Psychedelics in MDD & TRD: Not Quite Ready for Primetime

Poul Hansen Family Centre for Depression CPD Day

Susan Abbey, MD, FRCP

UHN Centre for Mental Health

Disclosures

- Inaugural Director, Nikean Psychedelic Psychotherapy Research Centre
- No $
- Lots of interest but also committed to “do no harm” with advocating for scientific rigour and social responsibility

Learning Objectives

At the end of the session participants will be able to:

- Describe recent research studies using psychedelic medicines to treat depression
- Summarize the implications for clinical practice and in particular how to respond to patient questions about psychedelics for depressive illness

Presentation Outline

- Why psychedelics?
- History of psychedelics use
- Paradigms for Psychedelic Therapies
- Psychedelics for mood
- Research studies
- Potential mechanisms of action
- Conclusions

During the decades during which they have been known in contemporary Western culture, the psychedelic drugs have been construed as agents that might assist in psychotherapy, produce spiritual transformation, enhance creativity, foster social chaos and moral breakdown, provide access to unexamined realms of a multifaceted reality, or provoke derangement, delusion and toxic psychoses.”

Mangini M. A Short, Strange Trip: LSD Politics, Publicity, and Mythology – From Discovery to Criminalization In CS Grob, J Grigsby. *Handbook of Medical Hallucinogens*, New York: Guildford Press, 2021, p 68

Why Psychedelics & Why Now?

- MDE is a major societal problem and source of enormous suffering
- Our treatments lack precision and take too long to work
- The potential value of psychedelics in both mental health treatment & optimizing mental health & the human experience has been recognized for millennia
- The study of psychedelics was promising in the 50's & 60's and shut down for sociopolitical reasons
- The current explosion in interest is a potent mix of hope, the current zeitgeist & profit

The Origins of Psychedelic Use in Indigenous Cultures

- Based in plant medicine & indigenous ceremonial use – 4000 BC to present across the globe

- Induction of non-ordinary states of consciousness in the service of healing, rites of passage & initiation, and connection

    - Mexico – Mazatec curanderos use mushrooms, peyote, salvia divinorum

    - Amazon – ayahuasca, tobacco, coca, san pedro cactus

    - Congo basin - Iboga

An Array of Terms

- Psychedelic
- Entheogen
- Hallucinogen
- Psychoplastogen

“Psychedelic”

- Dr. Humphry Osmond (Saskatchewan Hospital, Weybourne) introduced the term
  - 1953 – gave Aldous Huxley mescaline in LA while attending the American Psychiatric Association – Huxley wrote “The Doors of Perception” (1954)
  - 1956 – letter to Aldous Huxley - “To fathom hell or soar angelic / Just take a pinch of psychedelic”
  - 1957 – 1st use at a scientific meeting - New York Academy of Sciences
  - Derived from Greek = “manifesting the mind”
  - “clear, euphonius, and uncontaminated by other associations”

Dueling Contemporary Paradigms

Psychedelic as **molecule**.

Psychedelic as **catalyst** to be used in a psychotherapeutic environment.

Varying perspectives on the importance of **non-ordinary states of consciousness (NOSC)**

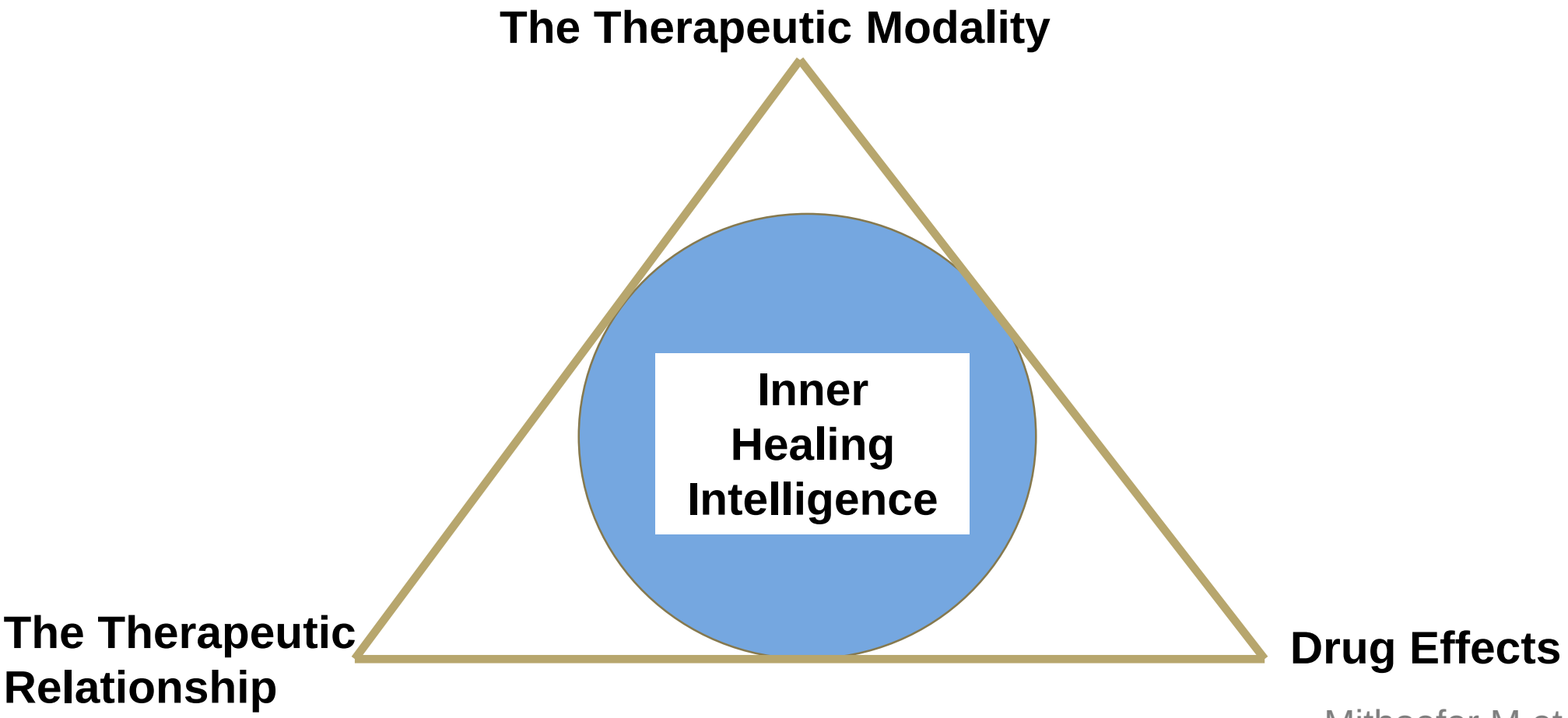
Non-Ordinary States of Consciousness (NOSC)

- Increasing interest in consciousness and “ordinary” and “non-ordinary” states of consciousness

- “Non-ordinary states of consciousness are characterized by dramatic perceptual changes, intense and often unusual emotions, profound alterations in the thought processes and behavior, and by a variety of psychosomatic manifestations.” Stan Grof

- Multiple pathways to NOCS in addition to psychedelics – meditation, hypnosis, breathwork, dance, lucid dreaming, sleep & food deprivation, medications, trance

What is Psychedelic-assisted Psychotherapy?



Mithoefer M et al. 2021

Principles of Psychedelic-Assisted Psychotherapy

- **Set** – mindset/intention of participant
- **Setting** – environment & therapeutic container of the therapists - use of music
- Co-therapists

Thanks to Emma Hapke

Three Phases of Psychedelic-Assisted Psychotherapy

- **Preparation** – 6-10 hours
- **Medicine Session** - ~ 8 hours
- **Integration** – 6-10 hours

Thanks to Emma Hapke

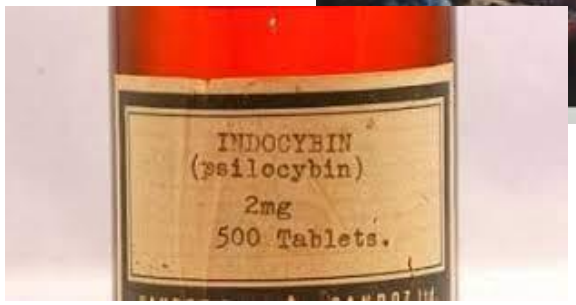
Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine)

- Naturally-occurring compound produced by ~200 species of fungi
- Active metabolite: *psilocin*
- Serotonin 2A receptor agonist
- Duration and quality of drug experience variable
  - Subjective effects usually begin 20-40 min after ingestion
  - Peak after 60-90 min
  - Total duration ~6 hours
- Physiologic effects:
  - Mild increases in BP and HR (transient, dose-dependent)
  - Headache, nausea, dizziness, fatigue

1957 – Life – Gordon Wasson
“Seeking the Magic Mushroom”

Modern History of Psilocybin

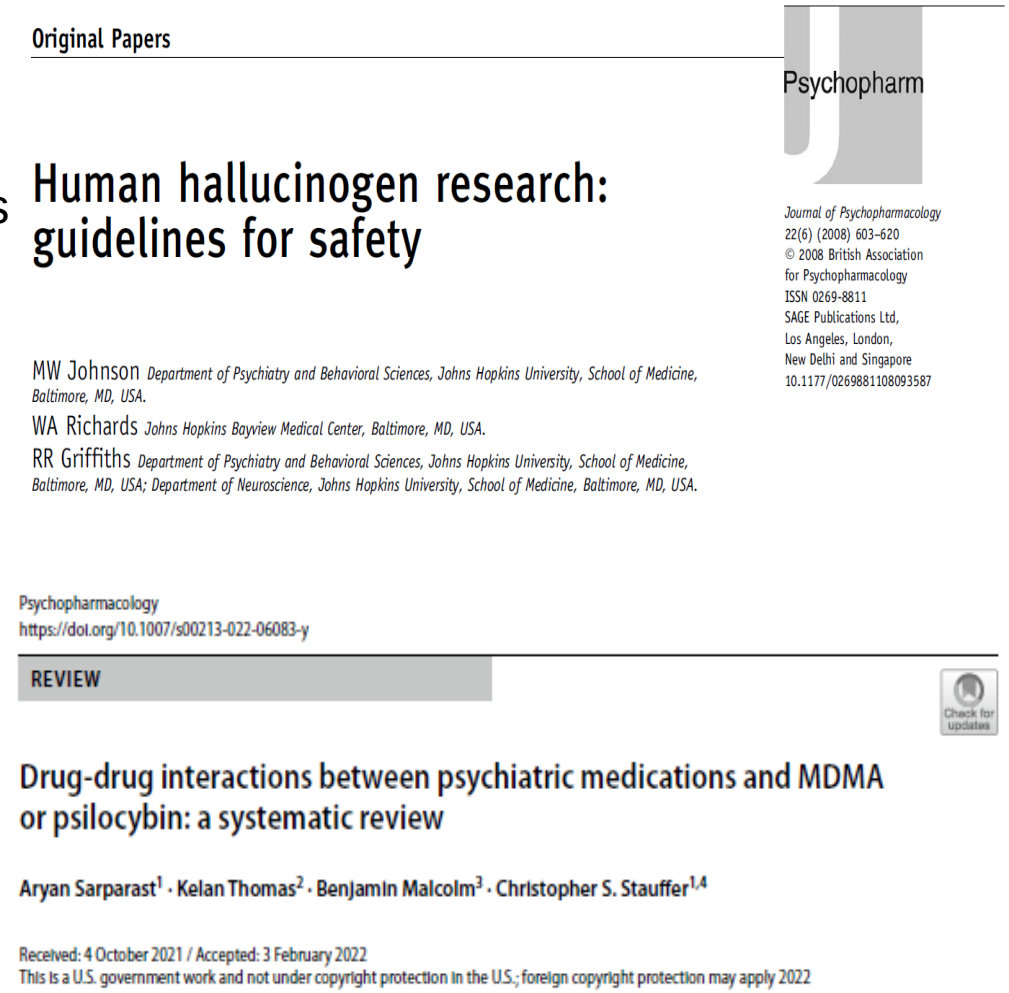
- 1955 – Gordan Wasson travels to Mexico and meets curandero Maria Sabina who guides him in a mushroom ceremony
- 1959 – Albert Hoffman synthesizes psilocybin
- 1961-1965 – Sandoz manufactures and distributes “Indocybin”
- 2006 – research resumes at Johns Hopkins University with healthy humans



Psilocybin – Safety Profile

- **Wide margin of safety**
  - Lethal doses estimated >1000-fold higher than therapeutic doses

- **Contraindications**:
  - Medical
    - Uncontrolled hypertension
    - Recent stroke or MI
    - Arrhythmias
    - CNS disease (mets, seizures)
    - Insulin-dependent diabetes
  - Psychiatric
    - Bipolar I or II disorder (personal or family hx)
    - Psychosis (personal or family hx)
    - Other “severe” disorders - BPD



Original Papers

Psychopharm

Human hallucinogen research: guidelines for safety

MW Johnson *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.*
WA Richards *Johns Hopkins Bayview Medical Center, Baltimore, MD, USA.*
RR Griffiths *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, School of Medicine, Baltimore, MD, USA; Department of Neuroscience, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.*

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REVIEW

Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review

Aryan Sarparast[1] · Kelan Thomas[2] · Benjamin Malcolm[3] · Christopher S. Stauffer[1,4]

Received: 4 October 2021 / Accepted: 3 February 2022

Psilocybin – Safety Profile

- Pharmacokinetics
  - Because minimal MAO reuptake inhibition (i.e., no SERT activity), serotonin toxicity unlikely
  - Drug-drug interactions & psychotropic meds:
    - Antidepressants
    - Antipsychotics
    - Mood stabilizers → lithium

- Persisting adverse effects rare
  - HPPD (Hallucinogen Persisting Perception Disorder)
  - Addiction
  - Psychosis vs. “spiritual emergency”
  - No driving on session day

- “Behavioural toxicity” & psychological risks

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Peer-Reviewed Publication of Non-Pharma Sponsored Trials

1. **Carhart-Harris et al. (2016/2018)**
   - Open-label feasibility study, TRD, n=12/20, 🍄🍄, 6-mo f/u
     → No SAEs
     → Significant reduction in depressive symptoms, associated w/ ratings of acute experience

2. **Davis et al. (2021)**
   - RCT (waitlist control), MDD, n=24, 🍄🍄, 4-week f/u
     → Large effect size & high rates or response and remission
   - Guskayan et al (2022) – 12-month f/u → sustained sig. depression scores, response & remission rates

3. **Carhart-Harris et al. (2021)**
   - RCT (psilocybin vs. escitalopram – "double dummy"), MDD, n=59, 🍄🍄, 6/week f/u
     → On primary outcome (QIDS), no sig diff btw groups
     → Overall rates of AEs similar, but anxiety, dry mouth, sexual dysfunction, flat affect in SSRI group only

Total Number of People with MDE/TRD Treated with Psilocybin in Randomized Peer-Reviewed Studies

51

Carhart-Harris et al, 2016

- Open-label feasibility study
- 12 patients (6 M, 6 W) with moderate-severe unipolar TRD of long-standing nature received two oral doses of psilocybin (10 mg and 25 mg) 7 days apart in a “supportive setting” – 5/12 had previously used psilocybin
- Primary outcome for feasibility – patient-reported intensity of psilocybin’s effects
- Evidence for safety & tolerability
- Depressive symptoms reduced following 25 mg dose at 1 week and 3 months

Carhart-Harris et al. *Lancet Psychiatry.* 2016, 3:619-627

Carhart-Harris et al, 2018

- Six-month f/u data of the 2016 cohort that had been supplemented with an additional 8 patients for a total sample of 20
- Of the 9 responders at 5 weeks – 3/9 relapsed at 6 month and 6/9 maintained response
- Effect size at 6 months – Cohen's d – 1.7

Carhart-Harris RL, et al. *Psychopharmacology* 2018, 235:399-408

Davis et al 2021

- Center for Psychedelic and Consciousness Research, Johns Hopkins
- Randomized, waiting list-controlled clinical trial – 2 sessions of psilocybin in the context of supportive psychotherapy – randomization to treatment immediately or 8/52 delay
  - moderate (20mg/70 kg) then high (30 mg/70 kg) ~ 1.6 weeks apart
- Primary outcome – depression severity – GRID-HAMD
- Secondary outcomes – QIDS-SR (Quick Inventory of Depressive Symptomatology – Self-Rated)

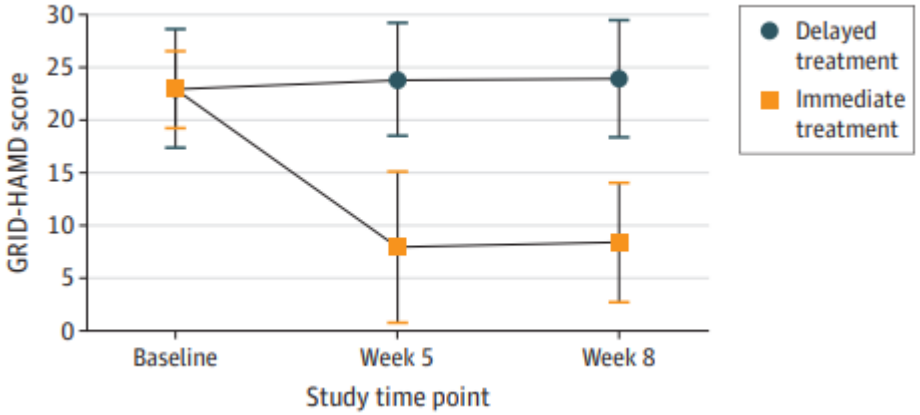
Davis AK et al. *JAMA Psychiatry*, 2021:78(5):481-489

Davis et al, 2021

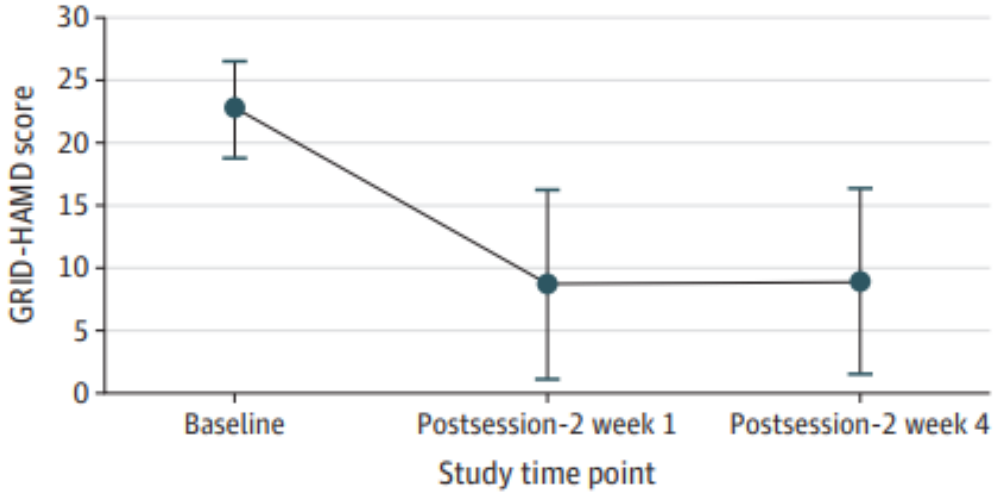
- 800 screened → 70 assessed → 27 enrolled → 24 completed
- Participants
  - Moderate or severe depression (GRID-HAMD ≥ 17)
  - Time in current major depressive episode – 24.4 (22) mo
  - Lifetime psychedelic use 0.8 (1.9)
  - Age – 39.8 (12.2) yr – 21 – 75
  - Sex - F 16 (67%), M 8
  - Education – 20 Bachelor's degree or higher
  - Married – 46%
  - Employment status – 63% FT, 17% PT, 21% unemployed

Davis et al 2021

- Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups



- Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 5 Postsession-2 Follow-up in the Overall Treatment Sample



Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder – A Randomized Clinical Trial. *JAMA Psychiatry*. 2021:78(5):481-489. Figure 3 & 4; p. 486

Davis et al 2021

Week	Response (≥ 50% reduction in score)	Remission (≤ 7 GRID-HAMD)	Effect Size (Cohen's d)
1 following session 2 of active dose	17 (71%)	14 (58%)	2.3 (95% CI 1.5-3.1)
4 following session 2 of active dose	17 (71%)	13 (54%)	2.3 (95% CI 1.5-3.1)

Gukasyan et al 2022

- Center for Psychedelic and Consciousness Research, Johns Hopkins
- 12 month f/u of Davis et al 2021 randomized, waiting list-controlled clinical trial of 2 sessions of psilocybin in the context of supportive psychotherapy
- 24 patients followed at 1, 3-, 6- and 12- month follow-up
- 12 month follow-up
  - Response = 75%
  - Remission = 58%
  - No serious adverse events
  - No use of psilocybin outside of the study context
  - Participant ratings of personal meaning, spiritual experience and mystical experiences of sessions predicted ↑ well-being but did not predict improvement in depression

Davis et al 2001

- Side-effects
  - 1 participant had DBP > 100 mm Hg but resolved spontaneously & didn't impact session
  - ½ of participants reported challenging emotional or physical experiences
  - Mild to moderate transient headache
    - 16/48 sessions (33%)
    - post session in 14/48 sessions

Carhart-Harris et al 2021

- NEJM paper of psilocybin vs. escitalopram
- Phase 2, double-blind, randomized controlled trial
- Moderate to severe MDD
- Received either:
  - 2 separate doses of 25 mg psilocybin 3/52 apart plus 6/52 of daily placebo
  - 2 separate doses of 1 mg psilocybin 3/52 apart plus 6/52 of escitalopram (10 mg weeks 1-3, 20 mg weeks 4 – 6)
- Primary outcome – change in QIDS-SR-16

Carhart-Harris R et al. *NEJM* 2021; 384:1402-1411

Carhart-Harris et al 2021

- Participants
  - 1000 screened (most were volunteers - 891 did not meet inclusion criteria) & 50 declined → 103 formally screened → 59 enrolled → 27 completed psilocybin and 24 completed escitalopram
  - Mean age – 41 (21-64)
  - Mostly white, university educated, long duration of illness
  - # of previously trialed psychiatric medications ~ 2
  - # of prior psychotherapy – 91.5%
  - Baseline HAMD-D – screening 17 required, at pretreatment baseline range 11 – 26 – average 19.2 in psilocybin group & 18.4 in escitalopram group
  - Baseline QIDS-SR-16 – range 6-23

Carhart-Harris R et al. *NEJM* 2021; 384:1402-1411

Carhart-Harris et al 2021

- Results
  - Change in QIDS-SR-16 scores did not differ significantly between trial groups
  - Secondary outcomes mostly favored psilocybin over escitalopram but confidence intervals were not adjusted for multiple comparisons
  - When cued to report on specific emotional and side-effect-related phenomena through the PTCS

Carhart-Harris R et al. *NEJM* 2021; 384:1402-1411

Qualitative Research

- Watts et al. (2017)
  - participants from Carhart-Harris Imperial College of London open-label trial (n=20)
  - thematic analysis of participant perspectives of psilocybin treatment and its comparison with other treatments
  - 2 main change processes
    - **Disconnection → connection**
    - **Avoidance of emotion → acceptance**
- Davis et al. (2021)
  - Johns Hopkins waitlist control RCT participants
  - **Emotional release and resolution** - peace, acceptance, letting go (of pain, sadness, trauma)

Watts R, et al. *J Human Psychol* 2017, 57(5):520-564

Davis AK, et al. *JAMA Psychiatry*, 2021:78(5):481-489

“…unlike with recreational users we found that very few of the depressed patients enjoyed the experience. They found confronting their depressive thoughts and memories quite challenging but afterwards almost all felt the experience had been worthwhile.”

Nutt 2019

Nutt D, *Dialogues Clin Neurosci* 2019; 21(2):139-147, p. 145

Pharma Sponsored: Compass Pathways – Proprietary Psilocybin Preparation – "COMP360"

****Caveat**: "topline results" = press-release only (i.e., no peer-reviewed publications)

Design: Phase IIb, DB-RCT, placebo-controlled, n=233 (multi-site), TRD, 🔔 (1mg vs. 10mg vs. 25mg) single dose

- Characteristics of "psychological support" unclear

Preliminary efficacy: rapid, significant reductions in depression scores (MADRS) ~ 6 points in 25 mg group

- "Positive" findings at 3-week mark
- 12 week sustained response in 24.1% receiving 25 mg dose vs. 10% in those receiving 1 mg

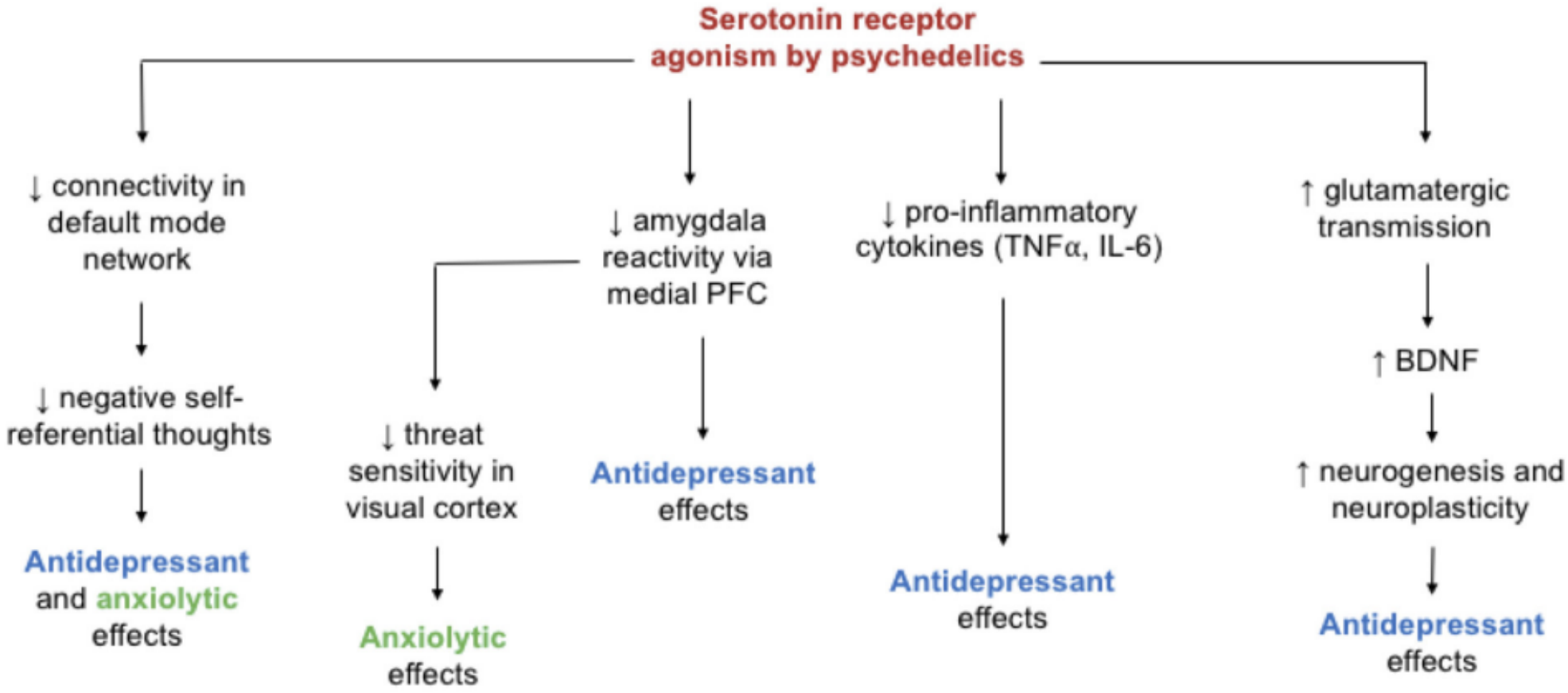
Safety: **12 SAEs (incl. suicidal behaviour, self-injury, and SI – primarily among those who failed to respond to therapy) – more frequent in 25mg group than the 10mg or 1mg groups

Limitations of Current Research

- Research base is currently limited – clinicaltrials.gov lists almost 30 trials
- Existing research has major limitations
  - Blinding – big challenges!
    - Effect size likely overestimated in early trials.
    - Integrity needs to be assessed.
  - Expectancy confound
  - Short f/u periods
  - Poor characterization of psychotherapy component
- External validity
  - Highly motivated patients
  - Previous psychedelic experiences
  - Diversity issues
- Conflicts of interest

Serotonin Receptor Agonism & Psychedelics – Multiple Neurobiological Mechanisms Mediating Anti-depressant and Anxiolytic Effects

Muttoni S. *J Affect Disorder*. 2019:258:11-24. p. 12



Therapeutic Mechanisms - ? Transdiagnostic

- **Neurobiological**
  - ↑ neuronal plasticity
  - ↓ "modularity" of brain regions/networks = greater global integration of brain function
  - ↓ default mode network activity
  - "Reset" of the brain

- **Psychological**
  - ↑ psychological flexibility
  - ↑ mindfulness
  - ↑ insight
  - ↑ cognitive flexibility
  - ↑ resilience
  - ↑ creativity
  - ↑ connectedness
  - ↑ openness to experience

- **Experiential**
  - NOSCs
  - Emotional breakthrough
  - Psychological insight

- **Spiritual**

Mechanisms

- Neuroimaging baseline & 1 day post dose in Carhart-Harris study
  - Decreases in fMRI brain network modularity = global increase in brain network integration
  - 5-HT2A receptor-rich higher order functional networks became more functionally interconnected and flexible after psilocybin treatment
  - These changes are not observed with escitalopram

Microdosing of Psilocybin (and Other Psychedelics)

- Alternative paradigm – developed underground so inconsistencies in definition – typically 10-20% of full dose used regularly (1 – 3 x per week)
- Lots of interest but limited evidence to guide us
- Some evidence that both LSD (10-20 mcg) and psilocybin (<1-3 mg) have subtle, positive effectives on cognitive processes and affective processes – and may induce cognitive flexibility and decrease rumination

Kupyers KPC. *Ther Adv Psychopharmacol* 2020; 10:1-15

Microdosing of Psilocybin

- Balázs Sigeti, 2021– “self-blinding citizen science”
  - Online instructions on how to incorporate placebo control into their microdosing practice without clinical supervision
  - 191 participants (1630 signed up → 240 started → 191 completed)
  - Psychedelic of choice – psilocybin containing mushrooms 23%, legal LSD analogues 14%, black market LSD 61%
  - All psychological outcomes improved significantly from baseline to after the 4 weeks long dose period however the placebo group also improved and no significant between group differences were observed
  - Small but significant microdose vs. placebo differences but can be explained by breaking blind
  - Anecdotal benefits of microdosing can be explained by placebo effect

Szigeti B et al. *e-Life* 2021; 1-:e62878

Take Home Messages

- Hopeful but “not ready for primetime” just yet

UHN Centre for Mental Health