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


Critical Elements of Psychedelic-Assisted Psychotherapy

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


“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

“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
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


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.

Ketamine

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

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

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


Effects of Schedule I Drug Laws

- Many psychoactive drugs are used recreationally.

- Possession of cannabis, 3,4-methylenedioxymethylamphetamine (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.


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-methylenedioxymethylamphetamine (MDMA; also known as ecstasy)
  - Psychedelics


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)


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


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

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

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

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

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

“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


Classes of Psychedelics

- Phenethylamines
  - Mescaline

- Tryptamines
  - DMT (ayahuasca)
  - Psilocybin

- Ergolines
  - LSD

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’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"


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.


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


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.


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

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’)

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

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


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 significant role in pain perception.


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

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-HT$_{2A}$ agonists inhibit activity in the default mode network


Mechanisms of Psychedelic Antinociceptive Effect

- The 5-HT 2A receptor may have 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

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.

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.