Chronic pain and psychedelics: a review and proposed mechanism of action

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ABSTRACT

The development of chronic pain is a complex mechanism that is still not fully understood. Multiple somatic and visceral afferent pain signals, when experienced over time, cause a strengthening of certain neural circuitry through peripheral and central sensitization, resulting in the physical and emotional perceptual chronic pain experience. The mind-altering qualities of psychedelics have been attributed, through serotonin 2A (5-HT_{2A}) receptor agonism, to 'reset' areas of functional connectivity (FC) in the brain that play prominent roles in many central neuropathic states. Psychedelic substances have a generally favorable safety profile, especially when compared with opioid analgesics. Clinical evidence to date for their use for chronic pain is limited; however, several studies and reports over the past 50 years have shown potential analgesic benefit in cancer pain, phantom limb pain and cluster headache. While the mechanisms by which the classic psychedelics may provide analgesia are not clear, several possibilities exist given the similarity between 5-HT_{2A} activation pathways of psychedelics and the nociceptive modulation pathways in humans. Additionally, the alterations in FC seen with psychedelic use suggest a way that these agents could help reverse the changes in neural connections seen in chronic pain states. Given the current state of the opioid epidemic and limited efficacy of non-opioid analgesics, it is time to consider further research on psychedelics as analgesics in order to improve the lives of patients with chronic pain conditions.

INTRODUCTION

Psychedelics are a class of drugs that alter perception and consciousness.[1 2] Psychedelic substances have been used in various ways throughout different cultures for centuries. In recent history, these substances were stigmatized in the USA and worldwide, with only a recent resurgence of clinical interest into their potential medical benefits. This newfound interest, along with advances in research methodology, has demonstrated the potential benefit of psychedelics for many psychiatric disorders, including depression, anxiety and addiction.[3 4] There is also evidence that psychedelic drugs may possess antinociceptive effects in chronic pain conditions. The development of chronic pain is a complex mechanism that is still not fully understood. Multiple somatic and visceral afferent pain signals, when experienced over time, cause a strengthening of certain peripheral and central nociceptive circuits through sensitization, resulting in the physical and emotional experience of chronic pain. The mind-altering qualities of psychedelics have been attributed, through serotonin-2A receptor (5-HT_{2A}) activation, to alterations of the functional connectivity (FC) of brain regions also known to play prominent roles in pain perception and neuropathic states. This review will cover the historical significance of psychedelics, will provide an overview of their safety and classification, and will discuss the potential mechanisms of action of psychedelics in relation to chronic pain.

HISTORICAL BACKGROUND

A wide variety of chemical compounds that can induce marked alterations of perception, affect and consciousness have been classified as psychedelic drugs.[5] These compounds are often referred to as 'hallucinogens' because they produce profound alterations of visual, auditory and tactile perception. Psychedelic drugs have played a prominent role in spiritual and religious ceremonies in numerous cultures. The Aztecs and other indigenous groups from Central and North America have been using *teonanácatl* mushrooms for religious and divinatory purposes for thousands of years. The medicinal, religious and ceremonial use of peyote (*Lophophora williamsii*), a cactus species containing mescaline, by tribal groups native to North America can be traced back 5700 years.[6] *Ayahuasca* (meaning 'vine of the souls') is a potent hallucinogenic beverage used by indigenous groups throughout the Amazon basin of South America. This beverage has been used since antiquity to diagnose and cure disease and to induce mystical and spiritual states. Modern Brazilian syncretic religious groups continue to use ayahuasca as a sacrament during religious ceremonies.

The usage of psychedelics has continued in the modern era. In 1938, a Swiss chemist named Albert Hofmann synthesized lysergic acid diethylamide (LSD), but its potent psychoactive effects were not discovered until 1943.[7] After the first European clinical trials published in 1947, LSD began to be studied by American psychiatrists in 1949 as a tool to induce a so-called 'model psychosis.'[8] In 1958, Hofmann and his colleagues isolated psilocybin and psilocin from *Psilocybe mexicana*, one species of hallucinogenic mushrooms.

During the following decades, modern scientific exploration of psychedelics accelerated and numerous studies were conducted with these substances, laying much of the groundwork for what is currently known about their pharmacodynamic

effects. In 1954, Woolley and Shaw first proposed that LSD may act by interfering with the action of serotonin in the brain.[6] In addition to examining the pharmacological properties of psychedelic drugs, clinical studies were also conducted to evaluate their potential use as therapeutic agents. Although many of these trials were poorly designed and lacked proper controls and blinding, considerable evidence did emerge indicating these substances likely possess clinical efficacy in the treatment of anxiety, depression and substance abuse.[7] In the 1960s and 1970s, both LSD and psilocybin were used to relieve psychological distress and facilitate psychotherapy in patients with cancer.[9]

LSD and psilocybin gained significant notoriety in the USA during the late 1960s as the recreational use of these compounds became more common. As the non-medical use of psychedelics increased, these substances received more coverage by media platforms, and they became synonymous with the American counterculture. Sensationalism in news reports about hallucinogens, along with fears that the use of these substances could result in psychological decompensation, antisocial behavior and chromosome damage, leads to the institution of strict legal controls over hallucinogen possession. In 1970, the Controlled Substances Act classified psychedelics as Schedule 1 drugs, deeming them to have no accepted medical use. Unfortunately, the scheduling of hallucinogens created substantial barriers that made it virtually impossible for researchers to conduct clinical research with these molecules in human subjects.[6 8] Although human studies with hallucinogens have cautiously resumed in recent years, there are still many barriers to research with psychedelics due to their DEA Schedule 1 status, limiting the amount of work that is being conducted with these substances.

Efficacy, tolerability and safety

Psychedelics are powerfully psychoactive substances but are generally considered safe from a physiologic perspective.[6] Furthermore, when compared with usage of methamphetamine, cannabis and alcohol, the recreational use of classical psychedelics (eg, LSD and psilocybin) is associated with a lower rate of required emergency medical treatment.[6 10] Numerous studies find that lifetime use of psychedelics is not associated with future development of mental health disorders, increased rates of panic attacks or decreased cognitive function.[2 6 11–17]

Nevertheless, psychedelic drugs must be used with caution. Specific areas of concern with the administration and study of psychedelics include acute psychological distress, self-harm, physiologic toxicity, physical dependence/withdrawal and prolonged psychosis/perceptual abnormalities.[8]

Physiologic toxicity

Numerous studies have confirmed that classical hallucinogens such as LSD, mescaline and psilocybin do not cause neurotoxic effects, organ damage or lasting neuropsychological deficits.[8 12 13] LSD is known to have a high margin of safety with individuals having survived after taking very high doses.[18] Acute hallucinogen intoxication can cause physiological side effects such as dizziness, tremor, nausea or paresthesias, which are typically well tolerated, even at high doses. Additionally, moderate increases in heart rate and blood pressure may be seen.[8 9] Contrary to some early claims, several studies have shown that LSD use is not a significant risk factor for chromosomal abnormalities or teratogenic effects.[8]

Newer synthetic phenethylamine hallucinogens, such as the '2C-X' compounds (4-substituted derivatives of 2,5-dimethoxyphenethylamine), bromo-Dragonfly and *N*-benzylphenethylamines ('NBOMes'), have resulted in numerous cases of toxicity as well as fatalities.[19–23] The most common side effects produced by these synthetic phenethylamines include tachycardia, hypertension, hyperthermia and agitation. More serious effects include seizures, rhabdomyolysis, vasospasm, metabolic acidosis and organ failure. While studies do indicate that certain synthetic phenethylamines have a less favorable safety profile compared with classical hallucinogens such as LSD and psilocybin, more research is needed in this area.[6]

Acute psychological distress and self-harm

Acute psychologic distress is perhaps the most common adverse reaction associated with the use of psychedelic drugs. An individual who experiences a 'bad trip' may exhibit profound anxiety, panic, dysphoria or paranoia.[8] These symptoms may lead to self-harm or aggression toward others. In 2016, a survey of nearly 2000 individuals with a history of psilocybin ingestion inquiring about their worst 'bad trip' found that 39% ranked the 'trip' as one of the top five most challenging experiences of their lifetime. In 11% of the individuals, the experience put themselves or others at risk for physical harm. Factors that seemed to influence the likelihood of having a 'bad trip' included the estimated dose, emotional state before the hallucinogen was ingested, physical comfort and social support during the experience.[24]

Physical dependence/withdrawal

Although use of hallucinogens may interfere with daily routines (ie, overuse can interfere with responsibilities and relationships), these drugs do not produce physiologic dependence, addiction or withdrawal symptoms.[8] The classical psychedelics have been shown in several non-human models to lack reinforcing properties that result in self-administration compared with addictive substances such as cocaine, alcohol, amphetamines and opioids.[25 26]

Prolonged psychosis/perceptual abnormalities

Although rare, a concerning potential side effect of psychedelic use is prolonged psychosis, potentially lasting days or months. In a survey of researchers who had administered LSD or mescaline to healthy subjects, only 1 participant out of 1200 experienced prolonged psychosis, a rate of 0.8 per 1000 individuals. Of note, this subject had an identical twin with schizophrenia.[8 27] In patients where psychotherapy was combined with the administration of LSD, the rate of prolonged psychosis persisting for >48 hours was 1.8 per 1000.[28] The biggest risk factors for prolonged psychosis are a pre-existing mental illness or a family history of mental illness.[8]

An additional concern associated with hallucinogen use is the risk of prolonged or re-occurring perceptual abnormalities. This condition, known as hallucinogen persisting perception disorder (HPPD), occurs when an individual experiences perceptual alterations similar to those experienced during previous episodes of hallucinogen intoxication, sometimes resulting in distress or impaired functioning.[8] As early as the 1950s, it was reported that some LSD users may experience 'flashbacks' (transient hallucinogen-like perceptual alterations), although reports showed these episodes were rare, short lived and not qualifying as HPPD.[28]

Safe administration of psychedelics

Given these areas of concern, guidelines for safely studying hallucinogens were published in 2008.[8] The authors stress several factors that should be addressed prior to the administration of

Table 1 Safe conditions for administration of psychedelics[8]

Factor	Optimum conditions	Comments
Selection of patients	► Pregnant women excluded ► No personal or family history of mental illness (schizophrenia, bipolar disorder, etc) ► No significant cardiovascular medical history ► Not taking additional psychoactive medications (Antidepressants, antipsychotics, lithium, etc) ► Adequate presession preparation (description of what to expect, common experiences, etc)	Psychedelics can induce transient tachycardia and/or hypertension.
Selection of administrators	► Individuals whom administer psychedelics should be proficient at monitoring for potential side effects, or causes of medical concern ► Excellent rapport with patients (often developed during prior visits/sessions) ► Proficient in relaxation techniques such as meditation, yoga or mindfulness ► Consider multiple administrators of varied gender, race and ethnicity	The administrator has a profound effect on the psychedelic session and will act as a 'guide' for the patient through their psychedelic 'trip.' Increased presession anxiety or stress correlates to a negative experience.
Selection of environment	► Esthetically pleasing setting (living-room-like setting) ► Minimize outside distractions (television, telephones) ► Physicians available if medical intervention is needed	Avoidance of clinical or laboratory setting in order to avoid presession anxiety.

hallucinogens. These factors are outlined in table 1, and include proper selection of patients, administrators and an esthetically pleasing environment in which to conduct administration.[8]

Substance class

Hallucinogens are generally defined as agents that alter thought, perception and mood without producing memory impairment, delirium or addiction. However, this definition is broad and includes a variety of agents that belong to multiple drug classes, such as cannabinoids, N-Methyl-D-aspartic acid (NMDA) receptor antagonists, gamma-Aminobutyric acid (GABA)-A receptor agonists, entactogens such as 3,4-Methylenedioxymet hamphetamine (MDMA), as well as the classical hallucinogens such as LSD, mescaline and psilocybin. It is now recognized that classical hallucinogens produce similar discriminative stimulus effects, induce the head twitch response (HTR) in rodents and act as agonists of the serotonin-2A (5-HT_{2A}) receptor. Classical hallucinogens, also known as serotonergic hallucinogens, are compounds that can be divided into three main classes of alkaloids: phenethylamines, tryptamines and ergolines.[2]

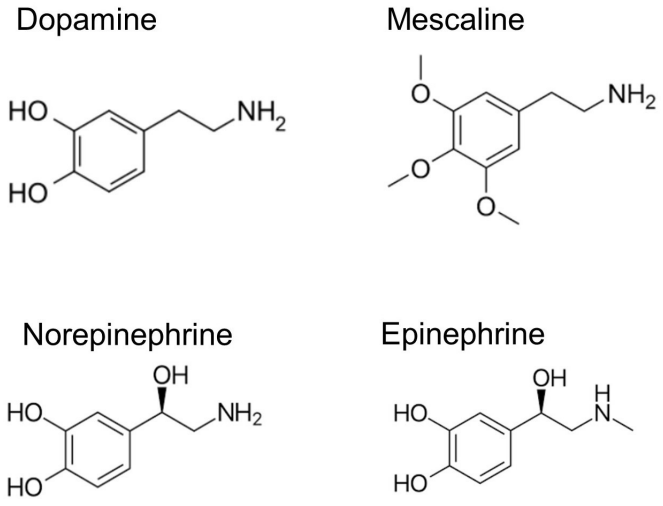

Figure 1 Phenethylamine compounds: (Black and white) An example of the chemical structure of several different phenethylamine compounds.

Phenethylamines

The phenethylamine class is similar in chemical structure to norepinephrine, epinephrine and dopamine (figure 1), with mescaline being the prototypical phenethylamine psychedelic drug. Mescaline has been used as a template for a myriad of designer hallucinogens, including the 2C-X compounds and NBOMes such as 25I-NBOMe and 25B-NBOMe.

Tryptamines

The second class of serotonergic hallucinogens are based on the tryptamine chemical scaffold. Tryptamine hallucinogens are structurally similar to serotonin (figure 2). *N,N*-Dimethyltryptamine (DMT) and psilocybin are the most well-known tryptamine hallucinogens. DMT is the active ingredient in ayahuasca. Psilocybin is the active ingredient in 'magic mushrooms' and undergoes *O*-dephosphorylation to psilocin, which is an active metabolite.

Ergolines

The third class of serotonergic hallucinogens are tetracyclic ergoline derivatives. The prototypical member of this class is LSD. In recent years, several other members of this class, including 1-propionyl-LSD (1P-LSD), 6-allyl-6-nor-lysergic acid diethylamide (AL-LAD) and lysergic acid 2,4-dimethylazetidide (LSZ), have been distributed as designer drugs.[29 30]

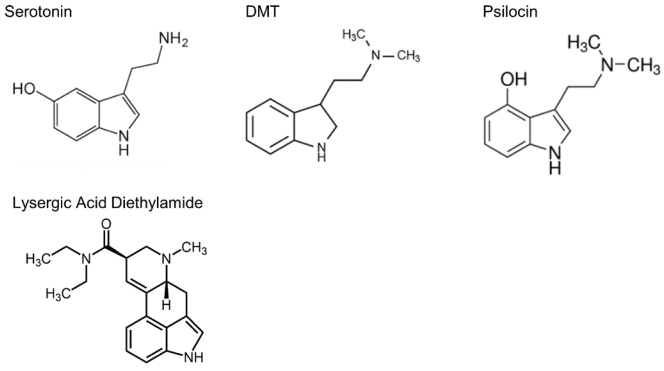

Figure 2 Tryptamines and ergolines: (Black and white) An example of the chemical structure of several different tryptamine and ergoline compounds. DMT, *N,N*-Dimethyltryptamine.

NON-ANALGESIC EFFECTS OF PSYCHEDELICS

Terminally ill patients are likely to encounter chronic pain, along with emotional, existential or spiritual suffering. The experience of suffering often creates a sense that life is not worth living among these patients.[11] Psychedelics are a class of medications that have been shown to be associated with therapeutic benefits for people with anxiety and depression. Even after the initial phase of the hallucinogenic experience resolves, patients report heightened cognitive clarity and an increased emotional receptivity.[11] Studies with single session administrations of LSD, psilocybin and MDMA have shown alleviation of anxiety and depression which may persist for weeks, or even months.[11] While there is variability between individuals' experiences with psychedelics, commonly reported aspects include enhanced/renewed recognition of intrinsic meaning of life, a closer connection to loved ones, nature and God.[31] These non-analgesic effects of psychedelics may be particularly useful in a patient population that is living with a terminal illness.

PSYCHEDELIC MECHANISM IN RELATION TO CHRONIC PAIN

This section will discuss what is known regarding the molecular mechanisms of psychedelic compounds, their local and global effects within the nervous and immune systems, and how this relates to chronic pain.

Molecular mechanism

The primary mechanism of action of psychedelics is via activation of the serotonin 5-HT_{2A} receptor, which is a G protein-coupled receptor encoded by the *HTR2A* gene.[32] Phenethylamine hallucinogens are typically selective for 5-HT_2 subtypes, including 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} sites. Tryptamine hallucinogens bind non-selectively to most 5-HT receptors and may also bind to the σ1 receptor, the trace amine receptor and the 5-HT transporter (SERT). Ergolines, by contrast, display high affinity for most 5-HT, dopaminergic and adrenergic receptors.[32]

Downstream effects: modulation of gene expression and inflammation

Several studies have looked at the downstream effects of psychedelics on gene expression. Nichols *et al* demonstrated that a single dose of LSD upregulates several transcripts in the prefrontal cortex via 5-HT_{2A} activation, including *neuron-derived orphan receptor 1* (*nor1*), *ania3*, *krox-20* (*egr-2*), *map kinase phosphatase 1* (*mkp1*), *core/enhancer binding protein β* (*C/EBP-β*) and *arrestin domain containing 2* (*arrdc2*).[33–35] Many of those genes appear to be involved in synaptic plasticity. 5-HT_{2A} receptor activation by psychedelics increases the expression of immediate early genes (IEGs), including *c-fos*, *period-1*, *egr-1* and *egr-2*, in mouse somatosensory cortex (SSC).[36 37] By contrast, although the non-hallucinogenic 5-HT_{2A} agonist lisuride increased the expression of *c-fos* in mouse SSC, it had no effect on *period-1*, *egr-1* or *egr-2* expression. Administration of 2,5-dimethoxy-4-iodoamphetamine (DOI) to rats increases brain-derived neurotrophic factor (BDNF) mRNA levels in frontal, temporal and parietal cortices.[38] According to a recent clinical trial, administration of ayahuasca also increases the level of BDNF in serum.[39] DOI and LSD also increase the expression of the IEG *Arc* (*activity-regulated, cytoskeleton-associated protein*) in cortex.[34 40] The ability of 5-HT_{2A} receptor activation to increase *Arc* expression is reportedly linked to effects on BDNF and glutamatergic signaling.[40 41]

Studies have also examined the effect of psychedelics on inflammatory responses. The hallucinogen *R*-(–)−4-iodo-2,5-dimethoxyamphetamine (*R*-(–)-DOI) is a potent inhibitor of tumor necrosis factor α (TNF-α)-mediated inflammatory pathways in primary rat aortic smooth muscle cells in vitro,[42] as well as in the vasculature and small intestine when administered in vivo.[43] At the present time, it is not clear whether other 5-HT_{2A} agonists have similar effects on TNF-α pathways.

Normally, descending inhibitory 5-HT pathways help to modulate the transmission of pain signals in the spinal cord and decrease the sensitivity of dorsal horn neurons by inhibiting the c-fiber responses of wide dynamic range neurons.[44–49] It has been suggested that malfunction of these descending inhibitory pathways plays a role in the development of hyperalgesia and allodynia.[50–52] In rat models, these descending inhibitory effects of 5-HT are mediated by activation of 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3 and 5-HT_4 receptors, but after nerve ligation, only activation of the 5-HT_{2A} subtype resulted in persisting 5-HT descending inhibition, suggesting a role for the latter receptor in pain caused by nerve injury.[50 53 54]

The 5-HT_{2A} receptor may play a role in hyperalgesia and neuropathic pain. 5-HT_{2A} mRNA are expressed by dorsal root ganglia (DRG) neurons.[53 56] DRG neurons are depolarized by 5-HT_{2A}.[57] 5-HT_{2A} receptors in the DRG have been shown to potentiate inflammatory pain.[28 58] Consistent with those findings, 5-HT_{2A} antagonists reduce pain responses to inflammatory stimuli.[28 58–60] Rats and mice treated with 2′,3′-dideoxycytidine (ddC), a reverse transcriptase inhibitor used to treat patients with HIV, or vincristine, a chemotherapeutic agent, show evidence of thermal allodynia and mechanical hypersensitivity. The allodynia and hypersensitivity can be reversed by the selective 5-HT_{2A} antagonist, glemanserin, and do not occur in 5-HT_{2A} receptor knockout mice.[61 62] These effects likely occur because ddC and vincristine increase 5-HT_{2A} receptor expression in dorsal horn, which sensitizes spinal nociceptive responses. 5-HT_{2A} receptors in the spinal cord have also been shown to undergo upregulation in models of inflammatory pain.[58 63]

Brain FC

Recent advances in brain imaging technology have allowed the mapping of neural connectivity within the brain. The identification of connections called resting-state networks and the temporal connection between anatomically separate areas called FC has helped show how brain regions are connected and the patterns of connection that are associated with neuropathology or psychological phenomena.[2 64] These brain network dynamics are revealed through fMRI resting state FC analysis. This work has identified brain connectivity networks that are essential for integration of information for complex cognitive function. Healthy brain networks have a characteristically efficient organization. There is growing evidence that disruption of these efficient networks is associated with several neurological conditions including but not limited to depression, anxiety, trauma, addiction, as well as many chronic pain states such as somatoform pain disorder, fibromyalgia, rheumatoid arthritis, centralized pain, chronic pelvic pain, lumbar back pain and phantom limb pain.[65–82] In evaluating the FC changes between healthy volunteers and subjects with chronic pain conditions, the common reorganization was in the extent of the association between prefrontal cortex and the insula. The extent of this reorganization was a function of the intensity of the chronic pain and its duration.[83]

Several imaging studies have demonstrated that psychedelics alter established patterns of connectivity within the brain by

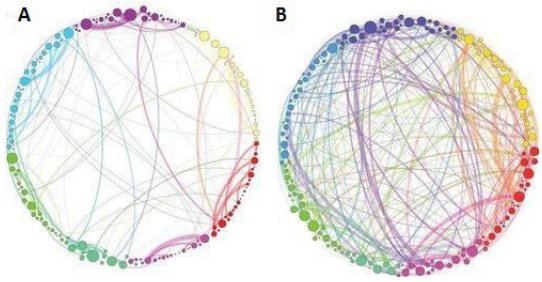

Figure 3 (COLOR) (A) A circular connectogram showing normally communication between distinct hubs. (B) Markedly increased intercommunity crosstalk after psilocybin administration.

reducing the stability and integrity of established brain networks and by increasing the global integration between established brain networks.[1 84–86] In patients with phantom limb pain, mental imagery exercises have been shown to decrease pain as well as reduce cortical reorganization, as seen on fMRI.[15] An fMRI study of mirror visual feedback (MVF) therapy in patients with phantom limb pain found that reduction in phantom pain after MVF therapy was associated with increased activity in the prefrontal cortex.[87] In a recent case report, a patient who combined MVF therapy and psilocybin had a profound pain response compared with the use of MVF alone, suggesting possible synergistic effects.[88]

How might this work? In analyzing a series of fMRI studies involving psilocybin, Carhart-Harris *et al* proposed that psychedelics 'disintegrate' brain networks and increase the 'repertoire of connectivity motifs' that form and fragment within a network. They suggest that psychedelics may have therapeutic potential in psychiatric conditions by disrupting spatiotemporal patterns of brain activity but that these drug-induced changes may need to be mediated by other therapeutic processes such as coadministered psychotherapy.[89] Psychedelics extend local functional connections to become more global with many additional brain regions and after the normal organization is disrupted there is emergence of strong, topologically long-range functional connections that are not present in the normal state.[7 74] Nichols *et al* hypothesized that after the psychedelic-induced brain network disruption, the formation of long-range functional connections may be solidified through local anti-inflammatory effects to allow 'healthy' reconnections as the drug wears off.[2] As an illustration of psychedelic induced connection disruption (figure 3), Petri *et al* produced a circular connectogram comparing the homological scaffolds showing strikingly different connectivity structure between placebo (A) and psilocybin (B) administration.[74]

Making the case for psychedelics for chronic pain

The literature on classic psychedelics and chronic pain is limited but does include several indicators that these agents have analgesic potential (table 2). There are a handful of articles including case reports, case series, retrospective surveys and prospective non-randomized trials of either psilocybin or LSD in chronic pain conditions. The earliest published studies on psychedelics and analgesia are works from Dr Eric Kast in the mid-1960s on analgesic response to LSD for cancer pain.[47 50] In these studies, LSD not only acutely outperformed 2 mg of PO hydromorphone or 100 mg of PO meperidine but also produced analgesia that persisted for an average of 3 weeks after LSD administration.[47] There were two case series in the 1960s and 1970s that demonstrated positive results in the use of LSD for phantom limb pain.[76 90]

More recently, two retrospective cross-sectional surveys of patients with cluster headache showed that the use of hallucinogens such as LSD and psilocybin was associated with a reduction in headache severity and an extension of remission periods.[77 91] Psilocybin was reported to be roughly as effective as high flow oxygen in aborting cluster headaches and was more effective than oral or intranasal triptan administration but less effective than triptan administration by the subcutaneous route. Psilocybin and LSD were also used to prevent cluster headaches and were evaluated by users to be more effective than conventional pharmaceutical agents including verapamil, prednisone, topiramate and melatonin. Additionally, the use of hallucinogens for headache prevention was relatively infrequent compared with conventional pharmaceutical treatments, which typically require daily administration for this indication.[91] A qualitative evaluation of online headache discussion forum posts on the use of psychedelics for cluster headache and migraine headache found that self-treatment with psychedelics was reported to be effective for lessening the frequency and severity of attacks. A number of patients reported complete remission of symptoms and periodic use to maintain remission. In co

ntrast to psychedelics, the authors found highly variable reports of efficacy when cannabis was self-administered as a treatment, worsening symptoms in some patients and improving symptoms in others.[78]

In a recent case series, five patients with cluster headache were treated with the non-hallucinogenic LSD analog 2-bromo-lysergic acid diethylamide (BOL-148).[92] Administration of three doses of BOL-148 (30 µg/kg by mouth) over 10 days resulted in a pronounced and long-lasting reduction in headache severity and frequency in four of five patients, while the fifth patient experienced a 30% reduction in attack severity that persisted for ~4 months. Consistent with previous clinical experience, the patients treated with BOL-148 experienced minor side effects but hallucinogenic effects did not occur. These findings indicate that the psychedelic effects produced by LSD and psilocybin may not play a role in their therapeutic action in patients with cluster headache.[83 93 94]

The mechanisms by which chronic pain develops are not completely understood but likely involve a complex interplay between somatic and visceral afferent input, peripheral and central sensitization, emotional state, and behavior and cognition. Distraction and changes in mood can have a powerful effect on the perception of pain.[95] Recent randomized double-blind trials demonstrated psilocybin can relieve anxiety and depression in patients with life-threatening cancer.[9 96 97] There is also evidence that specific 5-HT_{2A} gene polymorphisms are associated with fibromyalgia, chronic widespread pain and pelvic pain, further demonstrating a significant role of the 5-HT_{2A} receptor in pain perception.[98 99]

There are several mechanisms whereby psychedelic drugs could potentially produce antinociceptive effects in chronic pain states. First, 5-HT_{2A} receptor activation causes upregulation of genes associated with neuroplasticity and suppresses TNF-α-induced inflammation. Moreover, treatment with psychedelic drugs causes downregulation of 5-HT_{2A} receptor binding sites.[91 100–102] Agonist-induced downregulation of the 5-HT_{2A} receptor is not linked to changes in the level of 5-HT_{2A} mRNA), but rather likely occurs due to redistribution of the receptor from the cell surface to intracellular compartments.[88 103–106] Although as far as we are aware, studies have not examined whether psychedelic drugs induce 5-HT_{2A} internalization in dorsal horn neurons, such an effect could potentially counteract the sensitization of spinal nociceptive responses in neuropathic pain states.

Table 2 Summary of studies investigating psychedelics' role in pain states

Authors	Condition	Psychedelic	Study type	Method	Results
Fanciullacci *et al* (1977)[90]	Phantom limb pain	LSD	Case series Seven volunteers with phantom limb pain	Week 1: Daily placebo Week 2: LSD 25 µg QD Week 3 & 4: LSD 50 µg QD Weeks 5–9: Daily placebo	71% had improvement in pain with at least 50% reduction in analgesic use
Ramachandran *et al* (2018)[86]	Phantom limb pain	Psilocybin with mirror therapy	Case report	Patient-reported psilocybin use with ongoing mirror visual feedback therapy	Pain relief and pain duration were both positively correlated with estimated psilocybin dose. Pain relief duration was increased when high dose psilocybin was combined with mirror therapy (~12 → 24 hours).
Schindler *et al* (2015)[108]	Cluster headaches	LSD and psilocybin	Cross-sectional retrospective survey	Clusterbusters.org medication use survey 496 responders	Psychedelics were comparable with or more effective than most conventional medications, with increased effectiveness in shortening cluster periods. Subhallucanigenic doses were also efficacious.
Sewell *et al* (2006)[109]	Cluster headaches	LSD and psilocybin	Cross-sectional retrospective survey	53 patients with cluster headaches who had used LSD or psilocybin for cluster headache treatment	85% of psilocybin users noted aborted attacks. 52% of psilocybin users and 89% of LSD users reported cluster period termination. 95% of psilocybin users and 80% of LSD users reported extension in remission periods.
Karst et al. (2010)[92]	Cluster headaches	2-bromo-LSD (BOL-148)	Case series	Five patients suffering from cluster headache were treated with the non-hallucinogenic LSD analog 2-bromo-lysergic acid diethylamide (BOL-148)	Pronounced and long-lasting reduction in headache severity and frequency in four of five patients. The fifth patient experienced a 30% reduction in attack severity that persisted for ~4 months.
Kast & Collins (1964)[110]	Cancer, ischemic, or neuropathic pain	LSD	Prospective non-randomized trial with comparison to hydromorphone and meperidine; 50 subjects	50 hospitalized patients Breast CA w/ metastasis, (10) Cervix CA w/ metastasis, (13) Pancreatic CA (4) Liver CA (2) Larynx CA w/ metastasis, (4) Lung CA w/ metastasis, (6) Herpes zoster (1) Gangrene of foot/leg (10)	Three hours after administration, LSD was significantly better than both meperidine and hydromorphone ($p<0.001$). 48.9% of patients were free of pain after 19 hours.
Andreasen *et al* (2017)[19]	Cluster headache and migraine headache	LSD and psilocybin	Qualitative thematic analysis of online headache forum discussions	Thematic analysis of user online discussions of LSD and psilocybin use for cluster headache and migraine headache	LSD and psilocybin reported to reduce frequency and severity of headache attaches for both cluster and migraine headache
Kutch *et al* (1967)[76]	Phantom limb pain	LSD	Case series; eight subjects	Eight patients with phantom limb pain or phantom limb sensation	Significant and sustained reduction in phantom limb sensation in seven of eight subjects and phantom limb pain in five of six subjects

LSD, lysergic acid diethylamide.

The transition from acute pain to chronic pain, especially in patients with neuropathic pain, has been shown to involve neuroplasticity or other changes in nervous system structure and function. These neuroplastic changes have been detected at multiple levels of the central nervous system, ranging from the spinal cord to the cortex.[107] Given the accumulating evidence of altered brain FC in chronic pain states, the ability of psychedelics to disrupt established brain connection patterns is perhaps the most intriguing potential analgesic mechanism for psychedelics. Should this prove to be the case, combining psychedelics with more traditional therapeutic modalities could result in synergistic therapeutic benefits. Potential psychedelic co-therapeutic modalities include MVF therapy, physical therapy, nerve blocks, neuromodulation techniques or others with the goal of reversing some of the neuroplastic changes that resulted in the chronic pain state.

Future research

"According to clinicaltrials.gov, there are now well over 200 active and/or completed clinical trials examining the effects and mechanisms supporting the impact of psychedelic agents on a spectrum of health outcomes. However, there are none that are currently examining the impact of psychedelics on chronic pain. This recent increased interest in psychedelic calls for increased funding to better identify how psychedelics can be safely utilized to improve the human condition in an efficacious way. A major explanatory gap is identifying the active mechanisms supporting psychedelic-induced analgesia. Thus, there is need for studies focused on identifying physiological mechanisms supporting the pain relief across different chronic pain types and varying psychedelic products (ie, psilocybin; LSD). Figure 4 depicts a potential algorithm for 5-HT2A agonist psychedelics and subtypes of chronic pain. By focusing on specific types of pain, we can help

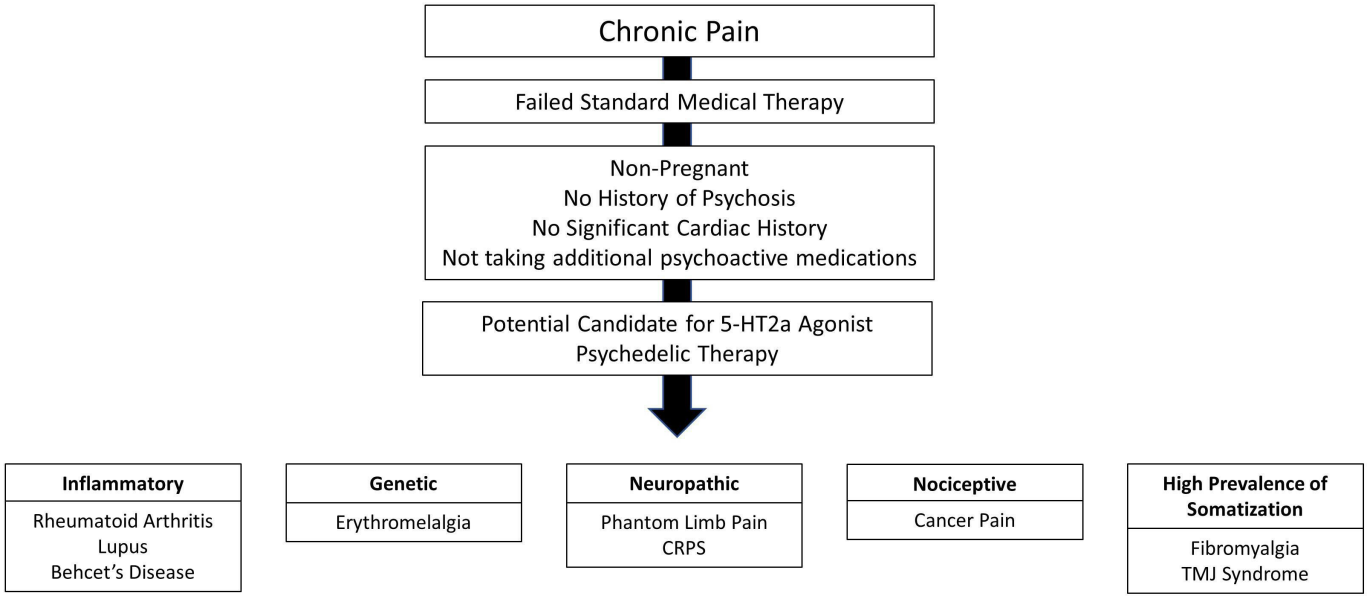

Figure 4 (Black and white) Proposed methodology to better elucidate 5-HT_{2A} agonist psychedelic mechanism of action for chronic pain. 5-HT2A, serotonin 2A; CRPS, Complex Regional Pain Syndrome ; TMJ, Temporomandibular Joint Syndrome.

better determine which types of chronic pain psychedelics are best utilized as well as guide elucidation of the major driving mechanism of action for psychedelics in chronic pain. Another important bridge for this gap is the utility of placebo-controlled trials and determining the appropriate dosages to elicit reliable changes in pain relief. As delineated in this review, there are a lot of promising and converging lines of evidence for the use and utility of psychedelic therapies across a range of health outcomes."

CONCLUSION

Psychedelics have been used in many cultures for thousands of years and recently there has been a resurgence of interest in using them to treat psychiatric conditions. These substances have a generally favorable safety profile, especially when compared with opioid analgesics. Clinical evidence to date for their use for chronic pain is limited; however, several studies and reports over the past 50 years have shown potential analgesic benefit in cancer pain, phantom limb pain and cluster headache. While the mechanisms by which the classic psychedelics may provide analgesia are unclear, several possibilities exist given the similarity between 5-HT_{2A} activation pathways of psychedelics and the nociceptive modulation pathways in humans. Additionally, the alterations in FC seen with psychedelic use suggest a way that these agents could help reverse the pathologic changes in neural connections seen in chronic pain states. Given the current state of the opioid epidemic and limited efficacy of non-opioid analgesics, it is time to consider further research on psychedelics as analgesics in order to improve the lives of patients with chronic pain conditions.

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