Lucy in the Sky without Pain : Psychedelics for Chronic Pain ?

SPS & SGPMR Joint Congress 2025, Aarau : Rehab Meets Pain Meets Rehab

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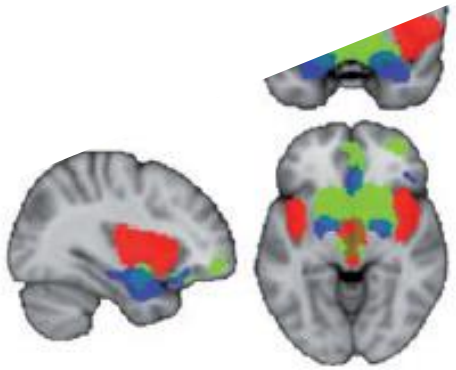
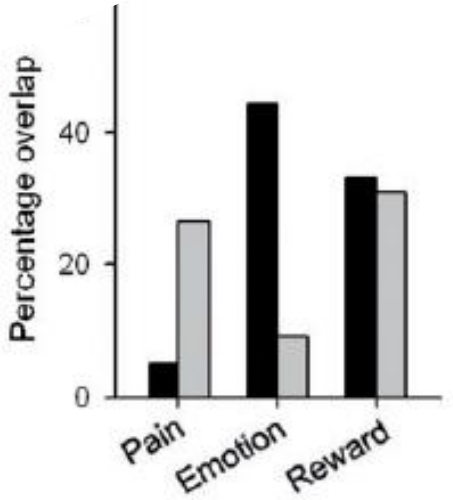
1. Introduction





"An emotional basis of chronic pain opens a new horizon of opportunities for developing treatment strategies beyond the repeated sole use of acutely acting analgesics"

Hashmi et al (2013), Zieglgänsberger et al (2022)

Pharmacological deadlock

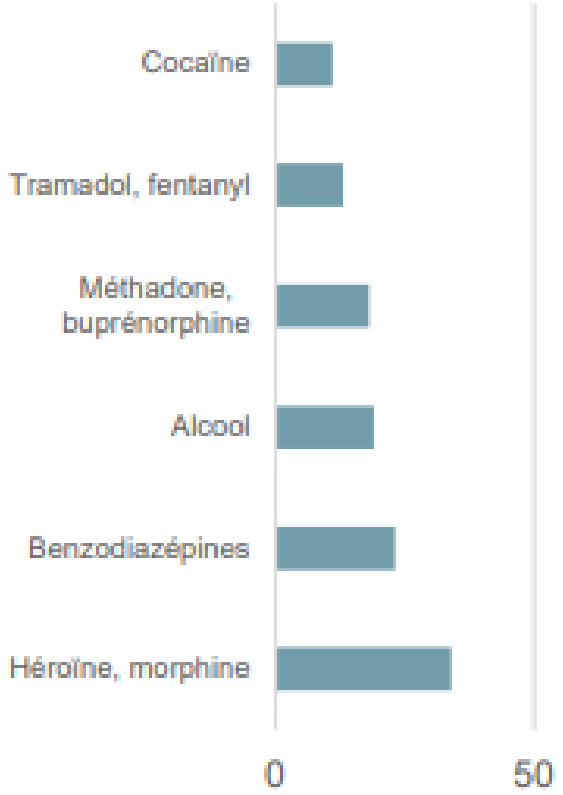
What works ?

- No moderate/high evidence for the benefit of pharmacological treatment vs. Placebo
- No evidence for long-term benefit (> 1 year) of opioids vs. no opioids
- Evidence ++ of risks associated with long-term opioid use

- **«The Opioid Overdose Epidemic»**
- Opioid-related overdoses (USA):
  - 1999 -> 2023 : x10
    - 806,000 deaths ; 217 people per day
    - 308,000 deaths from prescription drug overdoses
  - In 2023, 8.6 million cases of opiate misuse (prescription), 2/3 of which were to treat pain

- In Switzerland:
  - 1995 -> 2016 : ↓ 2/3 (376 vs 136 deaths)

www.cdc.gov, Cochrane Library (2023), www.suchtmonitoring.ch



Substances en cause dans les décès liés à la consommation de drogue (IML Zurich, Bâle, Aarau, analyses de A. Oestreich)

www.bag.admin.ch, Nutt (2007 and 2010)

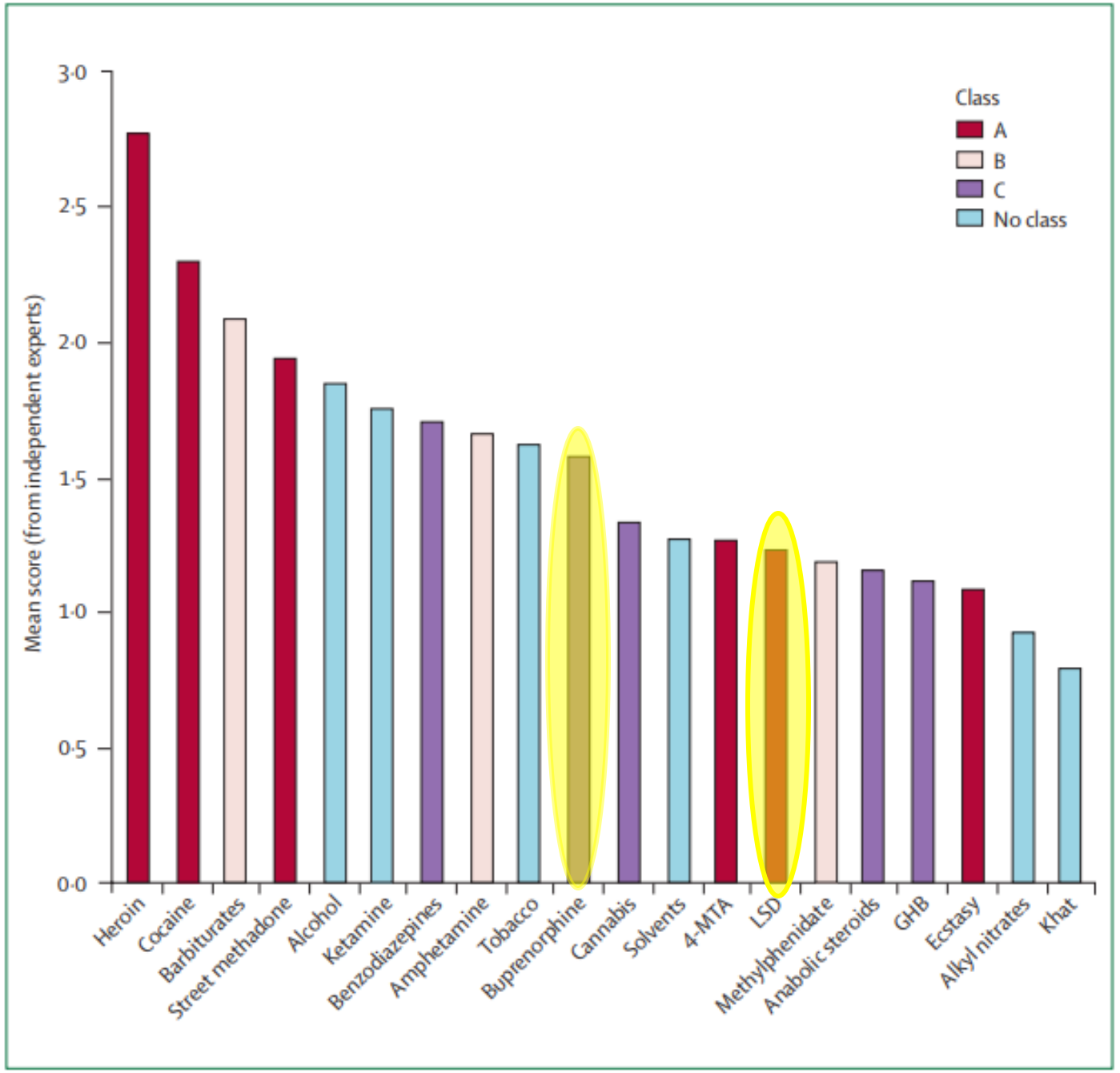


Figure 1: **Mean harm scores for 20 substances**
Classification under the Misuse of Drugs Act, where appropriate, is shown by the colour of each bar.

2. A bit of history…

Ritualistic and indigenous use

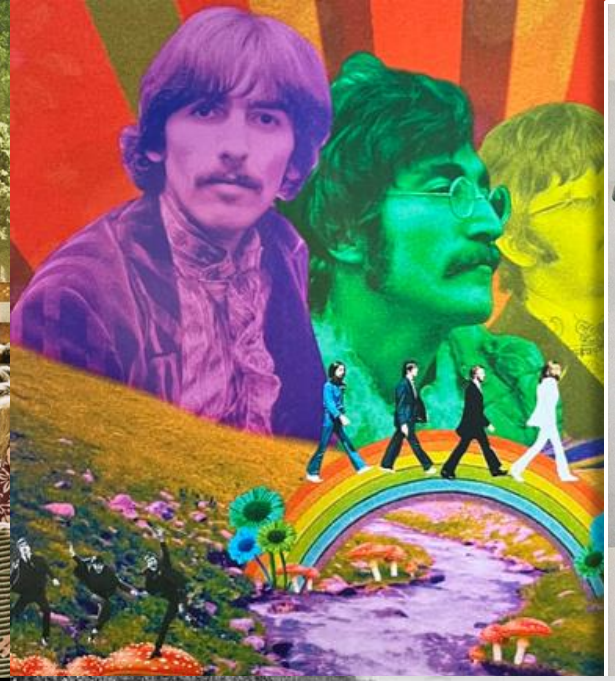
www.wikipedia.com, www.researchgate.net, www.fs.usda.gov, collections.gilcrease.org, mometo.net

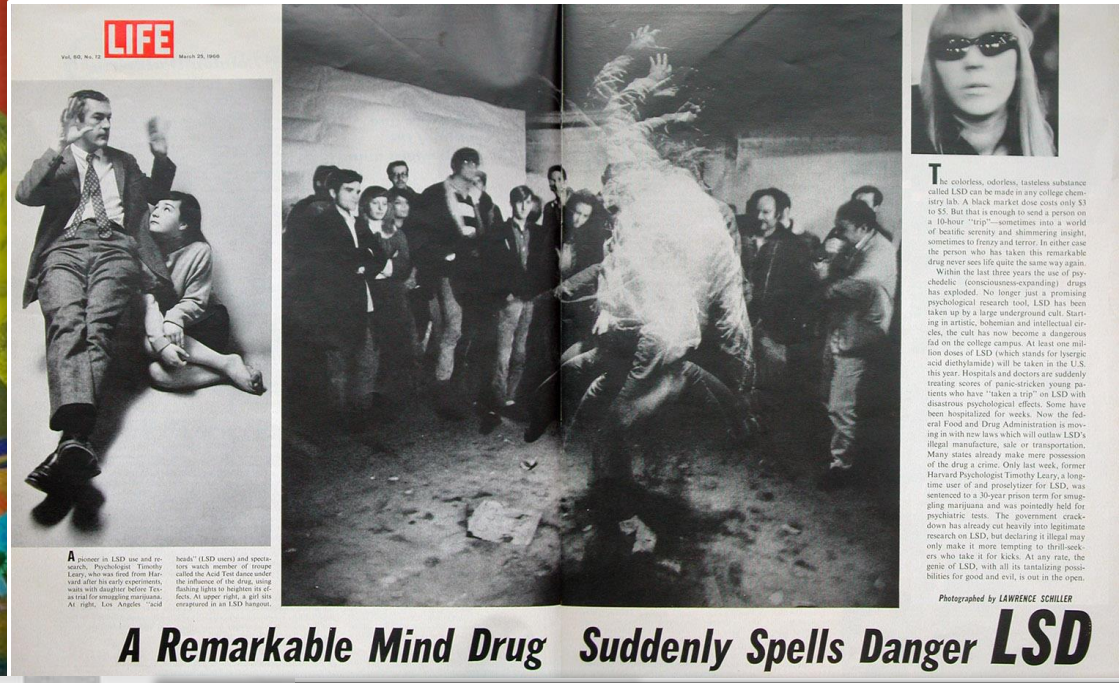
20th century

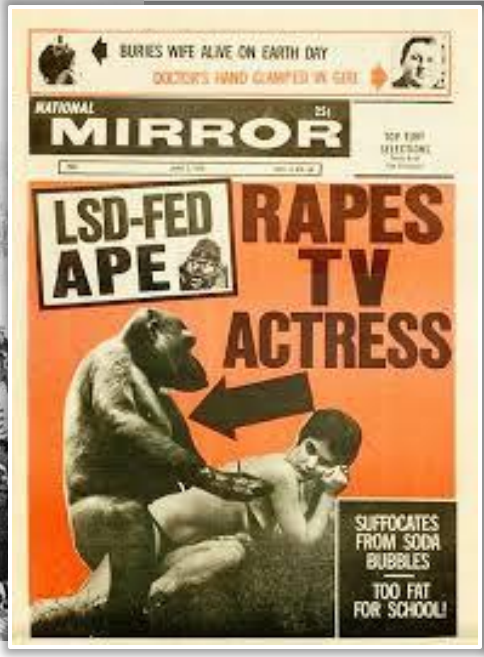
- **Scientific interest**
  - 1938 : LSD discovered by Dr. Albert Hofmann in Basel (Sandoz laboratory), then went on to isolate psilocin + psilocybin
  - Psycho[illegible]imeti[illegible]
  - «Truth s[illegible]rainwashing serum» (Nazi, CIA USA)
  - Research and studies in psychiatry with promising results

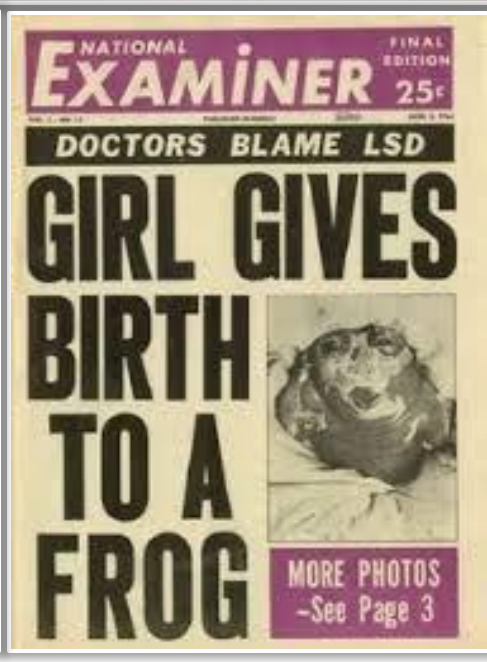
«*SET AND SETTING*»

Williams (1999) ; Hand et al (2016); Borgelt et al (2013)









www.vanityfair.com,Wikipedia Commons, www.vinylpussycat.com, www.nytimes.com, www.magnumphotos.com, www.reddit.com, dangerousminds.net, www.life.com

The Mail on Sunday August 8, 2004

Nobel Prize genius Crick was high on LSD when he discovered the secret of life

By Alun Rees

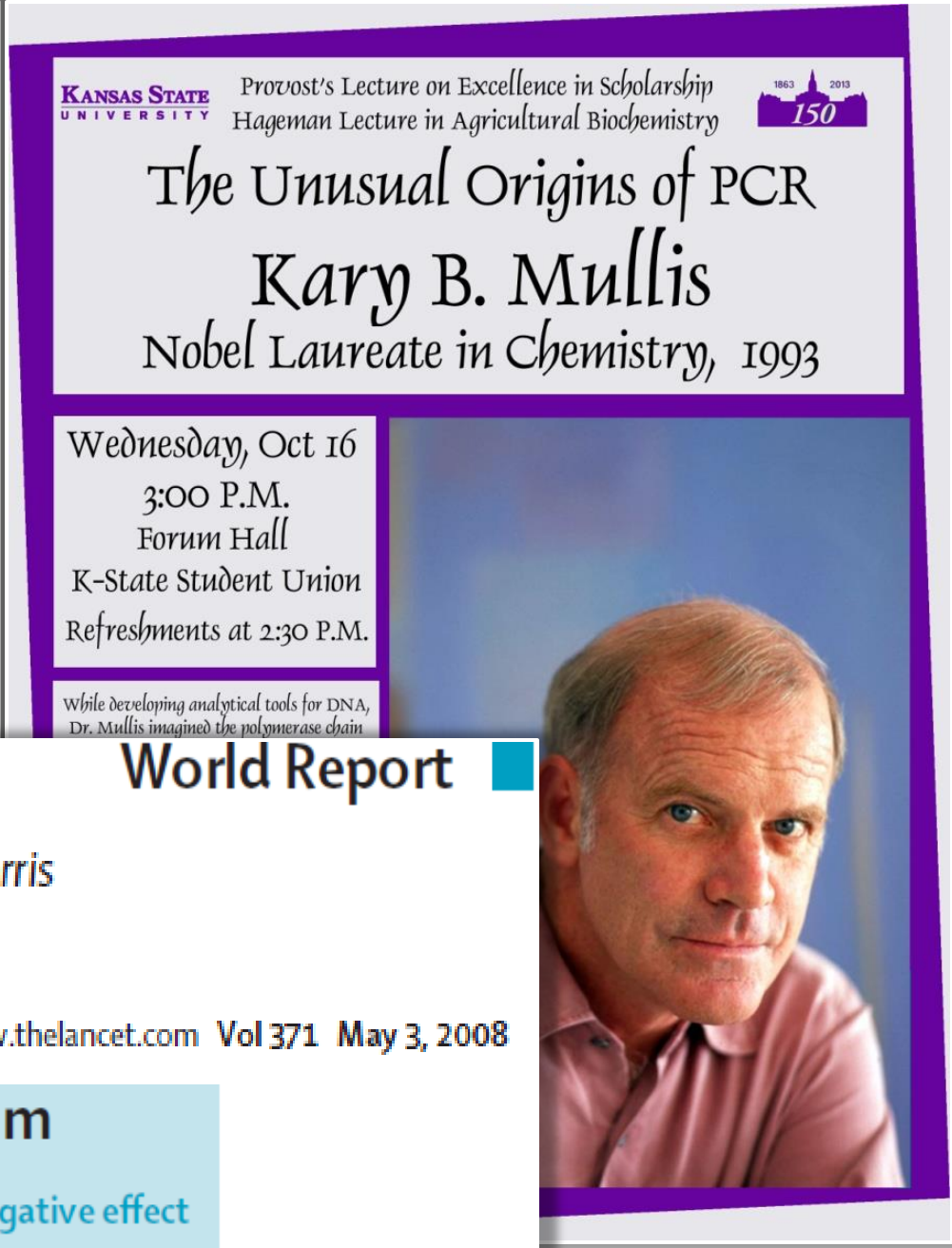
FRANCIS CRICK, the Nobel Prize-winning father of modern genetics, was under the influence of LSD when he first deduced the double-helix structure of DNA nearly 50 years ago.

The abrasive and unorthodox Crick and his brilliant American co-researcher James Watson famously celebrated their eureka moment in March 1953 by running from the now legendary Cavendish Laboratory in Cambridge to the nearby Eagle pub, where they announced over pints of bitter that they had discovered the secret of life.

Crick, who died ten days ago, aged 88, later told a fellow scientist that he often used small doses of LSD – then an experimental drug used in psychotherapy – to boost his powers of thought. He said it was LSD, not the Eagle's warm [illegible] him to unravel the [illegible] the discovery th[illegible] Nobel Prize.

Despite his Estal[illegible] Crick was a devo[illegible] Aldous Huxley, w[illegible] his experiments [illegible] another hallucinog[illegible] the short stories [illegible] Perception and H[illegible] became cult texts [illegible] the Sixties and Sev[illegible]

SPACED OUT: LSD was



World Report

Kelly Morris

www.thelancet.com Vol 371 May 3, 2008

Research on psychedelics moves into the mainstream

The backlash against the recreational use of psychedelic drugs in the 1960s had a negative effect on research into their potential therapeutic benefit. But now attitudes are changing and work in this area is being revitalised, with several early-stage trials underway. Kelly Morris reports.

Reemergence of scientific research

Since the 1990s

- Clinical research on psychiatric disorders
  - Depression
  - Anxiety
  - Addiction
  - End of life

  - -> **Efficacy, security, mechanisms**

Persistant pain and mood disorders?

- Bidirectional relationship
  - 60% of patients with persistant pain present depressive symptoms
  - Presence of one or the other increases risk to develop the other

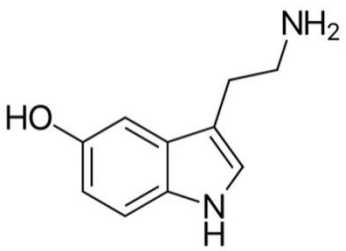
Muttoni et al (2019), De Gregario et al (2021), Nichols (2016), Byock (2013), Carhart-Harris (2018), Bondesson et al (2018), Hooten (2016), Holmes (2013), Sheng (2017)

3. A bit of chemistry…

«Classic» serotoninergic hallucigens

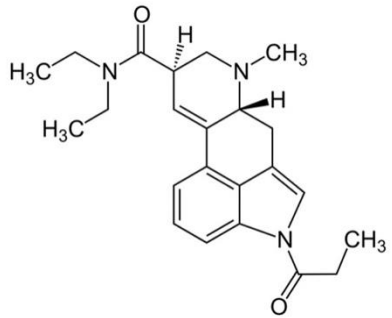
- **Activation 5-HT_{2A} receptor**

  - **Altered thoughts, perception, mood, cognitive functions** : mystical / spiritual / oceanic experience, expanding consciousness, feeling of unity, sacredness, transcendence...
  - Even after the end of the subjective experience, people describe increase in cognitive clarity, emotional receptivity, connection with loved ones, nature, God... for weeks -> months…
  - No interference with memory, no delirium, no physiological dependence, no addiction, no withdrawal symptoms



5-hydroxytyrptamine
(Serotonin)

1.2



Lysergic acid diethylamide
(LSD)

1.3

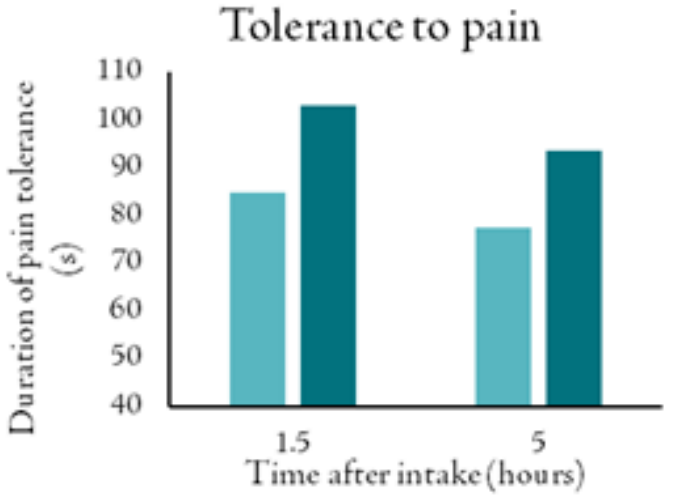
Kooijman et al (2023), Castellanos et al (2020), Nichols (2016), Thompson (2020)

www.researchgate.net/figure/Ayahuasca-prepared-from-B-caapi-and-P-viridis-Chemical-structures-for-harmine-1_fig1_359682544

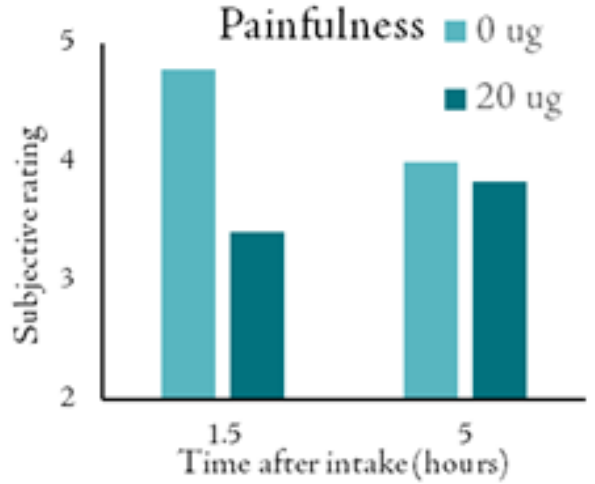
4. Proposed mecanisms

Pharmacological…

- **Pain modulation** (action on descending pathways)
- 3 doses sub-hallucinogenic (micro-doses) LSD vs placebo (healthy subjects, double blinded, «Cold Pressor Test») -> increased pain tolerance and decreased pain intensity with LSD



- Action on **central sensitisation** (via **neuroplasticity**)
- psychedelics induce molecular and cellular adaptations related to neuroplasticity via expression of plasticity-related genes and proteins, including Brain-Derived Neurotrophic Factor (BDNF)



- **Anti-inflammatory** (inhibition of molecular pathways)
- TNF-α, NF-ƙB

Kooijman et al (2023), Viguier et al (2013), Ramaekers et al (2021), Flanagan (2018), de Vos et al (2021)

Functional connectivity

Impact on the **Default Mode Network**

- = network of brain regions active at rest, essential for everyday consciousness, involved in introspection and self-reflection
  - Key regions: emotion and memory (vs. sensorimotor cortex)
  - Disruption/hyperactivity associated with mood disorders and chronic pain

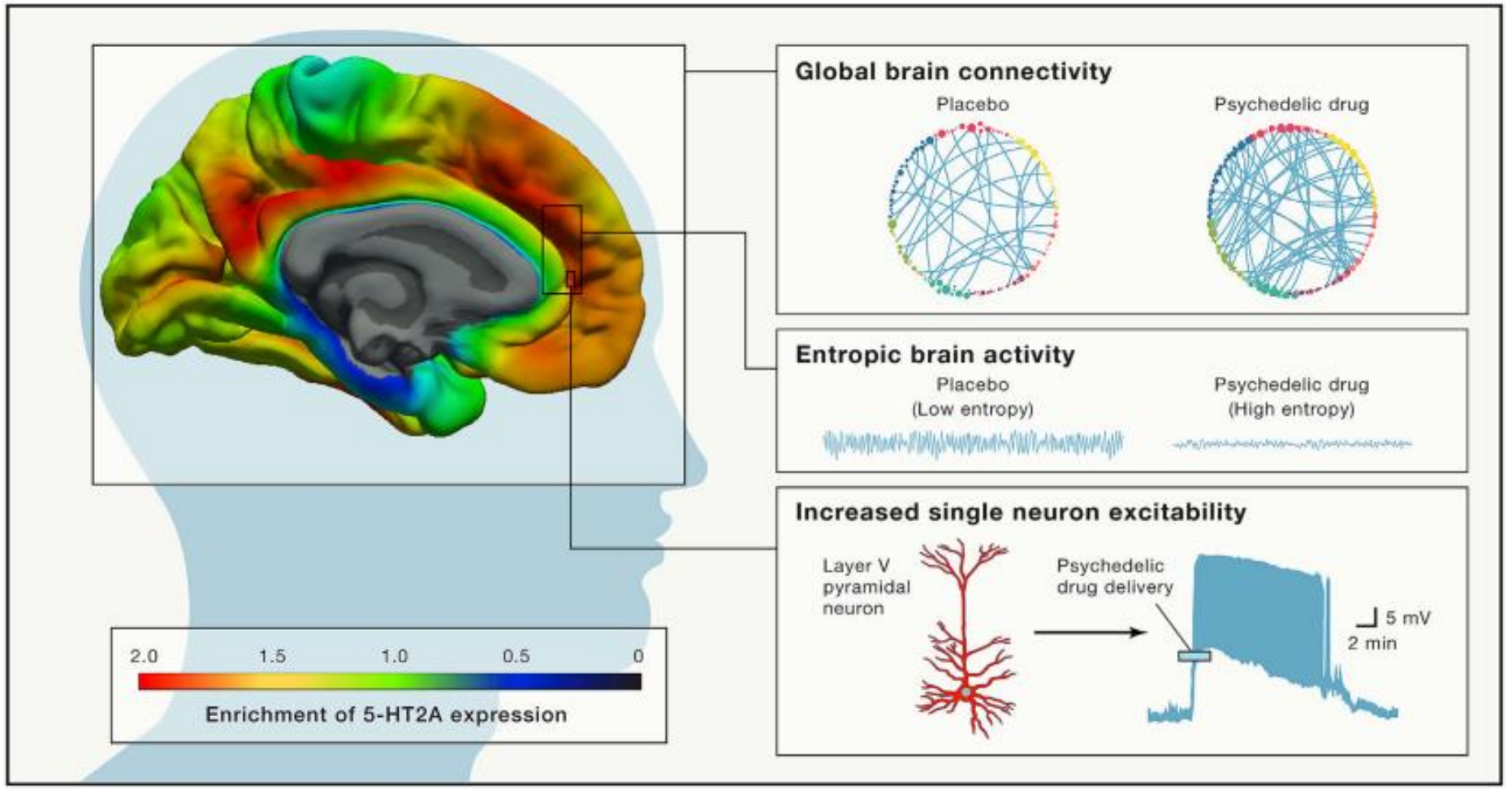
Temporary reopening of **« social reward learning critical period »**

- = period in childhood when we learn appropriate social behaviour, such as empathy, cooperation, tolerance, but also anxiety, shyness, stress management, coping with physical or emotional trauma, etc.)

- Improved **interoception** (= perception of bodily sensations and internal state of the body), increased **cognitive flexibility**, learning new **'healthy' behaviours**

Kooijman et al (2023), Elman et al (2022), Castellanos et al (2020), Siedel et al (2011)

Action on three cerebral levels…



"Psychedelics likely work by dysregulating activity in systems and circuits that encode negative habits of thought and behavior, allowing them to recalibrate as the acute effects of the drugs subside."

Carhart-Harris RL et al, 2014, 2018, Nutt et al, 2020

Window of opportunity to restore function or reset the interpretation network (brain) and pain transmission system

5. What does the literature say?

•Pathology	•Observed benefits of pyschedelic assisted therapy
•Cluster headache	•↓ frequency and intensity of attacks
•Neoplastic pain	•↓ intensity of the pain, ↑ mood, ↑ QoL
•Phantom limb pain	•Easier emotional processing, ↓trauma-related symptoms, change in body image perception
•CRPS	•↓ pain intensity, ↑ mood
•Fibromyalgia •Chronic back pain	•Studies ongoing...

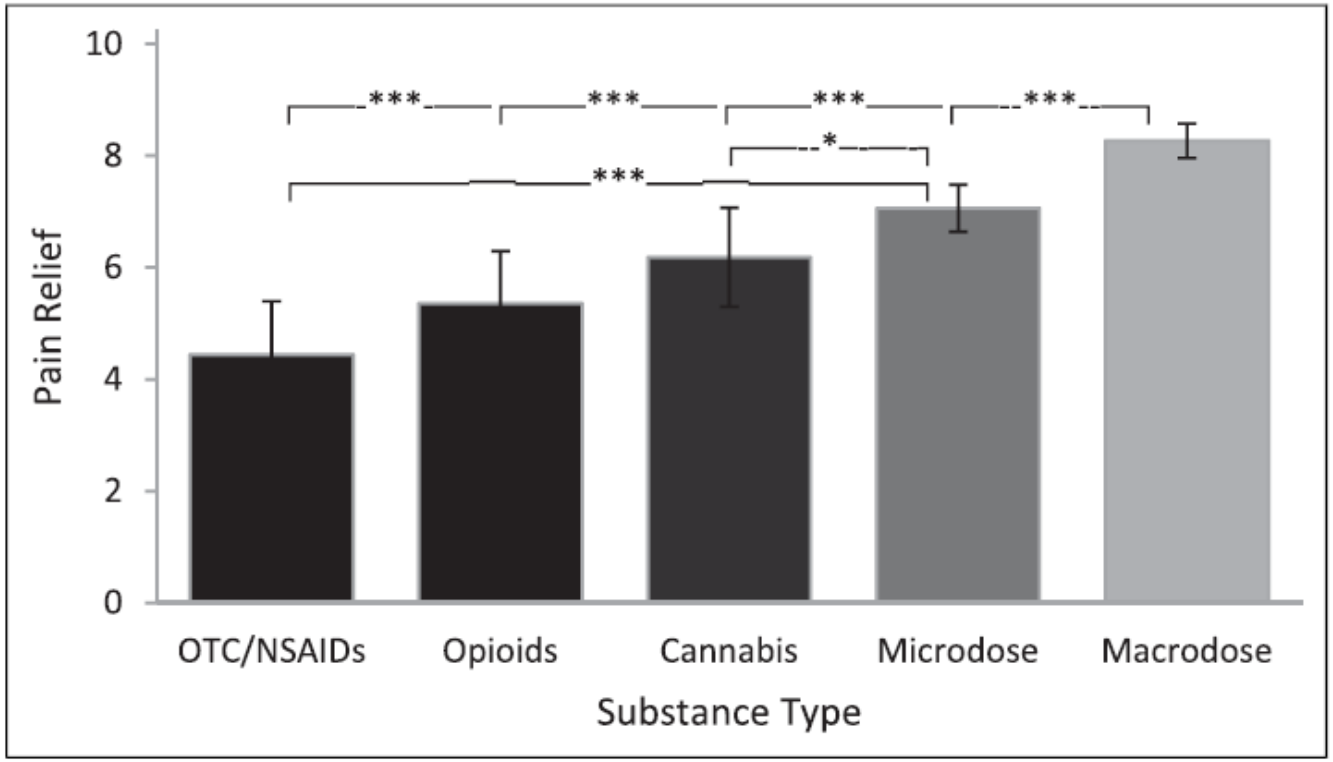
Kooijman et al (2023), Sewel et al (2006), Schindler (2022), Schindler et al (2020), Ramachandan et al (2018), Lyes et al (2023), Jevotovsky et al (2023)

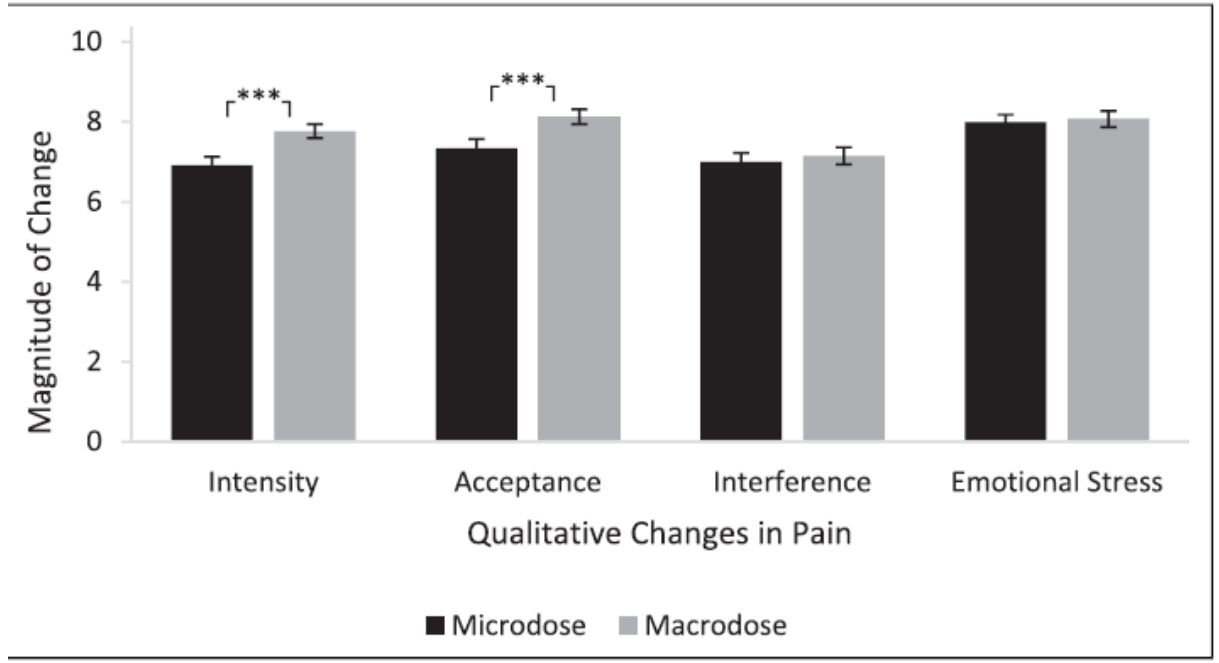
British Journal of Pain
Volume 16, Issue 6, December 2022, Pages 619-631

https://doi.org/10.1177/20494637221114962

Article

Analgesic potential of macrodoses and microdoses of classical psychedelics in chronic pain sufferers: a population survey





Bonnelle et al (2022)

6. Is it safe?

Side effects

- **Physical effects**
- Acute: dizziness, tremors, nausea, tingling, slight ↑ heart rate/blood pressure, sleep disturbances: ALL well tolerated and temporary

- **Psychological effects:** may interfere with daily routine.
- Tolerance and cross-tolerance: LSD 1x/3 days, psilocybin 1x/7 days.
- No physiological dependence, addiction or withdrawal symptoms upon cessation

- **Acute psychological distress** = 'bad trip', challenging experience
- Anxiety, panic, feeling of unease, paranoia: resolves
- Factors: dose, 'set and setting' (= emotional state, physical comfort, psychological/social support, preparation)

- **Prolonged psychosis**
- Risk 0.8/1000 healthy subjects, 1.8/1000 sick subjects (similar to psychotherapy)
- Risk factor +++: pre-existing psychiatric illness (schizophrenia spectrum disorder) in the patient or their family

- **Hallucinogen persisting perception disorder** = 'flashbacks', resolves
- A few cases described for several million users

- **Overdose ?** NONE
- 8 cases of inhalation of MASSIVE doses described (mistaken for cocaine), no deaths

Nichols (2016), Johnson et al (2008), Kooijman et al (2023), Passie et al (2008)

7. Clinical possibilities and future research

Pre-clinical research, clinical trials

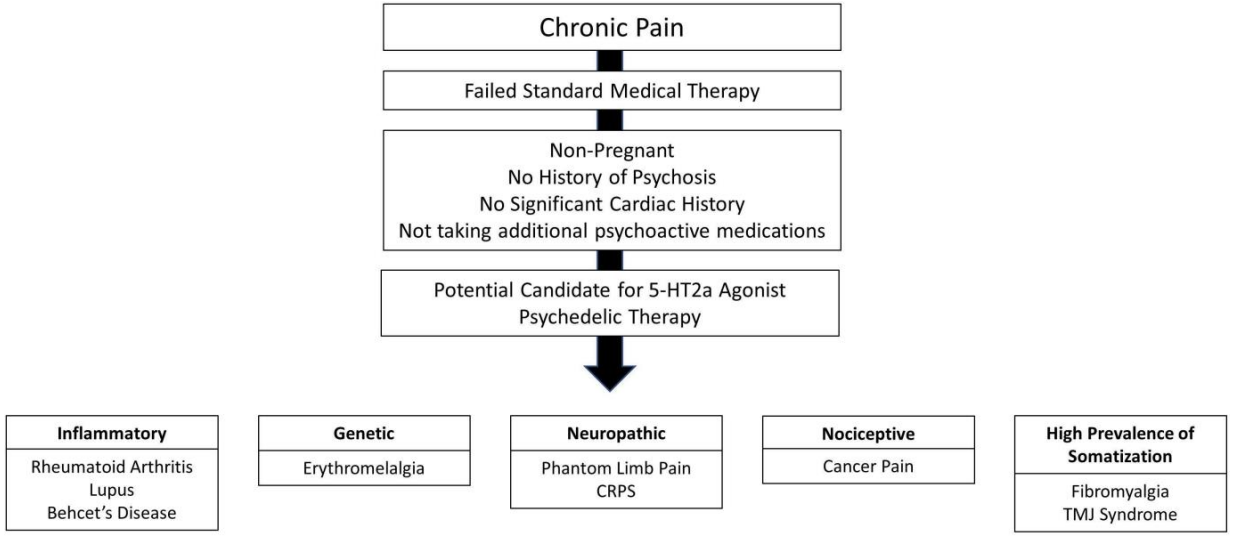
Table 1. Challenges and Research Needs: Pre-clinical Research

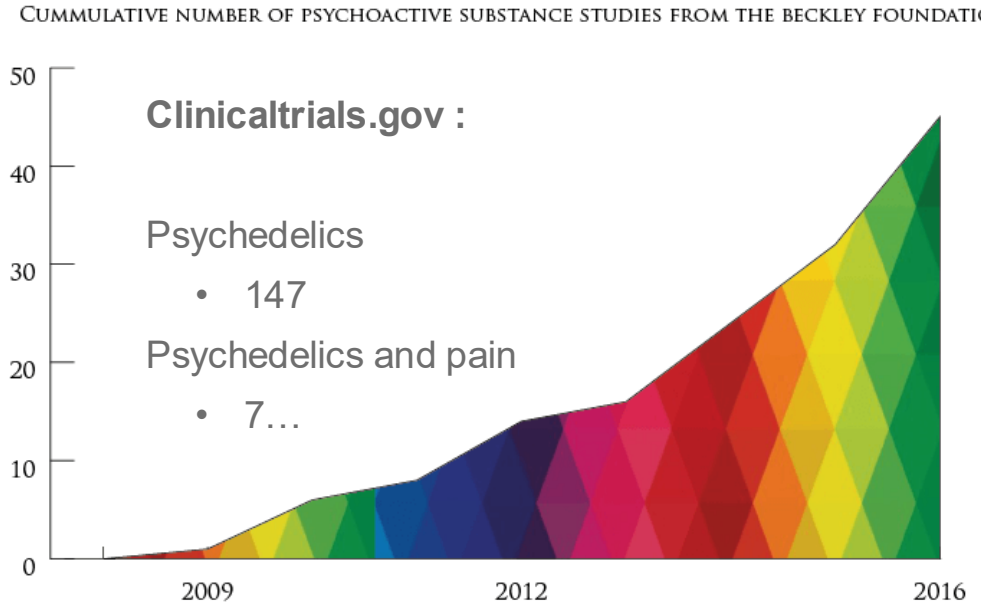
1. Preclinical studies of psychedelic analgesic targets and pathways
   - Receptor occupancy – ex vivo or in vivo
   - Behavioral pharmacology with either agonist/antagonist studies or compound/ knockout mouse to determine target
   - EEG/imaging

2. Preclinical studies of psychedelic effects in nociceptive, neuropathic, inflammatory, musculoskeletal, cancer, and other pain models using both evoked and spontaneous measures
   - Pharmacokinetics of parent and primary metabolite
   - Blinding, randomization, appropriately powered
   - Dose response, not single-dose studies
   - Oral route of administration if to be taken that way clinically to reflect metabolism and adsorption rates
   - Inclusion of comparator "positive control" (eg, gabapentin for neuropathic pain, NSAID for inflammatory pain)
   - Long-term monitoring after compound elimination
   - Multiple dosing studies to establish tolerance
   - Two independent cohorts to increase confidence in results

3. Establishing biomarkers
   - electroencephalography
   - Imaging (especially pharmacologic functional magnetic resonance imaging)

4. Evaluating Safety
   - Cardiovascular risk (eg, many psychedelics bind to 5-HT_{2B} receptors where agonism is a known risk for valvular heart disease)
   - Drug discrimination (level of generalization to known psychedelics and relationship with efficacious analgesic dose)
   - Abuse potential (eg, self-administration)
   - Plasma hormones (eg, prolactin), which could be dose limiting





Dworkin et al (2022), Castellanos et al (2020), The UC Berkeley Center for the Science of Psychedelics – BCSP, www.beckleyfoundation.org,

Barriers…

- **Blinding impossible.**
- To circumvent: use non-inert placebo?

- **Set and setting.**
- Essential +++
- Requires:
  - Trained personnel
  - Time
  - Specific location
- Increases variability between studies ++
- Increases costs

- **Same constraints for implementing therapies after studies!**

Dworkin et al (2023)

Other avenues to explore …

- **Co-therapeutic modalities**
- Mirror therapy (case study with psilocybin shows synergistic effect on phantom limb pain)
- Physiotherapy
- Hypnosis
  - Psychedelics increase ‘suggestibility’
  - Hypnosis can recreate a ‘psychedelic-like’ experience
  - Combining these could recreate the psychedelic experience to regain the effect
- Nerve blocks...

- **Other molecules**
- Non-hallucinogenic psychedelic analogues
- Microdosing
- ...however the results so far support the idea that the subjective experience is paramount for the therapeutic effect

Castellanos et al (2020), Ramachandran et al (2018), Lemercier & Terhune (2018), Czopek et al (2025)

Clinical possibility in Switzerland

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Federal Office of Public Health FOPH

Limited medical use of banned narcotics

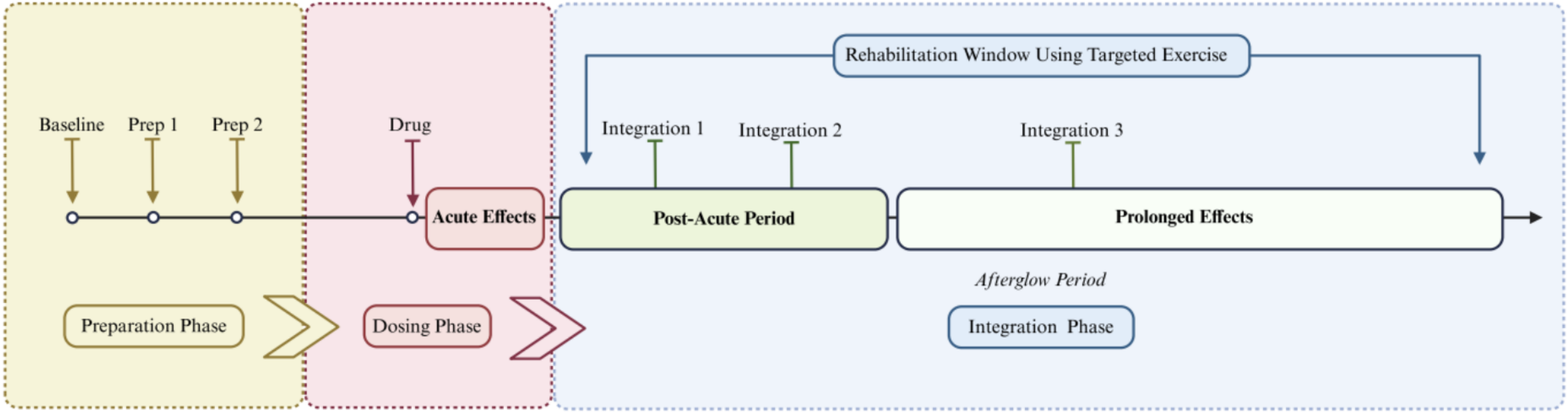
The FOPH may basically only issue exceptional licences for the medical use of banned narcotics for patients resident in Switzerland. Only the physician treating the patient may submit a corresponding application, which must include the patient's written consent.

Requirements

- patients are suffering from a usually incurable disease
- their suffering can be alleviated through consumption of the banned narcotic
- the available therapies have been exhausted and/or no alternative treatments are available

CRR TAP Program : Not a clinical trial !

- **Psychedelic-assisted therapy with 2-3 preparatory sessions, one dosing session (during which the medication is taken) and 2-3 integration sessions for patients with chronic pain (probably associated with a mental health diagnosis) that is resistant to all other treatments**
- Inpatient if possible



Cherup & Finan (2025)

CRR TAP Program: Not a clinical trial !

What do we hope for?

- Improvement in symptoms : pain intensity, frequency of painful episodes.
- Improvement in psychological distress : symptoms of depression and anxiety.
- Improvement in cognitive functioning : catastrophising, kinesiophobia, coping.
- Reduction in pain interference.

Inclusion criteria

- Age >25 years
- Persistant pain for > 2 years
- Available therapies have been exhausted and/or no alternative treatments are available
- Ability to participate in all prep and integration sessions

Exclusion criteria

- Comorbidity/history or family history (first degree) of schizophrenia spectrum disorders
- Comorbidity of bipolar or borderline disorder (for compliance reasons)
- Treatment with mirtazapine or trazadone at antidepressant doses
- Pregnancy
- Poorly controlled hypertension (>160 systolic)
- Insufficient understanding of french

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Thank you !

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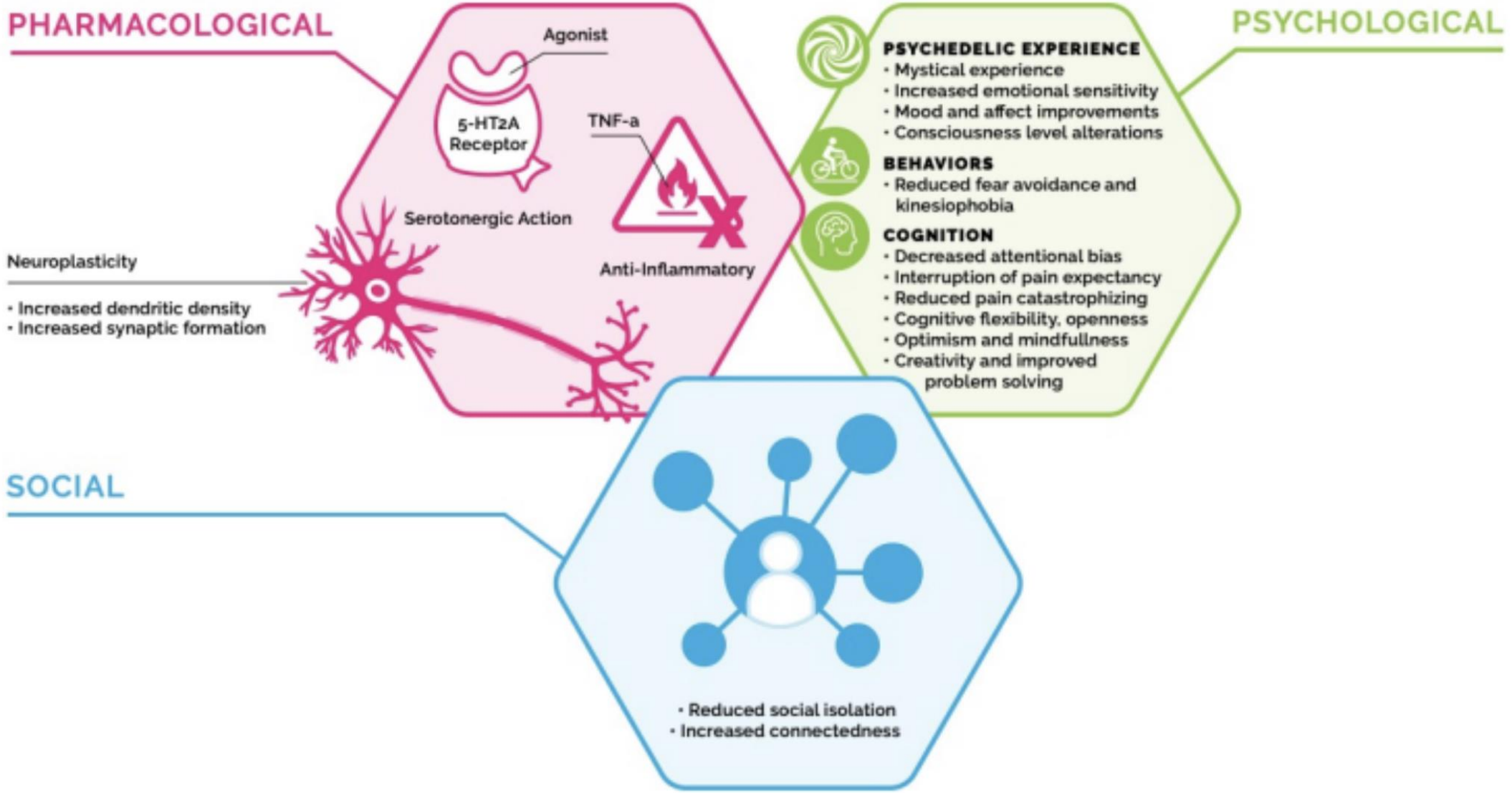
Psychedelics & Pain: Mechanisms



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