepartment of Psychology, University of Amsterdam, Amsterdam, The Netherlands; ^eDepartment of Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam University Medical Center, Amsterdam, The Netherlands; ^fAmsterdam Public Health, Amsterdam University Medical Center, Mental Health, Amsterdam, The Netherlands; ^gDepartment of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

Introduction: The positive results of MDMA from Phase 2 and 3 clinical trials in MDMA-assisted therapy (MDMA-AT) for the treatment of post-traumatic stress disorder (PTSD) call for a critical evaluation of its regulatory status within the European mental healthcare system. This is driven by the recent submission of MDMA-AT for FDA approval in the United States. Unless coordinated efforts in the European regulatory landscape start, there may be potential divergences in national regulatory strategies. Gaining insights from researchers and clinicians involved in the application of MDMA-AT may be useful in guiding the discussion of factors involved in its implementation.

Method: A comprehensive invitation-only survey was sent to researchers and clinicians involved in MDMA-AT clinical trials and contributors to the scientific literature on MDMA-AT from around the globe. This study aimed to collect opinions on clinical practices, training, and regulation worldwide, examining the global best practices and pitfalls to outline strategies for possible European implementation of MDMA-AT.

Results: The survey, which included responses from 68 experts, yielded a range of opinions where a large majority endorsed the need for training and standardization, emphasizing equity and access, stressing impediments in the national approval processes, and reflecting critically on anticipated spill-over effects of MDMA-AT in clinical settings.

Conclusion: The experts highlight the need for science-informed policy development, active regulatory involvement, and international cooperation to incorporate MDMA-AT into the European mental healthcare system in general and the treatment of PTSD in particular. The study emphasizes the importance of ongoing research, open professional discourse, and collaborative engagement to facilitate MDMA-AT's ethical and effective implementation.

ARTICLE HISTORY

Received 18 March 2024
Revised 1 July 2024
Accepted 2 July 2024

KEYWORDS

MDMA; PTSD; policy; regulation; research

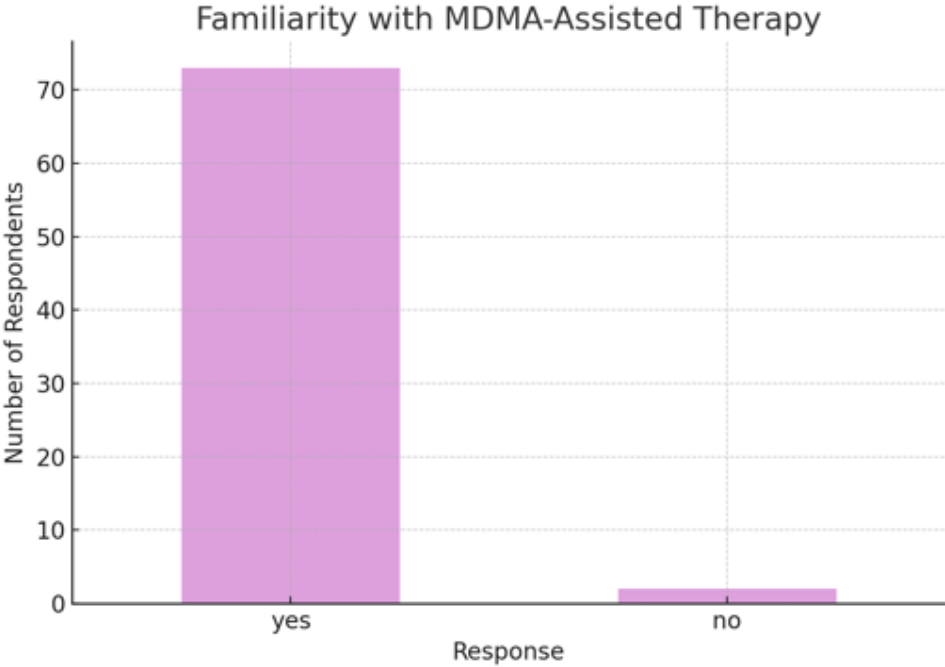
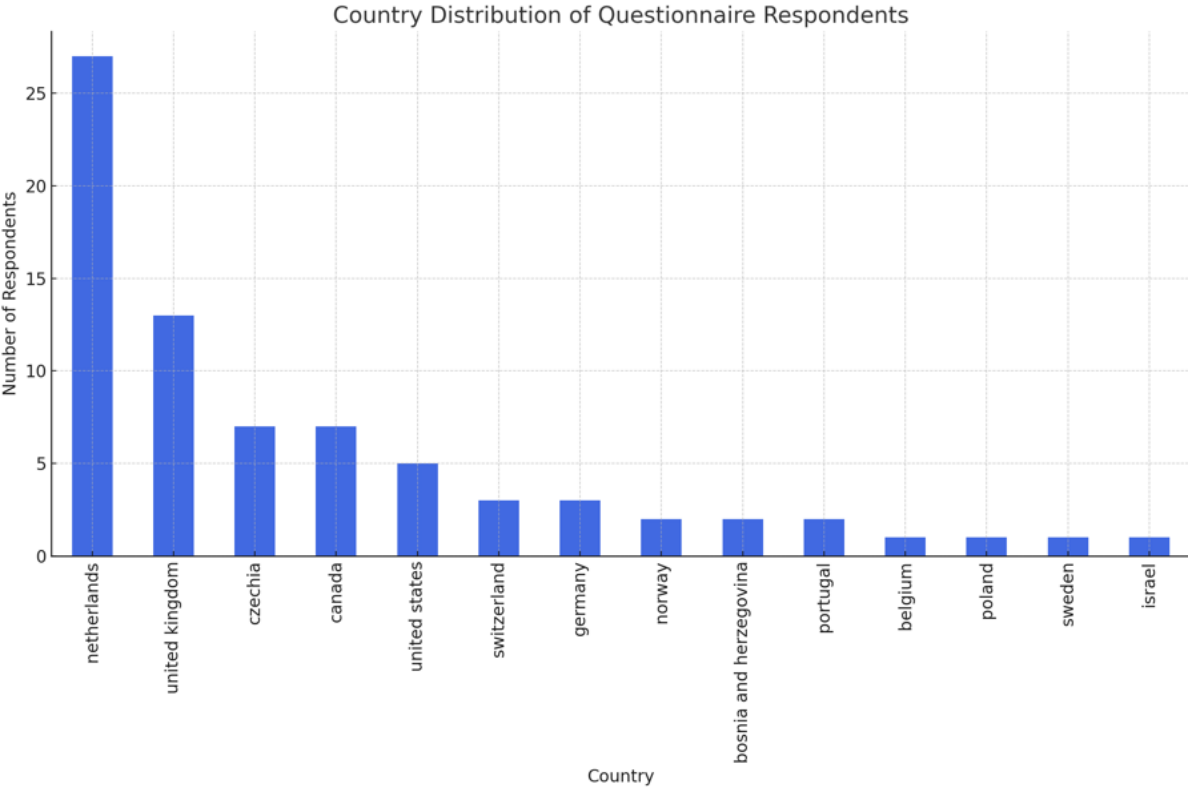
PALABRAS CLAVE

Terapia asistida por MDMA; MDMA; TEPT; política; regulación; investigación

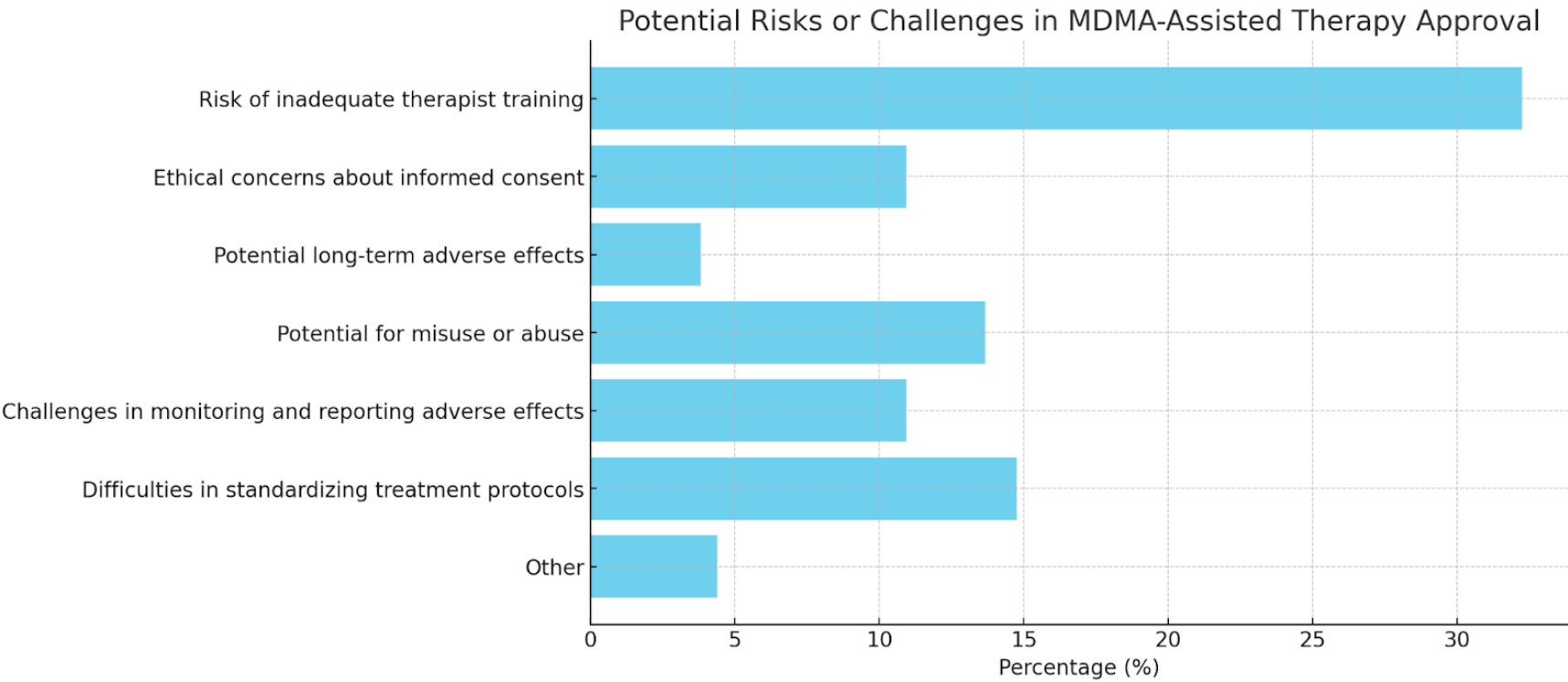
HIGHLIGHTS

- Positive clinical trials of therapy using MDMA for treating post-traumatic stress disorder (PTSD) call for a thorough review of its regulatory status in Europe, especially following its submission for approval in the United States.
- A global survey of 68

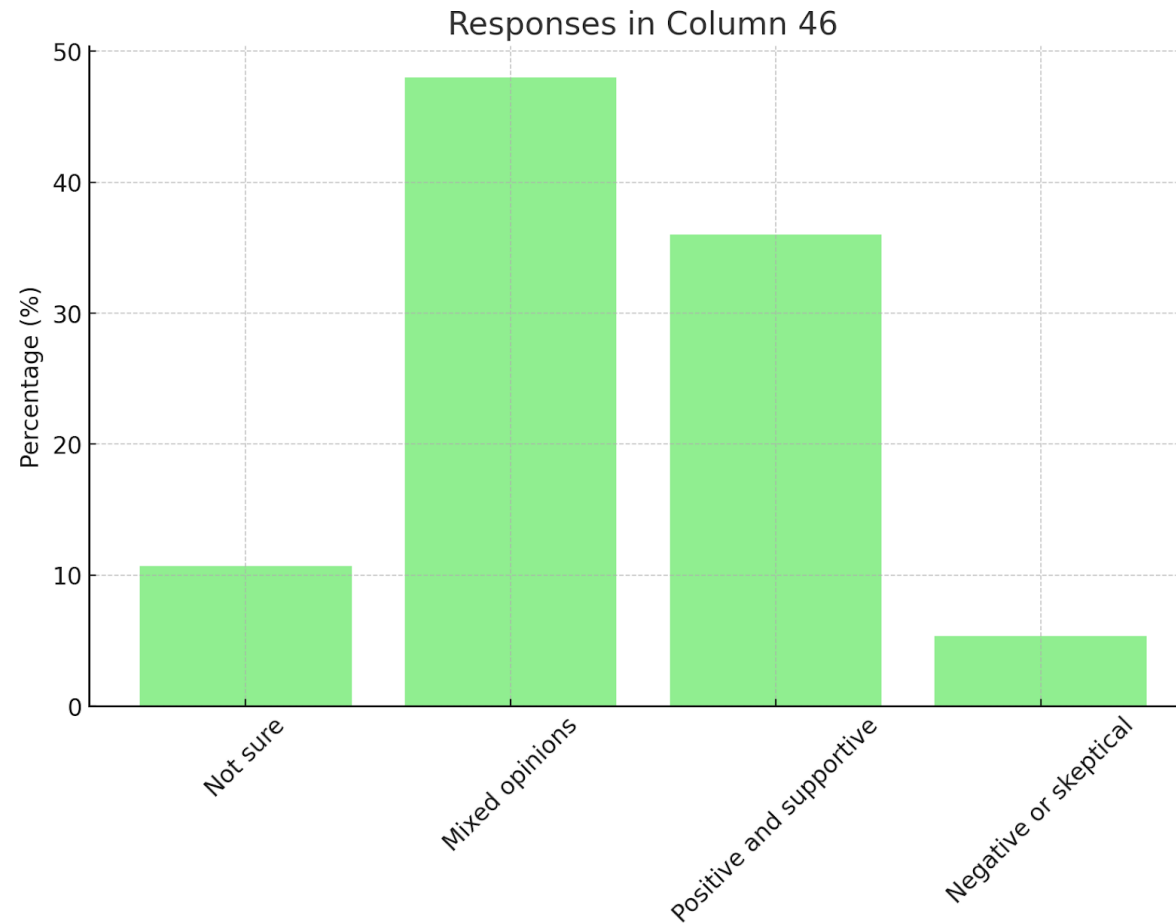
International Survey on MDMA-AT regulation (n=78)



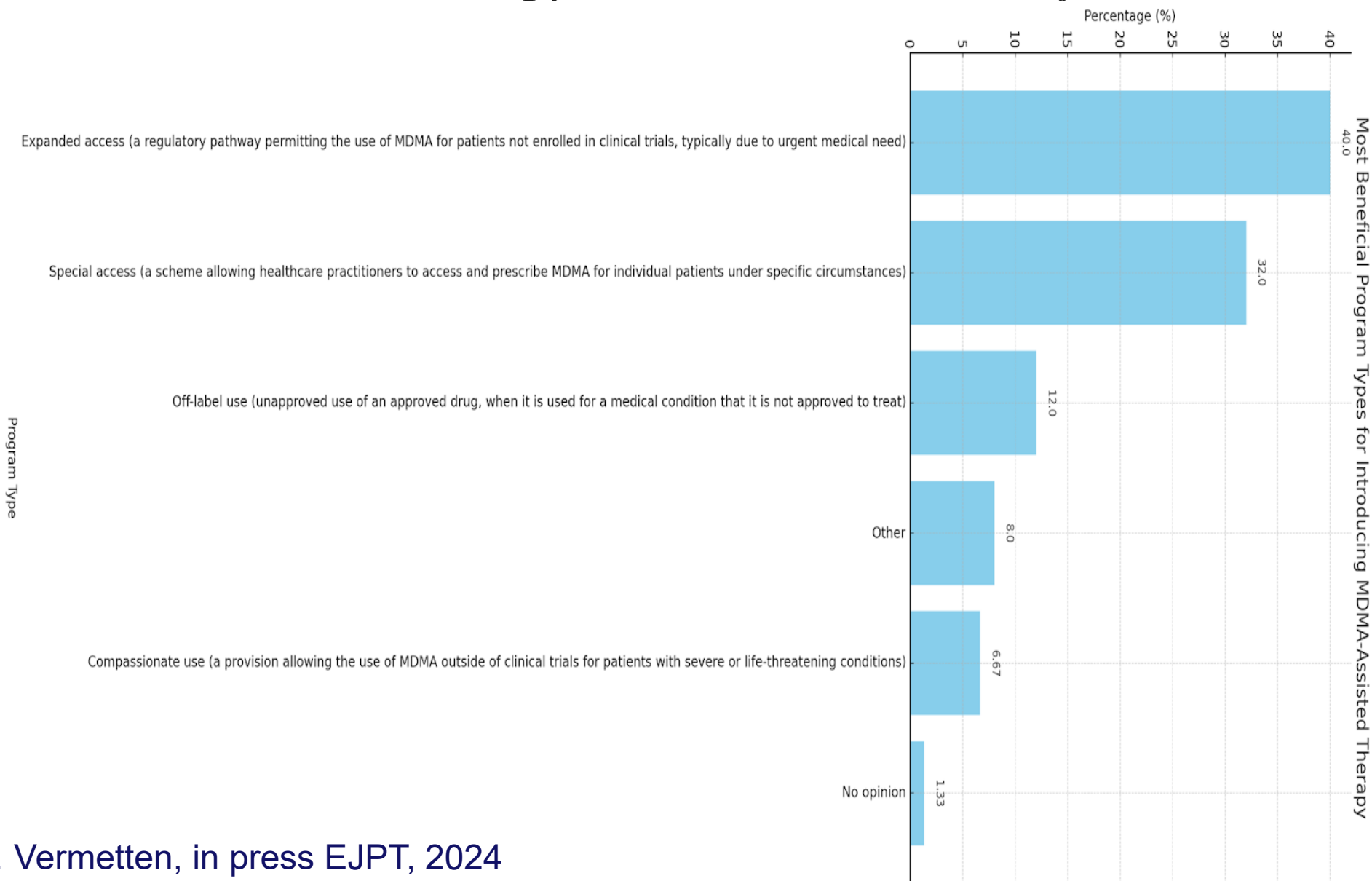
What potential risks or challenges do you foresee if MDMA-assisted therapy is approved? (Select all that apply)



How does the public perceive MDMA-assisted therapy in your country?



Which type of program would be most beneficial for introducing MDMA-assisted therapy in a controlled and safe manner?



Recommendations from focus groups of experts in MH:

- **Engage with Regulatory Bodies -** establishment of a clear regulatory pathway for approval with FDA and EMA.
- **Expand Training and Education** .. of healthcare professionals, gaining endorsement from key professional national organizations.
- **Promote International Collaboration -** build a broad base of support and shared knowledge.
- **Support Compassionate Use Programs -** pave the way for broader acceptance and regulatory approval.
- **Research on MDMA for Other Conditions** **obtaining real-world data** - more relaxed research environments that could facilitate therapy and data collection.
- **Build Public and Professional Support** for MDMA - AT - educational campaigns to dispel myths, share successful treatment outcomes, and build a strong base of advocates.
- **Address Ethical Considerations -** including patient consent, management of expectations.
- **Foster a Multi-Level Approach in Europe** that involves the EMA, European Commission, member states, and the dynamics within the European Parliament to harmonize the approach towards psychedelic therapy, in particular MDMA–AT for PTSD across Europe.

August 11



Poster by David Parker

Conditional approval?
ADComm: puritive recalibration?

*Metacognitive shifts –
recalibration/meaning making*

AT - training?

Europe?

– moral imperative -

June – August 2024

June 2024, the U.S. Food and Drug Administration's (FDA) Advisory Committee evaluated the approval of MDMA-assisted therapy (MDMA-AT) for treating post-traumatic stress disorder (PTSD).

-- The committee voted 9 to 2 against the therapy's efficacy and 10 to 1 against its safety, expressing concerns over trial design, potential bias, and cardiovascular risks associated with MDMA.

August 2024, the FDA declined approval, requesting additional Phase 3 trials to address these issues.

-- Significant setback for proponents of psychedelic therapies and delayed the potential introduction of the first new FDA-approved PTSD treatment in over two decades.



The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same.

Psilocybin and MDMA are poised to be the next big therapeutics since Prozac. Universities want to do what Wall Street does. Some worry a push to loosen regulations could bring unintended consequences.

FORUM – PSYCHIATRIC PRACTICE AND RESEARCH: THE VALUE OF INCREMENTAL AND INTEGRATIVE ADVANCES

Psychiatric diagnosis and treatment in the 21st century: paradigm shifts versus incremental integration

Dan J. Stein¹, Steven J. Shoptaw², Daniel V. Vigo³, Crick Lund⁴, Pim Cuijpers⁵, Jason Bantjes⁶, Norman Sartorius⁷, Mario Maj⁸

¹South African Medical Research Council Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, University of Cape Town, Cape Town, South Africa; ²Division of Family Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; ³Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada; ⁴Centre for Global Mental Health, Health Service and Population Research Department, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; ⁵Department of Clinical, Neuro and Developmental Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands; ⁶Alcohol, Tobacco and Other Drug Research Unit, South African Medical Research Council, Cape Town, South Africa; ⁷Association for the Improvement of Mental Health Programmes, Geneva, Switzerland; ⁸Department of Psychiatry, University of Campania "L. Vanvitelli", Naples, Italy

Stein et al., World Psychiatry, 2022



The BMJ

Cite this as: *BMJ* 2024;386:q1798

<http://dx.doi.org/10.1136/bmj.q1798>

Published: 13 August 2024

MDMA assisted therapy: Three papers are retracted as FDA rejects PTSD application

Elisabeth Mahase

Three research papers on MDMA assisted psychotherapy have been retracted by the journal *Psychopharmacology* because of “protocol violations amounting to unethical conduct” by researchers at a study site.

In the retraction notices the journal said that the authors were aware of the violations when they submitted the articles but failed to disclose them or remove the affected data from their analysis.¹⁻³ All three papers related to phase 2 randomised controlled trials for MDMA assisted therapy, with similar authors listed for all three papers.

Although the notices did not detail what the violations were, reports suggest that a trial investigator at one of the study sites engaged in an unethical sexual relationship with one of the trial participants.^{4,5} In a 2018 lawsuit that was settled out

regulatory approval for midomafetamine [MDMA] capsules.”

Lykos Therapeutics’ chief executive officer, Amy Emerson, who sits on the MAPS board of directors, said, “While conducting another phase 3 study would take several years, we still maintain that many of the requests that had been previously discussed with the FDA and raised at the Advisory Committee meeting can be addressed with existing data, post-approval requirements, or through reference to the scientific literature.”

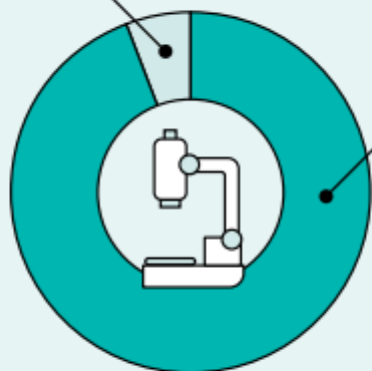
Emerson was listed as an author on two of the papers retracted by *Psychopharmacology*.

Reports show that the MDMA research presented in the three retracted papers did not form part of the company’s FDA application.

Dutch Perspective

Knowledge of the illegal ecstasy market through the Drugs Information and Monitoring System (DIMS)

5,6% contained no MDMA*



94,4% contained (a.o.) MDMA



*some samples contained caffeine, amphetamine or other drugs



"Moving MDMA to Schedule II means that less investigation capacity will be available to tackle and prosecute criminal organisations."



"If MDMA is moved to Schedule II, recreational users may potentially face less stigmatisation. The use of MDMA in mental health treatment may also raise fewer concerns."

Speed

MDMA

Crystal meth

Combination

(crystal methamphetamine)

(possibly MDMA)

10
0

2021

2022

2023



I. Self-medication



Users

People experiencing mental health complaints or pursuing personal growth



Substance Ecstasy



Location

At home or at social venues



Provider

Licensed therapist



Users

Individuals with psychological complaints



Substance MDMA



Location

Healthcare facility

II. Registered therapists acting ahead of regulation



Provider Commercial entity



Users

People experiencing mental health complaints or pursuing personal growth



Substance MDMA analogue, ecstasy, or truffles



Location

Business premises or on retreats

III. The grey economy: commercial parties

Home › Actualiteit › Artikelen › Onderzoek naar therapeutische toepassingen van psychedelica

Onderzoek naar therapeutische toepassingen van psychedelica

september 2024



Psychedelische middelen als ketamine, MDMA of psilocybine inzetten voor de behandeling van mensen met ernstige psychiatrische aandoeningen?

Dat is lang taboe geweest, maar binnen ZonMw wordt, in opdracht van het ministerie van VWS, verkend hoe subsidie voor onderzoek naar de toepassing van psychedelica in combinatie met psychotherapie effectief ingezet kan worden.

Onderwerpen

- Geneesmiddelen
- Mentale gezondheid
- Psychische klachten

Gerelateerde programma's

[Goed Gebruik Geneesmiddelen](#)

[Lees meer over het programma Goed Gebruik Geneesmiddelen](#)

[Bekijk alle lopende subsidies binnen het GGG-programma](#)

[Lees meer over het Onderzoeksprogramma ggz](#)

Contact

Candido da Silva
Programmamanager

070 349 54 64
Geneesmiddelen@zonmw.nl

Signalement

Therapeutische toepassingen van psychedelica

Kansen, uitdagingen en zorginnovatie voor behandelresistente psychiatrische aandoeningen



'the human connection'

frontiers | Frontiers in Psychiatry

ORIGINAL RESEARCH
published: 14 June 2022
doi: 10.3389/fpsy.2022.880442



Moral Injury and Recovery in Uniformed Professionals: Lessons From Conversations Among International Students and Experts

Jonathan Jin^{1†}, Kyle Weiman^{2†}, Suzette Bremault-Phillips^{2,3‡} and Eric Vermetten^{4**}

¹ Department of Psychiatry, University of Alberta, Edmonton, AB, Canada, ² Heroes in Mind, Advocacy and Research Consortium, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada, ³ Department of Occupational Therapy, Faculty of Rehabilitation Medicine, University of Alberta, Edmonton, AB, Canada, ⁴ Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands

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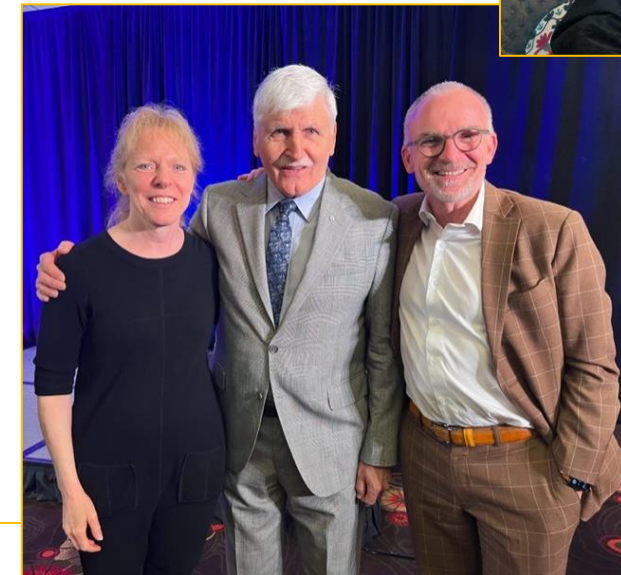
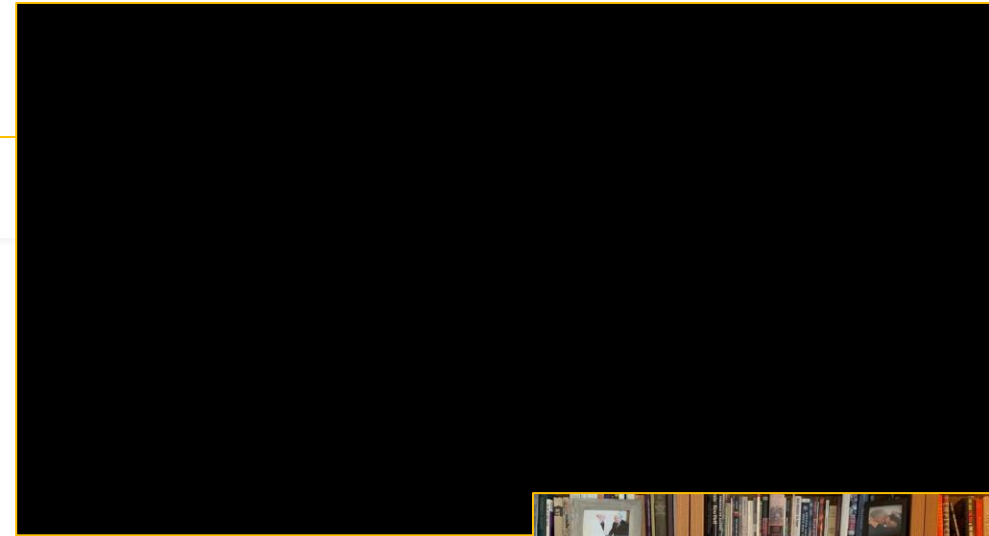
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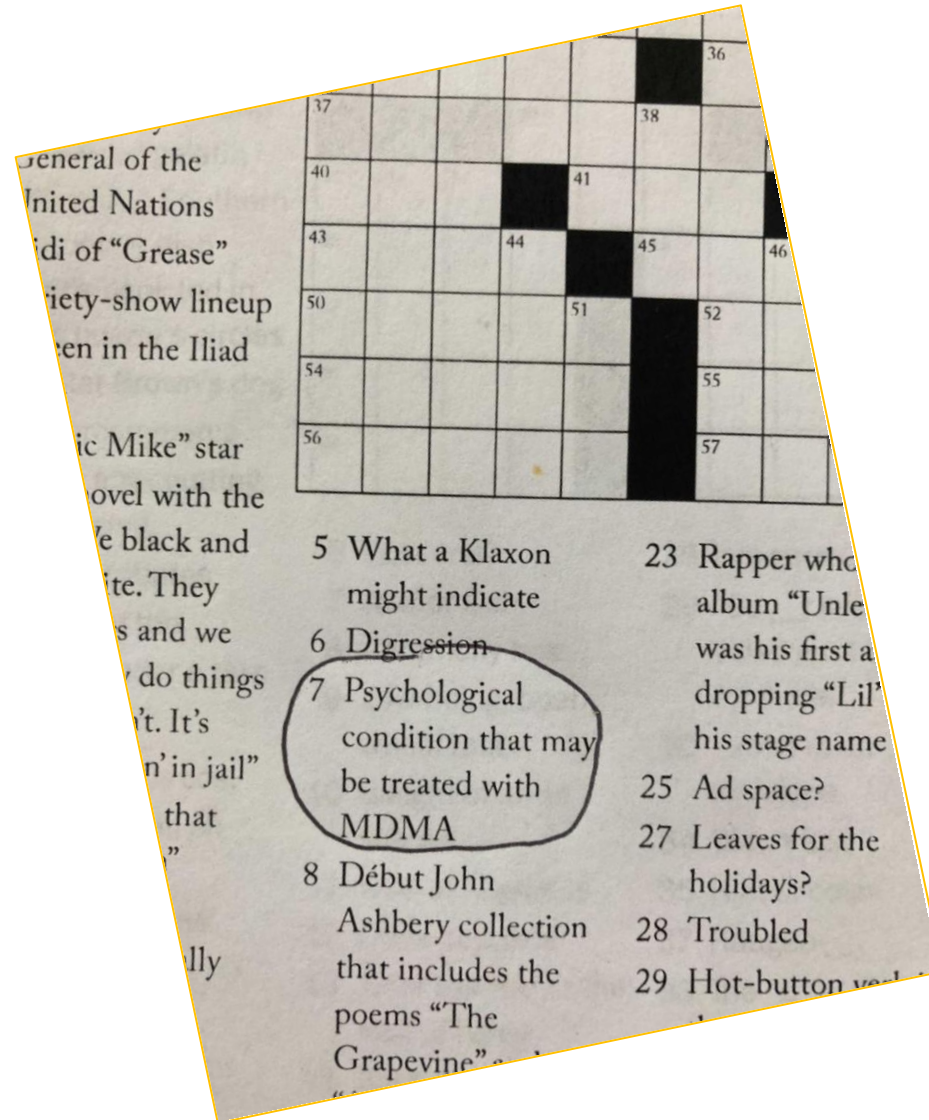
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Introduction: In the course of service, military members, leaders, and uniformed professionals are at risk of exposure to potentially morally injurious events (PMIEs). Serious mental health consequences including Moral Injury (MI) and Post-traumatic stress disorder (PTSD) can result. Guilt, shame, spiritual/existential conflict, and loss of trust are described as core symptoms of MI. These can overlap with anxiety, anger, re-experiencing, self-harm, and social problems commonly seen in PTSD. The experiences of General (retired) Romeo Dallaire and other international experts who have led in times of crisis can help us better understand MI and recovery.



crosswordpuzzle in New York Times (in 2022!)



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