Psychedelics in the treatment of addiction

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Bundesministerium für Bildung und Forschung

Psychedelic-assisted psychotherapy and EPIsoDE trial in Germany

More clinical trials to come

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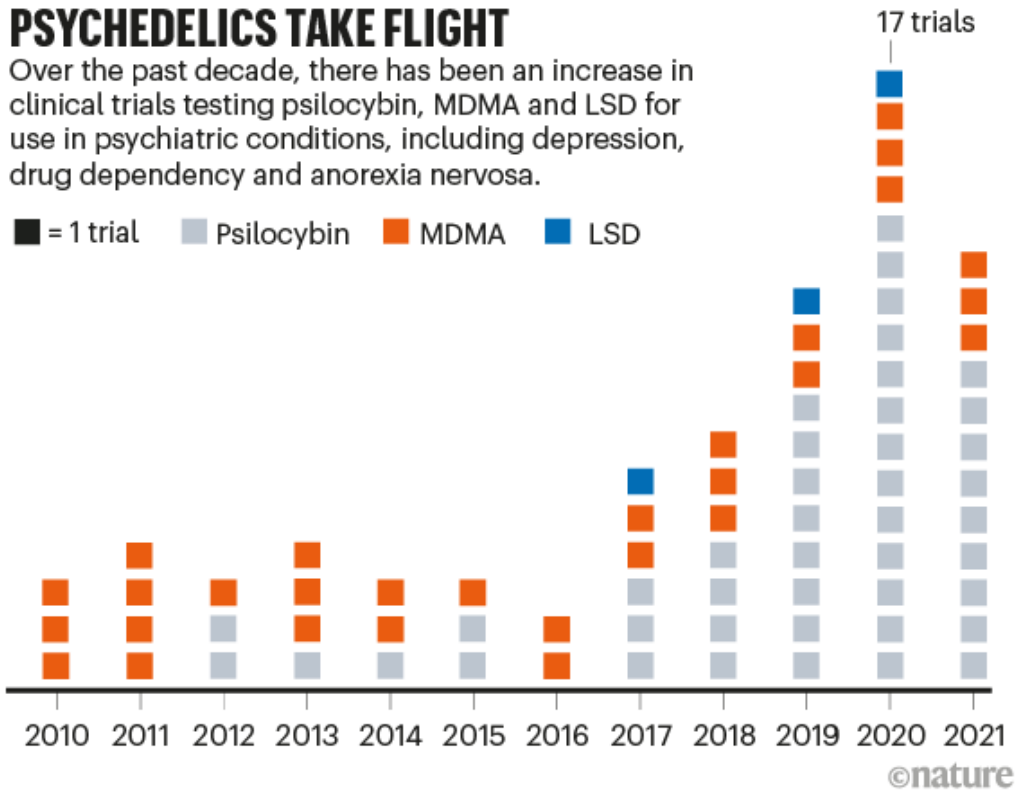
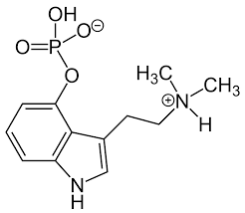


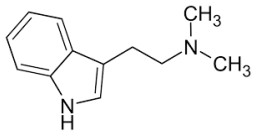
What are psychedelics?

Psilocybin

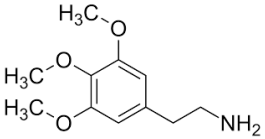


Ayahuasca/

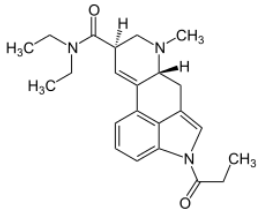
DMT+MAOI



Mescalin



LSD-25



European Neuropsychopharmacology
Volume 29, Supplement 1, 2019, Pages S304-S305

P.363

Psilocybin occupancy of brain serotonin 2A receptors correlates with psilocin levels and subjective experience: a [11C]Cimbi-36 PET study in humans

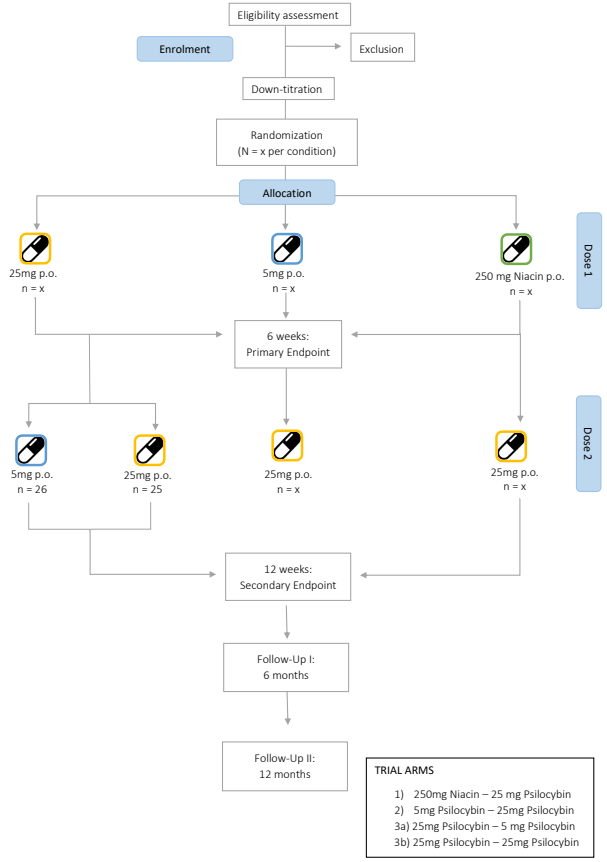
M.K. Madsen [1], D. Burmester [1], D.S. Stenbæk [1], S. Kristiansen [1], A. Dyssegaard [1], S. Lehel [2], K. Linnet [3], S.S. Johansen [4], C. Svarer [1], B. Ozenne [1], D. Erritzøe [5], P.M. Fisher [1], G.M. Knudsen [1]

biochemical commonality:
5HT-2A receptor agonism

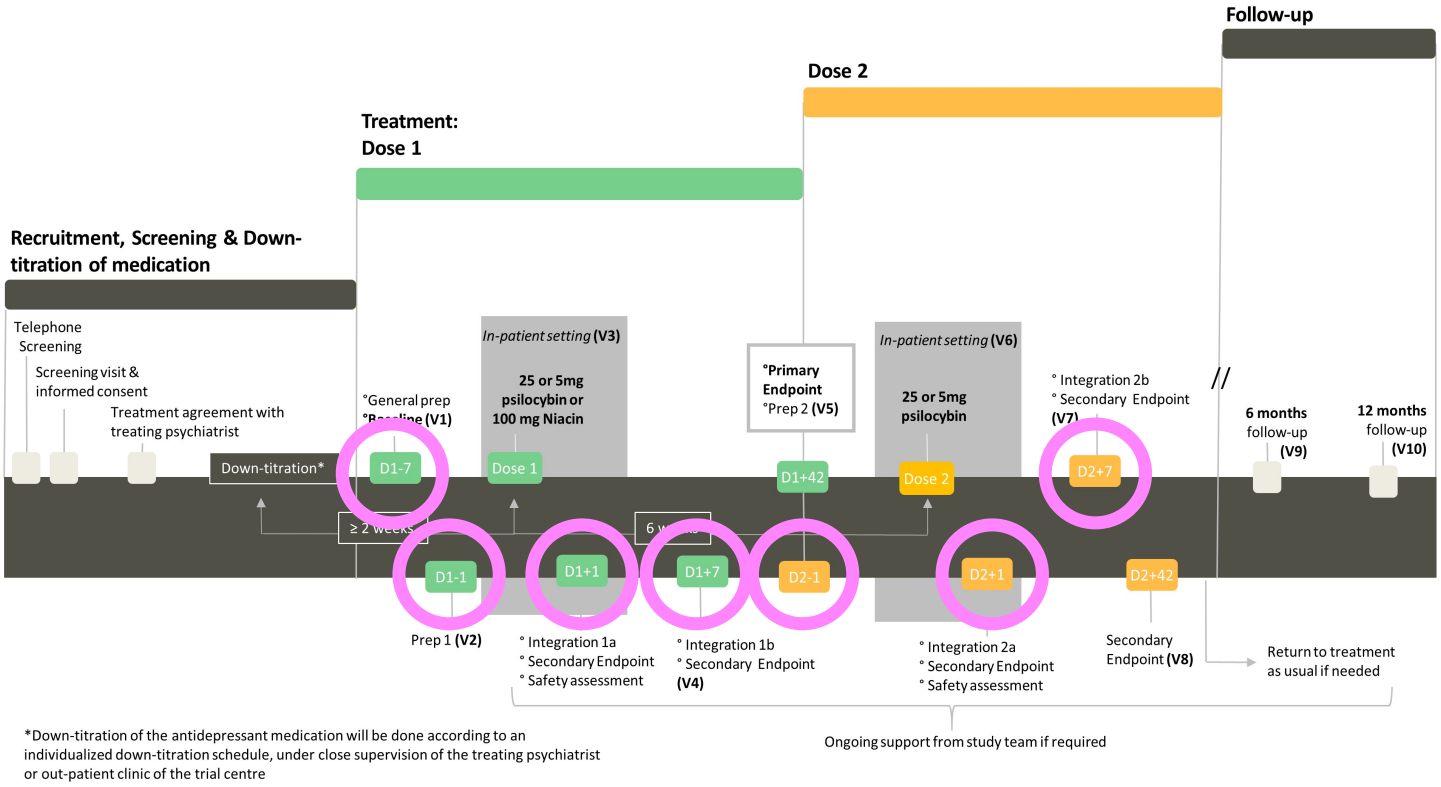
Design and „Setting“ of contemporary psychedelic therapy trials

- 3 phases: preparation, dosing session, integration
- high dose: 20-30 mg psilocybin
- Single or repeated dose
- sleep mask, selected emotionally evocative music, introspection
- therapist dyad (female and male)
- priority: safety
- Eclectic, rather supportive psychotherapy with elements from CBT, psychodynamic and mindfulness therapiy

EPIsoDE trial design



7 x 120 min. psychotherapy sessions



*Down-titration of the antidepressant medication will be done according to an individualized down-titration schedule, under close supervision of the treating psychiatrist or out-patient clinic of the trial centre

Metaanalysis psychedelics and depression

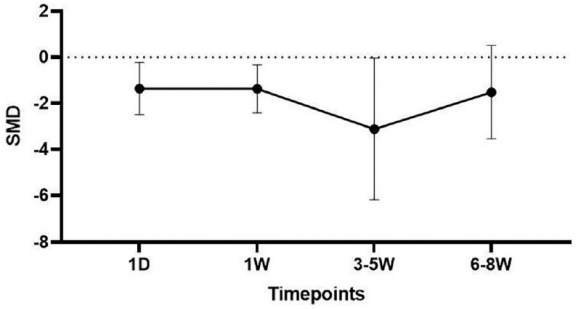


Fig. 3. Overall standardised mean differences between experimental and control at each time point of depressive score.

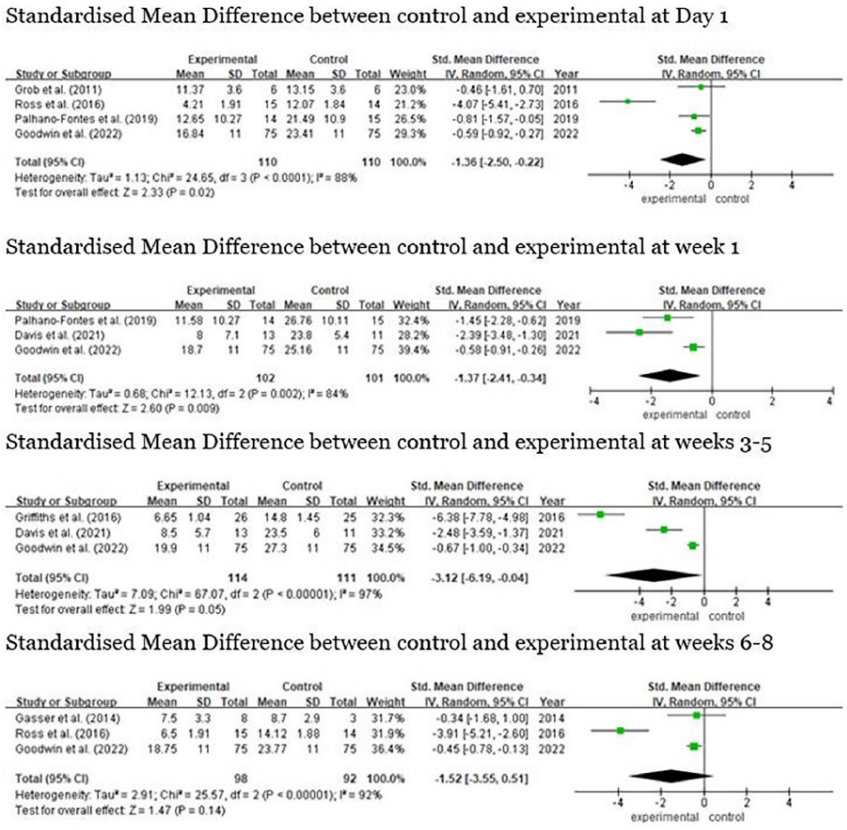


Fig. 2. Standardised mean differences between experimental and control at day 1, week 1, weeks 3–5, and weeks 6–8.

Safety and adverse events

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Review

Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review

Joost J Breeksema[1,2,3], Bouwe W Kuin[1], Jeanine Kamphuis[1], Wim van den Brink[4], Eric Vermetten[2] and Robert A Schoevers[1]

Psychopharm

Journal of Psychopharmacology
1–18

DOI: 10.1177/02698811221116926
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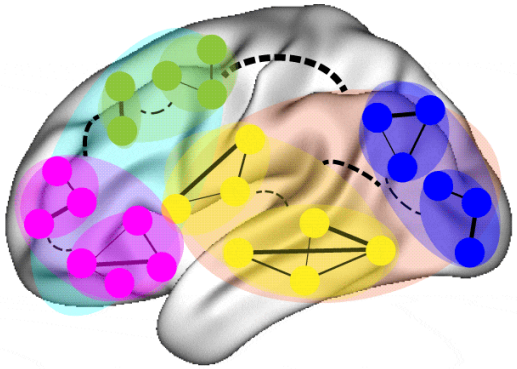
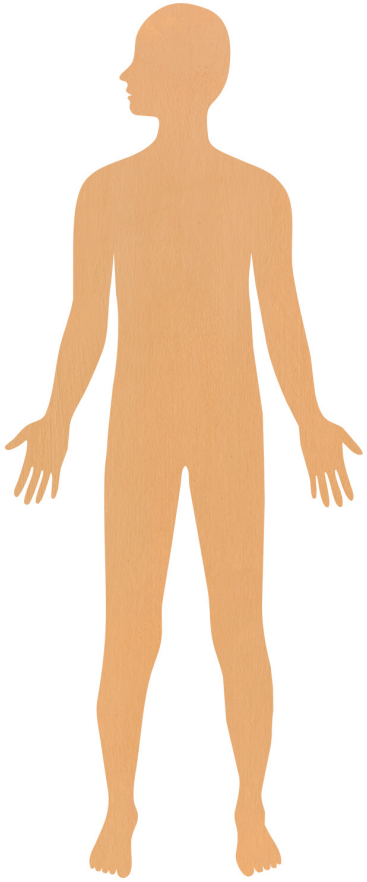
- N=598 (44 articles)
- „…treatments seemed to be overall well tolerated. **Nausea, headaches, and anxiety** were commonly reported acute AEs across diagnoses and compounds. Late AEs included headaches (psilocybin)…“
- „Qualitative studies suggested that **psychologically challenging experiences may also be therapeutically beneficial.**“

Mechanisms of action

Mechanisms of action: a complex interplay





Psychodynamic approach

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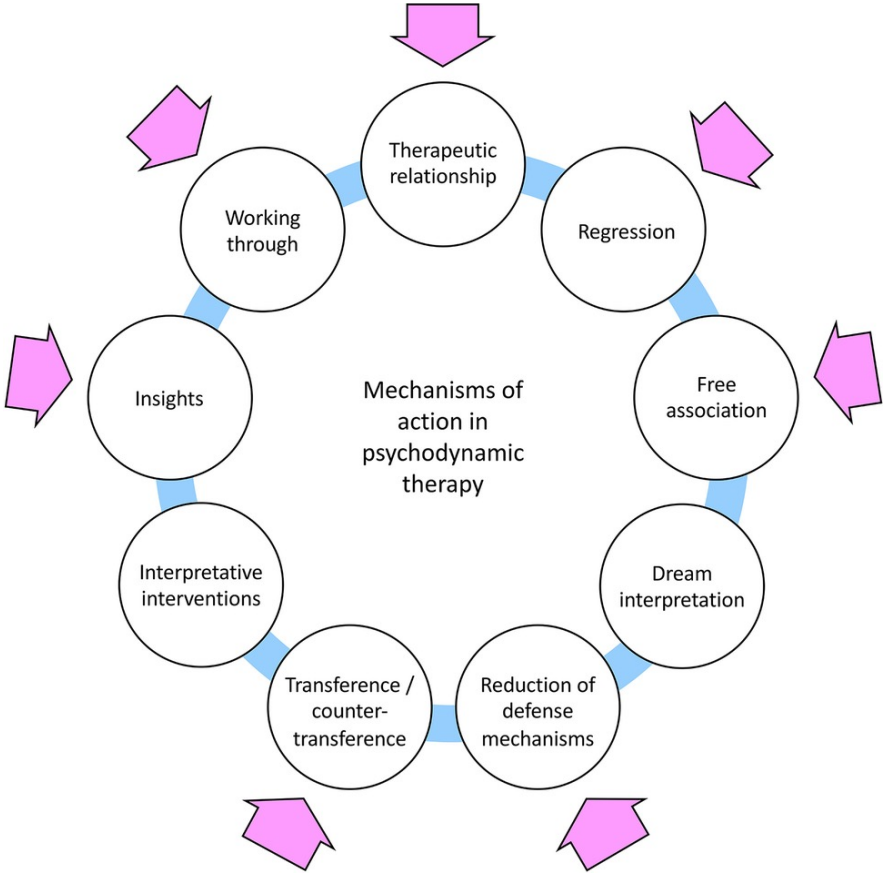
- Enhancement of psychoanalysis with several low/moderate dose psychedelic sessions
- > 700 publications 1953-1968
- > 6000 patients treated
- 2/3 of the patients improved
- no controlled trials



10.11.2020 | Psychotherapie | Fortbildung | Ausgabe 11/2020

Psychische Erkrankungen

Therapie mit Psychedelika - die Rolle der Psychotherapie

Zeitschrift: NeuroTransmitter > Ausgabe 11/2020

Autoren: Dr. med. Michael Koslowski, Dr. med. Felix Betzler, Prof. Dr. med. Gerhard Gründer, Dr. sc. hum. Henrik Jungaberle, Dr. rer. nat. Max Wolff

New Treatment Approaches in Therapy (A Heinz and N Romanczuk-Seiferth, Section Editors) | Open Access | Published: 13 November 2021

Novel Treatment Approaches for Substance Use Disorders: Therapeutic Use of Psychedelics and the Role of Psychotherapy

Michael Koslowski, Matthew W. Johnson, Gerhard Gründer & Felix Betzler

Current Addiction Reports (2021) | Cite this article

304 Accesses | 10 Altmetric | Metrics

Cognitive behavioural model


frontiers in Psychiatry | Psychopharmacology

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Hallucinogens and Entactogens: Establishing a New Class
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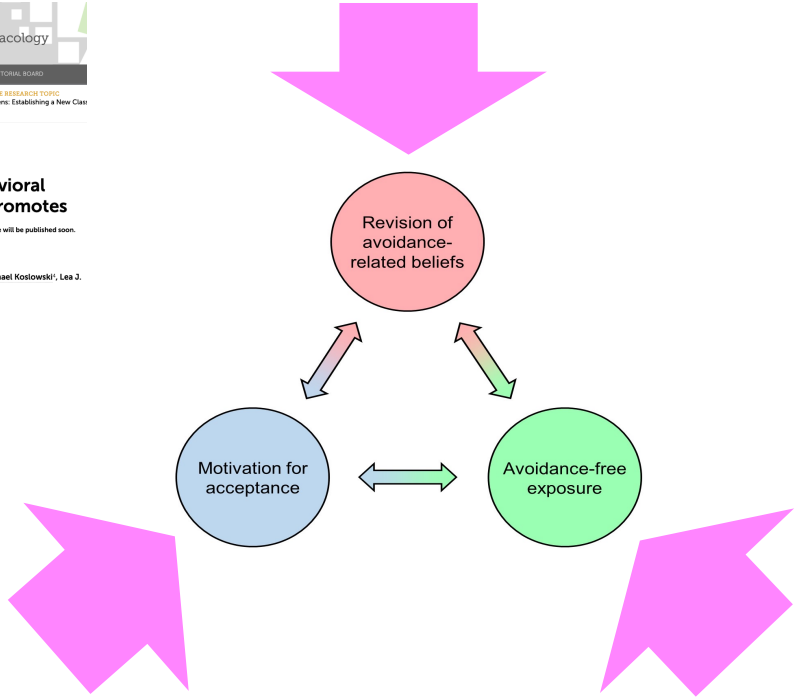
HYPOTHESIS AND THEORY ARTICLE

Front. Psychiatry | doi: 10.3389/fpsyt.2020.00005

Learning to Let Go: A Cognitive-Behavioral Model of How Psychedelic Therapy Promotes Acceptance Provisionally accepted The final, formatted version of the article will be published soon.

Notify me

Max Wolff[1, 2, *], Felix Betzler[1], Ricarda Evens[1], Gerhard Gründer[3], Michael Koslowski[4], Lea J. Mertens[5] and Henrik Jungaberle[1]



- **reinforced exposure** to internal events: painful emotions,memories,cognitions which are usually avoided
- "shaping" of acute experience, **favoring acceptance and reducing avoidance** (of negative emotions)
- revision of deeply rooted, rigid, **dysfunctional cognitions** about the self (worthlessness etc.)

Plans for further trials in Charité Berlin

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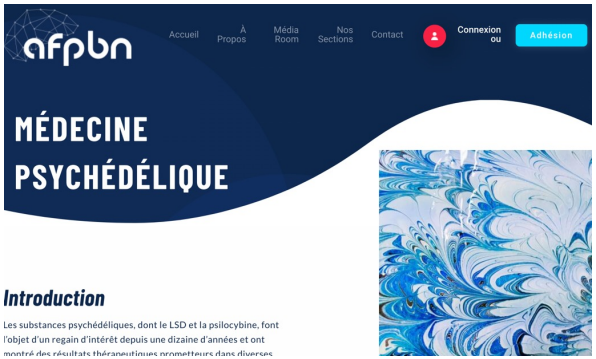
- Clinical trial with alcohol use disorder planned
- Participation in industry trials with short-lasting psychedelics: DMT, 5-MeO-DMT
- Negotiations with German authorities about cost-effectiveness and modalities for approval and reimbursement
- Survey studies on aspects of psychedelic therapy, harm reduction and recreational use
- Collaborations with research groups in France

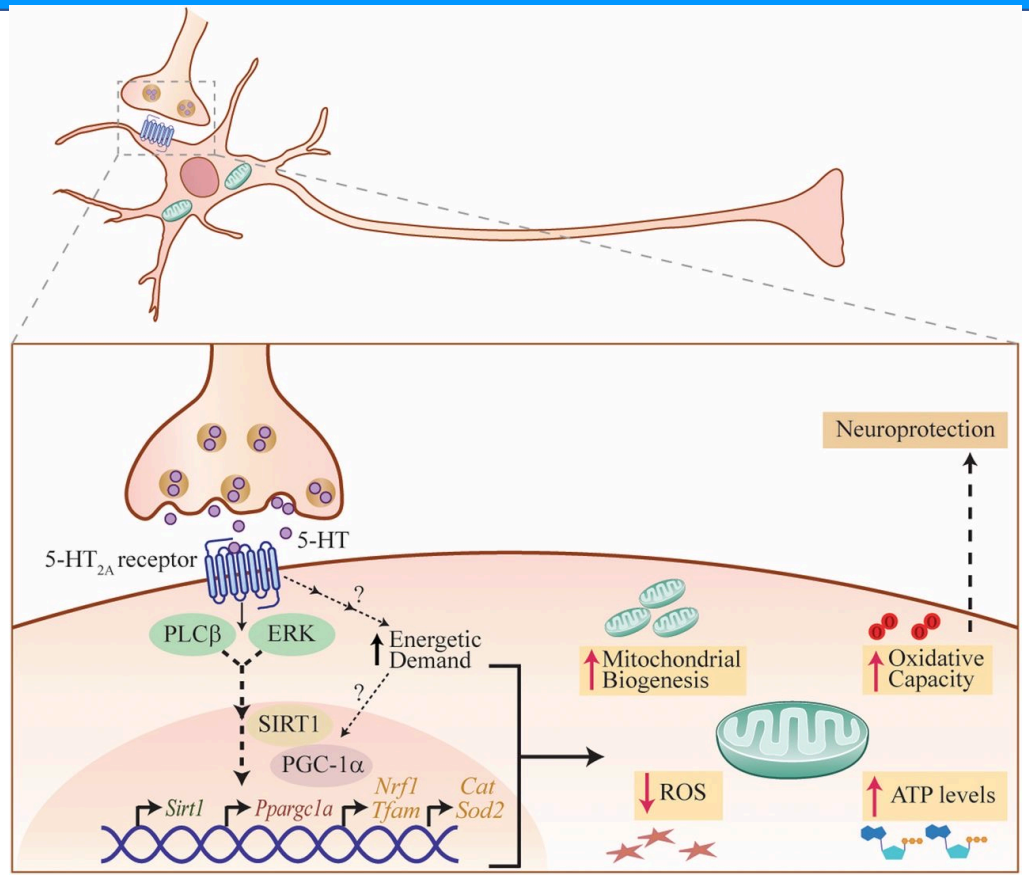
Psychedelic research and therapy in France - where do we stand?

- Symposia at psychiatry conferences
- Reviews and conceptual publications
- Animal studies on mechanisms of action (M. Nassila)
- Multiple clinical trials planned: services A. Benyamina, L. Mallet, R. Gaillard, Pitié-Salpetriere; Nimes, Montpellier etc.
- 2022: Section „Medecine psychedelique“ AFPBN
- Societé Psychedelique francaise (SPF)
- First clinical trial starting in Sep 2023 (Paris)
- Workshop March 2023 at Iméra Marseille
  - Exchange on study protocols
  - French-German collaborations
  - therapist training in French language



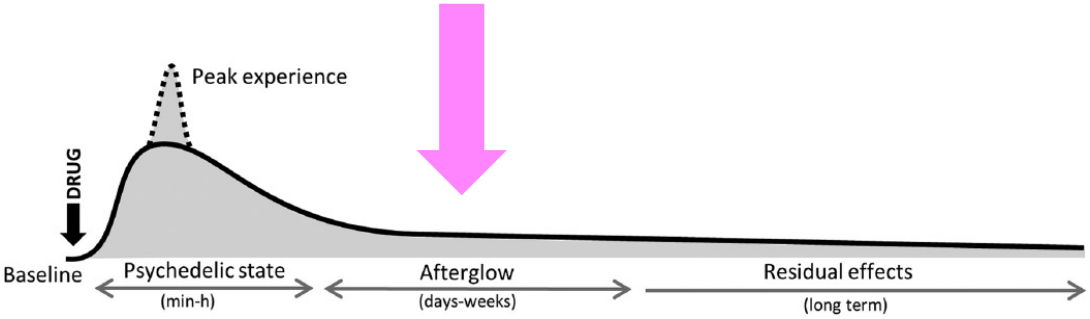
« Les thérapeutes ne pourront pas donner la main aux patients, comme ils le font aux Etats-Unis, les flics débarqueraient aussitôt ! », Luc Mallet, chercheur en neurosciences

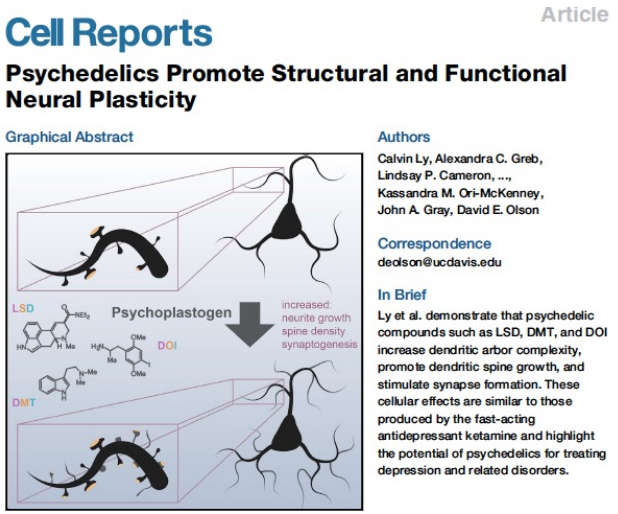
Neuron level: Stimulation of the serotonin 2A receptor



Fanibunda, et al. 2019

Neuron level: enhanced neuroplasticity




Article

Cell Reports

Psychedelics Promote Structural and Functional Neural Plasticity

Graphical Abstract

Authors

Calvin Ly, Alexandra C. Greb, Lindsay P. Cameron, ..., Kassandra M. Ori-McKenney, John A. Gray, David E. Olson

Correspondence

deolson@ucdavis.edu

In Brief

Ly et al. demonstrate that psychedelic compounds such as LSD, DMT, and DOI increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation. These cellular effects are similar to those produced by the fast-acting antidepressant ketamine and highlight the potential of psychedelics for treating depression and related disorders.

- subacute effects for 2 to 4 weeks after the psychedelic experience, with increased openness, well-being and cognitive flexibility
- Neuroplasticity: induction of dendritic spine growth, synapse formation
- ”psychoplastic window" during which psychotherapeutic interventions are more effective
- Other possible biological mechanisms: intracellular cascades (BDNF, mTOR), epigenetic changes, antioxidant and immunological effects etc.

Enhanced common factors of psychotherapy

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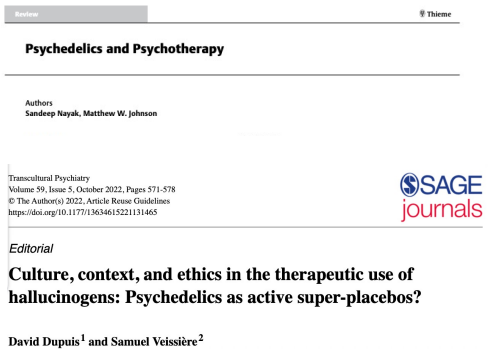

Review

Thieme

Psychedelics and Psychotherapy

Authors
Sandeep Nayak, Matthew W. Johnson

Transcultural Psychiatry
Volume 59, Issue 5, October 2022, Pages 571-578
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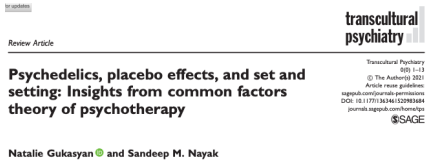
https://doi.org/10.1177/13634615221131465

SAGE journals

Editorial

Culture, context, and ethics in the therapeutic use of hallucinogens: Psychedelics as active super-placebos?

David Dupuis[1] and Samuel Veissière[2]



Review Article

transcultural psychiatry

Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy

Transcultural Psychiatry
0(0) 1–13
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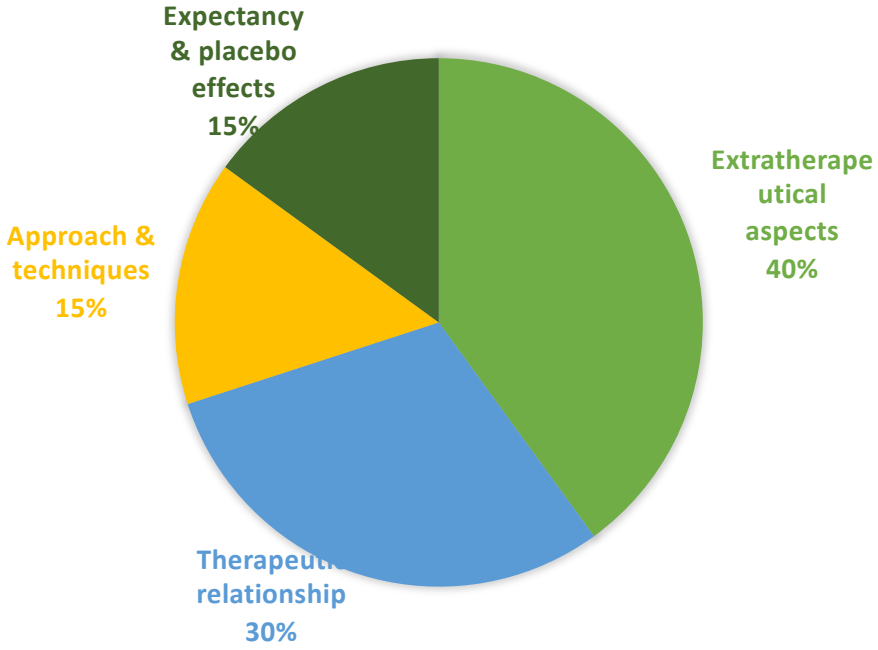
Natalie Gukasyan and Sandeep M. Nayak

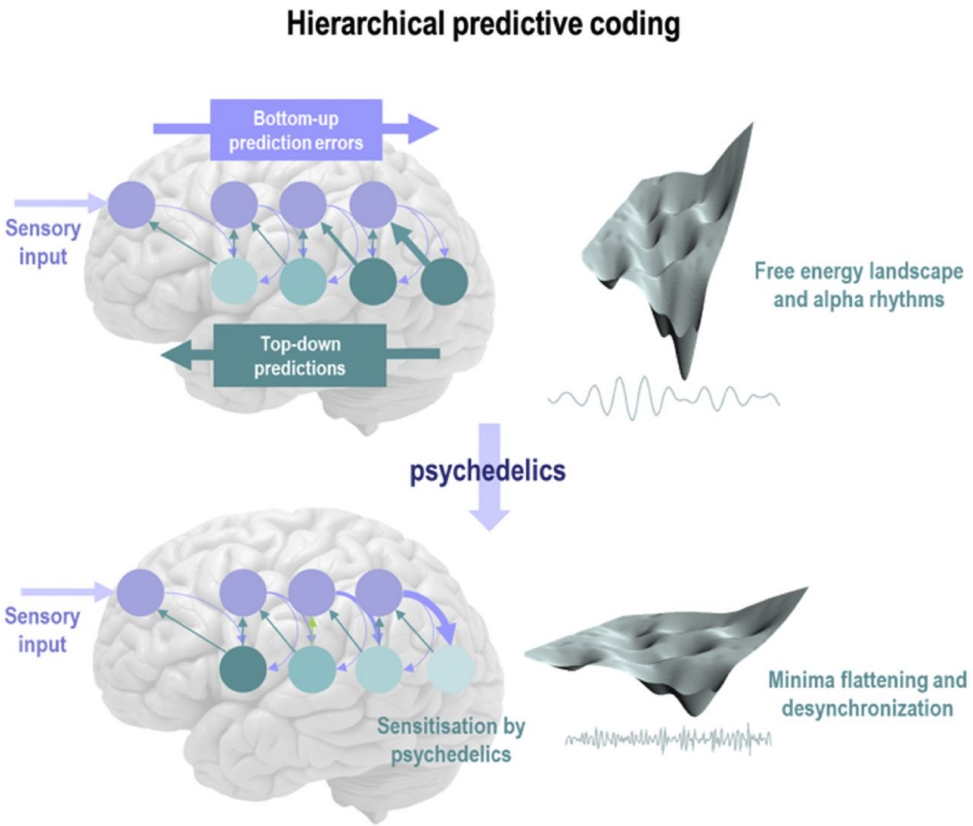
Psychedelics seem to enhance several **common factors** of effectiveness in psychotherapy :

- Patient-therapist Relationship
- working alliance
- Expectancy („super-placebos“ ?)
- Problem actualisation
- Motivation for change



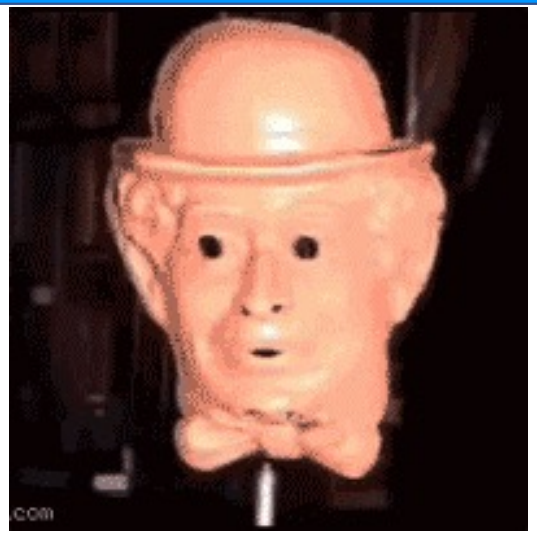
Asay, T. P., & Lambert, M. J. (1999)

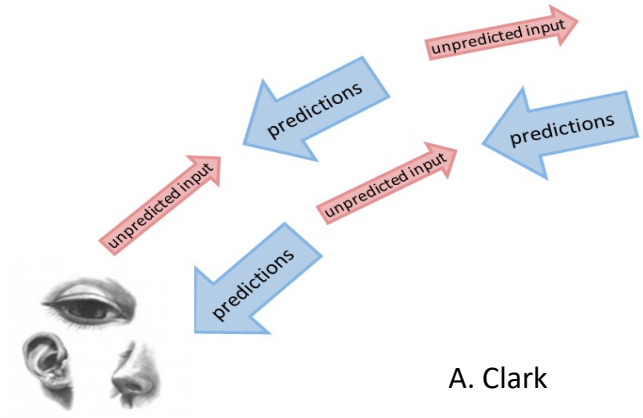
Network: disruption of predictive processing



- REBUS model (Carhart-Harris 2019) based on the predictive processing account (Clark 2013)
- Psychedelics reduce activity in cortical networks by agonism at 5HT-2A receptors
- decreased precision weighting in higher-level beliefs, about objects, time & space
- increase in "raw" information: perceptions, emotions, avoided/rejected content
- “ego dissolution”, disruption of narrative self-model
- increased global connectivity (e.g. synesthesia)

Network level: disruption of higher level predictions





A. Clark

- The hollow mask illusion: Based on a deeply rooted, unconscious belief, overriding contradictory perception: **„faces are always looking at me“**
- **Predective processing (PP)** model: We are constantly constructing and predicting a simplified, generative model of the world (C. Letheby)
- „perception is a controlled hallucination“ (A. Seth)
- Our self is a „virtual avatar“ (T. Metzinger)
- Modern version of **Kant´s** epistemology: the real world can never be percieved as such
- **REBUS** (Relaxed Beliefs Under pSychedelics) account applies the PP model to the psychedelic brain state

Psychedelics in the treatment of substance use disorders

Ongoing and planned trials in Germany

Psilocybin and TRD: COMPASS TRD Phase III

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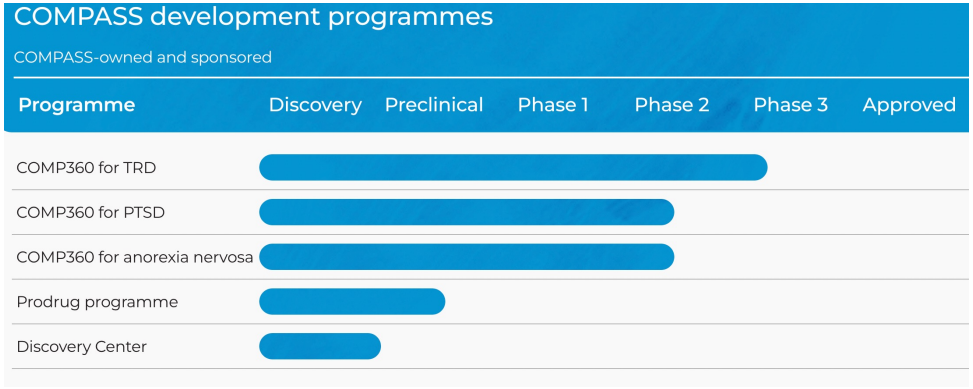
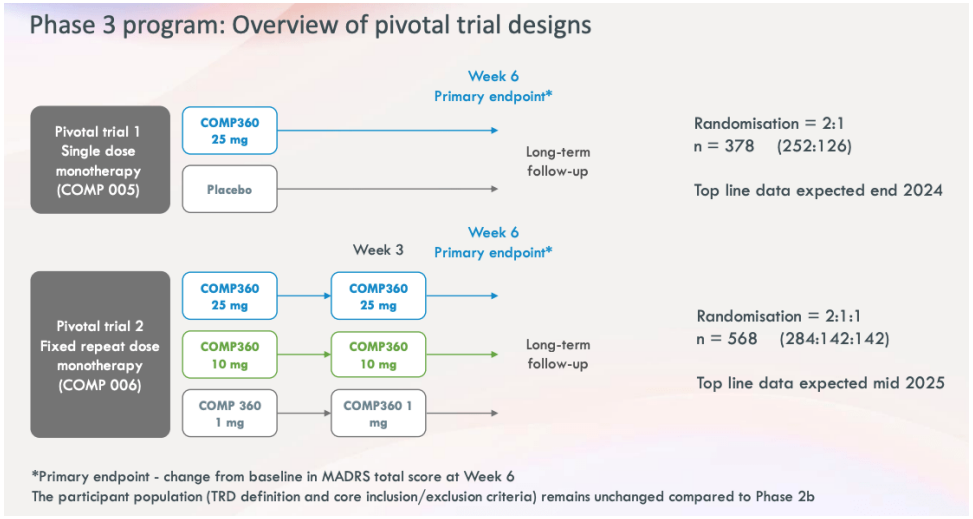
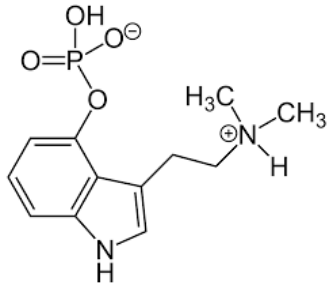




- Psilocybin single dose 25 mg
- Repeates dose 25 mg and 10 mg
- primary outcome parameter: MADRS (week 6)
- Start in 2023
- Multicenter study, with centers in Berlin, Paris and other cities



N,N-DMT and MDD: Small Pharma Phase IIb

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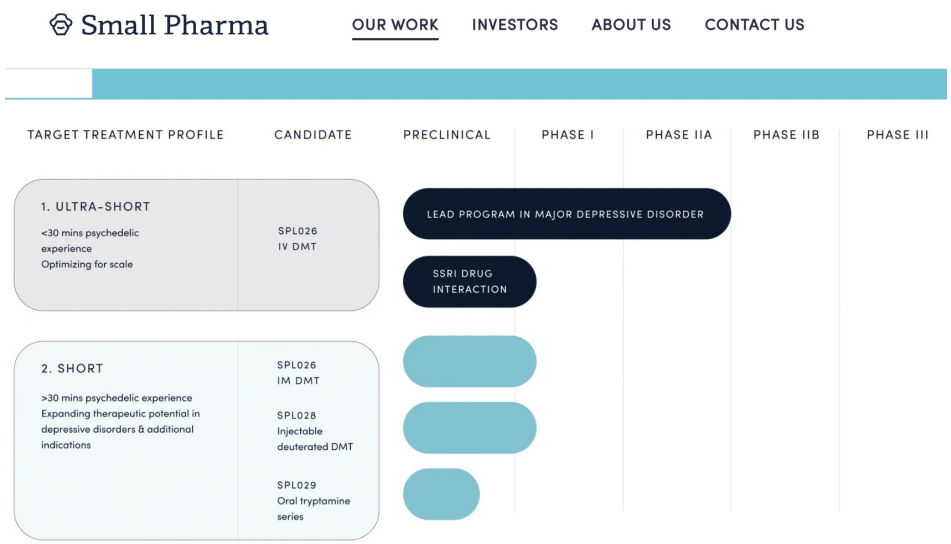
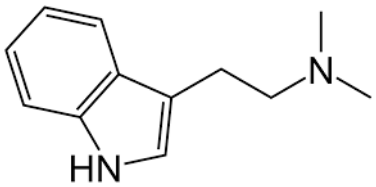


- Intravenous N,N-DMT (SPL026)
- Major depression (MDD)
- Psychological support
- Planned start in 2023
- Multiple sites (global), centers in Germany
- Phase IIa press release 01/2023: promising results

The highlights from the study are:



- **Primary endpoint** met with a statistically significant -7.4 point difference in MADRS between SPL026 (21.5mg) and placebo at two-weeks following a single dose with supportive therapy (p=0.02)
- **Fast antidepressant effect** with a statistically significant difference in MADRS of -10.8 versus placebo (p=0.002)
- **Durable antidepressant effect with** a 57% remission rate at 12-weeks following single dose of SPL026 with supportive therapy
- **Favourable safety and tolerability** profile demonstrated with no drug-related serious adverse events reported. All adverse events related to treatment were considered mild or moderate
- **No apparent differences** identified in antidepressant effect between a one and two dose regimen of SPL026

5-MeO-DMT and TRD: BeckleyPsytech Phase IIb

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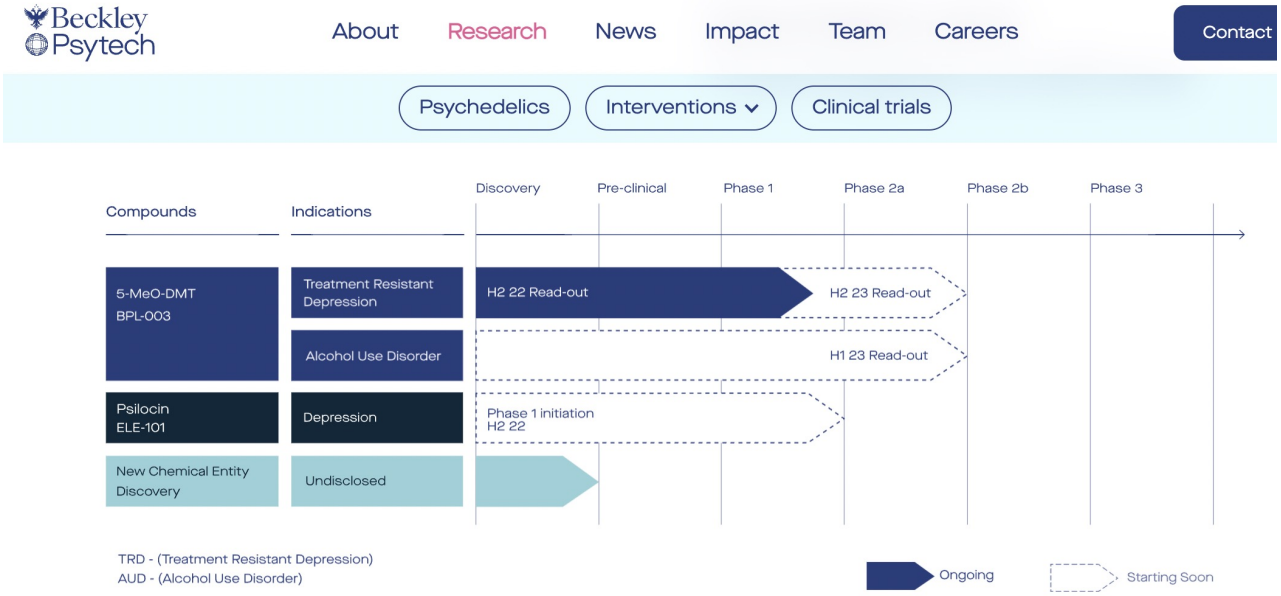

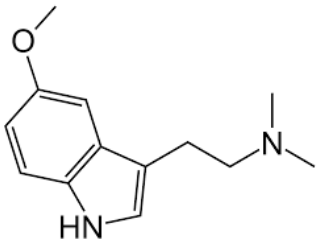

- Intranasal synthetic 5-MeO-DMT (BPL-003)
- Treatment-resistant depression (TRD)
- Randomized, blinded dose-finding study
- 3 doses: high, moderate, sub-perceptual
- primary outcome parameter: MADRS
- Psychological support
- Planned start in 2023
- 40 investigator sites in 7 different countries, centers in Germany

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The Role of Psychotherapy in psychedelic therapy & the EPIsoDE trial

Which psychotherapy is applied in current trials?

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Systematized Review of Psychotherapeutic Components of Psilocybin-Assisted Psychotherapy

David M. Horton, M.S., Blaise Morrison, Ph.D., Judy Schmidt, Ed.D.

TABLE 3. Structure and psychotherapy content of psilocybin sessions[a]

	Pretreatment			Treatment			Posttreatment		
Study	Sessions[b]	Hours[c]	Therapy content	Sessions[d]	Hours[e]	Therapy content	Sessions[f]	Hours[g]	Therapy content
Anderson et al., 2020 (9), group 1	5	7.5	Modified SEGT	1	8	Nondirective supportive	5	8	Modified SEGT
Anderson et al., 2020 (9), group 2	5	7.5	Modified SEGT	1	8	Nondirective supportive	7	11	Modified SEGT
Bogenschutz et al., 2015 (10)	4		MET	2	8	Nondirective supportive	6		MET
Carhart-Harris et al., 2016 (3)	1	4		2	6	Nondirective supportive	6		Integrative
Davis et al., 2021 (11)	2	6	Supportive therapy	2	7	Nondirective supportive	5	11	Integrative
Griffiths et al., 2016 (12)	2	8	Therapeutic relationship	2	8	Nondirective supportive	4	4	Support available as needed
Griffiths et al., 2018 (13), group 1	4	5	Therapeutic relationship, group sessions	2	7	Nondirective supportive	1	1	Journaling, group sessions
Griffiths et al., 2018 (13), groups 2 and 3	5	10	Therapeutic relationship, group sessions	2	7	Nondirective supportive	18	22	Journaling, group sessions
Grob et al., 2011 (14)	3		Supportive, existential	2	6	Nondirective supportive	3		Integrative, existential
Johnson et al., 2014 (15)	4	6	CBT	2	8	Nondirective supportive	12	9.5	CBT
Moreno et al., 2006 (16)	1		Therapeutic relationship	4	8	Nondirective supportive			
Nicholas et al., 2018 (17)	4	6	Supportive	3	8	Nondirective supportive	4	6	Integrative
Ross et al., 2016 (4)	3	6	Eclectic	2	8	Nondirective supportive	3	6	Eclectic

- **Commonalities:** 3-phase model; supportive setting in substance use session, with introspection and music.
- **Basics:** non-judgmental listening, empathic support and a strong therapeutic relationship
- **Psychotherapy methods:** MET, CBT, existential psychotherapy, SEGT*, psychodynamic therapy.
- **Psychotherapeutic techniques:** guided imagery, openended narrative writing, supportive touch, reality orientation, empathic support, nonjudgmental listening

*Supportive-Expressive Group Therapy

Patient statements: typical experiences

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„Excursions into grief, loneliness and rage, abandonment. Once I went into the anger it went ‘pouf’ and evaporated. I got the lesson that you need to go into the scary basement, once you get into it, there is no scary basement to go into [anymore].“

„[I] became myself at age 7, after my [grandparent] had died. I totally was back there, so vivid, so real, I had the emotions that I would have felt at the time: fearful, why did this happen, the naivety, the shock and confusion. I was getting overly upset and my parents were saying `boys don’t cry.`“

Watts et al 2017

Psychodynamic approach

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REVIEW article
Front. Pharmacol., 02 March 2018 | https://doi.org/10.3389/fphar.2018.00172

Unifying Theories of Psychedelic Drug Effects

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frontiers in Psychology

CONCEPTUAL ANALYSIS
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Entropy, Free Energy, and Symbolization: Free Association at the Intersection of Psychoanalysis and Neuroscience

Thomas Rabeyron[1,2] and Claudie Massicotte[3]*

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Psychopharmacology
https://doi.org/10.1007/s00213-019-05391-0

THEORETICAL AND METHODOLOGICAL PERSPECTIVE

Embedding existential psychology within psychedelic science: reduced death anxiety as a mediator of the therapeutic effects of psychedelics

Sam G. Moreton[1] · Luke Szalla[1] · Rachel E. Menzies[2] · Andrew F. Arena[2]

Received: 7 May 2019 / Accepted: 4 November 2019
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Converging theories on dreaming: Between Freud, predictive processing, and psychedelic research

Michael Koslowski[1,2*†], Max-Pelgrom de Haas[1,2†] and Tamara Fischmann[2,3]

- Phenomenological similarities to **dreams**: Access to unconscious processes
- shift from rational logical thinking (psychoanalytic: secondary process, "I") to **associative thinking** (primary process, "It")
- confrontation with **repressed fear of death** (existential psychotherapy)
- intensified **symbol formation**
- correction of early dysfunctional **object relations**
- Disruption and change of implicit **relational models**

ACT: a promising therapeutic framework for psychedelic therapy

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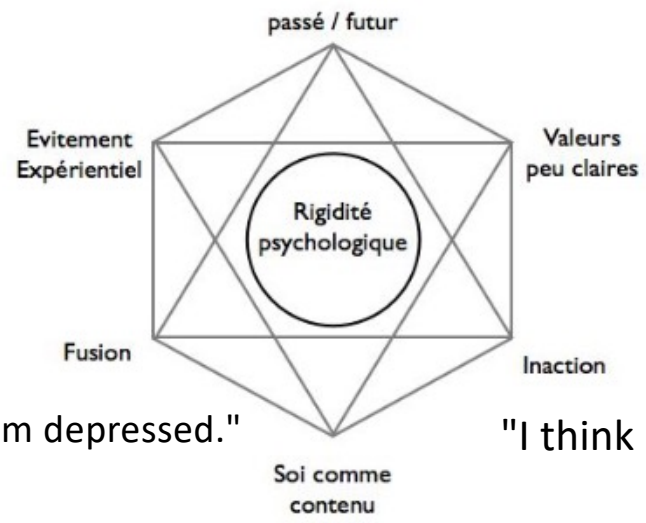
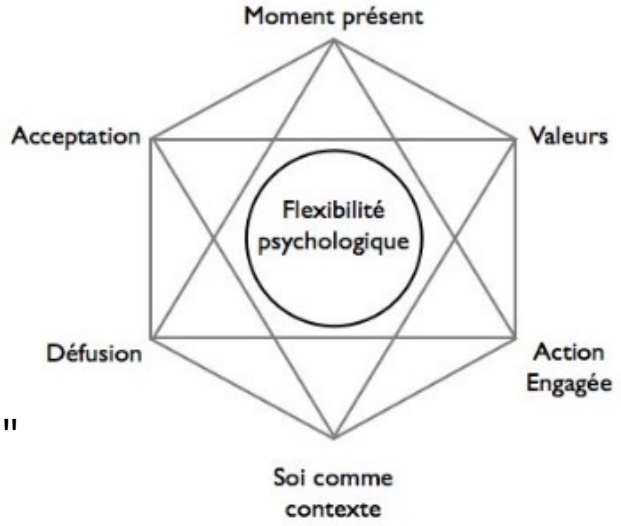
"I'm never gonna make it."



"I'm depressed."

"I'm worthless"

presence (mindfulness)



"I think I'm depressed."

"I observe my thoughts"

ACT = Acceptance and Commitment Therapy

Psychedelic integration: Review

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Psychedelic integration: An analysis of the concept and its practice

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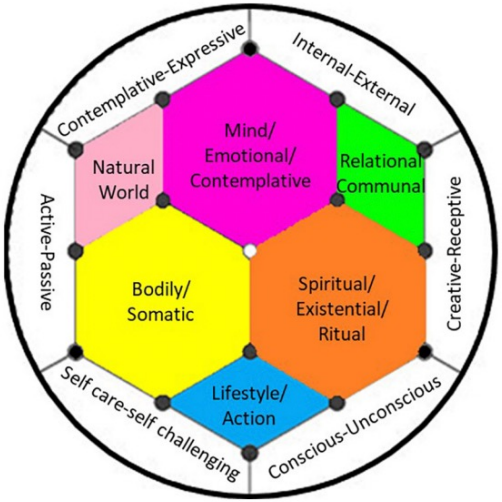

FIGURE 1
Synthesized model of integration: The hexagon reflects six interconnected domains of existence, with the more personal ones toward the center. The outer ring reflects continuums on which integration activities can be placed. The goal is a balance of integration activities addressing all domains of living.

TABLE 1 Comparison of integration models with resulting synthesized model of integration.

Model (Author)	Domains					
Synthesized Model of Integration	**Mind/emotional/ contemplative**	**Bodily/somatic**	**Spiritual/existential/ ritual**	**Lifestyle/ action**	**Relational/ communal**	**Natural world**
Visionary Plant Medicine Integration (Coder, 2017)	Inner listening, reflection, creative	Physical care, time/space	Spiritual practice, meaning making	Cultivating virtues	Turning outward	Nature and grounding
Holistic Model for a Balanced Life (Bourzat and Hunter, 2019)	Mind	Body	Spiritual	Sharing	Community	Nature
Realms of Integration (Buller and Moore, 2019)	Mental/Intellect	Mind-body, surroundings	Spiritual	Lifestyle/career	Relationships	
SAFETY (Westrum and Dufrechou, 2019)	Psychological (Transpersonal)	Somatic	Spiritual/existential/ritual		Social/Communal	
Nature Contact (Gandy et al., 2020)	Psychological (Nature-based)	Affective	Mystical/Awe			Nature relatedness
Psychedelic Harm Reduction and Integration (Gorman et al., 2021)	Psychological (Transtheoretical)	Somatic	Spiritual/mystical	Harm reduction		
Psychedelic Inclusive Model of the Psyche (Ortigo, 2021)	Psychological (Jungian, Transpersonal)	Body	Spiritual/mystical	Behavior		
Psycho-Spiritual Integration Process (Cohen, 2017)	Psychological (Jungian)	Somatic	Psychospiritual			
Acceptance and Commitment Therapy (Sloshower et al., 2020)	Psychological (ACT)			Behavior change		
Psychological Flexibility Model (Watts and Luoma, 2020)	Psychological (ACT)			Behavior change		

Integration groups in the EPIsoDE trial

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Adaa.org

- **Problem:** Only 4 x 120 min. integration sessions part of the protocol
- Many patients still in ongoing psychotherapeutic process at the end of the trial
- Therapists often lack knowledge about psychedelic therapy effects
- sometimes therapy cannot start right away after the trial

- **Consequence:** creation of post-study integration groups
- monthly meetings, 6-12 participants, guided by 2 therapists/psychiatrists
- ZI Mannheim: 6 x 90 min. online + 1 x presence
- Charité Berlin: 2 groups (online, presence), each 6 x 90 min.
- Similar concept, partly manualized
- Centered around the psychedelic experience, and what it means to the person, the course of depression, relationships

Yale Depression therapy manual based on ACT

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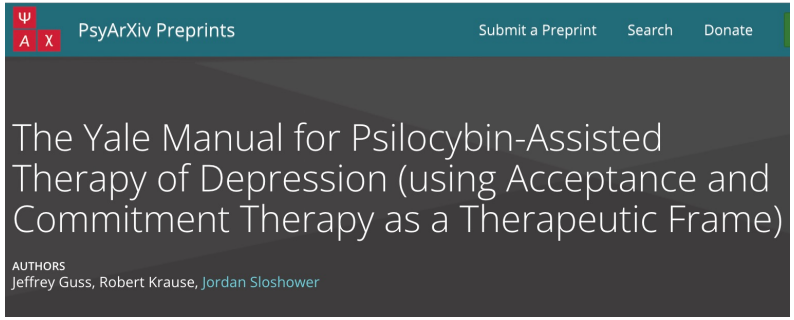
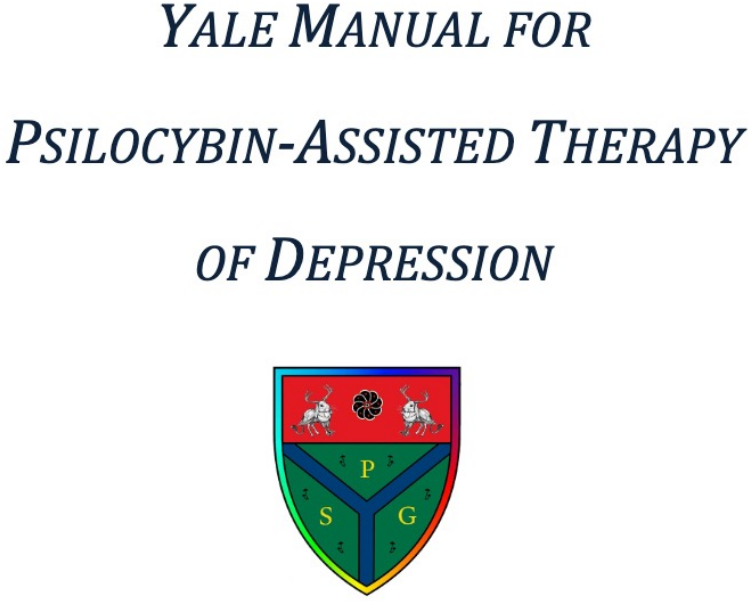


https://psyarxiv.com/u6v9y/



Therapy Manual of the EPIsoDE trial

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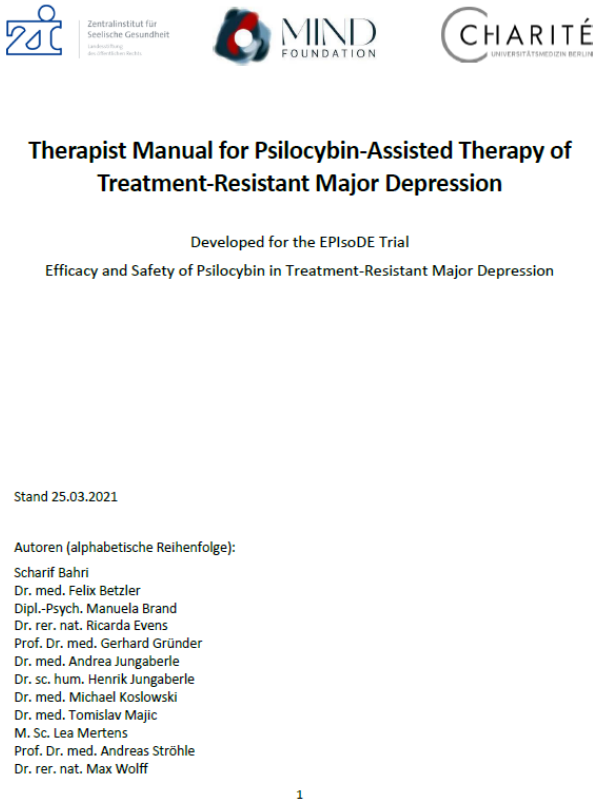

Therapist Manual for Psilocybin-Assisted Therapy of Treatment-Resistant Major Depression

Developed for the EPIsoDE Trial

Efficacy and Safety of Psilocybin in Treatment-Resistant Major Depression

Stand 25.03.2021

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1

- **Therapy manual** developed on the basis of existing manuals (NYU, Usona, MAPS, etc.)
- **3-phase model**:
  - **1. Preparation:** information, therapeutic relationship, detailed history of depression, biography; breathing exercise; formation of an "intention“ for the session
  - **2. Dosing**: support, check-ins, safety, debriefing
  - **3. Integration:** relationship between psychedelic experience and depression/current conflicts/dysfunctional interactions, depressive beliefs, application of insights to daily life, etc.
- Behavioral and psychodynamic elements
- Standardization
- Integration group 6 months after trial (online & presence)

Therapy Manual: Preparatory sessions

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7.2 General Prep

The General Prep session should have an approximate duration of 100 minutes. Whenever required, therapists may suggest a short break. The following should be covered in this session (see General Prep Checklist; Appendix A):

- Introduce yourselves and give an overview of preparatory sessions (~10 min)
- Discuss topics relevant to the patient´s depression (~30-45 min)
- Discuss previous treatments (~10 min)
- Discuss the patient´s expectations and hopes regarding treatment with psilocybin (~10-25 min)
- Discuss agreements necessary for study participation (~5 min)
- Hand over patient information on dosing sessions (~10 min)
- Clarify organizational issues (~5 min)
- Close the session (~5 min)

Documents needed for this session:

- General Prep Checklist (Appendix A)
- Print-out of Scheduling Form (Appendix C)
- Session Summary Form (Appendix D)
- Handout – Patient Information on Dosing Sessions (Appendix G)
- Biographical Questionnaire (prepared by the patient; Appendix X)

Sample statement:

« Our first preparatory session today is about us getting to know you further and you getting to know both of us even better as well. Above all, we want to learn more about your life and your depression. At the end we will discuss some organizational things. In the second preparatory session next week, we will go over typical experiences that are common in dosing sessions and discuss possible ways to deal with challenging or difficult experiences. We will also go over the schedule for the day of the substance session and answer any questions you may have. If you are bringing a support person next week, we would like to meet her or him at the end of the session. »

Therapy Manual: Preparatory sessions

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7.3 Prep 1/Prep 2: Before the First/Second Dosing Session

The Prep 1 and Prep 2 sessions should have an approximate duration of 100 minutes. Whenever required, therapists may suggest a short break. The Prep 2 session held before the second dosing session should be very similar to the Prep 1 session held before the first dosing session. Therapists should keep in mind that the patient may have received either nicotinamide or low-dose psilocybin during their first dosing session. It is therefore important to repeat the education on possible effects of psilocybin and how to handle challenging experiences with the patient. The following should be covered in Prep 1 and Prep 2 sessions (see Prep 1 and 2 Checklist; Appendix E):

- Ask for open questions from the previous session and give an overview of the session structure (~5 min)
- Guided mindfulness exercise (see Appendix F) (~10 min)
- Discuss common experiences in dosing sessions (~10 min)
- Discuss potential for challenging experiences and how to handle them (~20 min)
- Introduce physical space, music, and eyeshades (~5 min)
- Set an intention for the dosing session (~10 min)
- Discuss dosing day structure, instructions, and recommendations (~20 min)
- Meet the support person (if applicable; ~10 min)
- Clarify organizational issues (~5 min)
- Close the session (~5 min)

Documents needed for this session:

- Print-out of Scheduling Form (Appendix C)
- Session Summary Form (Appendix D)
- Prep 1 and 2 Checklist (Appendix E)
- Instructions for Mindfulness Exercise (Appendix F)
- Handout – Patient Information on Dosing Sessions (Appendix G)

Sample statements:

"Leaning into" the experience:

“A very important technique in dealing with challenging experiences is to consciously go even further into the experience.

Whenever you experience something that scares you, try to lean into it. This going into the experience makes the experience much more bearable than if you try to escape the experience somehow.

If you encounter something you are afraid of, try to be curious and open anyway. Don't run away from it, but go to it. Ask, "What are you doing here? What can I learn from you?"

If you feel like you're melting, dissolving, or exploding, don't fight it, let it happen. Melt, dissolve, explode! We will always be with you and keep you safe.“

Therapy Manual: Dosing sessions

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8.4.3.2 Guidelines for Handling Psychological Distress

During preparatory sessions, therapists have discussed with the patient potential challenging experiences and techniques for handling them (Section 7.3.4). At the beginning of dosing sessions (Section 8.4.2), therapists will encourage patients to respond to overwhelming challenges by reaching out to therapists. Nevertheless, therapists should remain alert and aware for signs of agitation, anxiety, and continued psychological distress, as verbal or gestural communication on the part of the patient may be hindered due to the effects of the study medication.

Interventions for handling psychological distress can be broadly distinguished with respect to the following characteristics:

- **Engagement** versus **disengagement** from the process that is experienced as distressful
- **Promoting self-efficacy** versus **supporting the patient**

As a general rule, self-efficacy and engagement interventions should be preferred over support and disengagement interventions whenever possible (talking through before talking down). Support and disengagement interventions should be used sparingly, and only when deemed absolutely necessary due to the severity of distress experienced by the patient. The Accordingly, the list below can be read as a gradient from "earlier" (first choice) to "later" (last resort) interventions:

1) **Promoting self-efficacy for engagement** (e.g., "You can do it"; "Would you like to try and go deeper?"; "Do you notice any changes when you pay close attention?")
2) **Supporting engagement** (e.g., "We are with you while you go through this"; "Should I hold your hand?"; "We will go through this together")
3) **Promoting self-efficacy for disengagement** (e.g., "Follow your breath […] observe the sensation of breathing in and out")
4) **Supporting disengagement** (e.g., "I will now mute the music for a while"; "Would you like a glass of water?")

Sample statements (short, simple):

Therapeutic touch:

"If you like, I will hold your hand."
"Do you want to take my hand?"

Guiding attention to the music:

"Follow the music."
"Let the music carry you."

Going back to the intention:

"Go back to your intention."

Guided breathing exercises:

"Breathe into the feeling."
"Let the breath flow... Observe how the breath flows in and out... Just observe."

Rescue medication:

"We have now weighed things up together and think the time has come to make things a little easier for you with a medicine. If you take this tablet, you will feel better quickly."

Therapy Manual: Integration sessions

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9.2 Integration 1a and 2a Sessions – One Day after Dosing Sessions

9.2.1 Session Structure

The Integration 1a and 2a sessions will be held on the day following dosing sessions, and will take place in the dosing session room whenever possible. Whenever possible, both therapists should be present during these sessions. These sessions should have a duration between 60 and 120 minutes. Whenever required, therapists may suggest a short break. The following should be covered in the Integration 1a and 2a sessions (see Integration 1a and 2a Checklist; Appendix O):

- Give an overview of the session structure (~5 min)
- Obtain a comprehensive overview of the patient's experience (~15-35 min)
- Help the patient relate their experience to their larger personal context (e.g. biography, everyday life, relationships) (~15-35 min)
- Encourage the patient to think about how to integrate gained insights and perspective shifts into everyday life (~15-35 min)
- Clarify organizational issues (~5 min)
- Close the session (~5 min)

Documents needed for this session:

- Print-out of Scheduling Form (Appendix C)
- Session Summary Form (Appendix D)
- Integration 1a and 2a Checklist (Appendix O)

Sample statements:

Resuming the experience:

"Please describe your experience in as much detail as possible."

Challenging experiences:

"Did you experience certain feelings, thoughts or sensations as difficult or challenging during the session? Can you describe these experiences for us? What do you think about them now, as we sit here together?"

Relate to depression and life situation:

"What does your experience yesterday have to do with you as a person, with your life, or with your relationships?"

„Hat diese Erfahrung einen Einfluss darauf, wie Sie Ihre Depression sehen?"