Identification of methodological issues and how to overcome them

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Conflict of Interest

Chair of the Psychedelic Working Group and excutive committee member (past-president) of the European College of Neuropsychopharmacology (ECNP)

Served as

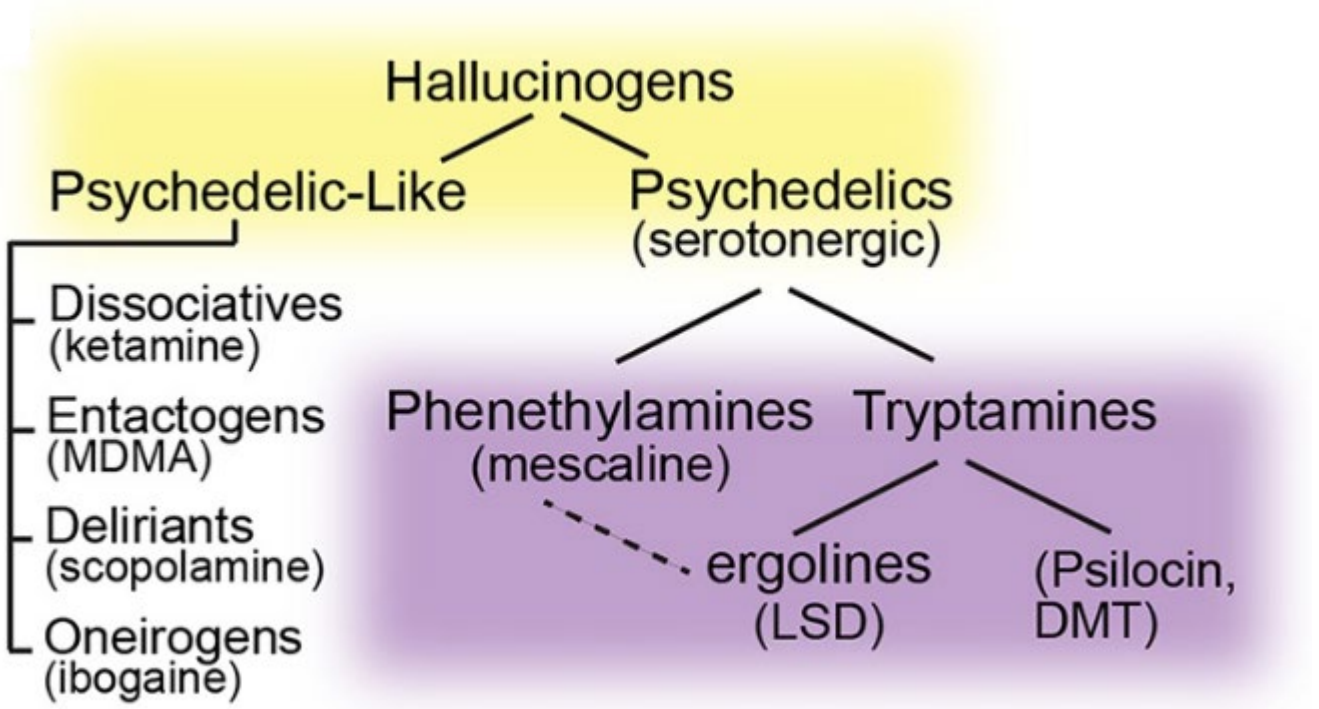
- a speaker for Angelini, Abbvie, Cybin, and H. Lundbeck
- an advisor for Sanos, Onsero, Pangea Botanica, Gilgamesh, Pure Technologies
- a research site for Reunion and Delix Therapeutics

Overview

Methodological issues and how to overcome them

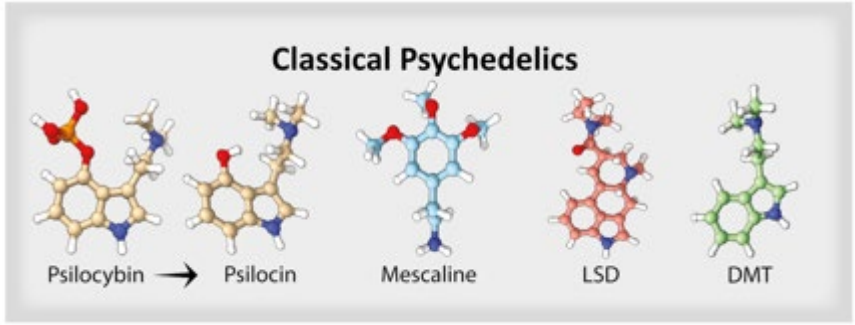
- Placebo, blinding, and expectations
- Dosing and maintenance of effect
- Safety and adverse events
- Setting and psychological support/psychotherapy
- Questions

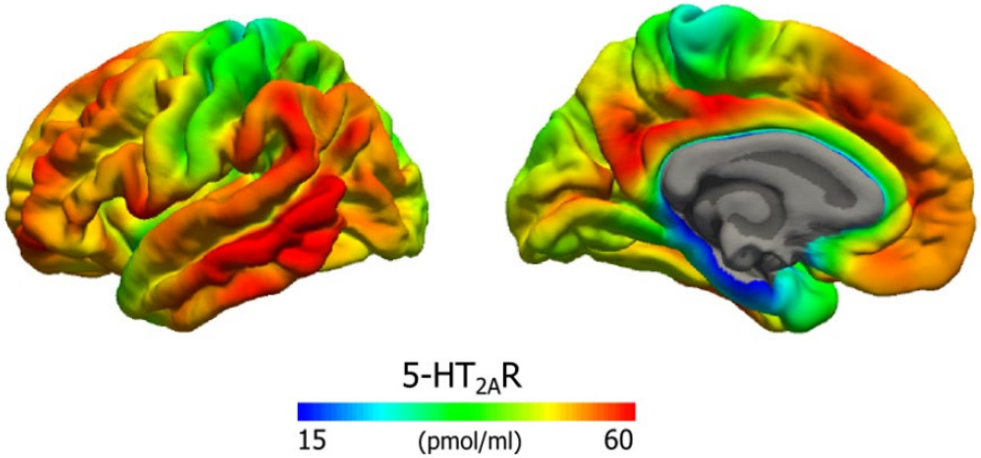
Nomenclature



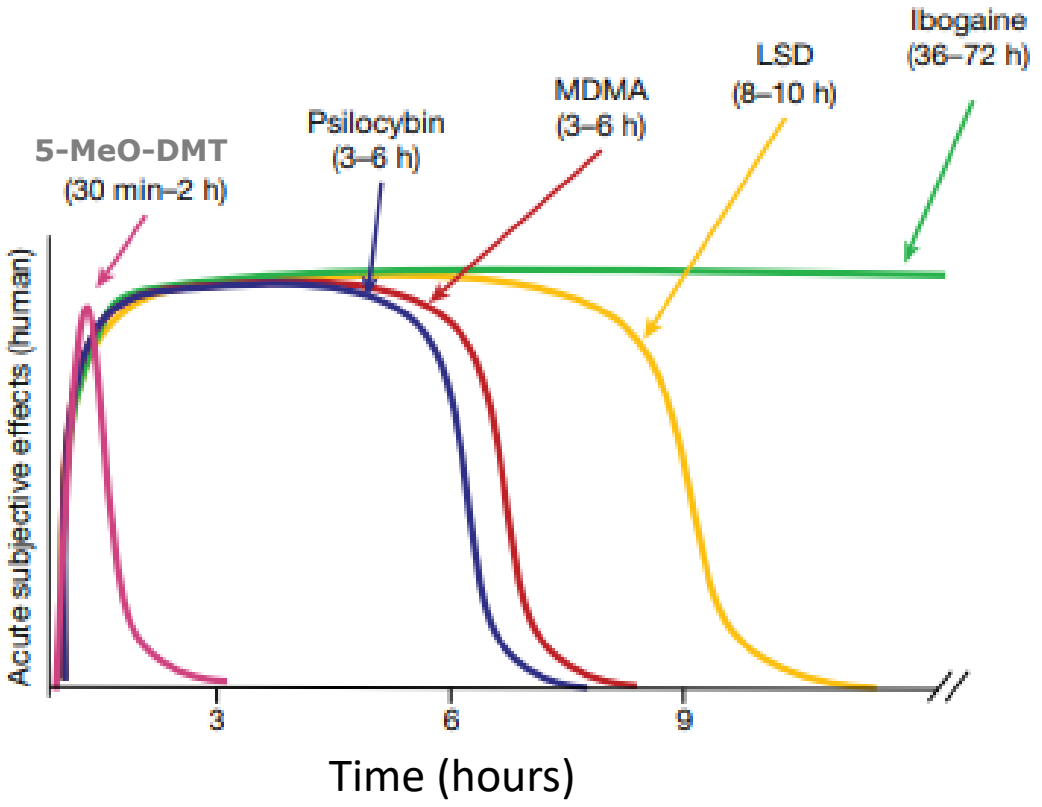
Grieco et al, J Neurosci 2022

The psychedelic experience is contingent on 5-HT$_{2A}$ receptor stimulation of classical psychedelics





Beliveau et al, J Neurosci, 2017



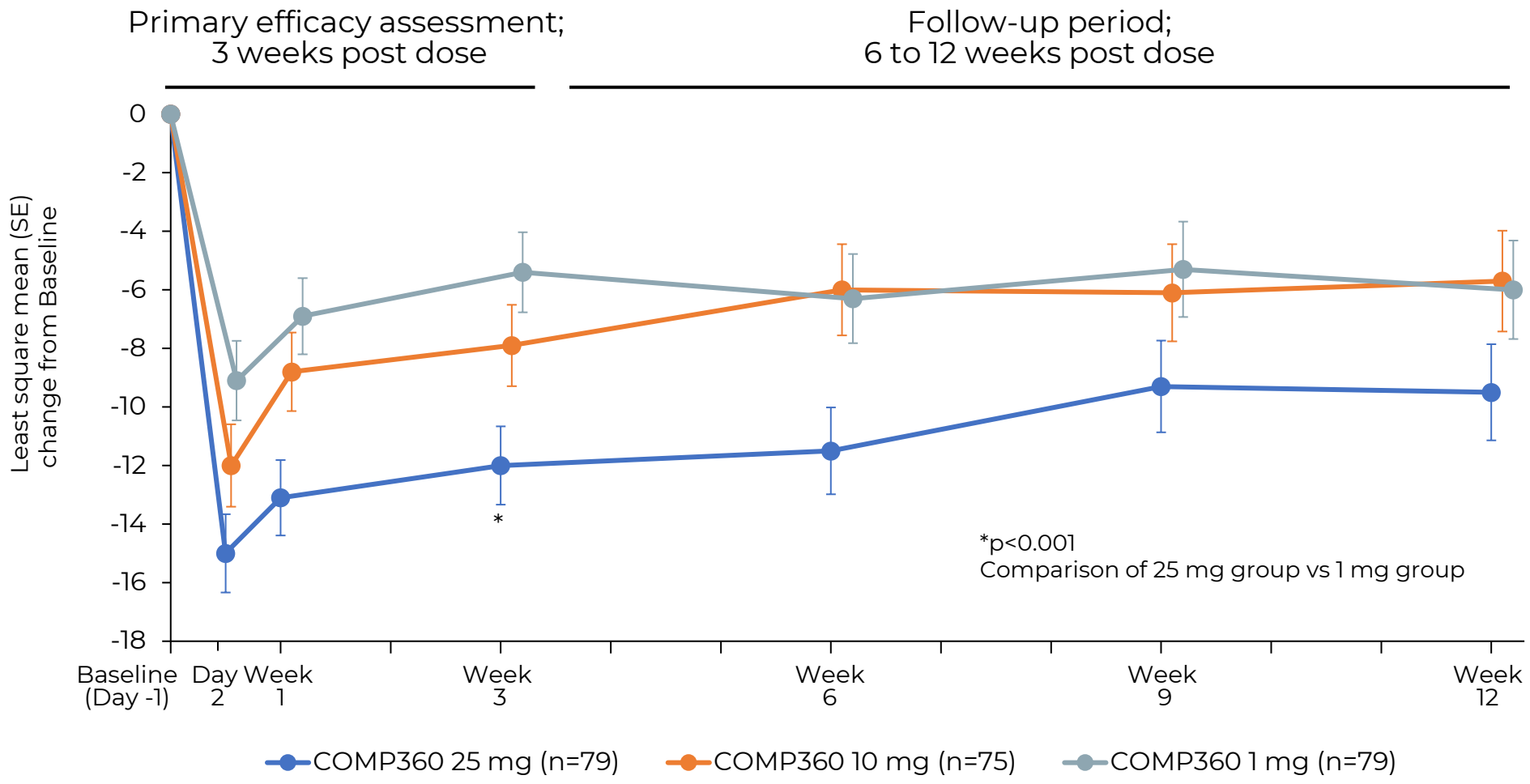
Modified from Nardou et al, Nature, 2023

Blinding, placebo, and expectations

- With psychedelic doses, patients and investigators invariably know that they are getting active drug
- Placebo effects (even) hard(er) to discern
- Patients expectations *may* mean that placebo experience is disappointing
- Solutions include:
  - Incorporate different doses of active compound in the trial design
  - Monitor subjective intensity of the psychedelic experience, patient's guess of dose and expectation
  - Use of independent and blinded external raters

IV Efficacy, Safety, and Tolerability of COMP360

Change from Baseline in MADRS total score up to Week 12 (full analysis set)



MADRS: Montgomery-Åsberg Depression Rating Scale; n: Number of participants; SE: Standard error
Goodwin GM, et al. *N Engl J Med*. 2022;387(18):1637-1648.

CYB003: Phase 1/2a Trial Design

Study Design:

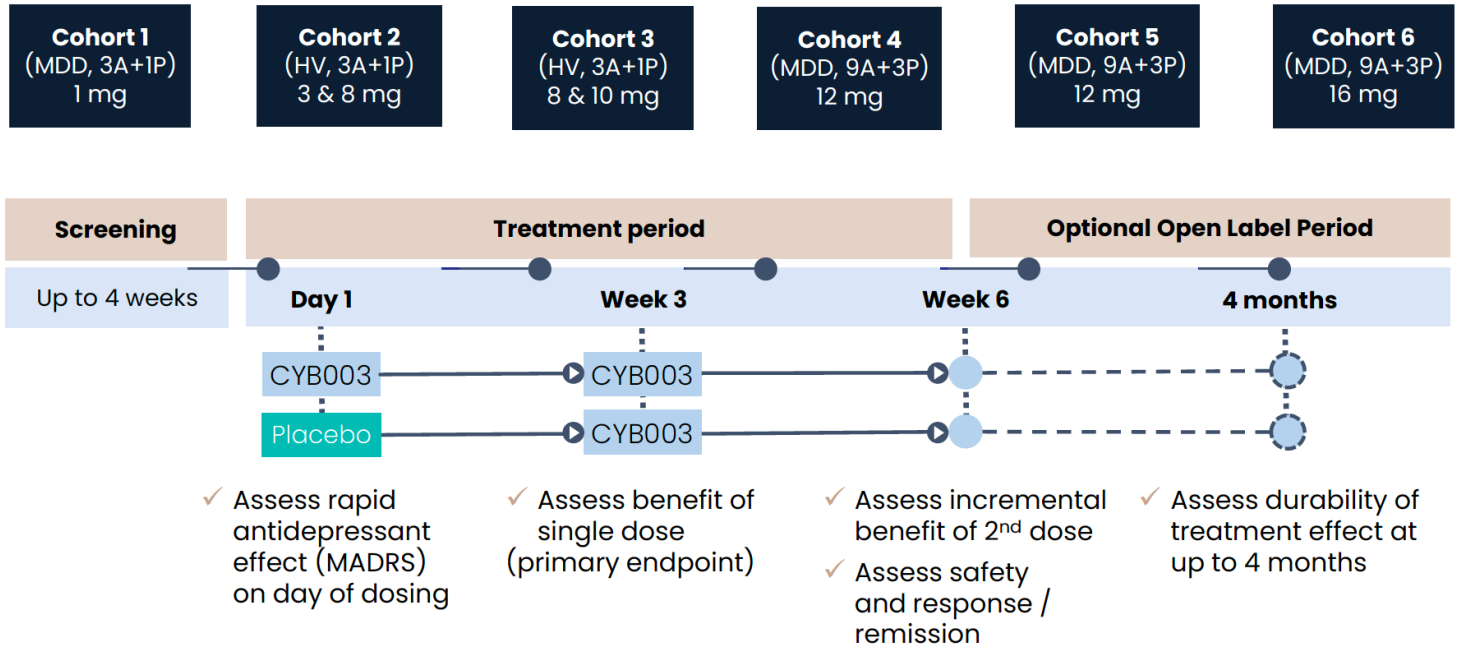
- ✓ Randomized, double-blind, placebo-controlled trial

Key Inclusion Criteria:

- ✓ Men and women, 21 to 65 years old
- ✓ Moderate to severe MDD (MADRS ≥ 21)
- ✓ Inadequate response to antidepressant medication

Endpoints:

- ✓ Reduction in depression symptoms (change in MADRS score) at Week 3 after a single dose*
- ✓ Change in MADRS score at Day 42, after second dose
- ✓ Safety, PK and tolerability



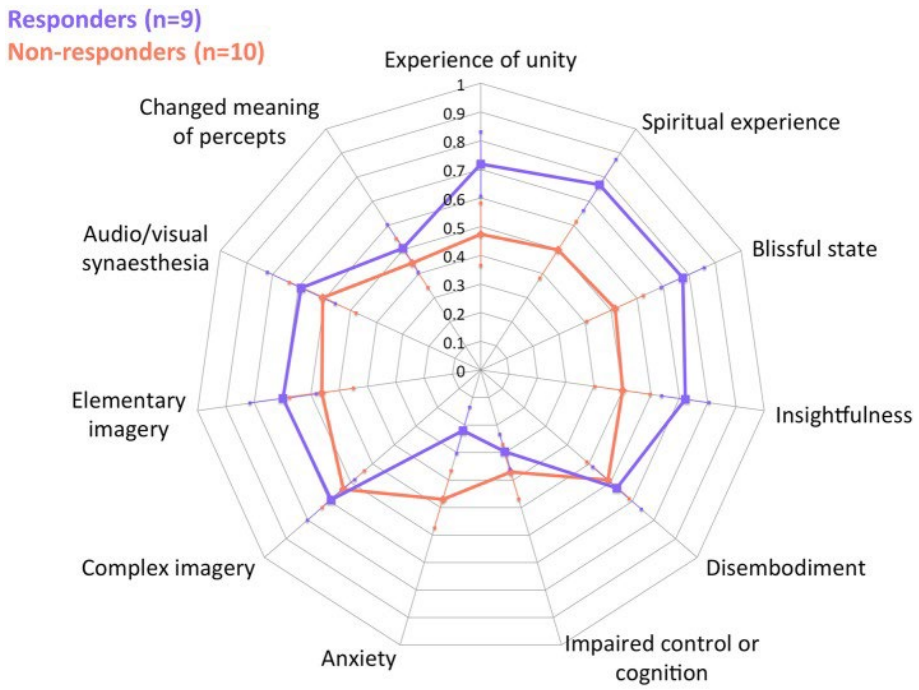
**** Patients allowed to remain on stable doses of antidepressant medications***

MDD: participants with major depressive disorder; HV: healthy volunteers; Primary efficacy assessed at Week 3; Optional 12 week follow up to assess durability of effects

Note:
**All data presented are preliminary.*

Dosing and maintenance of effect

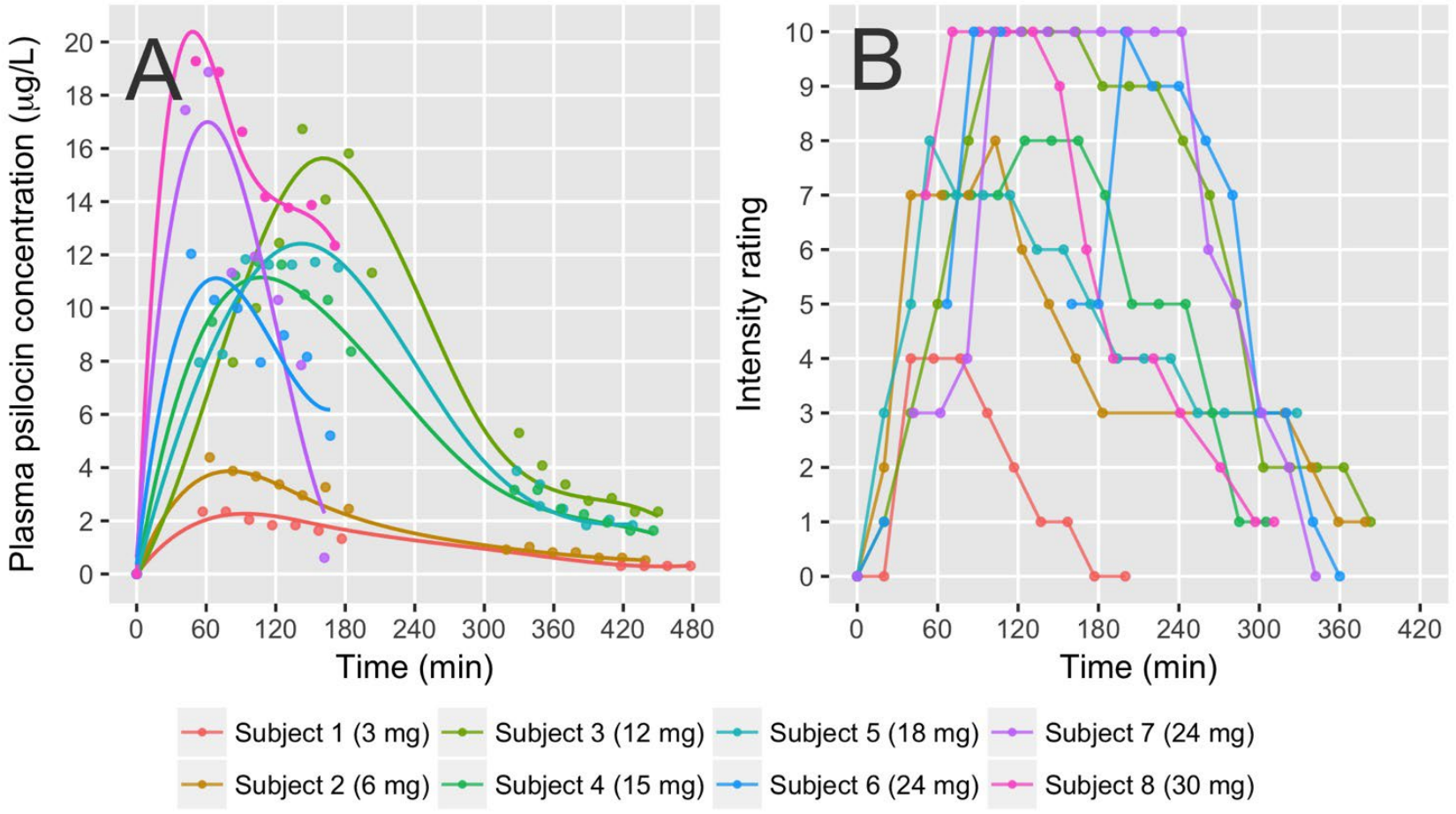
- The relationship between characteristics of the acute psychedelic experience (e.g., MEQ) and clinical improvement should be characterised
- Should concomitant treatments (e.g., SSRI's) be abandoned?
- Long-term (> 6 months) therapeutic effects monitored – with or without other treatments?
- Is one dose enough?
- Need for individualised dosing due to interindividual variability in drug metabolism, age, sex, or personality ?



Altered State of Consciousness (ASC)
Roseman et al, Front Pharmacol 2018

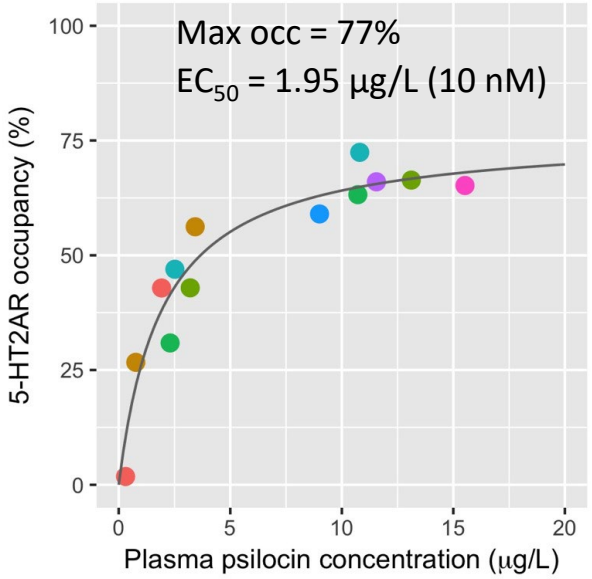
Psilocin levels and subjective effects

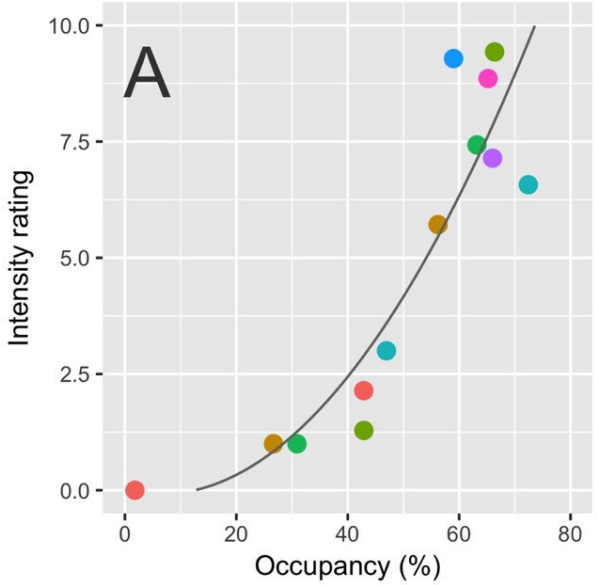
- Plasma psilocin levels
- Subjective experience intensity

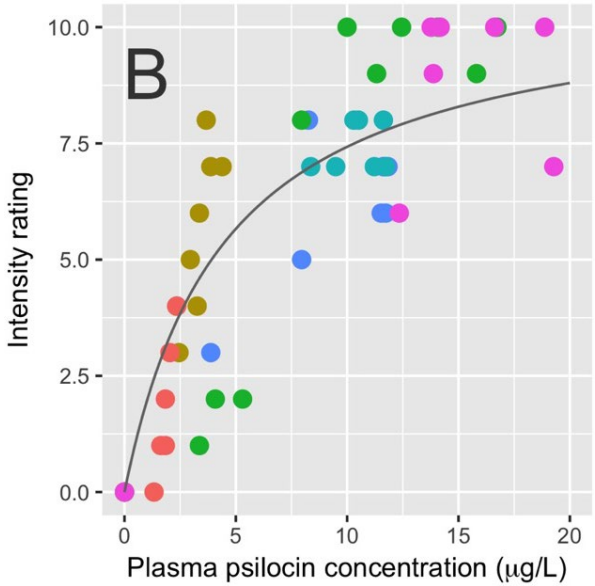


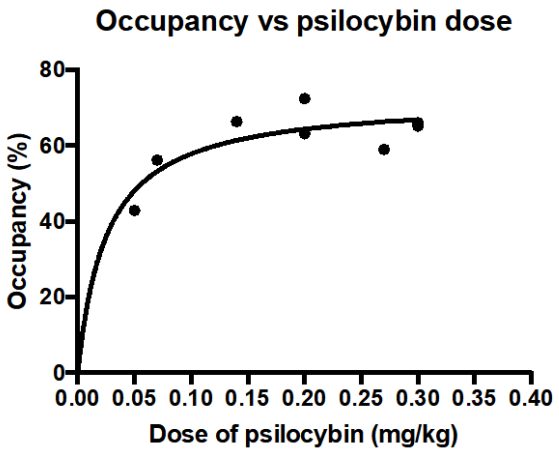
Madsen et al., *Neuropsychopharmacol 2019*

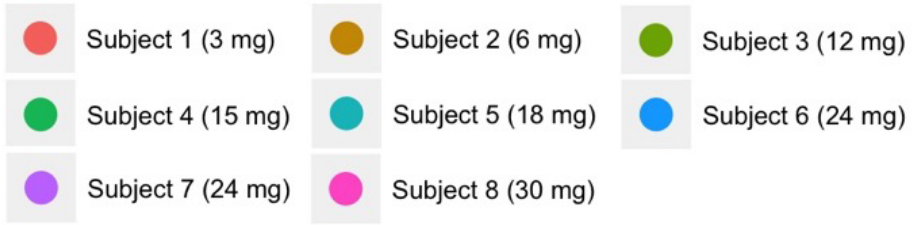
5-HT_{2A} receptor occupancy, dose, p-psilocin, and the subjective intensity of the psychedelic experience











Madsen et al., Neuropsychopharmacology 2019

Safety and adverse events

- Acute effects
  - Transiently elevated blood pressure and tachycardia
  - Nausea
  - Headaches
  - Anxiety (with derealization)
  - Harms to self and other

- Late effects
  - Flash-backs
  - Potential personality changes
  - Altered metaphysical beliefs
  - Psychosis
  - Suicidality?

Schlag et al, J Psychopharmacol 2022

Setting and psychological support/psychotherapy

Is it

- psilocybin-assisted psychotherapy *or*
- psychotherapy-assisted psilocybin therapy *or*
- psychologically supported psilocybin therapy?

How much does the setting matter?

Settings during the psilocybin psychedelic experience

		MR	Room	
Acute experience	MEQ - mystical	2.0	3.6	p=0.007
	MEQ - positive mood	2.5	3.8	p=0.01
	ASC - spiritual	13.7	47.2	p=0.008
	ASC - blissful state	37.1	66.0	p=0.02
12 weeks later	PEQ - SumPositive	6.8	47.7	p=0.008

Johansen et al, in prep

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