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The Doors of Perception: Psychedelics in Pain Management

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Disclosure

Maria Mangini PhD FNP-BC has nothing to disclose.

Learning Objectives

- Review the history of psychedelics in medicine
- Discuss the mechanisms by which psychedelics work in humans
- Describe the use of psychedelics in psychiatry and pain medicine

Popular Press

- Dean J: How MDMA went from club drug to “Breakthrough Therapy.” Wall Street Journal 2017
- Hochman D: How to talk to your kids about drugs when everyone is doing them New York Times 2019
- Oaklander: This Will Change Your Mind About Psychedelic Drugs. Time 2018
- Pollan M: The Treatment Trip. The New Yorker 2015
- Rubin, E: Excitement and Concerns About Therapies Using Psychedelics Psychology Today 2018

A Sample of Peer-reviewed Journals

Simonsson, O., Sexton, J. D., & Hendricks, P. S. (2021). Associations between lifetime classic psychedelic use and markers of physical health. *Journal of Psychopharmacology*, *35*(4), 447-452.

Carhart-Harris RL, Roseman L, Bolstridge M, et al. (2017) Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports:7*; 13187.

Sessa B (2017) MDMA and PTSD treatment: PTSD: From novel pathophysiology to innovative therapeutics. *Neuroscience Letter: 649*; 176–180

Nichols D.E., Johnson M.W., Nichols C.D. (2017) Psychedelics as Medicines: An Emerging New Paradigm. Clinical Pharmacology & Therapeutics. 101(2):209-219.

Daly E.J., Singh J.B., Fedgchin M., et al. (2018) Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry: 75(2): 139–148

Soussan C., Andersson M., Kjellgren A. (2018) The diverse reasons for using Novel Psychoactive Substances - A qualitative study of the users' own perspectives. International Journal of Drug Policy: 52:71-78.

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: a review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, *45* (7), 486-494.

Nutt, D., & Carhart-Harris, R. (2021). The current status of psychedelics in psychiatry. *JAMA Psychiatry*, *78*(2), 121-122

Critical Elements of Psychedelic-Assisted Psychotherapy

- Drug
- Set
- Setting
  - Includes therapeutic clinician-client relationship
- Matrix

Chwelos N, Blewett DB, Smith CM, et al. (1959) Use of d-lysergic acid diethylamide in the treatment of alcoholism. *Quarterlly Journal of Studies on Alcohol:*20, 577-90.

Eisner, B. (1997). Set, setting, and matrix. *Journal of Psychoactive Drugs*, *29*(2), 213-216.

“Hallucinogens”

Mind altering substances that induce experiences that are qualitatively different from those experienced in ordinary consciousness.

- Irony of Hallucinogenic Drugs
  - Hallucination --- an experience involving the apparent perception of something not present
  - Hallucinations are vivid, substantial, and are perceived to be located in external objective space

A Wide Range of Substances

Mind-Altering Drugs

- Psychedelics
  - psychoactive drugs whose primary action is to alter the thought processes of the brain
- Empathogens or Entactogens
  - produce experiences of emotional communion, oneness, relatedness, emotional openness
- Disociatives
  - reduce or block signals to the conscious mind from other parts of the brain, typically the physical senses
- ßDeliriants
  - Anticholinergics which are antagonists for the acetylcholine receptors

Hallucinogens

- Common Misinterpretation
  - It has been thought that the effects of hallucinogens mimic psychological conditions.
    - For example, many people believe the use of hallucinogens mimics or will lead to the following:
      - Psychosis
      - Schizophrenia
      - Thought disorder

Yaden, D. B., Yaden, M. E., & Griffiths, R. R. (2020). Psychedelics in psychiatry—keeping the renaissance from going off the rails. JAMA Psychiatry: 78(5):469-470

“Classic” Psychedelics

- The classic psychedelics exert primary activity as agonists at the 5-HT2A receptor
  - lysergic acid diethylamide [LSD]
  - psilocybin
  - dimethyltryptamine [DMT]
  - mescaline
- Many are found in plants or fungi used traditionally

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The Entactogens or Empathogens

- MDMA, MDA, MDEA, MDOH, MBDB, 6-APB, methylone, mephedrone, αMT, and αET, MDAI among others.

- Most are phenethylamines and amphetamines

The Entactogens or Empathogens

- Produce experiences of emotional communion, oneness, relatedness, emotional openness

- Particularly seen with
  - 3,4- Methylenedioxymethamphetamine (MDMA)
  - Known as the street drug: Ecstasy, Mollie

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, P. M., Wymer, J., . . . Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry*, 5(6), 486-497.

Sessa, B. (2017). MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics." *Neuroscience Letters, 649*, 176-180.

Dissociatives

- **Dissociatives**
  - distort perceptions of sight and sound
  - produce feelings of detachment – dissociation – from the environment and self.
  - Include;
    - PCP (Phencyclidine)
    - Ketamine.
    - DXM (Dextromethorphan)
    - Salvia divinorum.

- Ketamine
  - the most accessible of the agents now being used for psychedelic-assisted psychotherapy
  - an NMDA receptor antagonist, but it may also have other activity.

Riggs, L. M., & Gould, T. D. (2021). Ketamine and the future of rapid-acting antidepressants. *Annual Review of Clinical Psychology, 17*(1), 207-231.

Ketamine

Mion G. (2017). History of anaesthesia: the ketamine story - past, present and future. *European Journal of Anaesthesiology 34*, 571–575.

Ketamine

Mathew, S. J., & Zarate, C. A., Jr. (2016). *Ketamine for treatment-resistant depression: the first decade of progress*. Switzerland: Adis

Ketamine

- Many properties make ketamine a good candidate for treating depression and anxiety
  - –inexpensive
  - –easy to administer by multiple routes.
  - –rapid onset of action
  - –minimal side effects when used at subanesthetic doses
  - –may be given and an adjuvant to opiates

Irwin, S. A., Iglewicz, A., Nelesen, R. A., Lo, J. Y., Carr, C. H., Romero, S. D., & Lloyd, L. S. (2013). Daily Oral Ketamine for the Treatment of Depression and Anxiety in Patients Receiving Hospice Care: A 28-Day Open-Label Proof-of-Concept Trial. *Journal of Palliative Medicine, 16*(8), 958-965

Historic Research

- LSD psychoactive properties discovered by Albert Hofmann 1943
- Hundreds of trials 1950s and 1960s involving thousands of patients
- 130 NIH-funded studies
- Research encouraged by Bill Wilson of AA
- Results were generally reported as positive and encouraging in disorders including anxiety, depression, alcoholism and addiction

Nutt, D., & Carhart-Harris, R. (2021). The current status of psychedelics in psychiatry. *JAMA psychiatry*, *78*(2), 121-122.

Historic Research

- Studies in the late 1960s and early 1970s with lysergic acid diethylamide (LSD) and psilocybin
- Patients with terminal cancer
  - –rapid and sustained reduction in anxiety
  - – improvement in mood
  - –enhanced quality of life patients with terminal cancer
- Treatment-resistant alcoholics

Grof S, Goodman LE, Richards WA, et al. (1973) LSD-assisted psychotherapy in patients with terminal cancer. *International Pharmaco-psychiatry* 8: 129–144alcoholism: meta-analysis of randomized controlled trials. *Journal of Psychopharmacology*

Mangini M (1998) Treatment of alcoholism using psychedelic drugs: a review of the program of research. *J Psychoactive Drugs 30*:381–418.

Effects of Schedule I Drug Laws

- Many psychoactive drugs are used recreationally
- Possession of cannabis, 3,4-methylenedioxy-N-methylamphetamine (MDMA; also known as ecstasy) and the classic psychedelics is stringently regulated.
- These controls make research into their mechanisms of action and potential therapeutic difficult and in many cases almost impossible.

Heal, D. J., Henningfield, J., Frenguelli, B. G., Nutt, D. J., & Smith, S. L. (2018). Psychedelics—Re-opening the doors of perception.

Nichols, D. E. (2016). Psychedelics. *Pharmacological reviews*, *68*(2), 264-355.


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Exceptions to Schedule I Drug Laws

- Allowed to be used as treatments for medical conditions
  - Opiates
  - Cocaine
  - Some stimulants (amphetamines)
  - Cannabis (recently, in some states, not federally)

- Not available for therapeutic use
  - 3,4-methylenedioxy-*N*-methylamphetamine (MDMA; also known as ecstasy)
  - Psychedelics

Nutt, D. J., King, L. A., & Nichols, D. E. (2013). Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Reviews Neuroscience*, *14*(8), 577-585.

Rucker, J. J. (2015). Psychedelic drugs should be legally reclassified so that researchers can investigate their therapeutic potential. *BMJ*, *350*.

Adverse Effects

- Adverse effects of the classic psychedelics
  - –Acute increases in anxiety, fear, heart rate and blood pressure
    - limited to the time of drug action
  - –Dangerous behavior
  - –Delayed onset headache
  - –Persisting perceptual disorder (HPPD)

Halpern, J. H., Lerner, A. G., & Passie, T. (2016). A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. *Behavioral Neurobiology of Psychedelic Drugs* (Vol. 36). 333-360.

Johnson MW, Sewell RA, Griffiths RR.(2012) Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug Alcohol Dependence;123*:132–40

Tupper, K. W., Wood, E., Yensen, R., & Johnson, M. W. (2015). Psychedelic medicine: a re-emerging therapeutic paradigm. *CMAJ*, *187*(14), 1054-1059.

Historic Users

- Lifetime use of classic psychedelics at the population level is associated with decreased psychological distress
- Individual instances of harm may be overshadowed by instances in which people experience benefit or no harm
- Clinical studies of the pre-prohibition era generally found good safety and therapeutic potential for psychedelics in treating conditions such as alcoholism, end-of-life anxiety, and even pain

Martinotti, G., Santacroce, R., Pettorruso, M., Montemitro, C., Spano, M. C., Lorusso, M., ... & Lerner, A. G. (2018). Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. *Brain sciences*, *8*(3), 47.

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., ... & Kuypers, K. P. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, *35*(4), 398-405.

Hendricks PS, Thorne CB, Clark CB, et al.(2015) Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *Journal of Psychopharmacology*; 29:280-8.

Cessation of Research

- Methodological challenges
  - Disagreements about controlled trials
  - Difficulties with double-blinding
  - Lack of standardized treatment
- Concern about untoward effects
  - Potential precipitation of psychotic breaks
  - Hallucinogen Persisting Perception Disorder (HPPD)
  - Role in social change

Oram M. (2014) Efficacy and enlightenment: LSD psychotherapy and the drug amendment of 1962. *Journal of History of Medicine & Allied Sciences*;69:221-50.

Quiescence of Research

- Effective termination of research in the 1970s
- Decades of inactivity
- Cautious resumption of Phase I volunteer research in the 1990s
- Rigorous clinical treatment studies in the 21st century

Belouin, S. J., & Henningfield, J. E. (2018). Psychedelics: Where we are now, why we got here, what we must do. *Neuropharmacology*, *142*, 7-19.

Experience from Previous Research

- Positive
  - current methodological designs
  - ethical strictures
  - clinical protocols
- Negative
  - lack of informed consent
  - unsupported claims about purported benefits
  - encouragement for non-clinical use

Contemporary Clinical Protocols

- Manualized treatment
- Fully informed consent
- Sessions take place in health care facilities
- Quiet room
- Comfortable décor/ minimal hospital equipment

Byock, I. (2018). Taking psychedelics seriously. *Journal of Palliative Medicine*, *21*(4), 417-421.

Contemporary Clinical Protocols

- Careful screening of patients
  - Exclusions:
    - personal or family history of psychosis or bipolar disorder
- Two-person co-therapist team
  - Therapists present throughout
  - Minimal interaction
- Patient encouraged to engage in self-reflection

Tupper, K., Wood, E., Yensen, R., & Johnsom, M. (2015). Psychedelic medicine: A re-emerging therapeutic paradigm. *Canadian Medical Association Journal , 187*(4), 1054-1059.

Contemporary Clinical Protocols

- Psychedelic drugs are used as adjuncts to psychotherapy.
  - Preparatory counseling
  - Variable psychotherapeutic interventions
  - Follow-up sessions
- Psychedelic-assisted treatment research
  - anxiety
  - addiction
  - PTSD

Wheeler, S. W., & Dyer, N. L. (2020). A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice*, *7*(3), 279.

“Hallucinogens”

- Alter thought, perception and mood without producing memory impairment, delirium or addiction
  - –cannabinoids,
  - –N-Methyl-D-aspartic acid (NMDA)receptor antagonists
  - – gamma-Aminobutyric acid (GABA)-A receptor agonists,
  - – entactogens such as 3,4-Methylenedioxymethamphetamine (MDMA)
  - –classical psychedelics (serotonergic psychedelics)
    - three main classes of alkaloids:
      - –phenethylamines, tryptamines and ergolines

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: a review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, *45*(7), 486-494.

Nichols DE. (2016) Psychedelics. *Pharmacological Review:68*: 264–355

Classes of Psychedelics

- Phenethylamines
  - Mescaline
- Tryptamines
  - DMT (ayahuasca)
  - Psilocybin
- Ergolines
  - LSD

Nichols DE. (2016) Psychedelics. *Pharmacological Review:68*: 264–355

LSD as an Analgesic Agent

- LSD first suggested to interfere with serotonin action in 1954
- Studies in “in gravely ill patients who complain[ed] of severe intolerable pain”
  - –Precipitous (12 hour) drop in pain with ~ 3 weeks decreased intensity
  - –Degree and duration of pain relief greater than hydromorphone and meperidine

Kast, E. (1966). Pain and LSD-25. *A theory of attenuation of anticipation. In LSD: The Consciousness Expanding Drug. D. Solomon, Ed*, *239*, 254.

Woolley DW and Shaw E. (1954) A biochemical and pharmacological suggestion about certain mental disorders. *Proceedings of the National Academy of Science USA* ***40***:228–231

Kast's Studies

- "Sensory" vs "affective" pain

- Kast proposed four factors as mechanisms to explain the analgesic potential of LSD:
  - Loss of ability to anticipate pain
  - Expansion of "immediate sensory life"
  - Change in the meaning of pain
  - Ability to separate self from pain
- Theory of "attenuation of anticipation"

Gerard, F. (1990) Pain, Death and LSD: A Retrospective of the Work of Dr. Eric Kast. In: Lyttle, T. (Ed.*) Psychedelic Monographs and Essays #5,* 114-121

Kast, E. C., & Collins, V. J. (1964). Study of lysergic acid diethylamide as an analgesic agent. *Anesthesia & Analgesia*, *43*(3), 285-291.

LSD as an Analgesic Agent

- Two case series in the 1960s and 1970s of LSD for phantom limb pain.
- Two retrospective cross-sectional surveys of patients with cluster headache
  - LSD and psilocybin
  - reduction in headache severity
  - extension of remission periods
- Very few trials assessing the effectiveness of psychedelics in the management of acute or chronic pain since 1977.

Kikkert S, Johansen-Berg H, Tracey I, et al.(2018) Reaffirming the link between chronic phantom limb pain and maintained missing hand representation. *Cortex:106*, 174–84.

Kutch JJ, Ichesco E, Hampson JP, et al.(2017) Brain signature and functional impact of centralized pain: a multidisciplinary approach to the study of chronic pelvic pain (MAPP) network study. *Pain: 158*, 1979–91.

Lambru G and Matharu M (2011) Serotonergic agents in the management of cluster headache. *Current Pain & Headache Report 15*: 108–117.

LSD as an Analgesic Agent

- LSD can be effective:
  - cluster headache AND migraine
  - prophylactic AND acute treatment
  - used infrequently or at non-hallucinogenic doses.
- Cluster headache patients reported
  - cluster period termination
  - extension of the remission period

Sewell RA, Halpern JH and Pope HG, Jr (2006) Response of cluster headache to psilocybin and LSD. Neurology 66: 1920–1922.

Andersson M, Persson M and Kjellgren A (2017) Psychoactive substances as a last resort—A qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduction Journal 14*: 60.

Hutten N, Mason NL, Dolder PC, et al. (2019) Self-rated effectiveness of microdosing with psychedelics for mental and physical health problems among microdosers. *Frontiers in Psychiatry 10*: 672.

Schindler EA, Gottschalk CH, Weil MJ, et al. (2015) Indoleamine hallucinogens in cluster headache: Results of the Clusterbusters medication use survey. *Journal of Psychoactive Drugs 47*: 372–381.

Efficacy, Tolerability and Safety

- Generally considered physiologically safe
- Lower rate of required emergency medical treatment than other drugs
- Not associated with future development of mental health disorders, increased rates of panic attacks or decreased cognitive function.
- LSD use is not a significant risk factor for chromosomal abnormalities or teratogenic effects.

Johnson M, Richards W, Griffiths R. (2008) Human hallucinogen research: guidelines for safety. *Journal of Psychopharmacology;22*:603–20.

Gable RS. (2004) Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction:99*, 686–96.

Efficacy, Tolerability and Safety

- Most common adverse reaction:
  - –acute psychologic distress
- Low risk of physical dependence/withdrawal
  - –psychedelics lack reinforcing properties that result in self-administration
- Perceptual abnormalities
  - –hallucinogen persisting perception disorder (HPPD)
- Prolonged psychosis risk factors:
  - – pre-existing mental illness
    - family history of mental illness

Strassman RJ. (1984) Adverse reactions to psychedelic drugs. A review of the literature. *Journal of Nervous & Mental Disease ;*172:577–95

Halpern, J. H., Lerner, A. G., & Passie, T. (2016). A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. IN: Halberstadt, A. L., Vollenweider, F. X., & Nichols, D. E. (Eds.). (2018). *Behavioral Neurobiology of Psychedelic Drugs* (Vol. 36). Springer., 333-360.

Physiologic Toxicity

- Newer synthetic phenethylamine hallucinogens
  - numerous cases of toxicity as well as fatalities.
- '2 C-X' compounds
  - 4-substituted derivatives of 2,5-dimethoxyphenethylamine (bromo-Dragonfly)
  - N-benzylphenethylamines ('NBOMes')

Srisuma S, Bronstein AC, Hoyte CO. (2015) NBOMe and 2C substitute phenylethylamine exposures reported to the National poison data system. *Clinical Toxicology:53*, 624–8.

Mechanisms in Depression, Addiction & OCD

- Neuroimaging studies:
  - psychedelics probably work by disrupting brain systems and circuits that encode repetitive thoughts and behaviors.
- Psychedelic experience opens a therapeutic window
  - can lead to a recalibration of one's spectrum of associations
- A new paradigm psychiatric medicine
  - drug-facilitated psychotherapy or psychedelic-assisted therapy

Carhart-Harris RL, Nutt DJ. (2017) Serotonin and brain function: a tale of two receptors. *Journal of Psychopharmacology*. 31(9):1091-1120.

Mechanisms of Analgesia

- Psychedelics may alleviate pain:
  - by producing psychedelic effects that indirectly affect the final experience of pain
    - the psychological view
  - by actions with physiological systems directly involved in pain and its modulation
    - the pharmacological view

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., ... & Kuypers, K. P. (2021). A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, *35*(4), 398-405.

Whelan, A., & Johnson, M. I. (2018). Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role? *Pain Management, 8*(3), 217-217–229.

Mechanisms of Analgesia: Psychological View

- Evidence tentatively suggests benefits in addiction, treatment-resistant depression, terminal-illness-related anxiety, obsessive-compulsive disorder, cluster headaches and pain
- Psychedelics may alleviate pain indirectly through the action a psychedelic experience has on an individual's metacognitive interpretation of their pain.
- Distraction and changes in mood can have a powerful effect on the perception of pain
- Recent randomized double blind trials demonstrated psilocybin can relieve anxiety and depression in patients with life-threatening cancer
- The 5-HT 2A receptor may have a a significant role in pain perception

Garcia-Romeu, A., & Richards, W. A. (2018). Current perspectives on psychedelic therapy: use of serotonergic hallucinogens in clinical interventions. *International Review of Psychiatry*, *30*(4), 291-316.

Ross S, Bossis A, Guss J, et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology ;30:1165–80.*

Mechanisms of Analgesia

- Still not fully understood

- Psychedelics can “reset” areas of functional connectivity (FC) in the brain
  - prominent role in many central neuropathic states
  - attributed to serotonin 2A(5-HT_{2A}) receptor agonism
  - could help reverse the changes in neural connections
    - cluster headache, complex regional pain disorder, phantom limb pain, tinnitus

- Promotes neuroplasticity
  - new functional brain connections and pathways to form in regions that support body self-image and pain experience

- Could facilitate a “restart mechanism” that modulates the feeling of pain
  - similar to mindfulness meditation

Rhodes, C (2020) Psychedelics for chronic pain: Is it time? *Practical Pain Management 20* (6)

Mechanisms of Analgesia: Pharmacological View

- LSD, psilocybin and psilocin have affinity for 5-HT receptors
- 5-HT_{2A} activation pathways of psychedelics and nociceptive modulation pathways are similar
- Serotonin 2A (5-HT_{2A}) receptor agonism
  - ’reset’ areas of functional connectivity (FC) in the brain prominent roles in many central neuropathic states.
- Alterations in FC suggest that psychedelics could help reverse neural connections changes in chronic pain states
- 5-HT2A agonists inhibit activity in the default mode network

Castellanos, J. P., Woolley, C., Bruno, K. A., Zeidan, F., Halberstadt, A., & Furnish, T. (2020). Chronic pain and psychedelics: a review and proposed mechanism of action. *Regional Anesthesia & Pain Medicine*, *45*(7), 486-494.

Machek, S. B. (2019). Psychedelics: Overlooked clinical tools with unexplored ergogenic potential. *Journal of Exercise and Nutrition*, *2*(3).

Mechanisms of Psychedelic Antinociceptive Effect

- The 5-HT 2A receptor may have a a significant role in pain perception
  - 5-HT 2A receptor activation causes upregulation of genes associated with neuroplasticity and suppresses TNF-α-induced inflammation
- Psychedelics may alleviate pain directly
  - 5-HT2A receptor binding at the rostral ventromedial medulla
    - enhancement of descending pain inhibitory pathways.
  - 5-HT 2A internalization in dorsal horn neurons
    - can counteract the sensitization of spinal nociceptive responses
- Analgesic properties may be due to psychedelic-induced reductions in tumor necrosis factor alpha

Ramaekers, J. G., Hutten, N., Mason, N. L., Dolder, P., Theunissen, E. L., Holze, F., ... & Kuypers, K. P. (2021). A low dose of LSD decreases pain perception in healthy volunteers. *Journal of Psychopharmacology*, *35*(4), 398-405.

Practice Points

- Drugs such as LSD and psilocybin may interact with endogenous systems in the brainstem and spinal cord that utilize 5-HT such as those involved with inhibition of onward transmission of nociceptive information

- LSD and psilocybin interact with brain regions associated with the default mode network that generates a resting conscious state of awareness.

- There is insufficient evidence to determine whether LSD and psilocybin may be of benefit for patients with persistent pain in the presence and absence of neuropsychiatric ailments

Whelan, A., & Johnson, M. I. (2018). Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role? *Pain Management, 8*(3), 217-217–229.

Practice Points

- There have been very few trials assessing the effectiveness of psychedelics in the management of acute or chronic pain since 1977.

- There are reports that self-medication with psychedelics is superior to current medications in the treatment of cluster headaches and a small-case series demonstrated 2-bromo-lysergic acid diethylamide improved cluster headache symptoms and frequency of attacks.

- Small studies without controls suggest potential benefit for malignant and neuropathic pain.