What Can be Learned From Altered States?

The Renaissance of Psychedelic-Assisted Psychotherapy

2022 JGH Department of Psychiatry Research Day

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Presenter Disclosure

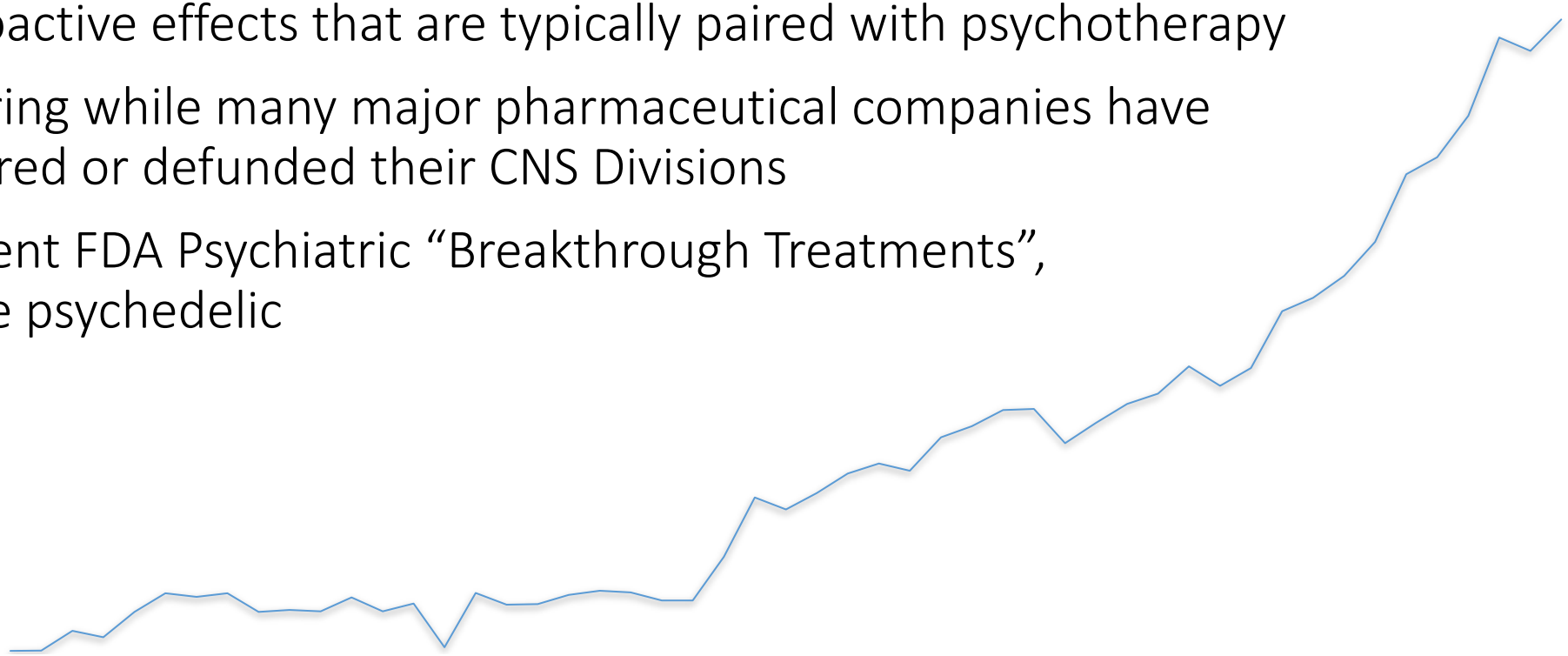
- **Grants/Research Support:**
  - The Quebec Network on Suicide, Mood Disorders and Associated Disorders (RQSHA)
  - Jewish General Hospital Department of Psychiatry financial support
- **Speakers Bureau/Honoraria:**
  - Medical Doctor Psychotherapy Association of Canada (teaching)
- **Consulting Fees:**
- **Other:**
  - Unpaid scientific advisor for Wake Networks Incorporated
  - Unpaid guide trainer for Therapsil
  - Co-created course on ketamine for Psychedelic.Support

Presenter's Background

- Since 2018, operating intravenous ketamine for treatment-resistant depression clinics at the Douglas and, as of 2021, at the JGH
- About 300 ketamine infusions administered to highly refractory patients from across Quebec along with Dr. Nicolas Garel (R5 Psychiatry)
  - Unipolar and bipolar depression
  - Universally
- Pursuing psychedelic biopsychosocial approaches to enhancing and prolonging ketamine's efficacy
- Our (intense) experiences with this population have taught us a great deal about the psychedelic and conventional psychiatric models
  - E.g., the ubiquity of broken brain narratives in this population

The Psychedelic Renaissance

- Explosive interest in a variety of drugs with powerful, transient psychoactive effects that are typically paired with psychotherapy
- Occurring while many major pharmaceutical companies have shuttered or defunded their CNS Divisions
- Of recent FDA Psychiatric “Breakthrough Treatments”, 4/8 are psychedelic



Ketamine Publications by Year

(Similar for Psilocybin)

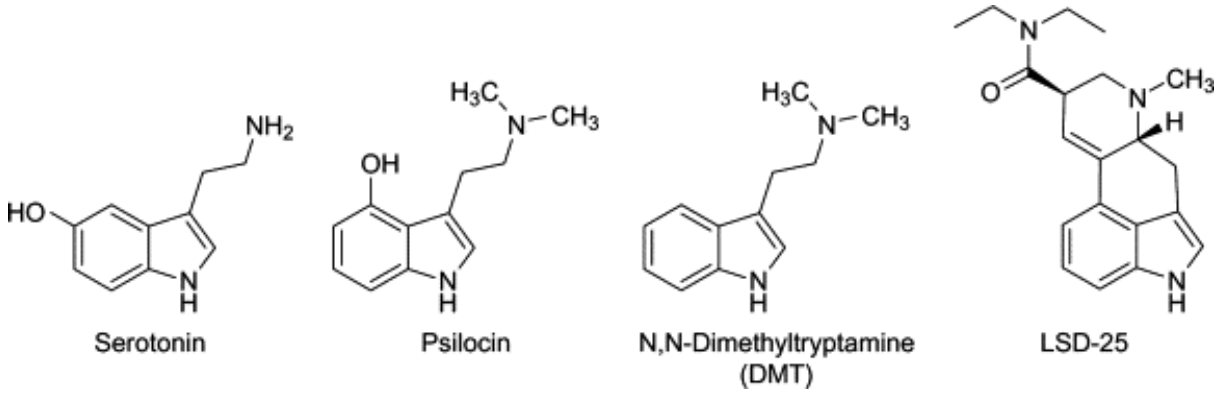
1. Prevalence, Severity, and Unmet Need for Treatment of Mental Disorders in the WHO JAMA. 2004;291(21):2581. doi:10.1001/jama.291.21.2581
2. Wegener G, Rujescu D. The current development of CNS drug research. Int J Neuropsychopharmacol. 2013;16(7):1687-1693. doi:10.1017/S1461145713000345

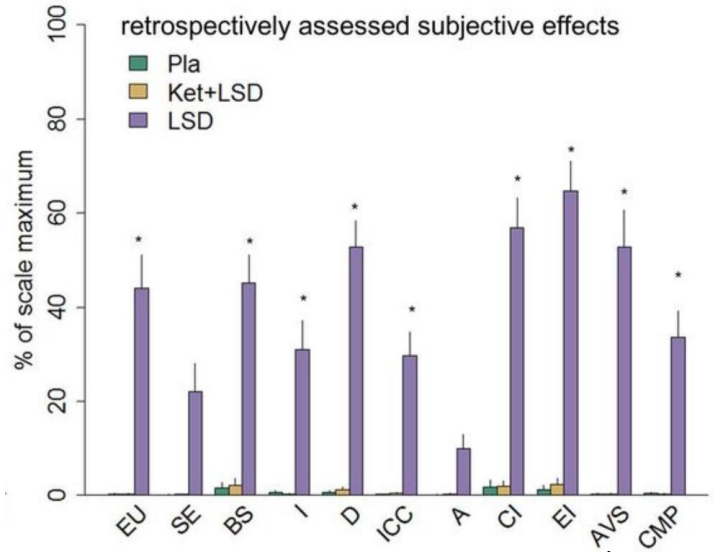
New Psychedelic Research Centers:

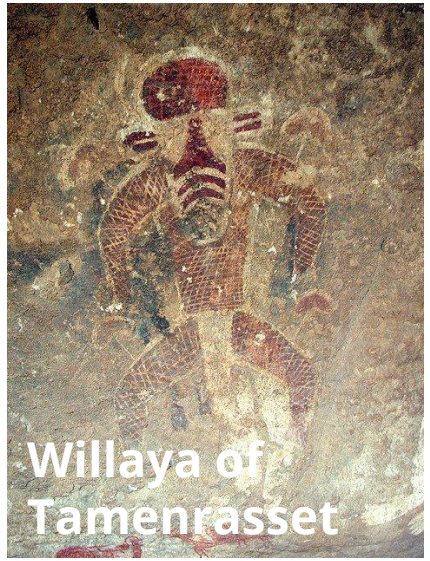
- Imperial College London (2019)
- John Hopkins (2020)
- Stanford (2020)
- California, Berkeley (2020)
- University of Toronto (2021)
- University of New York (2021)
- Harvard University (2021)
- University of California in San Francisco (2021)
- Mount Sinai (2021)
- University of Calgary (2021)
- Queens University (2021)
- University of Texas (2021)
- University of Sidney (2022)
- Naropa University (2022)

What is a (Serotonergic) Psychedelic?

- A neologism coined in 1953 by Canadian psychiatrist Humphrey Osmond from the Greek *psyche* (mind/soul) and *delos* (reveal/manifest)
- Molecules' origins can be traced variously to:
  - 6,000 BC North Africa
  - Aztec Rituals
  - 20th Century Switzerland
- Defining feature: **5-HT$_{2A}$ agonism**
  - Neural and subjective effects blocked by Ketanserin (**5-HT$_{2A}$ antagonist)**
- Pharmacokinetics vary greatly





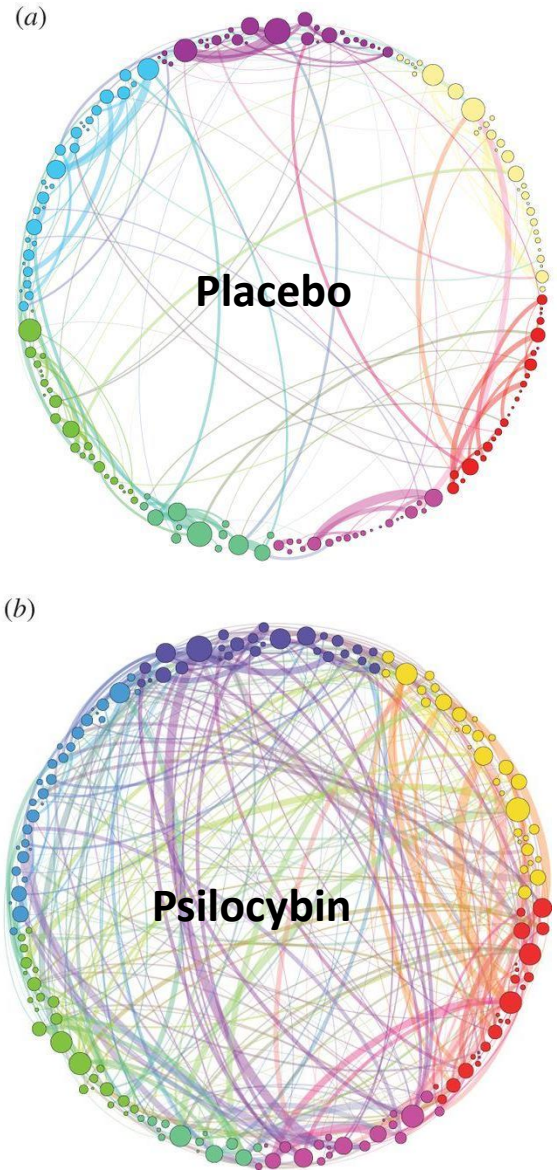


Preller et al. 2018 eLife 2018;7:e35082 DOI: 10.7554/eLife.35082

Neural Effects of $5HT_{2a}$ Agonism

- Neurophysiological effects
  - Pyramidal cell activation
  - Modulates neuronal gain
  - Excites a subtype GABAergic interneurons
- Regional effects, e.g.,
  - Increased amygdala cerebral blood flow *during* acute drug effects
  - Decreased amygdala cerebral blood flow *after* acute drug effects
- Acute neural circuit effects
  - Decrease in *intra-* functional neural circuit integrity
  - Increase in *inter-* functional neural circuit communication
- Post-acute neural circuit effects
  - Default Mode Network integrity decreased *during* drug effects
  - Default Mode Network integrity increased *after* drug effects

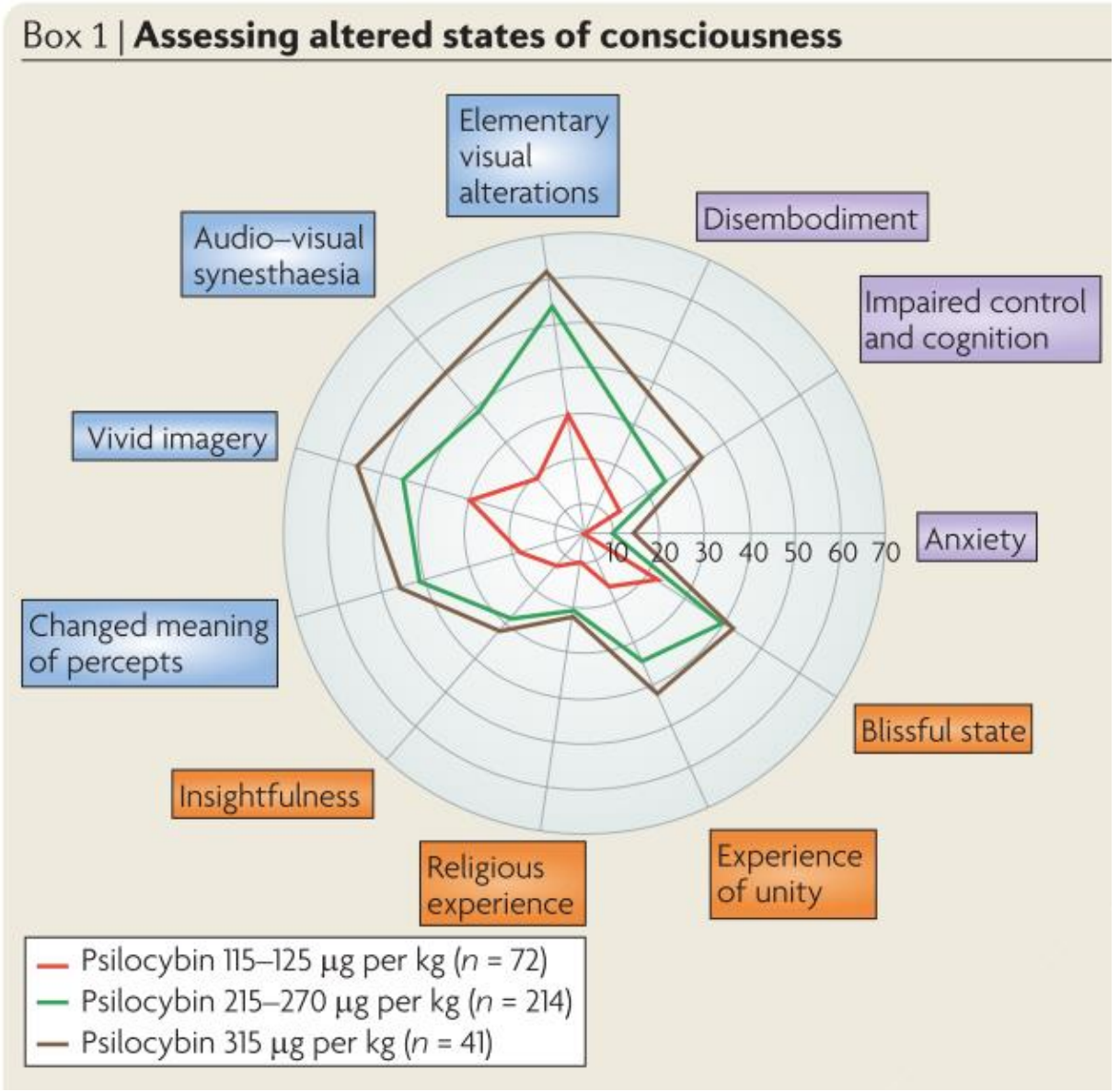
Global Connectivity



Petri G et al. 2014. J Royal Soc Interface doi: 10.1098/rsif.2014.0873

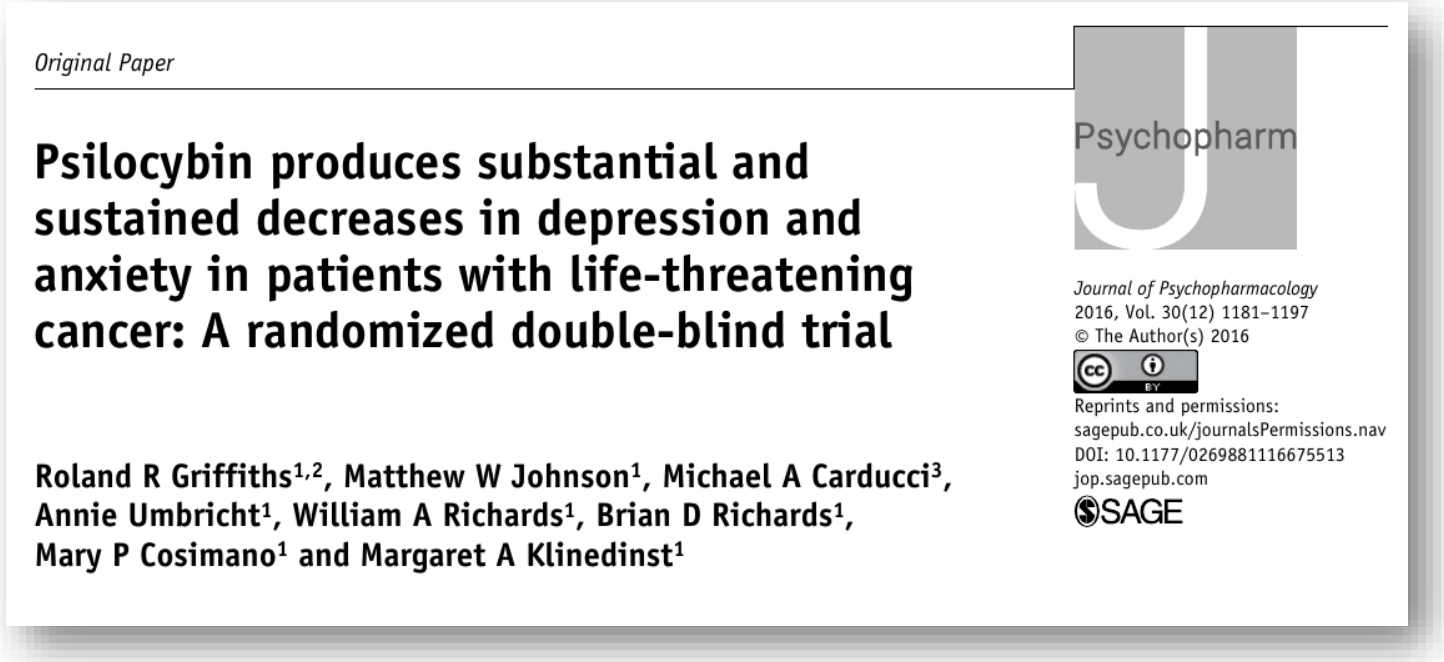
Phenomenology

- Hallucinations/illusions
- Alteration or dissolution of ones sense of self
  - Experiences of unity, “bliss”, mystical experiences
  - Altered meaning, emotional release
  - Disembodiment
- “Set and Setting” amplifiers:
  - Internal environment (mind**set**)
  - External environment (physical **setting**)



Vollenweider FX, Kometer M. **The neurobiology of psychedelic drugs: implications for the treatment of mood disorders.** Nat Rev Neurosci. 2010;11(9):642-651. doi:10.1038/nrn2884

Beginning of My Interest in Altered States I:
Can One Experience Change Your Life?



Original Paper

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths[1,2], Matthew W Johnson[1], Michael A Carducci[3], Annie Umbricht[1], William A Richards[1], Brian D Richards[1], Mary P Cosimano[1] and Margaret A Klinedinst[1]

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(12) 1181–1197

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DOI: 10.1177/0269881116675513
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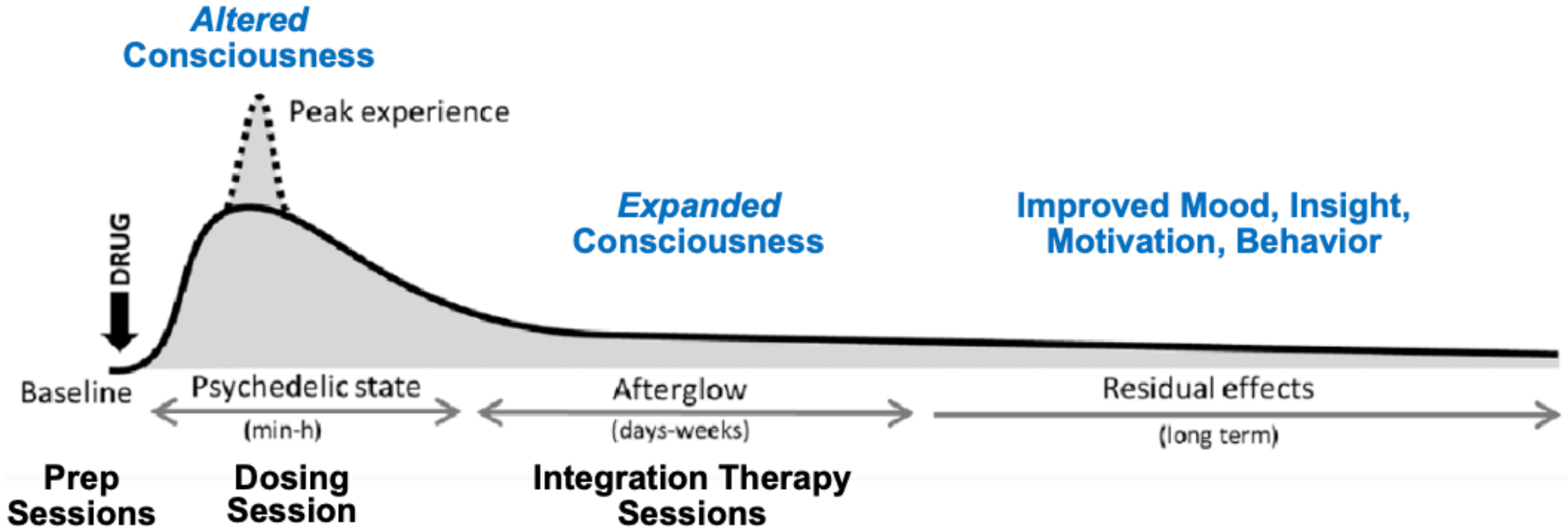
- Double-blind cross-over of 51 patients of placebo-like dose of psilocybin versus high-dose psilocybin, with psychedelic psychotherapy
- Significant, sustained reductions in anxiety and depression persistent at 3 years follow-up, strongly correlated with aspects of the drug experience (e.g., mystical-like experiences)
- At 6 months, 67% of patients rated the high-dose as one of the top 5 most personally meaningful experiences of their lives (versus 24% who received low-dose)
- Similar findings in addictions, major depression and treatment-resistant depression

Psychedelic Therapy Process and Postulates

- Mystical/peak experiences can produce profound, lasting benefits
- Psychedelic guides:
  - Create conditions for these experiences to arise with a psychedelic
  - Help patients to “integrate” these experiences
- Common themes of such experiences in patients with terminal illnesses:
  - Interconnectedness of everything
  - “All is love”
  - Undying nature of the soul
- Such experiences can have clear therapeutic effects against existential distress and other psychiatric conditions like depression (at least to some extent)

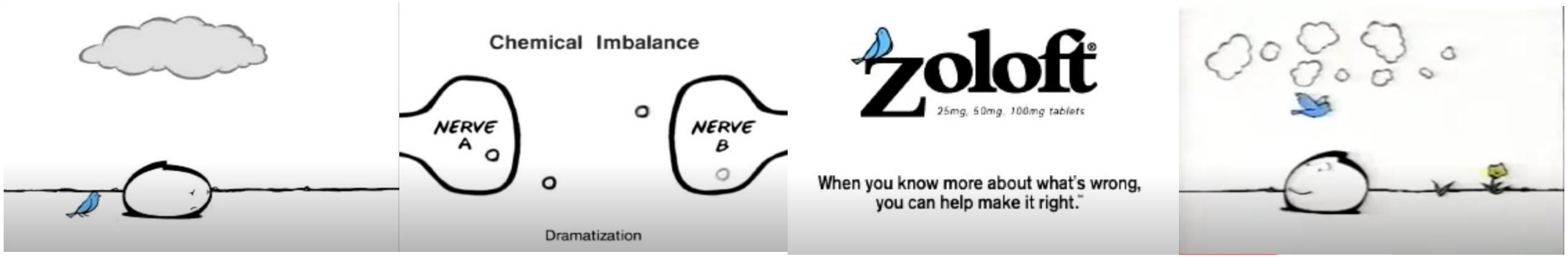


Question to Ponder

How can depression be effectively treated by:

- Antidepressants (e.g., bupropion),
- Antipsychotics (e.g., aripiprazole), *and*
- “Pro-psychotics” (e.g. psilocybin)?

Beginning of My Interest in Altered States II: Antidepressants and "Broken Brains"



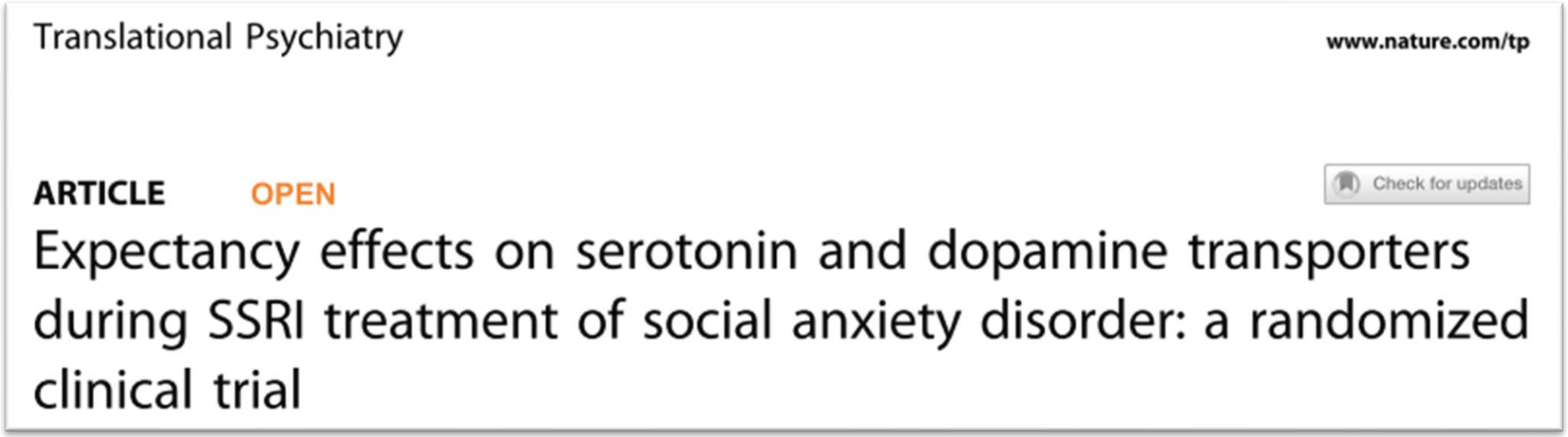
- Depression is a medical illness
- Antidepressants act biologically
- Prescriber's job: find the right medication, help patients titrate the dose and manage side effects
- Concomitant psychotherapy largely seen as acting independently

From Disease-Centered to Drug-Centered

- Decades of research have produced no evidence that psychiatric medications *correct* disease states
  - Possible exception: addictions
- Yet psychiatric medications produce states that can be highly therapeutic
- Much like psychedelics, their effects depend on illness/treatment narratives (akin to *set* and *settings)*:
  - Expectancy
  - Therapeutic alliances
  - Personality structures
  - Culture
  - Environment

Disease centred model	Drug centred model
Drugs correct an abnormal brain state	Drugs create an abnormal brain state
Drugs as disease treatments	Psychiatric drugs as *psychoactive drugs*
Therapeutic effects derived from effects on (presumed) disease pathology	Useful effects are a consequence of the drug induced state

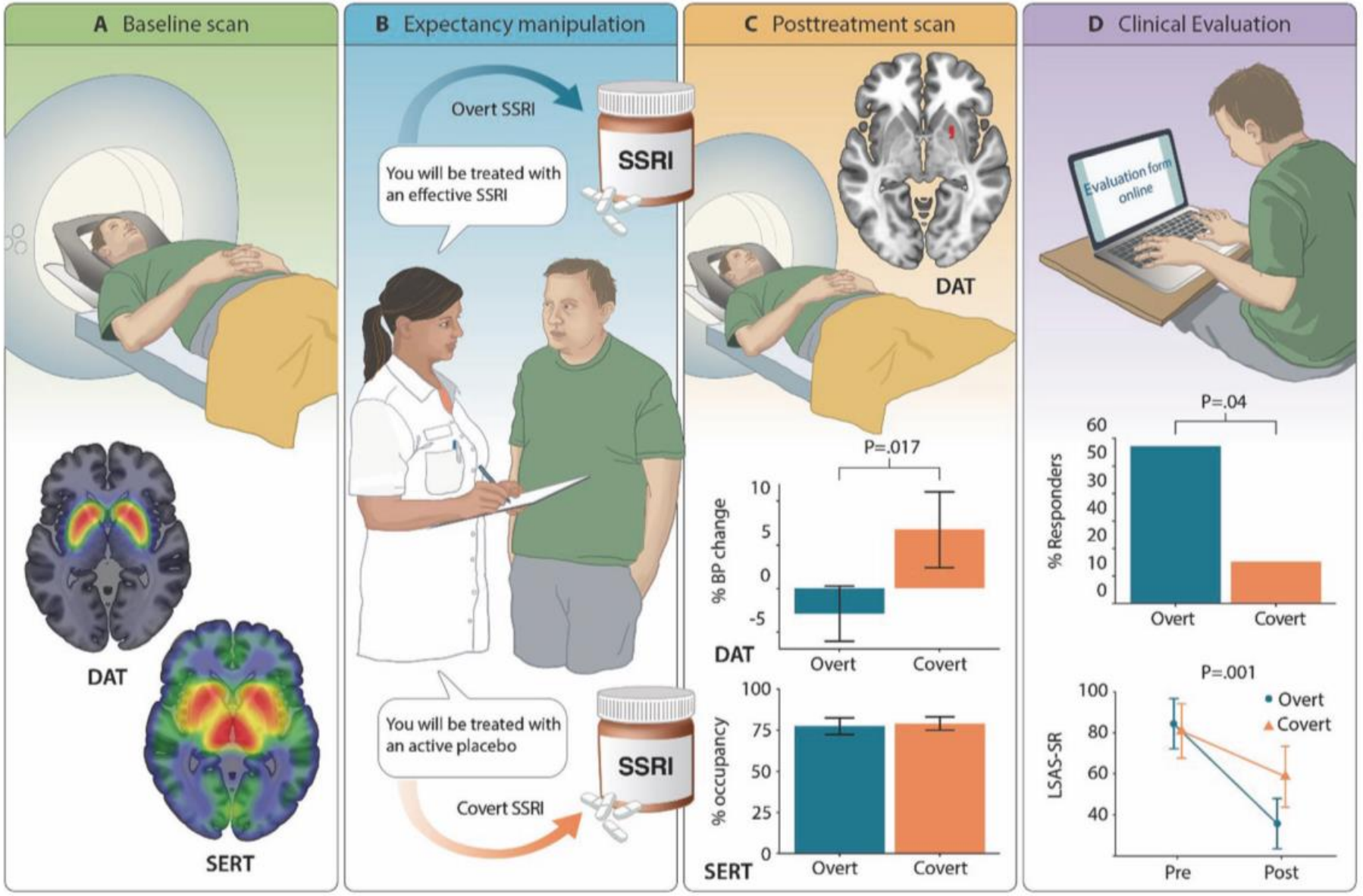
Moncrieff J. Epidemiol Psychiatr Sci. 2018 Apr;27(2):133-140. doi: 10.1017/S2045796017000555. Epub 2017 Oct 12.



- RCT (n=27) of social anxiety disorder who received covert or overt escitalopram (20mg) over 9 weeks
  - Overt group: active drug + therapeutic narrative
  - Covert group: active drug + non-therapeutic narrative ("active placebo")
- Outcomes:
  - Standardized scale of social anxiety (Leibowitz Social Anxiety Scale)
  - Pre-post Positron Emission Tomography probe of serotonin and dopamine transporter occupancy

Hjorth, OR et al. *Translational Psychiatry* 11, no. 1 (2021): 559. https://doi.org/10.1038/s41398-021-01682-3.

- Response rates:
  - **Overt group: 57%**
  - **Covert group: 15%**
- No difference in serotonin transporter occupancy
- Dopamine transporter occupancy:
  - Decreased in overt group
  - Increased in overt group
  - Decrease correlated with overall clinical response



Narratives and Drug Effects

- Similar response rates are seen in various RCTs of escitalopram versus placebo for Social Anxiety Disorder
  - E.g., one 12-week trial from 2005 (n=358) using the same outcome: 54% response
- Both studies find active drug + therapeutic narrative superior
- Narratives shape therapeutic benefits, to a greater extent than drug effects

Social Anxiety Response Rates	Active Drug	Placebo
Therapeutic Narrative	≈ 55%	≈ 40%
Inactive Narrative	≈ 15%	?

Depress Anxiety . 2004;19(4):241-8. doi: 10.1002/da.20014
Hjorth, OR et al. *Translational Psychiatry* 11, no. 1 (2021): 559. https://doi.org/10.1038/s41398-021-01682-3.

A Similar (Unintentional) Experiment:

Is bupropion effective when it’s presented as a smoking cessation aid?

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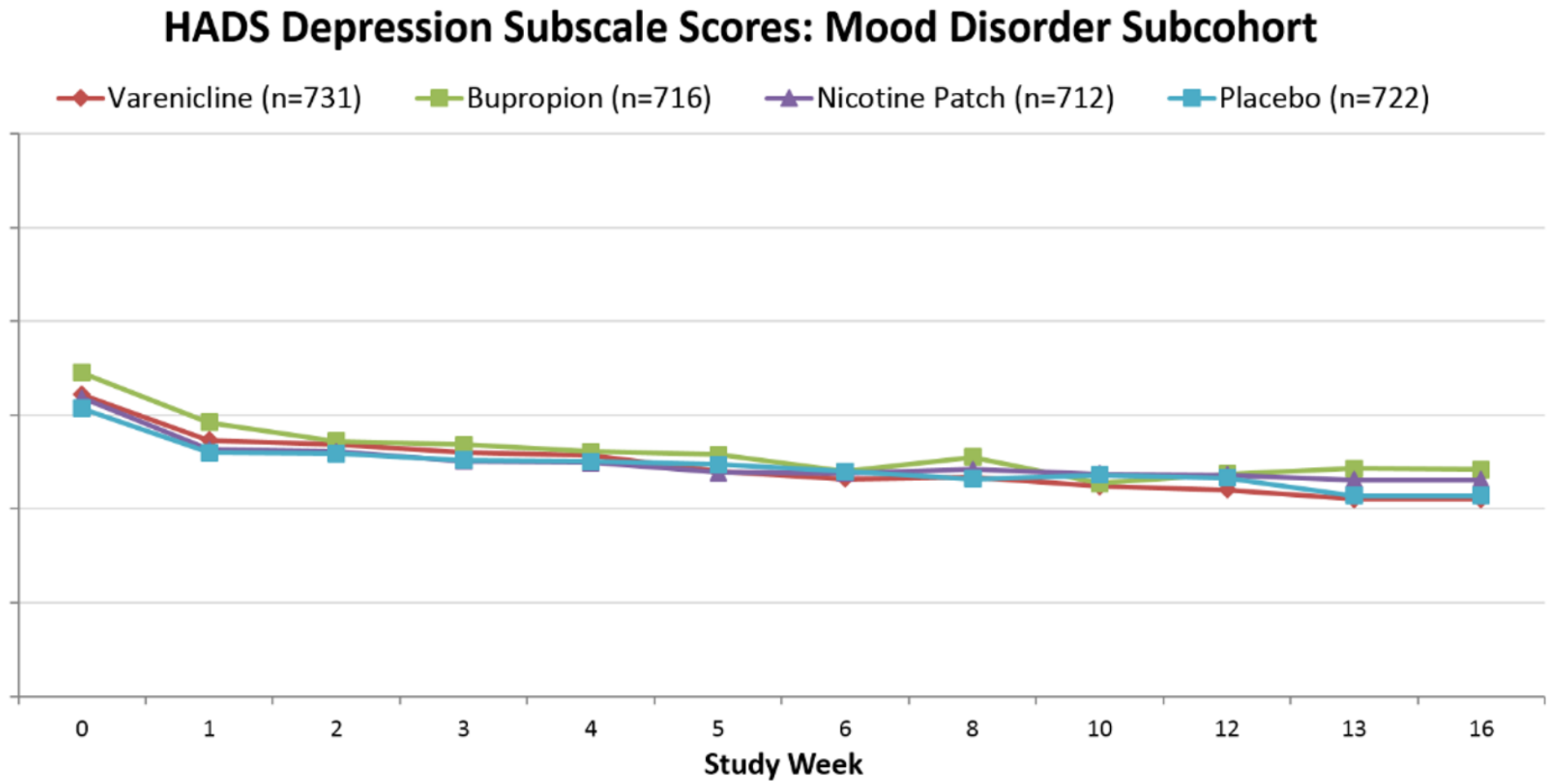


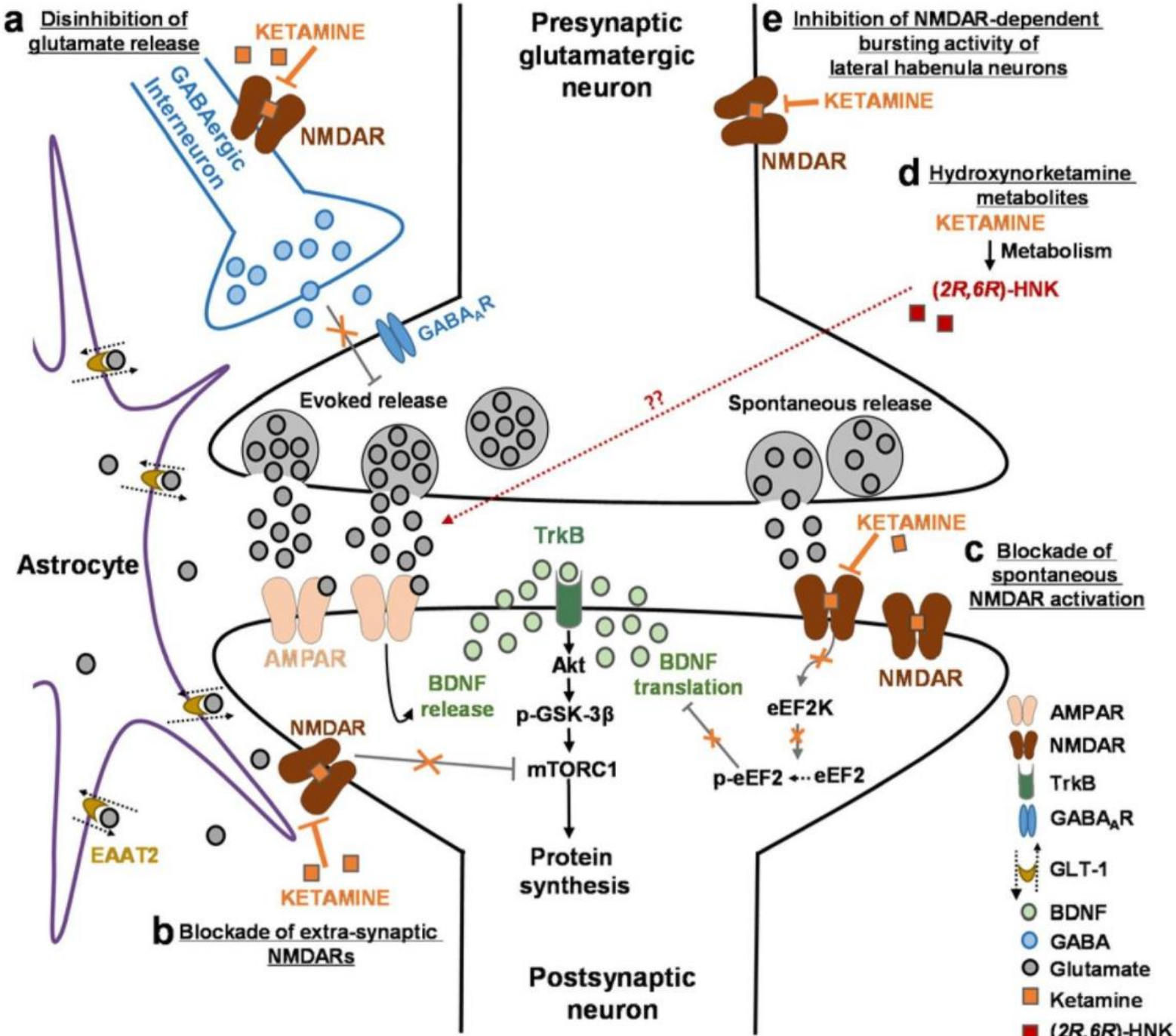
Proposal: Learning From Altered States

- All psychotropic drugs produce altered states of consciousness
  - Not cures of illnesses and not placebos
  - Efficacity and tolerability of these states are shaped by how they are understood (*set* and *setting*)
- Exploring experiences and understandings of psychotropic drugs yields rich information
  - Calmed versus numbed? Adherent or starting/stopping? Low mood or broken brain?
- Psychedelic drugs are less exceptional than they may appear, but more acute and dramatic
  - This acuity can greatly enhance experiential learning for patient and therapist

Ketamine Historical Overview

- An arylcyclohexylamine, developed in 1962 as a novel anesthetic
- Known as a “dissociative” for its capacity to engender states of analgesia and reduced interactivity
  - Original proposed term for its effects: “dreaming”
- Patented in 1963 in Belgium as a veterinary anesthetic and approved by the FDA in 1970
- Added to WHO list of Essential Medications in 1985, largely due to **Vietnam**
- Widely used for ER procedural sedation since 1990[2]
- Classified as Schedule III in 1999 by the FDA following its proliferation as a “club drug”
- First reported uses in a psychedelic model in the 1970s[1]
- First-use in “treatment-resistant depression” in 2000[3]

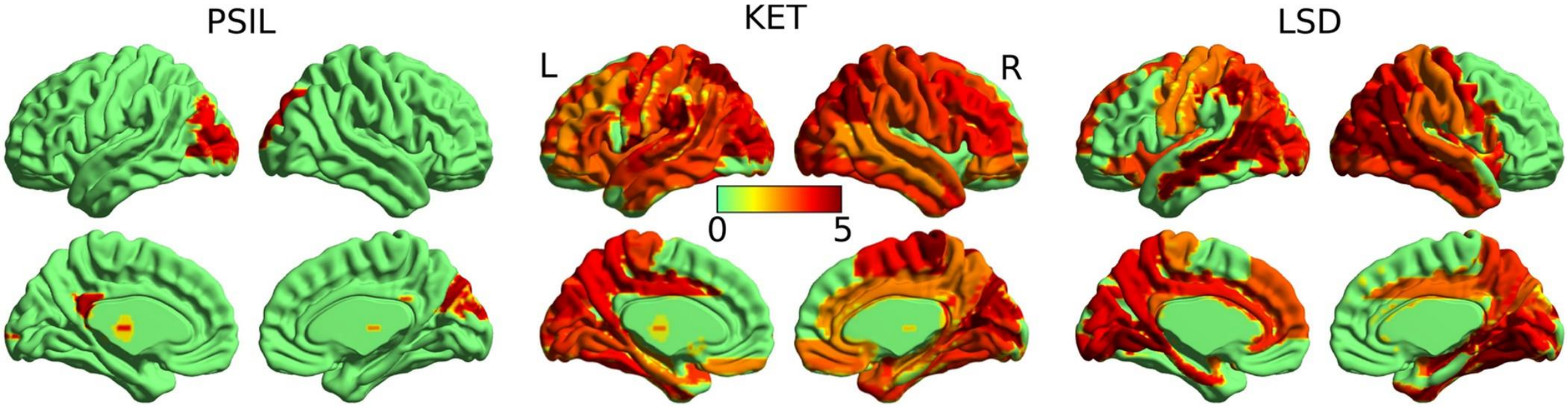
1. Kolp, E. *et al.* Ketamine Psychedelic Psychotherapy: Focus on its Pharmacology, Phenomenology, and Clinical Applications. *Int. J. Transpers. Stud.* **33,** 84–140 (2014).
2. Green, S. M. & Johnson, N. E. Ketamine sedation for pediatric procedures: Part 2, Review and implications. Ann. Emerg. Med. 19, 1033–1046 (1990).
3. Berman, R. M. et al. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 47, 351–354 (2000).



Mol Psychiatry. 2018 Apr; 23(4): 801–811. doi: 10.1038/mp.2017.255

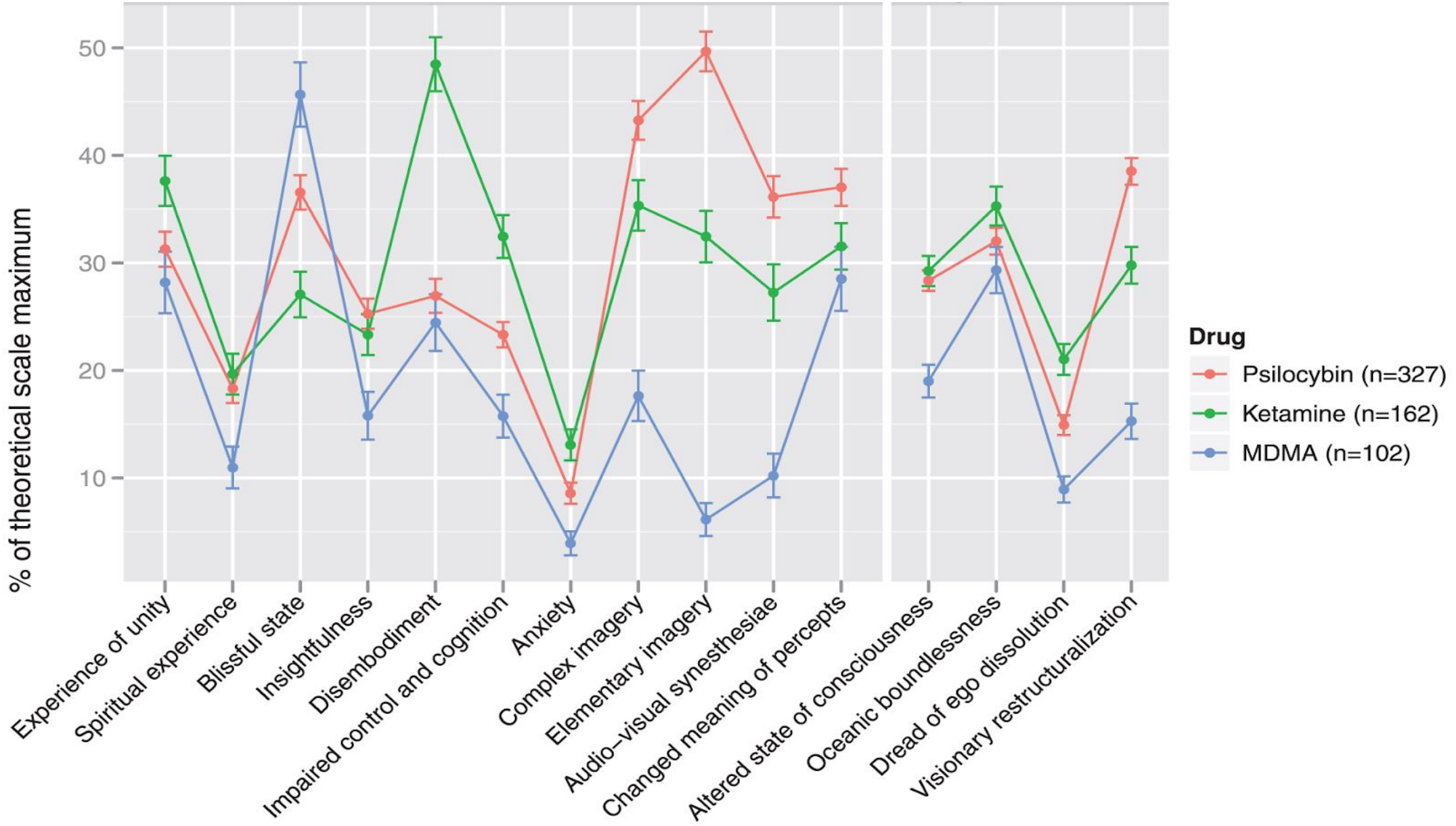
Remarkable Overlap in Neural Effects

Low-doses (<u>but not anesthetic doses</u>) of ketamine enhance the richness/diversity of information across the cortex (Lempel-Ziv neurocomplexity), much like serotonergic psychedelics



Schartner, M., Carhart-Harris, R., Barrett, A. et al. Sci Rep 7, 46421 (2017). Doi: 10.1038/srep46421

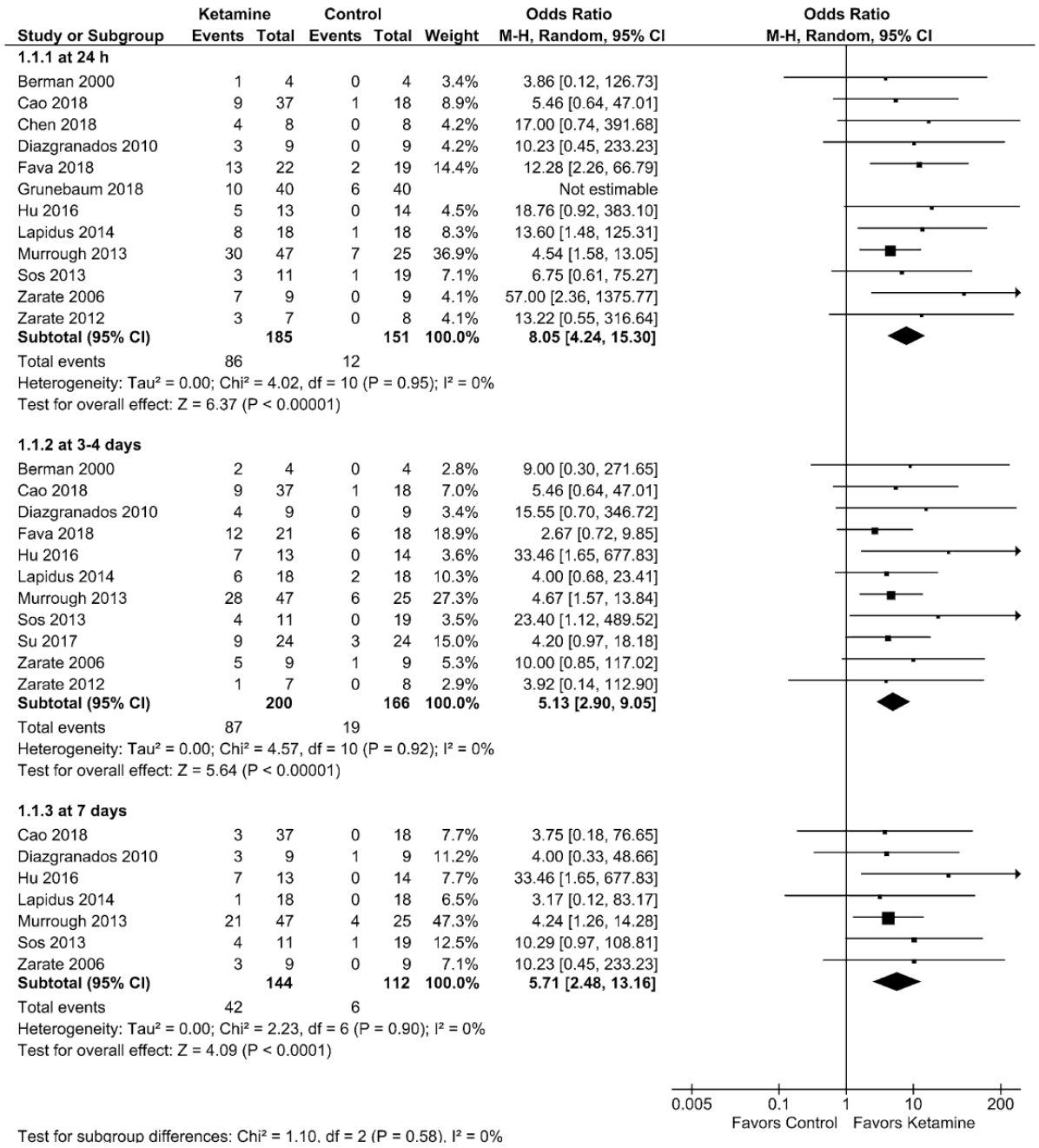
Significant Phenomenological Overlap Between Ketamine and Psilocybin



Vollenweider FX, Kometer M. Nat Rev Neurosci. 2010;11(9):642-651. doi:10.1038/nrn2884

Ketamine's Remarkable Efficacy

- Odds ratio of response to one infusion in Treatment Resistant Depression compared to <u>active placebo (midazolam)</u>:
  - 24h: 8.05
  - 3-4d: 5.13
  - 3-7d: 5.71
- For conventional antidepressants, odds ratios versus inactive placebos in treatment naïve patients: 1.37 to 2.13
- Benefits fade (days to weeks) but increase with serial treatments
- Reverses chronic-stress induced neuronal changes (neuroplasticity)
- CANMAT Level 1 Evidence



Kryst J et al. 2020. Pharm. Reports doi:10.1007/s43440-020-00097-z , Can J Psychiatry . 2021 Feb;66(2):113-125. doi: 10.1177/0706743720970860.

Our Approach: Enhancing the Biomedical Approach with Psychedelic Interventions

- Standard course:
  - Six 0.5mg/kg IV infusions 40-minute infusions (2/week x 2 weeks; weekly x 2 weeks)
- ≥ 2 assessment/preparation sessions beforehand:
  - **Standard psychiatric assessment**: diagnosis, alternative medications, contraindications
  - **Psychedelic preparation**: careful exploration of narratives around illness and treatment, behavioural activation and self-care strategies
- Psychedelic treatment adjuncts:
  - A pleasant setting
  - Psychedelic frame: encouragement to be open, curious about altered state, practice “letting go”
  - Eyeshades to encourage inward focus
  - Accompaniment and concurrent psychotherapy
  - Intention setting, thought defusion, meditation exercises
  - 1h of debriefing after infusion

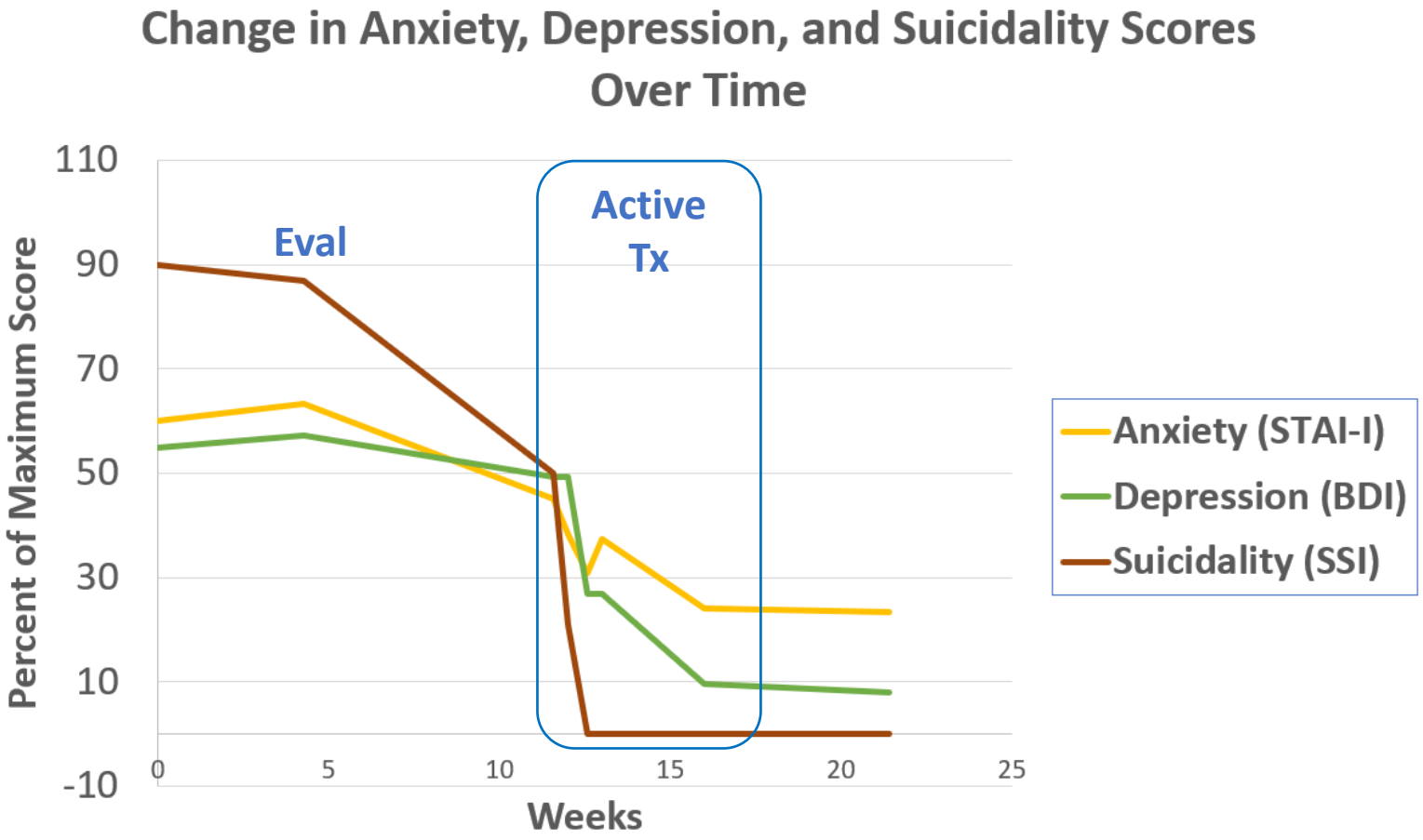
Music Study
Clinicaltrials.gov: NCT04701866

Music as an Intervention to Improve Hemodynamic Tolerability of Ketamine in Depression

- 30 patients receiving our hybrid approach for 6 infusions over 4 weeks, randomized to receive (carefully curated) music or not during all treatments
- The first study of music with ketamine
- The first psychedelic RCT to randomize patients to music or not
- All patients' sessions recorded and one post-treatment 2-hour phenomenological interview
- Primary outcome: reduced blood pressure increase
- Secondary outcomes:
  - Measures of experience: mystical experience questionnaire, emotional breakthrough inventory
  - Change in symptoms at 4 weeks and 8 weeks: depression, anxiety, suicidality

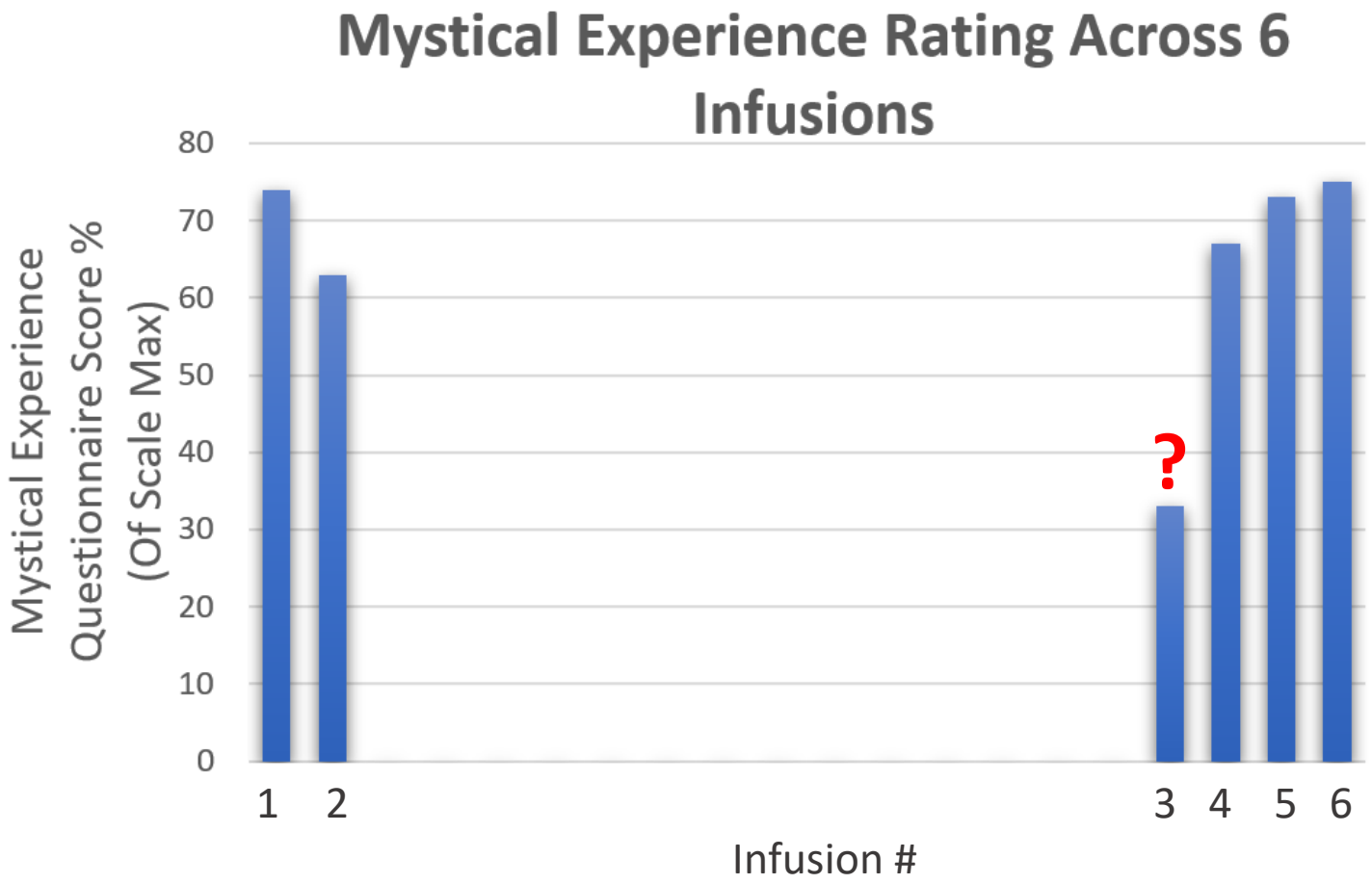
Case Example 1 – MAiD for Depression

- Female, ≈ 60 y.o., actively requesting MAiD for depression
- Failed:
  - Two courses of ECT
  - Months of TMS
  - >15 psychotropes
  - > 10 years psychotherapy
- Described each treatment as proof of her being a failure



Case Example 2 – Mental Priming

- Female, ≈ 30 y.o., admitted for depression/suicidality
- Benzodiazepines stopped
- Two infusions administered then discharged
- 6 months later, received infusions as outpatient
- First outpatient treatment: experience totally different than rest



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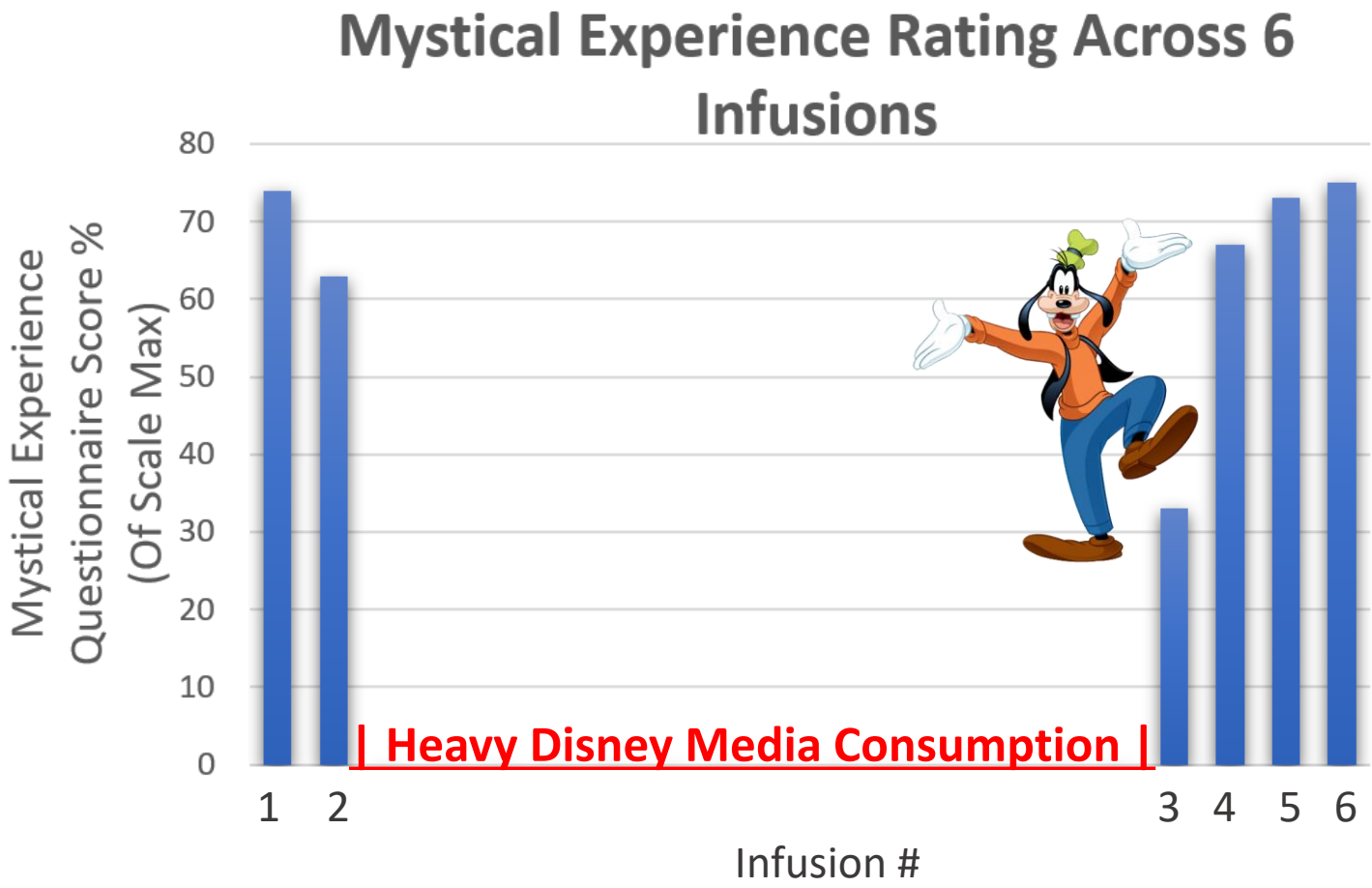
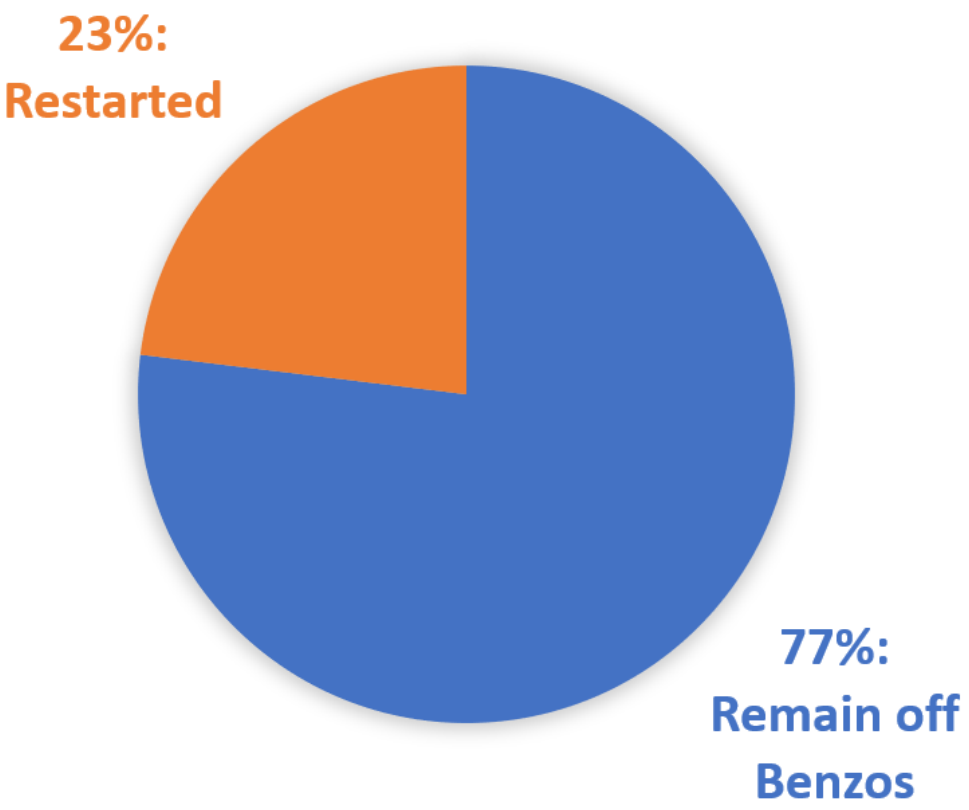
- Two infusions administered then discharged
- 6 months later, received infusions as outpatient
- First outpatient treatment: experience totally different than rest
- From experience, patient reduced Disney media consumption from 6h/day to 0.5-1h/day
- This change maintained at 1 year later



Case Example 3 – Benzodiazepine Deprescribing

- Many of our referred patients are on significant doses of benzodiazepines
- We attempt to discontinue benzodiazepines due to:
  - Biological interactions
  - To cultivate new skills for tolerating distress
- Retrospective cohort study of 17 patients, being led by Dr. Nicolas Garel:
  - 13/17 were successfully weaned during treatment
  - 10/13 remain off benzodiazepines since
    - Follow-up varies from 1 month to 2 years
  - 12/13 described ketamine-therapy process as “helpful” or “extremely helpful”



Suggested Conclusions

- Considering effects of all psychotropes, especially antidepressants, as altered states has benefits:
  - Drug effects are often overpowered by *set* and *setting* (explanatory framework, mindset, therapeutic alliance, personality, culture, environment)
  - Subjective effects can be rich sources of diagnostic information
  - Links between conventional and psychedelic combinations (and psychotherapy) become clear
- Psychedelic combinations are not wholly unique, but are particularly powerful due to richness of information and acuity of effects
- For some patients, this acuity *can* lead to durable breakthroughs

Subjective effects depend on:

- Biology/Pharmacology
- Mindset: alliance, conscious/unconscious illness narratives, culture, etc.
- Setting (environment)

Three common factors for improvement:

- A real relationship
- Creation of expectation through explanation
- Enactment of health-promoting actions

Thank you for your attention.

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- Dr. Jessica Drury
- Justin Lessard-Wajcer BSc
- Dr. Vincent Dagenais-Beaulé
- Elena Willis MA
- Dasha Sandra MSc
- Dr. Mendel Kaelen
- Dr. Michael Lifshitz
- Dr. Arwa El-Housseini
- Nick Murray

All Psychiatric Drugs

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Psychedelic Drugs

Medicine as medicine (present in animals/cells)

- Rapid symptomatic reduction
- Reversal of chronic stress-induced neural changes

Experience as medicine

- Reparative interactions (heightened with altered states)
- Reformulated narratives
- Profound exposure to challenging thoughts/emotions/memories
- Increased interest in subconscious processes

Process as medicine

- Distress as meaningful
- Emotions as benign
- Self as context