From Taboo to Treatment: The Emergence of Psychedelics in the Management of Pain and Opioid Use Disorder

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October 30, 2023

Abstract

The rise of psychedelics in contemporary medicine has sparked interest in their potential therapeutic applications. While traditionally associated with countercultural movements and recreational use, recent research has shed light on the potential benefits of psychedelics in various mental health conditions. In this review, we explore the emerging role of psychedelics in the management of chronic pain and opioid use disorder (OUD), two critical areas in need of innovative treatment options. Pain control remains a significant clinical challenge, particularly for individuals with OUD and those who receive long-term opioid therapy (LTOT) who develop marked tolerance to opioid-induced analgesia. Despite the magnitude of this problem, there is a scarcity of controlled studies investigating pain management alternatives for these populations. Drawing from preclinical and human evidence, we highlight the potential of psychedelics to act on shared neurobiological substrates of chronic pain and opioid use disorder, potentially reversing pain- and opioid-induced neuroadaptations, such as central sensitization. We elaborate on the multifaceted dimensions of the pain experience (sensory, affective, and cognitive) and their intersections that overlap with opioid-related phenomena (opioid craving and withdrawal), hypothesizing how these processes can be modulated by psychedelics. After summarizing the available clinical research, we propose mechanistic insights and methodological considerations for the design of future translational studies and clinical trials, building on a shared clinical and neurobiological understanding of chronic pain and OUD. Our intention is to provide timely perspectives that accelerate the development and exploration of novel therapeutics for chronic pain and OUD amidst the escalating opioid crisis.

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Running Title: Psychedelics, Pain, Opioid Use Disorder

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ABSTRACT WORD COUNT: 249

MANUSCRIPT WORD COUNT: 7,998

REFERENCES: 148

FIGURES: 2

TABLES: 0

KEYWORDS: Nociception, Analgesia, Opioid Addiction, Hallucinogen, Drug Development

CONFLICTS OF INTEREST: The authors disclose no conflicts of interest. J.P.D. has been supported in clinical trials by Jazz Pharmaceuticals, specifically through medication provisions. Additionally, J.P.D. has been a compensated consultant for Boehriger Inhelheim.

FUNDING INFORMATION: J.P.D. is supported by the grants K23DA052682 and R21DA057240 from the National Institute on Drug Abuse (NIDA).

ABSTRACT

The rise of psychedelics in contemporary medicine has sparked interest in their potential therapeutic applications. While traditionally associated with countercultural movements and recreational use, recent research has shed light on the potential benefits of psychedelics in various mental health conditions. In this review, we explore the emerging role of psychedelics in the management of chronic pain and opioid use disorder (OUD), two critical areas in need of innovative treatment options. Pain control remains a significant clinical challenge, particularly for individuals with OUD and those who receive long-term opioid therapy (LTOT) who develop marked tolerance to opioid-induced analgesia. Despite the magnitude of this problem, there is a scarcity of controlled studies investigating pain management alternatives for these populations. Drawing from preclinical and human evidence, we highlight the potential of psychedelics to act on shared neurobiological substrates of chronic pain and opioid use disorder, potentially reversing pain- and opioid-induced neuroadaptations, such as central sensitization. We elaborate on the multifaceted dimensions of the pain experience (sensory, affective, and cognitive) and their intersections that overlap with opioid-related phenomena (opioid craving and withdrawal), hypothesizing how these processes can be modulated by psychedelics.

After summarizing the available clinical research, we propose mechanistic insights and methodological considerations for the design of future translational studies and clinical trials, building on a shared clinical and neurobiological understanding of chronic pain and OUD. Our intention is to provide timely perspectives that accelerate the development and exploration of novel therapeutics for chronic pain and OUD amidst the escalating opioid crisis.

1. INTRODUCTION

The renewed interest in psychedelics has sparked growing attention to their potential therapeutic applications, prompting a new wave of modern clinical studies and trials. While traditionally associated with counterculture movements and recreational use, leading to their scheduling under the Controlled Substances Act at the start of the 1970s, recent research has shed light on the potential benefits of psychedelics in various mental health conditions, and more recently, both pain and substance use disorders (SUDs).

The continuing opioid epidemic, which claimed over 100,000 lives in the United States in 2021,[1] is intertwined with the parallel crisis of chronic pain.[2] The initial wave of the opioid epidemic stemmed from the excessive prescription of opioids for chronic pain-related conditions.[3,4] Chronic pain not only serves as a precursor to possible opioid use disorder (OUD) but is also associated with poorer treatment outcomes for those with OUD, including sleep disturbances, diminished social functioning, and increased attrition rates from OUD treatment.[5,6]Despite the magnitude of this problem, there is a scarcity of controlled studies investigating pain management alternatives for those with OUD.[7] The three medications currently approved for OUD all exert their therapeutic benefits primarily through the mu-opioid receptor (MOR) and, given their various adverse effects, ranging from gastrointestinal and immune (e.g., methadone and buprenorphine) to hepatic (e.g., extended-release intramuscular naltrexone), there exists a great need for medications that work outside of this system.[8] Collectively, the challenges posed by opioid analgesic tolerance[9] and the escalation of the opioid epidemic, due to the widespread availability of fentanyl derivatives, further emphasize the urgency to explore novel, non-opioid therapeutics for pain and OUD.

The serotonergic psychedelics, or the "classic" psychedelics, are a class of compounds that exert their psychedelic effects primarily at the serotonin 2A (5-HT2A) receptors.[10] Common examples of serotonergic psychedelics include lysergic acid (LSD), psilocybin, ibogaine, noribogaine, ayahuasca, and N, N-dimethyltryptamine (DMT), which have been used in clinical trials investigating their utility independently for both pain and OUD since the 1960s.[11-13] Psilocybin, one of the most studied serotonergic psychedelics in modern trials, has shown efficacy in the treatment of other SUDs, such as alcohol use disorder (AUD)[14] and tobacco use disorder.[15]The potential efficacy of psilocybin for chronic pain in people receiving long-term opioid treatment (LTOT) is being tested in ongoing clinical trials.

This review will summarize the available data on the use of serotonergic psychedelics for the treatment of chronic pain and OUD. This review complements prior reviews on psychedelics [16-20] by presenting a synthesis of the mechanisms for how this class of compounds could be useful to treat OUD and chronic pain independently, as well as when these conditions co-occur. In addition, we propose mechanistic and methodological insights for future research needs, including trial design considerations in this area.

PSYCHEDELICS' GENERAL MECHANISM OF ACTION

Serotonergic psychedelics are either full or partial agonists at the 5-HT2A receptor. Psychedelics can also be classified based on their chemical structure.[21] The tryptamines, such as psilocybin, ayahuasca and DMT, contain an indole ring structure and are structurally similar to the neurotransmitter serotonin. The ergolines, such as LSD, contain the ergoline ring system and are derived from ergot fungi. Others, such as ibogaine and noribogaine, produce altered states of consciousness through serotonergic and other mechanisms.[21]

Preclinical studies using the head-twitch model in rodents, a behavior specifically mediated by 5-HT2A receptor agonism,[22]have shown that many psychedelics, such as LSD and psilocybin, reliably induce head-twitch responses,[23,24] thus providing evidence that psychedelics have serotonergic activity. By this mechanism these compounds are known to induce profound alterations in perception, cognition, and emotion.

Additionally, psychedelics appear to promote neuroplasticity[25] and facilitate changes in neural connectivity, potentially underpinning their therapeutic effects. Elucidating the complex mechanisms underlying the efficacy of psychedelics can inform the optimization of psychedelic therapies for both OUD and chronic pain.

3. PSYCHEDELICS'ANALGESIC MECHANISMS

Pain perception is a complex phenomenon involving somatosensory, cognitive, and affective components.[26] Serotonergic signaling has been implicated in the peripheral and central mechanisms of nociceptive transmission and modulation in both acute and chronic pain states.[27] Convergent preclinical and human findings support and strengthen the involvement of the 5-HT2A receptor in musculoskeletal pain perception, with relevance for clinical pain conditions. In addition, human studies have provided evidence for the involvement of 5-HT2A receptor in pain perception and processing. Associations have been found between the T102C polymorphism of the 5-HT2A receptor gene and fibromyalgia, and other genetic variations in 5-HT2A polymorphisms have been associated with chronic widespread pain.[28,29] Psychedelics, through these serotonergic and other properties, hold promise as novel analgesics by modulating multiple dimensions of the pain experience.

3.1 Modulation of bottom-up nociception

The somatosensory dimension of pain encompasses its intensity, quality, and spatial characteristics.[30] Mechanistic studies have demonstrated that 5-HT2A receptors are involved in the nociceptive transmission through the spinal cord[31] and that their activation can inhibit the descending nociceptive transmission in states of chronic and neuropathic pain.[27,32,33] 5-HT2A receptors are expressed in neurons in the dorsal root ganglia (DRG), nodule-like structures found on the posterior root of each spinal nerve, among other locations, which contain the cell bodies or afferent sensory neurons carrying pain signals back to the central nervous system (CNS). Therefore, the DRG are critical structures responsible for central pain sensitization, a mechanism by which the CNS becomes sensitized to nociceptive stimuli, promoting the maintenance of chronic pain states. Some of the analgesic properties of psilocybin, for instance, are believed to be mediated by downregulation of 5-HT2A receptor in the DRG.[34,35] This downregulation may counteract central pain sensitization.

3.2 Anti-inflammatory properties

Besides neural transmission, inflammation is another key mechanism involved in the pain experience. Chronic inflammation drives pain by sensitizing peripheral nociceptors.[36] This inflammatory process involves various mediators that can initiate and perpetuate chronic pain states.[36] Serotonergic agonism from psychedelics has the potential to inhibit inflammatory signaling mediated by TNF-alpha, NF-kB, and inflammatory cytokines.[37,38] This is thought to occur through activation of 5-HT2A receptors on immune cells. Hence, by suppressing key inflammatory mediators, these anti-inflammatory properties of psychedelics may also reduce inflammatory pain.

3.3 Neuroplastic effects

In addition to affecting the sensory and inflammatory aspects of pain, psychedelics may also influence chronic pain through their ability to promote neuroplasticity.[25] Neuroplasticity is the brain's ability to reorganize neural pathways and forge new connections.[39] Neuroimaging studies have revealed that chronic pain conditions such as chronic low back pain, complex regional pain syndrome, and osteoarthritis are all associated with altered functional connectivity between spatially distinct brain regions.[40-43] For example, functional MRI (fMRI) studies have demonstrated that chronic low back pain is associated with a reorganization of functional connectivity between sensory, cognitive, and limbic areas (e.g., *nucleus accumbens* and the prefrontal cortex [PFC]). It is also associated with a disruption of the default mode network (DMN) — a system of connected brain areas that show increased activity when the individual is passively resting and mind-wandering. These connectivity changes likely reflect maladaptive plasticity and reorganization of functional brain circuits due to persistent pain signaling.[40,41] By stimulating neural plasticity and regrowth of connections between brain cells,[44] psychedelics could potentially counteract these observed connectivity alterations and remodel the disrupted networks involved in pain. As a result, psychedelics could temporarily disrupt

these patterns of brain activity, providing a window for rewiring neural connections and restoring more optimal network functioning. This could potentially disentangle the clustering of sensory, cognitive, and affective components of pain, enabling a transformed understanding of the pain experience.

Relatedly, these compounds have been theorized to be linked with changes in entropy and complexity in brain dynamics,[45,46]leading to changes that may be helpful in breaking out of rigid cognitive and behavioral patterns. By disrupting these patterns, psychedelics may facilitate the adoption of more adaptive pain-related beliefs, thought processes, and actions.

3.4 Impact on negatively valenced emotional states related to the pain experience

Both opioid use and chronic pain can disrupt pain modulatory systems, altering not only nociception, the process of encoding noxious stimuli, but also the affective component of pain, which can culminate in pain catastrophizing. This maladaptive state of unrelenting pain is characterized by magnification (heightening the threat value of pain-related stimuli), helplessness (lack of control over pain), and rumination (having a reduced ability to divert one's focus away from pain-related emotions).

Beyond their impact on neural pathways, psychedelics could also influence the affective and psychological experience of pain, encompassing the feelings of unpleasantness, distress, suffering, and reactions to the long-term implications of living with chronic pain.[47] The anterior cingulate cortex (ACC) is a crucial area in processing the emotional and affective aspects of pain.[26,48] Psychedelics may modulate these affective aspects by altering activities in the ACC. Studies using task-free fMRI found that psilocybin reduces cerebral blood flow in the ACC, which was associated with the intensity of subjective effects of psilocybin.[49] As a result, it is possible that psychedelics might also have the potential to lessen these negative emotions associated with pain. This is supported by evidence suggesting that psilocybin may mitigate similar affective phenomena, such as depressive rumination and obsessive thinking,[50] which can resemble the fear of movement seen in chronic pain. Given that depressive and anxiety disorders often co-occur with chronic pain,[51] psychedelics may provide a more comprehensive treatment strategy by targeting these affective aspects, which can often be equally hard to discern and equally debilitating for these patients.

3.6 Cognitive and psychosocial effects

Pain also involves cognitive and behavioral processes such as attention, memory, and evaluation.[52] Psychological factors, such as coping strategies, significantly influence the overall experience of pain.[53] In patients with chronic low back pain, fear of movement, or *kinesiophobia* , is associated with increased activity in brain regions related to emotion and fear.[54] Higher levels of pain intensity can also lead these patients to engage in more perseverative thinking, such as worry and rumination, as they try to mentally problem-solve their pain.[55] In patients with chronic pain, these negative metacognitive beliefs are associated with higher emotional distress and lower mood.[56] Psychedelics may have the potential to facilitate changes in some of these harmful cognitive patterns by loosening rigid mindsets like functional fixedness, and by allowing greater problem-solving ability.[57] Additionally, psychedelics can induce a profound shift in consciousness, known as ego dissolution, with increased emotional sensitivity[58]that could facilitate changes in maladaptive cognitions and emotions related to pain. This may facilitate the revaluation of maladaptive beliefs and attitudes towards pain, potentially promoting confidence in one's ability to perform tasks despite pain (i.e., self-efficacy). Additionally, it has been suggested that psychedelics may impact automatic cognitive phenomena such as attentional bias – a process in which attention is preferentially captured by pain and its cues. It is also worth noting that abnormal attentional bias for pain and opioid cues have been respectively identified among those with chronic pain and OUD[59,60]; and attentional bias for both cues are potentially modifiable in individuals with chronic pain and OUD receiving methadone or buprenorphine.[61]

In addition to altering pain-related cognitions, psychedelics have been found to increase positive mood, feelings of social connectedness and interpersonal closeness.[62-64] A recent meta-analysis revealed a significant inverse association between positive mood and pain intensity in individuals with chronic pain.[65]Additionally, enhanced social functioning associated with psychedelics could potentially improve interpersonal interactions despite experiencing pain, and strengthen social support by improving openness and communication. To-

gether, these social and relational changes have the potential to improve coping and readjust maladaptive pain-related thoughts and behaviors.

In summary, psychedelics have the potential to improve pain management through their multidimensional impact on sensory transmission, inflammation, neuroplasticity, affect, anxiety, cognitive patterns, and behaviors. Although these findings are promising, further research is needed to comprehensively understand the various mechanisms by which psychedelics may alleviate distinct forms of chronic pain. Elucidating these mechanisms can further inform the development of interventions that leverage these pharmacological and psychological effects to reduce the suffering of patients with chronic pain (**Figure 1**).

4. CLINICAL APPLICATIONS OF PSYCHEDELICS FOR PAIN: CURRENT KNOWLEDGE

Early research beginning in the 1950s was focused on ways in which psychedelics could be used as an adjunctive to facilitate engagement in psychotherapeutic interventions. Regulatory restrictions on psychedelics in the early 1970s halted research. For chronic pain treatment, psychedelics have mainly been investigated in palliative care, cancer-related pain, headaches, and phantom limb pain.

4.1. Lysergic Acid Diethylamide (LSD)

Lysergic acid diethylamide (LSD) is a non-exclusive 5-HT receptor agonist that has been investigated for its potential analgesic properties. It also interacts with certain dopaminergic and adrenergic receptors.[66] Threshold dosages for psychedelic effects are as low as 20-30μg, although recreational dosages can range from 50-200μg.[66] LSD has a prolonged action, with effects that can persist for six to nine hours after ingestion.[66] Some of the putative analgesic mechanisms for LSD originate from both its general pharmacological action and its psychological effects: (1) anti-inflammatory action, for instance through inhibition of tumor necrosis factor (TNF) production[37]; (2) activation of inhibitory serotonergic descending pathways, inhibiting central sensitization[67]; and (3) modulation of emotional aspects of pain, potentially through alterations in consciousness, and/or the "psychedelic experience".[68]

Studies from the 1960s had suggested some evidence that LSD could attenuate pain in various conditions, including chronic pain syndromes and terminal illness. An early double-blinded trial including patients with multiple chronic pain conditions compared the analgesic action of two opioids, dihydromorphine (2 mg) and meperidine (100 mg), with an open-label arm in which participants received 100μg of LSD.[13] The study demonstrated that LSD had a more prolonged and effective analgesic potential, despite a slower onset of action. However, despite pain relief, patients were more likely to refuse the second administration of LSD, suggesting that its analgesic properties were accompanied by a lack of tolerability. This clinical trial was not only the first to explore the role of LSD for pain treatment, but through comments regarding "psychic work" and participants' "distraction from pain", it also hinted at early insights that pain is a multidimensional experience encompassing both biological and psychological components.

Recent studies, albeit limited, have reignited interest in the analgesic potential of LSD.[69] In 2021, a randomized, placebo-controlled, crossover human laboratory study administered low doses of LSD (5, 10, and 20 μg) and showed an increase in pain tolerance and reduction in pain unpleasantness, using the Cold Pressor Test (CPT), a well-established laboratory model of pain.[67] This study provided evidence that sub-hallucinogenic doses of LSD may produce analgesia in humans.

Preliminary evidence suggests that LSD may alleviate pain and improve the overall well-being of individuals suffering from chronic pain. Other areas of research interest include palliative care and cancer-related pain, headaches (including migraines and cluster headaches), and phantom limb pain.

4.1.1 Palliative care and cancer-related pain

Early reports of the use of LSD to mitigate cancer-related pain include examinations of a single dose of LSD in patients with various forms of metastatic cancers.[13] Among the 128 participants included in this study, a fraction had various forms of metastatic cancer (i.e., breast, cervical, lung, larynx, and pancreatic cancer).

A single 100μg dosage of LSD, administered orally, improved pain for up to two weeks, as measured by the numerical rating scale. No sensitivity analyses were reported for the participants with cancer pain.

Suggested mechanisms included "LSD produces an inability to maintain selective attention ", hinting at what is also called attentional bias. This effect was proposed as a psychological mechanism to explain the reduction of participants' concerns for pain, suffering, and death. They noted that "participants displayed a particular disregard for the gravity of their situation and talked freely about their impending death". Later studies published throughout this early period mostly replicated these early findings and emphasized the importance of "distracting patients from their pain" and reaching the "psychedelic experience" to achieve the best results.[70,71] Modern trials of LSD in those with palliative cancer states have continued, with a focus on mood, anxiety, and quality of life (QoL) outcomes. While few details have been specifically reported on the measurement of pain or the use pain as a primary outcomes measure, these studies provide the foundation on which to further study the unique biological, analgesic, and psychological effects, in the setting of cancer-related pain.

4.1.2 Headaches

The research investigating the analgesic potential of LSD in headaches has centered around both cluster-type headaches (CH) and migraine headaches. Both conditions are generally chronic but episodic in nature, making it important to distinguish between the specific use of medications in their treatment, namely, the use of medications for*prophylaxis* or for acute *abortive* treatment. Interestingly, medications commonly used to abort these types of headaches (many from the ergotamine and triptan families), partially share LSD's (a lysergamide) mechanism of action as 5-HT receptor modulators. The theoretical underpinnings of serotonin and possible role of LSD and its analogs can play in the role of these types of headaches have been considered since at least the 1960s. The use of non-hallucinogenic LSD-analogs and other lysergamides have been studied and used in the treatment of many of these headache disorders.[72] [73] Despite mechanistic plausibility, there have been no randomized clinical trials for LSD and migraines. Other clinical studies investigating three single doses of an LSD derivate (BOL-148, at a dose of 30 μg/kg/body weight) safely improved CH cycles or significantly improved frequency/intensity of episodes in four out of five patients.[73] Other qualitative studies with patients self-medicating with LSD reported prophylactic and acute abortive benefits.[74] Another preliminary study suggests that micro-dosing, or using sub-hallucinogenic dosages, of LSD may also be beneficial to prevent headache episodes.[75] In summary, the use of LSD for headaches holds promise as a therapeutic option, but research in the area is still in early stages.

Interviews with 53 patients living with CH who were using psilocybin or LSD without medical supervision to treat the condition, have found that seven of the eight participants who used LSD reported termination of cluster periods, and four of those reported that the substance significantly prolonged their periods of remission. [76]Online survey studies including 496 participants from a specific CH support group suggested that a single dose of LSD could prevent attacks, shorten, or even abort cluster episodes, or induce remission.[77] Several participants reported using small, sub-hallucinogenic doses, suggesting that a psychedelic experience may not be an essential component of therapeutic efficacy.

4.1.3 Phantom Limb Pain

Phantom limb pain (PLB) is a painful experience interpreted by patients after a limb amputation with few viable treatment options.[78] The causes of PLB are currently unclear, but it is hypothesized to result from the disruption of ascending and descending pain pathways that reorganize improperly, leading to an ongoing misinterpreted pain perception. LSD has been previously suggested as a possible treatment for PLB. Small case series demonstrated that intravenous infusion or bolus injection of LSD (10 ng/mL at 0.5 ml/min) was "curative" in two patients, "partially helpful" in three, and "ineffective" in two (although measurement and definition of benefit were not systematically described).[79] An additional study found significant benefits of LSD for PLB, with sustained self-reported pain reduction in seven out of eight participants.[80]

4.2. Psilocybin

4.2.1. *Palliative care and cancer-related pain*

In a randomized, double-blind, cross-over trial of very low (placebo-like) dose (1 or 3 mg/70 kg) vs. high dose (22 or 30 mg/70 kg) psilocybin that the substance is indeed able to increase well-being and life satisfaction among patients with cancer.[81]Unfortunately, this study did not include pain as an outcome, but mechanistic plausibility remains. Furthermore, psilocybin has been explored in the context of end-of-life care, where it may alleviate psychological distress associated with dying, enhance existential well-being and improve the quality of life.[81]

4.2.2. Headaches

Psilocybin has also been suggested to produce significant reductions in pain intensity and unpleasantness in patients with cluster headaches.[76] In survey studies, 22 of 26 patients taking psilocybin for cluster headaches reported that the substance was able to abort their crisis. Further, 18 participants reported an extension of remission periods after a single dose of psylocibin. The effectiveness of psilocybin for cluster headache in qualitative studies has reported that psilocybin is "perceived by participants to shorten/abort a cluster period and bring chronic cluster headache into remission more so than conventional medications".[77]

An exploratory double-blind, placebo-controlled, cross-over study investigated psilocybin for migraines. Ten adults with migraine received oral inactive placebo and psilocybin (0.143 mg/kg) in two test sessions spaced two weeks apart. Participants were closely tracked with headache diaries. Over the two weeks after a single dose administration, psilocybin was significantly more effective than placebo in reducing the frequency of migraines.[82] Overall, the research considering psilocybin and pain seems to progress alongside LSD studies; results are promising, yet in their early stages.

4.2.3. Chronic pain and LTOT

One planned eight-week open-label non-randomized study with a six-month follow of those with chronic pain on LTOT is ongoing. This study will investigate the effect of psilocybin and psilocybin-assisted therapy in one of two dosing sessions (25mg and 37.5mg) with the first occurring during the period of opioid tapering. [NCT05585229].[83]

4.3. Ayahuasca

Ayahuasca is a psychoactive substance, usually ingested as a beverage, decocted from *Banisteriopsis caapi* and *Psychotria viridis*plants. They are rich in DMT, a partial 5-HT serotonergic receptor agonist and have direct monoamine-oxidase A (MAO-A) inhibiting properties. Through both mechanisms, ayahuasca has psychedelic effects.[84] Ayahuasca has been historically and culturally used by those in several countries in Central and South America, however, it has recently been more widely used, particularly in religious and spiritual contexts.[85]

So far, no studies have investigated the role of ayahuasca in the management of pain as a primary outcome. One recent study included the Medical Outcomes Study 36-Item Short-Form (SF-36) as a secondary measurement including a subcomponent rating of participant's bodily pain.[86] In this report, the authors conducted two observational sub-studies: (1) one with first-time ayahuasca users (n = 40), and (2) adding a comparison group of long-term ayahuasca users (n = 23). Reported improvements in depression rates for first-time ayahuasca users and lower depression scores among long-term ayahuasca users were found. However, there were no significant changes in bodily pain for first-time ayahuasca users. In a similar study with 23 first-time ayahuasca users showed similar findings but with significant reductions in the bodily pain component of the SF-36 for a subgroup of participants (n = 8).[87] Despite the mechanistic plausibility of ayahuasca for pain treatment given its serotonergic and other relevant mechanisms of action, the literature on the topic is underdeveloped and the little available evidence is conflicting.

4.4. Ibogaine and Noribogaine

Ibogaine is an alkaloid substance obtained from the root bark of the shrub *Tabernanthe iboga,* endemic to Western African regions.[88] It has been historically used by indigenous communities in West Africa for

religious ceremonies, and also to treat fatigue.[88] Its ceremonial use is due to its*oneirophrenic* properties, which means it can invoke dream-like states without loss of consciousness.[88] While preclinical studies of ibogaine and noribogaine have suggested that both ibogaine and noribogaine dose-dependently increase the antinociceptive properties of morphine, making it a potential opioid-sparing strategy in pain management, no human laboratory clinical trials have investigated the use of ibogaine for pain.

Convergent preclinical models have suggested that ibogaine could be used as a modulator of morphine antinociception.[89,90]Co-administration of ibogaine in various doses (1-40mg/kg) and morphine (4 mg/kg) increased morphine-induced antinociception in a dose-dependent manner for rats in a heat-pain paradigm. Further, the administration of 40mg/kg of noribogaine, the primary metabolite of ibogaine, resulted in similar effects. Ibogaine enhances the pain-relieving effects of morphine in mice. After making all mice tolerant to morphine, researchers compared two groups: one given morphine alone and the other with morphine and varying doses of ibogaine or noribogaine. Both ibogaine and noribogaine were found to increase morphine's antinociception effects. To our knowledge, no studies have investigated whether patients receiving morphine could have analgesic effects maximized by ibogaine, thus reducing the total opioid requirement to alleviate pain.

5. CLINICAL APPLICATIONS OF PSYCHEDELICS FOR OPIOID USE DISORDER: CURRENT KNOWLEDGE

Most research on classic psychedelics' therapeutic effects on OUD has focused on opioid withdrawal. Other benefits like reduced opioid use from pain relief are less studied. Although these psychedelics are seen as having low abuse potential, their addiction risk in this group awaits thorough evaluation.

5.1. LSD

There are two studies from the early phase of psychedelic research that investigate the use of LSD in people with OUD. The first study, conducted in 1965, was an open-label controlled trial that included 70 patients with OUD, who had recently been hospitalized for treatment of opioid withdrawal.[12] The study found that orally administered LSD (at doses of 2ug/kg) was generally well tolerated with no participants requiring medications to counteract adverse effects, with only three participants reporting worsening of psychiatric symptoms. The study did not collect data on traditional OUD outcomes, pain, or functioning. The second study, conducted in 1973, was a randomized controlled trial that included 74 participants with OUD at a residential reentry program.[11] Participants were randomized to either a treatment (LSD 300ug-450ug) or control arm. The treatment arm consisted of living in a halfway house from four to six weeks and undergoing 24 hours of preparatory therapy over five weeks and one week of integration therapy post-LSD. At 12 months, 9/36 (25%) of treatment arm participants remained abstinent, compared to 2/37 (5%) of the participants the control group. There were no statistically significant group differences on changes in overall functioning. The authors report that 12 of the 13 of participants who had a "psychedelic peak experience" (using an unnamed questionnaire) appeared more likely to have higher "community adjustment scores" at 12 months. The design of this study makes it difficult to interpret the findings, as there was no control for the impact of the residential treatment component in the treatment arm. There are currently no registered studies planned investigating LSD for OUD or for those on LTOT.

5.2. Psilocybin

Psilocybin has been minimally studied in those with OUD, even though it is one of the most commonly investigated psychedelics in contemporary trials for psychiatric disorders.[91] Although there are limited preclinical investigations of psilocybin in animal models of opioid addiction, it has shown efficacy in the treatment of AUD[14] and tobacco use disorder[15] in modern trials. Other evidence has shown that in large samples of naturalistic use, the classic serotonergic psychedelics as a group have been shown to be associated with 27% reduced risk of past-year opioid dependence and 55% reduced risk of daily illicit opioid use.[92,93] When this relationship is assessed individually, there is some suggestion that lifetime psilocybin use may be associated with a 30% reduced odds of a past-year OUD diagnosis.[94]

There are several planned or ongoing registered studies examining the safety and efficacy of psilocybin in those with either OUD or who receive LTOT for chronic pain. One registered study plans an eight-week double-blind, controlled intervention of hallucinogenic psilocybin (30mg) versus a blinding dose of psilocybin (1mg), following an inpatient buprenorphine-naloxone induction for OUD [NCT06005662].[95] Primary outcomes include opioid abstinence (timeline follow-back [TLFB][96] and urine toxicology), treatment retention, and reduction in days using opioids (self-report and urine toxicology). Secondary measures include quality of life (World Health Organization Quality of Life-BREF [WHOQOL-BREF]), depression (Beck Depression Inventory II [BDII]), anxiety (State-Trait Anxiety Inventory [STAI]), and abstinence from other non-opioid substance use (TLFB).

A Phase 1 study investigating the safety of psilocybin in persons with OUD who were recently stabilized on buprenorphine-naloxone is also currently underway [NCT04161066].[97] This study aims to address two important questions; how psilocybin may impact the effectiveness of medications for OUD (MOUD) and how concurrent MOUD may affect psilocybin therapy. Assessments include safety and adverse events as well as opioid craving (opioid craving scale [OCS]) and opioid use (TLFB).

A planned randomized double-blind placebo-controlled study of those with OUD engaged in methadone treatment who are concurrently using other illicit opioids seeks to investigate primary outcomes of changes in non-medical opioid use (by self-report and urine toxicology) as well as quality of life (WHOQOL-BREF) [NCT05242029].[98]This study has two planned dosing sessions (at 40mg) with further randomization of the treatment group at the second dosing session to investigate the impact of two doses. Importantly, secondary outcomes include assessment of chronic pain, as well as measures of non-opioid substance use, mood, and sleep, which may help to further our understanding of psilocybin's utility as a treatment of co-occurring OUD and chronic pain.

5.3 Ayahuasca

There is one observational study investigating the effects of ayahuasca on substance misuse and psychological functioning in 12 participants with no specific psychiatric or SUD.[99] The intervention was a four-day retreat including two "ayahuasca ceremonies" (50-100mL of ayahuasca) and various addiction-related psychosocial intervention groups. As a major limitation, the diagnosis regarding opioid use (i.e., whether or not participants had OUD) entering the study was not reported; however, it is noted that some participants were receiving methadone treatment. The primary substance use measure was the Four-Week Substance Use Scale (4WSUS). Scores reportedly decreased for all substances except for cannabis; however, data on primary opioid use was not clearly reported. There was no observed difference in opioid use among participants when comparing the proportion who had used opioids at the baseline and the six-month follow-up. However, results showed statistically significant improvements in multiple psychological measures, including mindfulness, empowerment, hopefulness, quality of life-meaning, and quality of life outlook across the whole group — which is generally consistent with prior research on ayahuasca.[100] Other studies on ayahuasca have also suggested its effects on decreasing substance use and potentially mitigating other negative psychosocial effects of drug use, which may deserve future attention.[101] These themes also appear in qualitative work in those using ayahuasca for addiction-related issues in indigenous communities among whom SUD is prevalent.[102] At this time, however, there are no currently registered ayahuasca trials for OUD or opioid dependence.

5.4. Ibogaine and Noribogaine

The studies investigating the use of ibogaine and noribogaine for OUD and opioid withdrawal represents one of the larger collections of clinical studies of a psychedelic for these conditions. There is a large preclinical foundation exploring ibogaine and noribogaine in addiction paradigms and for opioid withdrawal.[103]

5.4.1. Ibogaine for OUD

An open-label study of 27 treatment-seeking participants with OUD and/or cocaine use disorder received a fixed-dose of either 500, 600, or 800 mg ibogaine HCl in a 12-day inpatient setting showed statistically

significant reductions in various subscales of the Heroin Craving Questionnaire (HCQN-29) by the time of discharge.[104]An open-label study of 14 participants with OUD who took ibogaine-HCl (10 mg/kg orally) showed temporary QTc prolongation on an electrocardiogram (EKG)—a condition that may elevate the risk of irregular heart rhythm and sudden death—and other side effects, including ataxia.[105] Both studies are limited by their small size, lack of blinding, and short duration/limited follow-up.

Other case series exist of patients who received treatments in countries where prescription ibogaine is legal. These studies reported reductions in Addiction Severity Index-Lite (ASI-Lite), and Subjective Opioid Withdrawal Scale (SOWS) up to one year post-treatment, with some suggestion of decreased family/social status problems.[106] Notable are the serious safety concerns raised within this study concerning a patient that died for which the cause was attributed to cardiac arrythmias post-ibogaine use. Another series of participants surveyed post-ibogaine treatment provide some indication suggesting that despite return to use in a large proportion of the sample one to two years after ibogaine exposure, there was some indication of decreased opioid use, improvements in mood and anxiety effects, and other improvements in psychosocial measures.[107] Other retrospective, observational and case series provide additional data concerning dosing and the effect of ibogaine on withdrawal and other addiction outcomes.[108,109]

There are two currently registered clinical trials investigating the use of ibogaine for OUD. One is a Phase 2 RCT including patients with OUD who receive methadone treatment who will be administered ascending doses of ibogaine for opioid withdrawal [NCT04003948].[110] The other is a Phase 1/2a dosing study of healthy volunteers followed by a randomized, double-blind, placebo-controlled study in patients seeking medically supervised opioid withdrawal treatment [NCT05029401].[111]

5.4.2. Noribogaine for OUD

Following an earlier Phase 1 study in healthy volunteers,[112] a double-blind placebo-controlled study was conducted in 27 patients receiving methadone treatment who were administered ascending doses (60, 120, and 240 mg) of noribogaine. The study investigated its effect on opioid withdrawal, safety, and pharmacokinetics.[112] There no statistically significant differences in opioid withdrawal symptoms (assessed using the Subjective Opioid Withdrawal Scale [SOWS], Objective Opioid Withdrawal Scale [OOWS], and Clinical Opioid Withdrawal Scale [COWS]). Additionally, there was no difference in time to restart opioid treatment. Conversely, noribogaine produced statistically significant dose- and concentration-dependent increases of QTc interval on the ECG, although no cardiac events were noted. To our knowledge, there are no currently registered trials for OUD involving noribogaine administration.

DISCUSSION

In this review, we have summarized mechanistic and clinical findings regarding the potential of serotonergic psychedelics to treat both chronic pain and OUD. As the opioid epidemic persists, it is imperative that future research be directed toward this intersection, employing rigorous methodologies to uncover the nuanced possible effects of psychedelics on chronic pain and OUD. This concerted effort is pivotal in advancing evidence-based treatments and ultimately alleviating the burden of chronic pain, while minimizing reliance on traditional opioid-based approaches, especially among persons with OUD. Overall, convergent evidence studies provide early clinical and translational support for the use of serotonergic psychedelics for chronic pain and OUD, offering insights into their neurobiological effects, and suggesting avenues for future mechanistic research and clinical trials.

The available literature regarding the role of psychedelics for pain management is nascent but promising. Despite the nuanced needs of each type of chronic pain, such as migraines or chronic low back pain, there seems to be some common ground upon which psychedelics can exert their analgesic effects. In short, psychedelics may have the potential to alleviate pain not only through direct biological and pharmacological mechanisms (e.g., anti-inflammatory properties and reduction of central sensitization), but also through cognitive and psychological pathways (e.g., through reducing attentional bias for pain and opioid cues; counteracting fear avoidance; improving mood; and alleviating pain catastrophizing).[113]

However, there are also key differences between these clinical populations that warrant considerations. Many chronic pain conditions for which psychedelic treatment have been promising for, such as migraines,[114] typically do not involve high opioid use rates. For other conditions, such as cancer-related pain and palliative pain, high doses of opioids are the norm.[115]Ultimately, different pain conditions have nuanced, variable factors that may impact their response to psychedelics and each one of them will require tailored protocols and monitoring procedures. While preliminary findings are promising for certain pain syndromes, more research is still needed to establish safety, effective dosing, and ideal administration settings across diverse chronic pain populations with varying clinical and psychosocial backgrounds.

As future clinical directions, we hypothesize that psychedelics may play a role in alleviating the burden of primarily through distinct mechanisms, as a function of the type of chronic pain and severity of opioid use at baseline. First, by alleviating episodes of acute pain, the need for high-potency analgesics such as opioids may be spared, thereby reducing the risks associated with opioids, including the potential for the development of OUD. Second, by alleviating multiple aspects of the pain experience and subjectively increasing well-being, psychedelics may have the potential to be used as co-adjuvants of a long-standing treatment for different forms of chronic pain, increasing analgesic effectiveness and potentially serving as an opioid-sparing strategy that reduces opioid-related adverse effects.

There is limited reporting across the psychedelic trials for OUD about concurrent MOUD or other treatments participants were receiving. Furthermore, the potential effects of psychedelics on different phases of OUD — ranging from current/active opioid use to acute withdrawal and later stages or recovery/maintenance — remain a critical area of inquiry, necessitating longitudinal studies to examine the full spectrum of therapeutic implications. Gaps exists about the possible effects of psychedelics in the role of psychosocial changes and changes in other recovery or harm reduction behaviors during the acute/longer term recovery phase in OUD. In addition, there is little data concerning the co-occurrence of chronic pain or changes in pain perception, despite the high rates of chronic pain in OUD.[116] The dearth of comprehensive research underscores a significant gap in the literature, leaving researchers with an incomplete understanding of the potential risks and benefits at this juncture.

Despite burgeoning interest in the therapeutic potential of psychedelics for both chronic pain and SUDs, studies that specifically address these conditions in tandem are scarce. In **Figure 2** , we propose various mechanisms of actions of psychedelics across the commonly discussed neurocircuitry of both addiction and its overlap with chronic pain. The biological, social, and psychological potential of these substances to influence these various neurobiological substrates with corresponding outcomes that can be assessed are described. The promising analgesic effects of classic psychedelics, the growing evidence for their utility in multiple SUDs and specifically in OUD, as well as their impact on clinical phenomena that are relevant for both chronic pain and addiction behaviors, suggest their potential as adjuncts or alternatives to traditional opioid agonist for both chronic pain and OUD.

Trial design considerations in psychedelic trials for those with pain and/or OUD

Here we lay out suggestions for future investigations and continued optimization for safety and trial design for patients with chronic pain, OUD, and/or those receiving LTOT. The goals of some of these suggestions are to optimize pain and OUD measures for trials that assess outcomes for either or both of these conditions. Specific recommendations regarding psychedelic clinical investigations were addressed in recent draft Food and Drug Administration (FDA) guidance documents and recent guidelines.[117] Kiluk and colleagues also reviewed clinical trial design challenges and opportunities for emerging treatments in OUD.[118,119] Addressing the existing methodological limitations is imperative for improved study design and a better understanding of the various possible uses for psychedelic medications for chronic pain and OUD, conditions with limited treatment options.

6.1.1. Choice of pain- and opioid-related outcomes

A careful selection of pain- and opioid-related outcomes is necessary to provide clinically relevant evidence. As discussed in this review, the pain experience is multifaceted, composed of sensory, affective, and cognitive

components. Therefore, a combination of mechanistic human laboratory studies and clinical trials broadly examining various components of the pain experience is warranted to understand the analgesic effects of psychedelics. Early analgesic signals may be identified using a combination of laboratory pain techniques, such as quantitative sensory testing (QST),[120] a psychophysical tool to reliably assess analgesia and pain modulation[121]; along with psychological constructs assessing cognitive-affective components of pain (i.e., pain attentional bias, pain catastrophizing, self-efficacy, and fear avoidance).[6,122] Quantifiable outcomes will be key to assessing pain-related functioning. These include measures of physical functioning and activity (e.g., pedometer count). The specific choice of pain-related outcomes can be tailored to the needs of each clinical population.

Likewise, the experience of using opioids, whether medically or non-medically, is also complex and multi-faceted. Human laboratory studies are well-suited to identify the potential therapeutic effects of early stages of opioid withdrawal, various types of opioid craving (e.g., pain-, stress-, and cue-induced craving), and acute changes in hedonic states associated with chronic opioid exposure (e.g., hypohedonia and anhedonia).[123,124] Longer-term clinical trials should include real-world outcomes such as the success of induction onto MOUD, treatment retention, adherence to MOUD, and the MOUD doses required to suppress craving and withdrawal. Studies specifically including persons with co-occurring OUD and chronic pain are required since a third of people with OUD also have chronic pain and this population has unique clinical needs and treatment trajectories. In summary, a comprehensive assessment of pain- and opioid-related outcomes is paramount to generate clinically pertinent evidence.

6.1.2 Concurrent opioid use or MOUDs

The use of psychedelics as an add-on to, or concurrently with medications that work at the MOR may have unintended effects. Being prepared to prevent or mitigate possible withdrawal states should be taken into consideration. The impact of possible withdrawal states on the subjective psychedelic experience should also be considered and timing of dosing of any concurrent MOR should be thoughtfully considered. For many studies of ibogaine and noribogaine, MOUD is commonly switched to shorter-acting medications such as controlled-release oral morphine products or other short-acting MOR agonists.[125] There are also possibly important safety concerns related to concurrent use of opioids and some psychedelics, which are reviewed below.

6.1.3 Subjective effects of psychedelics

There remains ongoing debate concerning the necessity for the hallucinogenic effects of psychedelics, with arguments both for and against their importance.[126,127] There is a suggestion that in both, at least, treatment-resistant depression and tobacco use disorder, the subjective components and quality of the acute psychedelic experience may be important for therapeutic efficacy,[128] while there remains some preliminary data in OUD this may be the case. Conversely, for cluster and migraine headaches, the acute subjective psychedelic effects may be independent from their clinical effects.[129] These studies were dovetailed by recent healthy human laboratory data, putting into question the therapeutic relevance of hallucinogenic effects for analgesia.[67] Measurement and investigation into the importance of hallucinogenic and subjective effects remains crucial to further our understanding of this phenomenon (and supposed "biological effects" from the "psychological effects") and the viability of sub-psychedelic dosing/microdosing paradigms and active control groups that receive low or blinding doses of psychedelics in some studies, which may have some effect on outcomes.

6.1.4 Psychedelic-assisted psychotherapy (PAP)

The role of psychedelic-assisted psychotherapy (PAP) is another important methodological concern in future trial design regarding investigations for chronic pain and OUD. Despite concomitant psychotherapy being a component of other modern trials of psilocybin for other SUDs,[14,130] protocols have included mostly manualized cognitive behavioral therapy- or motivational enhancement therapy-based interventions. The efficacy for evidence-based psychosocial treatments for chronic pain[131] and substance use[132] remain modest, with small to medium effect sizes across trials. As such, adjunctive psychedelics may increase the efficacy and/or engagement in evidence-based psychosocial treatments. The importance of psychotherapy during

these psychedelic trials on efficacy remains to be seen as there are exist few repeated evaluations or studies have not been powered to assess differences between groups on psychotherapy. Draft FDA guidance on psychedelic trials has also questioned the use of PAP as it raises concerns about standardization and the introduction of other forms of bias. The many types of PAP have been reviewed in detail, including discussions on trial design during each phase of psychedelic trial,[133,134] as have theoretical considerations for its use in other components of recovery and synergy with other treatment paradigms such as twelve-step facilitation (TSF).[135]

6.1.5 Treatment setting

There is a large variation across the existing studies for psychedelics for OUD studies in regard to treatment settings. For example, the early LSD studies were mostly carried out in residential settings, the study investigating ayahuasca was completed in a retreat setting, and many of the trials with ibogaine or noribogaine were carried out in various medical treatment centers. Pain studies have traditionally occurred in two settings: (1) human laboratory investigations and (2) real-word, ambulatory and emergency room studies. Treatment setting determination may also be influenced by which phase of treatment is being targeted (i.e., acute withdrawal) or by other safety concerns that may require continuous medical monitoring. Treatment setting is overall an important consideration for research design but also for real-world implementation if such psychedelic treatments receive regulatory approval.

6.1.6 Blinding and expectancy bias

The issue of blinding, blinding procedures, and blinding failures in psychedelic trials has received considerable attention in the literature.[136] While expectancy bias remains an issue for all clinical trials, expectancy bias has been well documented in the pain literature and should be thoughtfully considered in future trial designs around pain and psychedelics.[137] Systematic reviews of the RCTs of psychedelics have illustrated that many trials have used various forms of placebo groups including placebo control groups, inert placebo control, or active placebo control, or both, but there is room to improve on quality and blinding assessment and blinding failure in these trials.[138] Blinding integrity tools in the context of psychedelic micro-dosing studies have also been recently developed, as well as recommendations to improve blinding issues in psychedelic trials.[139] The impact of preparatory sessions on expectancy, as well as the set and setting and other controllable factors in psychedelics sessions, should be also thoughtfully considered as possible factors influencing outcomes.[140]

Specific safety considerations in psychedelic trials for those with pain and/or OUD

6.2.1 Addictive and "abuse potential"

Concerns about the addictive potential (development of hallucinogen use disorder [HUD]) or "abuse potential" of psychedelics have been raised as a common argument against the investigation of psychedelics for SUDs, since their historic scheduling as a Schedule I controlled substances (i.e., high potential for abuse and no currently accepted medical use). Still, the evidence to support the addictive potential of psychedelics is scant. Current FDA guidance for psychedelic trials outlines guidance for the assessment of this risk.[117]National Survey on Drug Use and Health (NSDUH) data reports the rates of HUD criteria by DSM-IV criteria very low amongst respondents that have used a hallucinogen (less than <1% for both meeting criteria for "abuse" and dependence). Other data from the NSDUH concerning serotonergic psychedelics specifically, commonly reports that past use of these compounds is associated with lower rates of certain SUDs (specifically meeting OUD criteria in some studies),[94]as do other studies of naturalistic psychedelic use reporting a decrease in the use of multiple substances including opioids.[93]In addition, some of the recent trials investigating psilocybin for MDD that have included longer term follow-up have noted no reported additional psilocybin use up to 12 months after the trial amongst participants.[141] Overall, only more data in study participants with co-occurring SUDs and/or chronic pain conditions and further, more specific FDA guidance around psychedelic studies will determine best practices for study design and risk assessment around the serotonergic psychedelics. Detailed discussions and considerations around assessing the abuse potential of psychedelics and their current drug scheduling have been reviewed in detail here.[142]

6.2.2 Other adverse effects

Generally, the classic psychedelics have been deemed to be relatively low risk for adverse events,[143] although there are special populations (such as older adults, and those with cardiac disorders) that have generally not been included in studies and deserve particular attention to possible cardiovascular adverse events including increased heart rate, blood pressure, and myocardial ischemia.[144] As a general concern for psychedelic trials, reports of suicidal ideation (SI), non-suicidal self-injurious behavior (NSSBI), and hospitalizations for severe depression have been reported in some recent trials of psilocybin for depression as have been noted in earlier trials of psychedelics for SUDs.[145]These serious psychological adverse events appear rare and may reflect baseline risk for participants with mood disorders and/or SUDs, and it is uncertain what additional risks that those with chronic pain may incur. In addition, risks of hallucinogen persisting perception disorder (HPPD) a low concern but possible concern.[146] Guidance suggests additional measurement of long term follow up for return to use or later overdose events which would shed light on other possible risks for psychedelics.[119] Notably, rigorous reporting of adverse events across psychedelic studies has varied and deserves attention in future trial design.[143]

Other serotonergic psychedelics have cardiovascular risks, including QTc prolongation and possible valvular disease, warranting adequate screening and monitoring of participants with OUD, whose QTc interval may be prolonged at baseline, and who may have underlying cardiac disorders as a consequence of intravenous drug use.[147,148] The concurrent use of methadone, which has relevant cardiac effects, and a psychedelic like ibogaine (also with well documented cardiac effects) may warrant additional safety monitoring.

Conclusion

Psychedelic-assisted interventions for chronic pain and OUD present a promising avenue for therapeutic innovation. Although preliminary evidence suggests potential benefits, more rigorous research is needed to establish the safety, efficacy, and optimal protocols for psychedelic-assisted interventions in these conditions. Future studies should focus on carefully selected, population-specific pain- and opioid-related outcomes, elucidating mechanisms of action, refining treatment protocols, and addressing safety concerns. This research is essential to ensure the responsible and evidence-based integration of psychedelics into research settings and potentially clinical practice. In the context of rapid attitudinal and regulatory changes regarding psychedelics, it remains to be seen whether their therapeutic potential for chronic pain and OUD — two of the most vexing problems of modern healthcare — can be fully realized.

REFERENCES

1. Spencer MR, Miniño AM, Warner M. Drug Overdose Deaths in the United States, 2001-2021. *NCHS Data Brief* . Dec 2022;(457):1-8.

2. Ciccarone D. The triple wave epidemic: Supply and demand drivers of the US opioid overdose crisis. *Int J Drug Policy* . Sep 2019;71:183-188. doi:10.1016/j.drugpo.2019.01.010

3. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction.*Annu Rev Public Health* . Mar 18 2015;36:559-74. doi:10.1146/annurev-publhealth-031914-122957

4. Vital signs: overdoses of prescription opioid pain relievers and other drugs among women–United States, 1999-2010. *MMWR Morb Mortal Wkly Rep* . Jul 5 2013;62(26):537-42.

5. Barry DT, Beitel M, Joshi D, Schottenfeld RS. Pain and substance-related pain-reduction behaviors among opioid dependent individuals seeking methadone maintenance treatment. *Am J Addict* . Mar-Apr 2009;18(2):117-21. doi:10.1080/10550490902772470

6. Mun CJ, Beitel M, Oberleitner L, et al. Pain catastrophizing and pain acceptance are associated with pain severity and interference among methadone-maintained patients. *J Clin Psychol* . Dec 2019;75(12):2233-2247. doi:10.1002/jclp.22842

7. Oliveira D, Fontenele R, Weleff J, Sofuoglu M, De Aquino JP. Developing non-opioid therapeutics to alleviate pain among persons with opioid use disorder: a review of the human evidence. *International Review of Psychiatry* . 2023:1-20. doi:10.1080/09540261.2023.2229430

8. Fuehrlein BS, Ross DA. Opioid Use Disorder: A Desperate Need for Novel Treatments. *Biol Psychiatry* . Apr 1 2017;81(7):e43-e45. doi:10.1016/j.biopsych.2017.01.014

9. De Aquino JP, Parida S, Avila-Quintero VJ, et al. Opioid-induced analgesia among persons with opioid use disorder receiving methadone or buprenorphine: A systematic review of experimental pain studies. *Drug Alcohol Depend* . Nov 1 2021;228:109097. doi:10.1016/j.drugalcdep.2021.109097

10. Nichols DE. Psychedelics. *Pharmacol Rev* . Apr 2016;68(2):264-355. doi:10.1124/pr.115.011478

11. Savage C, McCabe OL. Residential psychedelic (LSD) therapy for the narcotic addict. A controlled study. *Arch Gen Psychiatry* . Jun 1973;28(6):808-14. doi:10.1001/archpsyc.1973.01750360040005

12. Ludwig AM, Levine J. A CONTROLLED COMPARISON OF FIVE BRIEF TREATMENT TECHNIQUES EMPLOYING LSD, HYPNOSIS, AND PSYCHOTHERAPY. *Am J Psychother* . Jul 1965;19:417-35. doi:10.1176/appi.psychotherapy.1965.19.3.417

13. Kast EC, Collins VJ. STUDY OF LYSERGIC ACID DIETHYLAMIDE AS AN ANALGESIC AGENT. *Anesth Analg* . May-Jun 1964;43:285-91.

14. Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* . Oct 1 2022;79(10):953-962. doi:10.1001/jamapsychiatry.2022.2096

15. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse* . Jan 2017;43(1):55-60. doi:10.3109/00952990.2016.1170135

16. Mosca A, Chiappini S, Miuli A, et al. Ibogaine/Noribogaine in the Treatment of Substance Use Disorders: a Systematic Review of the Current Literature. *Curr Neuropharmacol* . Oct 17 2022;doi:10.2174/1570159x21666221017085612

17. van der Meer PB, Fuentes JJ, Kaptein AA, et al. Therapeutic effect of psilocybin in addiction: A systematic review. *Front Psychiatry* . 2023;14:1134454. doi:10.3389/fpsyt.2023.1134454

18. Liester MB. A review of lysergic acid diethylamide (LSD) in the treatment of addictions: historical perspectives and future prospects. *Curr Drug Abuse Rev* . 2014;7(3):146-56. doi:10.2174/1874473708666150107120522

19. Bogenschutz MP, Johnson MW. Classic hallucinogens in the treatment of addictions. *Prog Neuropsychopharmacol Biol Psychiatry* . Jan 4 2016;64:250-8. doi:10.1016/j.pnpbp.2015.03.002

20. Rodrigues LS, Rossi GN, Rocha JM, et al. Effects of ayahuasca and its alkaloids on substance use disorders: an updated (2016-2020) systematic review of preclinical and human studies. *Eur Arch Psychiatry Clin Neurosci* . Jun 2022;272(4):541-556. doi:10.1007/s00406-021-01267-7

21. Kelmendi B, Kaye AP, Pittenger C, Kwan AC. Psychedelics. *Curr Biol* . Jan 24 2022;32(2):R63-r67. doi:10.1016/j.cub.2021.12.009

22. Nakagawasai O, Arai Y, Satoh SE, et al. Monoamine oxidase and head-twitch response in mice. Mechanisms of alpha-methylated substrate derivatives. *Neurotoxicology* . Jan 2004;25(1-2):223-32. doi:10.1016/s0161-813x(03)00101-3

23. Silva MT, Calil HM. Screening hallucinogenic drugs: systematic study of three behavioral tests. *Psychopharmacologia* . May 28 1975;42(2):163-71. doi:10.1007/bf00429548

24. Yamamoto T, Ueki S. The role of central serotonergic mechanisms on head-twitch and backward locomotion induced by hallucinogenic drugs.*Pharmacol Biochem Behav* . Jan 1981;14(1):89-95. doi:10.1016/0091-3057(81)90108-8

25. de Vos CMH, Mason NL, Kuypers KPC. Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Front Psychiatry* . 2021;12:724606. doi:10.3389/fpsyt.2021.724606

26. Price DD. Psychological and neural mechanisms of the affective dimension of pain. *Science* . Jun 9 2000;288(5472):1769-72. doi:10.1126/science.288.5472.1769

27. Bardin L. The complex role of serotonin and 5-HT receptors in chronic pain. *Behav Pharmacol* . Sep 2011;22(5-6):390-404. doi:10.1097/FBP.0b013e328349aae4

28. Bondy B, Spaeth M, Offenbaecher M, et al. The T102C polymorphism of the 5-HT2A-receptor gene in fibromyalgia. *Neurobiol Dis* . Oct 1999;6(5):433-9. doi:10.1006/nbdi.1999.0262

29. Nicholl BI, Holliday KL, Macfarlane GJ, et al. Association of HTR2A polymorphisms with chronic widespread pain and the extent of musculoskeletal pain: results from two population-based cohorts.*Arthritis Rheum* . Mar 2011;63(3):810-8. doi:10.1002/art.30185

30. Talbot K, Madden VJ, Jones SL, Moseley GL. The sensory and affective components of pain: are they differentially modifiable dimensions or inseparable aspects of a unitary experience? A systematic review.*Br J Anaesth* . Aug 2019;123(2):e263-e272. doi:10.1016/j.bja.2019.03.033

31. Okamoto K, Imbe H, Morikawa Y, et al. 5-HT2A receptor subtype in the peripheral branch of sensory fibers is involved in the potentiation of inflammatory pain in rats. *Pain* . Sep 2002;99(1-2):133-43. doi:10.1016/s0304-3959(02)00070-2

32. Patel R, Dickenson AH. Modality selective roles of pro-nociceptive spinal 5-HT(2A) and 5-HT(3) receptors in normal and neuropathic states.*Neuropharmacology* . Dec 2018;143:29-37. doi:10.1016/j.neuropharm.2018.09.028

33. Liu QQ, Yao XX, Gao SH, et al. Role of 5-HT receptors in neuropathic pain: potential therapeutic implications. *Pharmacol Res* . Sep 2020;159:104949. doi:10.1016/j.phrs.2020.104949

34. López-Giménez JF, González-Maeso J. Hallucinogens and Serotonin 5-HT(2A) Receptor-Mediated Signaling Pathways. *Curr Top Behav Neurosci* . 2018;36:45-73. doi:10.1007/7854_2017_478

35. Haleem DJ. Serotonin-1A receptor dependent modulation of pain and reward for improving therapy of chronic pain. *Pharmacol Res* . Aug 2018;134:212-219. doi:10.1016/j.phrs.2018.06.030

36. Seifert O, Baerwald C. Interaction of pain and chronic inflammation.*Z Rheumatol* . Apr 2021;80(3):205-213. Wechselwirkungen von Schmerz und chronischer Entzündung. doi:10.1007/s00393-020-00951-8

37. Flanagan TW, Nichols CD. Psychedelics as anti-inflammatory agents.*Int Rev Psychiatry* . Aug 2018;30(4):363-375. doi:10.1080/09540261.2018.1481827

38. Abbott FV, Hong Y, Blier P. Activation of 5-HT2A receptors potentiates pain produced by inflammatory mediators.*Neuropharmacology* . Jan 1996;35(1):99-110. doi:10.1016/0028-3908(95)00136-0

39. Puderbaugh M, Emmady PD. Neuroplasticity. *StatPearls* . StatPearls Publishing

40. Shen W, Tu Y, Gollub RL, et al. Visual network alterations in brain functional connectivity in chronic low back pain: A resting state functional connectivity and machine learning study. *Neuroimage Clin* . 2019;22:101775. doi:10.1016/j.nicl.2019.101775

41. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. *PLoS One* . 2014;9(9):e106133. doi:10.1371/journal.pone.0106133

42. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics.*J Neurosci* . Feb 6 2008;28(6):1398-403. doi:10.1523/jneurosci.4123-07.2008

43. Baliki MN, Petre B, Torbey S, et al. Corticostriatal functional connectivity predicts transition to chronic back pain. *Nat Neurosci* . Jul 1 2012;15(8):1117-9. doi:10.1038/nn.3153

44. Ly C, Greb AC, Cameron LP, et al. Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Rep* . Jun 12 2018;23(11):3170-3182. doi:10.1016/j.celrep.2018.05.022

45. Hipólito I, Mago J, Rosas FE, Carhart-Harris R. Pattern breaking: a complex systems approach to psychedelic medicine. *Neurosci Conscious* . 2023;2023(1):niad017. doi:10.1093/nc/niad017

46. Carhart-Harris RL, Chandaria S, Erritzoe DE, et al. Canalization and plasticity in psychopathology. *Neuropharmacology* . Mar 15 2023;226:109398. doi:10.1016/j.neuropharm.2022.109398

47. Gracely RH, Harte SE. Emotional/Affective Aspects of Pain. In: Binder MD, Hirokawa N, Windhorst U, eds. *Encyclopedia of Neuroscience* . Springer Berlin Heidelberg; 2009:1092-1095.

48. Kasanetz F, Acuña MA, Nevian T. Chapter 18 - Anterior cingulate cortex, pain perception, and pathological neuronal plasticity during chronic pain. In: Rajendram R, Patel VB, Preedy VR, Martin CR, eds. *The Neurobiology, Physiology, and Psychology of Pain* . Academic Press; 2022:193-202.

49. Carhart-Harris RL, Erritzoe D, Williams T, et al. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin.*Proc Natl Acad Sci U S A* . Feb 7 2012;109(6):2138-43. doi:10.1073/pnas.1119598109

50. Barba T, Buehler S, Kettner H, et al. Effects of psilocybin versus escitalopram on rumination and thought suppression in depression.*BJPsych Open* . Sep 6 2022;8(5):e163. doi:10.1192/bjo.2022.565

51. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med* . Nov 10 2003;163(20):2433-45. doi:10.1001/archinte.163.20.2433

52. Dick BD, Rashiq S. Disruption of attention and working memory traces in individuals with chronic pain. *Anesth Analg* . May 2007;104(5):1223-9, tables of contents. doi:10.1213/01.ane.0000263280.49786.f5

53. Linton SJ, Shaw WS. Impact of psychological factors in the experience of pain. *Phys Ther* . May 2011;91(5):700-11. doi:10.2522/ptj.20100330

54. Meier ML, Stämpfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S. Neural Correlates of Fear of Movement in Patients with Chronic Low Back Pain vs. Pain-Free Individuals. *Front Hum Neurosci* . 2016;10:386. doi:10.3389/fnhum.2016.00386

55. Schütze R, Rees C, Smith A, Slater H, O'Sullivan P. Metacognition, perseverative thinking, and pain catastrophizing: A moderated-mediation analysis. *Eur J Pain* . Jan 2020;24(1):223-233. doi:10.1002/ejp.1479

56. Ziadni MS, Sturgeon JA, Darnall BD. The relationship between negative metacognitive thoughts, pain catastrophizing and adjustment to chronic pain. *Eur J Pain* . Apr 2018;22(4):756-762. doi:10.1002/ejp.1160

57. Sweat NW, Bates LW, Hendricks PS. The Associations of Naturalistic Classic Psychedelic Use, Mystical Experience, and Creative Problem Solving. *J Psychoactive Drugs* . Nov-Dec 2016;48(5):344-350. doi:10.1080/02791072.2016.1234090

58. Millière R, Carhart-Harris RL, Roseman L, Trautwein FM, Berkovich-Ohana A. Psychedelics, Meditation, and Self-Consciousness.*Front Psychol* . 2018;9:1475. doi:10.3389/fpsyg.2018.01475

59. MacLean RR, Sofuoglu M, Brede E, Robinson C, Waters AJ. Attentional bias in opioid users: A systematic review and meta-analysis. *Drug Alcohol Depend* . Oct 1 2018;191:270-278. doi:10.1016/j.drugalcdep.2018.07.012

60. Schoth DE, Nunes Vd Fau - Liossi C, Liossi C. Attentional bias towards pain-related information in chronic pain; a meta-analysis of visual-probe investigations. (1873-7811 (Electronic))

61. MacLean RR, Heapy AA, Waters AJ, et al. Integrating cognitive bias modification for pain and opioid cues into medication for opioid use disorder clinical care: Feasibility, acceptability, and preliminary results. (1879-0046 (Electronic))

62. Griffiths RR, Johnson MW, Richards WA, et al. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *J Psychopharmacol* . Jan 2018;32(1):49-69. doi:10.1177/0269881117731279

63. Forstmann M, Yudkin DA, Prosser AMB, Heller SM, Crockett MJ. Transformative experience and social connectedness mediate the mood-enhancing effects of psychedelic use in naturalistic settings. *Proc Natl Acad Sci U S A* . Feb 4 2020;117(5):2338-2346. doi:10.1073/pnas.1918477117

64. Weiss B, Nygart V, Pommerencke LM, Carhart-Harris RL, Erritzoe D. Examining Psychedelic-Induced Changes in Social Functioning and Connectedness in a Naturalistic Online Sample Using the Five-Factor Model of Personality. *Front Psychol* . 2021;12:749788. doi:10.3389/fpsyg.2021.749788

65. Ong AD, Thoemmes F, Ratner K, Ghezzi-Kopel K, Reid MC. Positive affect and chronic pain: a preregistered systematic review and meta-analysis. (1872-6623 (Electronic))

66. Whelan A, Johnson MI. Lysergic acid diethylamide and psilocybin for the management of patients with persistent pain: a potential role? *Pain Manag* . May 2018;8(3):217-229. doi:10.2217/pmt-2017-0068

67. Ramaekers JG, Hutten N, Mason NL, et al. A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers. *J Psychopharmacol* . Apr 2021;35(4):398-405. doi:10.1177/0269881120940937

68. Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majić T. Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review. *Prog Neuropsychopharmacol Biol Psychiatry* . Feb 2 2018;81:1-10. doi:10.1016/j.pnpbp.2017.09.012

69. Kooijman NI, Willegers T, Reuser A, et al. Are psychedelics the answer to chronic pain: A review of current literature. *Pain Pract* . Apr 2023;23(4):447-458. doi:10.1111/papr.13203

70. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry* . 1973;8(3):129-44. doi:10.1159/000467984

71. Kurland AA. LSD in the supportive care of the terminally ill cancer patient. *J Psychoactive Drugs* . Oct-Dec 1985;17(4):279-90. doi:10.1080/02791072.1985.10524332

72. Fuentes JJ, Fonseca F, Elices M, Farré M, Torrens M. Therapeutic Use of LSD in Psychiatry: A Systematic Review of Randomized-Controlled Clinical Trials. *Front Psychiatry* . 2019;10:943. doi:10.3389/fpsyt.2019.00943

73. Karst M, Halpern JH, Bernateck M, Passie T. The non-hallucinogen 2-bromo-lysergic acid diethylamide as preventative treatment for cluster headache: an open, non-randomized case series. *Cephalalgia* . Sep 2010;30(9):1140-4. doi:10.1177/0333102410363490

74. Andersson M, Persson M, Kjellgren A. Psychoactive substances as a last resort-a qualitative study of self-treatment of migraine and cluster headaches. *Harm Reduct J* . Sep 5 2017;14(1):60. doi:10.1186/s12954-017-0186-6

75. Fadiman J, Korb S. Might Microdosing Psychedelics Be Safe and Beneficial? An Initial Exploration. *J Psychoactive Drugs* . Apr-Jun 2019;51(2):118-122. doi:10.1080/02791072.2019.1593561

76. Sewell RA, Halpern JH, Pope HG, Jr. Response of cluster headache to psilocybin and LSD. *Neurology* . Jun 27 2006;66(12):1920-2. doi:10.1212/01.wnl.0000219761.05466.43

77. Schindler EA, Gottschalk CH, Weil MJ, Shapiro RE, Wright DA, Sewell RA. Indoleamine Hallucinogens in Cluster Headache: Results of the Clusterbusters Medication Use Survey. *J Psychoactive Drugs* . Nov-Dec 2015;47(5):372-81. doi:10.1080/02791072.2015.1107664

78. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. *Pain Res Treat* . 2011;2011:864605. doi:10.1155/2011/864605

79. Fanciullacci M, Bene ED, Franchi G, Sicuteri F. Brief report: Phantom limp pain: sub-hallucinogenic treatment with lysergic acid diethylamide (LSD-25). *Headache* . Jul 1977;17(3):118-9. doi:10.1111/j.1526-4610.1977.hed1703118.x

80. Kuromaru S, Okada S, Hanada M, Kasahara Y, Sakamoto K. The effect of LSD on the phantom limb phenomenon. *J Lancet* . Jan 1967;87(1):22-7.

81. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial.*J Psychopharmacol* . Dec 2016;30(12):1181-1197. doi:10.1177/0269881116675513

82. Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin.*Neurotherapeutics* . Jan 2021;18(1):534-543. doi:10.1007/s13311-020-00962-y

83. Medicine USNLo. Standardized Natural Psilocybin-assisted Psychotherapy for Tapering of Opioid Medication. 2023.

84. McKenna DJ. Clinical investigations of the therapeutic potential of ayahuasca: rationale and regulatory challenges. *Pharmacol Ther* . May 2004;102(2):111-29. doi:10.1016/j.pharmthera.2004.03.002

85. Bouso CSaJC. Ayahuasca: From the Amazon to the Global Villag. Transnational Institute; 2015.

86. Jiménez-Garrido DF, Gómez-Sousa M, Ona G, et al. Effects of ayahuasca on mental health and quality of life in naïve users: A longitudinal and cross-sectional study combination. *Sci Rep* . Mar 5 2020;10(1):4075. doi:10.1038/s41598-020-61169-x

87. Barbosa PC, Cazorla IM, Giglio JS, Strassman R. A six-month prospective evaluation of personality traits, psychiatric symptoms and quality of life in ayahuasca-naïve subjects. *J Psychoactive Drugs* . Sep 2009;41(3):205-12. doi:10.1080/02791072.2009.10400530

88. Goutarel RG, Otto; Sillans, Roger. Pharmacodynamics and Therapeutic Applications of Iboga and Ibogaine. Psychedelic Monographs and Essays 1993 6 71-1111996.

89. Bagal AA, Hough LB, Nalwalk JW, Glick SD. Modulation of morphine-induced antinociception by ibogaine and noribogaine.*Brain Res* . Nov 25 1996;741(1-2):258-62. doi:10.1016/s0006-8993(96)00938-9

90. Sunder Sharma S, Bhargava HN. Enhancement of morphine antinociception by ibogaine and noribogaine in morphine-tolerant mice.*Pharmacology* . Nov 1998;57(5):229-32. doi:10.1159/000028246

91. Weleff J, Akiki TJ, Barnett BS. Bibliometric Analysis of Academic Journal Articles Reporting Results of Psychedelic Clinical Studies.*J Psychoactive Drugs* . Sep-Oct 2023;55(4):434-444. doi:10.1080/02791072.2022.2133757

92. Pisano VD, Putnam NP, Kramer HM, Franciotti KJ, Halpern JH, Holden SC. The association of psychedelic use and opioid use disorders among illicit users in the United States. *J Psychopharmacol* . May 2017;31(5):606-613. doi:10.1177/0269881117691453

93. Argento E, Socias ME, Hayashi K, et al. Psychedelic use is associated with reduced daily opioid use among people who use illicit drugs in a Canadian setting. *Int J Drug Policy* . Feb 2022;100:103518. doi:10.1016/j.drugpo.2021.103518

94. Jones G, Ricard JA, Lipson J, Nock MK. Associations between classic psychedelics and opioid use disorder in a nationally-representative U.S. adult sample. *Sci Rep* . Apr 7 2022;12(1):4099. doi:10.1038/s41598-022-08085-4

95. Medicine USNLo. Inpatient Buprenorphine Induction With Psilocybin for Opioid Use Disorder (BIPOD-In). ClinicalTrials.gov2023.

96. Sobell LC, Sobell MB. Timeline Follow-Back. In: Litten RZ, Allen JP, eds. *Measuring Alcohol Consumption: Psychosocial and Biochemical Methods* . Humana Press; 1992:41-72.

97. Medicine USNLo. Adjunctive Effects of Psilocybin and a Formulation of Buprenorphine. 2021.

98. Medicine USNLo. Psilocybin for Opioid Use Disorder in Patients on Methadone Maintenance With Ongoing Opioid Use. 2023.

99. Thomas G, Lucas P, Capler NR, Tupper KW, Martin G. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. *Curr Drug Abuse Rev* . Mar 2013;6(1):30-42. doi:10.2174/15733998113099990003

100. Hamill J, Hallak J, Dursun SM, Baker G. Ayahuasca: Psychological and Physiologic Effects, Pharmacology and Potential Uses in Addiction and Mental Illness. *Curr Neuropharmacol* . 2019;17(2):108-128. doi:10.2174/1570159x16666180125095902

101. Fábregas JM, González D, Fondevila S, et al. Assessment of addiction severity among ritual users of ayahuasca. *Drug Alcohol Depend* . Oct 1 2010;111(3):257-61. doi:10.1016/j.drugalcdep.2010.03.024

102. Argento E, Capler R, Thomas G, Lucas P, Tupper KW. Exploring ayahuasca-assisted therapy for addiction: A qualitative analysis of preliminary findings among an Indigenous community in Canada. *Drug Alcohol Rev* . Nov 2019;38(7):781-789. doi:10.1111/dar.12985

103. Mosca A, Chiappini S, Miuli A, et al. Ibogaine/Noribogaine in the Treatment of Substance Use Disorders: A Systematic Review of the Current Literature. *Curr Neuropharmacol* . 2023;21(11):2178-2194. doi:10.2174/1570159x21666221017085612

104. Mash DC, Kovera CA, Pablo J, et al. Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. *Ann N Y Acad Sci* . Sep 2000;914:394-401. doi:10.1111/j.1749-6632.2000.tb05213.x

105. Knuijver T, Schellekens A, Belgers M, et al. Safety of ibogaine administration in detoxification of opioid-dependent individuals: a descriptive open-label observational study. *Addiction* . Jan 2022;117(1):118-128. doi:10.1111/add.15448

106. Noller GE, Frampton CM, Yazar-Klosinski B. Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. *Am J Drug Alcohol Abuse* . 2018;44(1):37-46. doi:10.1080/00952990.2017.1310218

107. Davis AK, Renn E, Windham-Herman AM, Polanco M, Barsuglia JP. A Mixed-Method Analysis of Persisting Effects Associated with Positive Outcomes Following Ibogaine Detoxification. *J Psychoactive Drugs* . Sep-Oct 2018;50(4):287-297. doi:10.1080/02791072.2018.1487607

108. Mash DC, Duque L, Page B, Allen-Ferdinand K. Ibogaine Detoxification Transitions Opioid and Cocaine Abusers Between Dependence and Abstinence: Clinical Observations and Treatment Outcomes.*Front Pharmacol* . 2018;9:529. doi:10.3389/fphar.2018.00529

109. Malcolm BJ, Polanco M, Barsuglia JP. Changes in Withdrawal and Craving Scores in Participants Undergoing Opioid Detoxification Utilizing Ibogaine. *J Psychoactive Drugs* . Jul-Aug 2018;50(3):256-265.

doi:10.1080/02791072.2018.1447175

110. Medicine USNLo. Preliminary Efficacy and Safety of Ibogaine in the Treatment of Methadone Detoxification. 2022.

111. Medicine USNLo. A Study of Oral Ibogaine in Opioid Withdrawal. 2022;

112. Glue P, Lockhart M, Lam F, Hung N, Hung CT, Friedhoff L. Ascending-dose study of noribogaine in healthy volunteers: pharmacokinetics, pharmacodynamics, safety, and tolerability. *J Clin Pharmacol* . Feb 2015;55(2):189-94. doi:10.1002/jcph.404

113. Bornemann J, Close JB, Spriggs MJ, Carhart-Harris R, Roseman L. Self-Medication for Chronic Pain Using Classic Psychedelics: A Qualitative Investigation to Inform Future Research. *Front Psychiatry* . 2021;12:735427. doi:10.3389/fpsyt.2021.735427

114. Lipton RB, Buse DC, Friedman BW, et al. Characterizing opioid use in a US population with migraine: Results from the CaMEO study.*Neurology* . Aug 4 2020;95(5):e457-e468. doi:10.1212/wnl.0000000000009324

115. Paice JA, Bohlke K, Barton D, et al. Use of Opioids for Adults With Pain From Cancer or Cancer Treatment: ASCO Guideline. *J Clin Oncol* . Feb 1 2023;41(4):914-930. doi:10.1200/jco.22.02198

116. Delorme J, Kerckhove N, Authier N, Pereira B, Bertin C, Chenaf C. Systematic Review and Meta-Analysis of the Prevalence of Chronic Pain Among Patients With Opioid Use Disorder and Receiving Opioid Substitution Therapy. *J Pain* . Feb 2023;24(2):192-203. doi:10.1016/j.jpain.2022.08.008

117. Administration USFaD. Psychedelic Drugs: Considerations for Clinical Investigations. 2023.

118. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol* . Aug 2008;22(6):603-20. doi:10.1177/0269881108093587

119. Kiluk BD, Kleykamp BA, Comer SD, et al. Clinical Trial Design Challenges and Opportunities for Emerging Treatments for Opioid Use Disorder: A Review. *JAMA Psychiatry* . Jan 1 2023;80(1):84-92. doi:10.1001/jamapsychiatry.2022.4020

120. Mücke M, Cuhls H, Radbruch L, et al. Quantitative sensory testing (QST). English version. *Schmerz* . Nov 2021;35(Suppl 3):153-160. Quantitative sensorische Testung (QST). doi:10.1007/s00482-015-0093-2

121. Georgopoulos V, Akin-Akinyosoye K, Zhang W, McWilliams DF, Hendrick P, Walsh DA. Quantitative sensory testing and predicting outcomes for musculoskeletal pain, disability, and negative affect: a systematic review and meta-analysis. *Pain* . Sep 2019;160(9):1920-1932. doi:10.1097/j.pain.0000000000001590

122. Crombez G, Van Ryckeghem DML, Eccleston C, Van Damme S. Attentional bias to pain-related information: a meta-analysis. *Pain* . Apr 2013;154(4):497-510. doi:10.1016/j.pain.2012.11.013

123. Kiluk BD, Yip SW, DeVito EE, Carroll KM, Sofuoglu M. Anhedonia as a key clinical feature in the maintenance and treatment of opioid use disorder. *Clin Psychol Sci* . Nov 2019;7(6):1190-1206. doi:10.1177/2167702619855659

124. Saraiya TC, Jarnecke AM, Jones J, Brown DG, Brady KT, Back SE. Laboratory-induced stress and craving predict opioid use during follow-up among individuals with prescription opioid use disorder.*Drug Alcohol Depend* . Aug 1 2021;225:108755. doi:10.1016/j.drugalcdep.2021.108755

125. Glue P, Cape G, Tunnicliff D, et al. Ascending Single-Dose, Double-Blind, Placebo-Controlled Safety Study of Noribogaine in Opioid-Dependent Patients. *Clin Pharmacol Drug Dev* . Nov 2016;5(6):460-468. doi:10.1002/cpdd.254

126. Olson DE. The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects. *ACS Pharmacol Transl Sci* . Apr 9 2021;4(2):563-567. doi:10.1021/acsptsci.0c00192

127. Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. *ACS Pharmacol Transl Sci* . Apr 9 2021;4(2):568-572. doi:10.1021/acsptsci.0c00194

128. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. *Front Pharmacol* . 2017;8:974. doi:10.3389/fphar.2017.00974

129. Schindler EAD. Psychedelics in the Treatment of Headache and Chronic Pain Disorders. *Curr Top Behav Neurosci* . 2022;56:261-285. doi:10.1007/7854_2022_365

130. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction.*J Psychopharmacol* . Nov 2014;28(11):983-92. doi:10.1177/0269881114548296

131. Hoffman BM, Papas RK, Chatkoff DK, Kerns RD. Meta-analysis of psychological interventions for chronic low back pain. *Health Psychol* . Jan 2007;26(1):1-9. doi:10.1037/0278-6133.26.1.1

132. Dutra L, Stathopoulou G, Basden SL, Leyro TM, Powers MB, Otto MW. A meta-analytic review of psychosocial interventions for substance use disorders. *Am J Psychiatry* . Feb 2008;165(2):179-87. doi:10.1176/appi.ajp.2007.06111851

133. Brennan W, Belser AB. Models of Psychedelic-Assisted Psychotherapy: A Contemporary Assessment and an Introduction to EMBARK, a Transdiagnostic, Trans-Drug Model. *Front Psychol* . 2022;13:866018. doi:10.3389/fpsyg.2022.866018

134. Cavarra M, Falzone A, Ramaekers JG, Kuypers KPC, Mento C. Psychedelic-Assisted Psychotherapy-A Systematic Review of Associated Psychological Interventions. *Front Psychol* . 2022;13:887255. doi:10.3389/fpsyg.2022.887255

135. Yaden DB, Berghella AP, Regier PS, Garcia-Romeu A, Johnson MW, Hendricks PS. Classic psychedelics in the treatment of substance use disorder: Potential synergies with twelve-step programs. *Int J Drug Policy* . Dec 2021;98:103380. doi:10.1016/j.drugpo.2021.103380

136. Pronovost-Morgan C, Hartogsohn I, Ramaekers JG. Harnessing placebo: Lessons from psychedelic science. *J Psychopharmacol* . Sep 2023;37(9):866-875. doi:10.1177/02698811231182602

137. Henderson LA, Di Pietro F, Youssef AM, et al. Effect of Expectation on Pain Processing: A Psychophysics and Functional MRI Analysis.*Front Neurosci* . 2020;14:6. doi:10.3389/fnins.2020.00006

138. Hovmand OR, Poulsen ED, Arnfred S, Storebø OJ. Risk of bias in randomized clinical trials on psychedelic medicine: A systematic review.*J Psychopharmacol* . Jul 2023;37(7):649-659. doi:10.1177/02698811231180276

139. Szigeti B, Nutt D, Carhart-Harris R, Erritzoe D. The difference between 'placebo group' and 'placebo control': a case study in psychedelic microdosing. *Sci Rep* . Jul 26 2023;13(1):12107. doi:10.1038/s41598-023-34938-7

140. Gukasyan N, Nayak SM. Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy.*Transcult Psychiatry* . Oct 2022;59(5):652-664. doi:10.1177/1363461520983684

141. Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *J Psychopharmacol* . Feb 2022;36(2):151-158. doi:10.1177/02698811211073759

142. Henningfield JE, Ashworth J, Heal DJ, Smith SL. Psychedelic drug abuse potential assessment for new drug applications and controlled substance scheduling: A United States perspective. *J Psychopharmacol* . Jan 2023;37(1):33-44. doi:10.1177/02698811221140004

143. Breeksema JJ, Kuin BW, Kamphuis J, van den Brink W, Vermetten E, Schoevers RA. Adverse events in clinical treatments with serotonergic psychedelics and MDMA: A mixed-methods systematic review. *J Psychopharmacol* . Oct 2022;36(10):1100-1117. doi:10.1177/02698811221116926

144. Johnston CB, Mangini M, Grob C, Anderson B. The Safety and Efficacy of Psychedelic-Assisted Therapies for Older Adults: Knowns and Unknowns.*Am J Geriatr Psychiatry* . Jan 2023;31(1):44-53. doi:10.1016/j.jagp.2022.08.007

145. Goodwin GM, Aaronson ST, Alvarez O, et al. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *N Engl J Med* . Nov 3 2022;387(18):1637-1648. doi:10.1056/NEJMoa2206443

146. Halpern JH, Pope HG, Jr. Hallucinogen persisting perception disorder: what do we know after 50 years? *Drug Alcohol Depend* . Mar 1 2003;69(2):109-19. doi:10.1016/s0376-8716(02)00306-x

147. Rocha JM, Reis JAS, Bouso JC, Hallak JEC, Dos Santos RG. Identifying setting factors associated with improved ibogaine safety: a systematic review of clinical studies. *Eur Arch Psychiatry Clin Neurosci* . Oct 2023;273(7):1527-1542. doi:10.1007/s00406-023-01590-1

148. McIntyre RS. Serotonin 5-HT(2B) receptor agonism and valvular heart disease: implications for the development of psilocybin and related agents. *Expert Opin Drug Saf* . Jul-Dec 2023;22(10):881-883. doi:10.1080/14740338.2023.2248883

FIGURE LEGEND

Figure 1. Pharmacological, psychological, and social mechanisms for how psychedelics may influence pain and pain-related behaviours.

Figure 2. Figure 2A. Overview of neurocircuitry of addiction.**Figure 2B.** Overlap of psychedelic mechanisms as they may theoretically influence specific areas of the neurocircuitry of addiction as relevant to both pain and opioid use disorder.

FIGURES

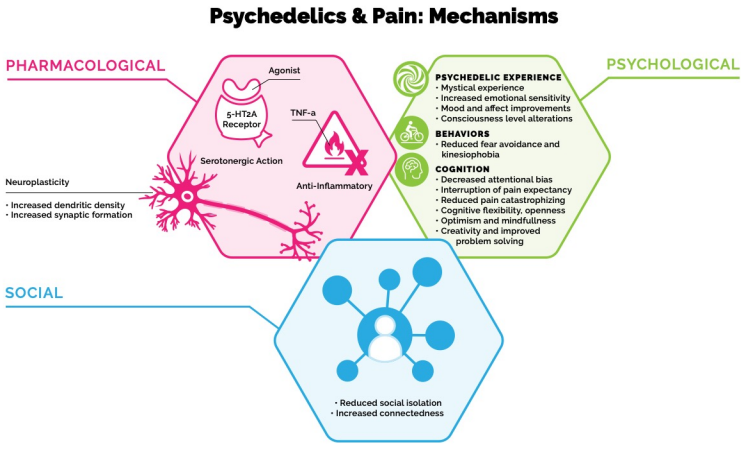


Figure 1. Pharmacological, psychological, and social mechanisms for how psychedelics may influence pain and pain-related behaviours.

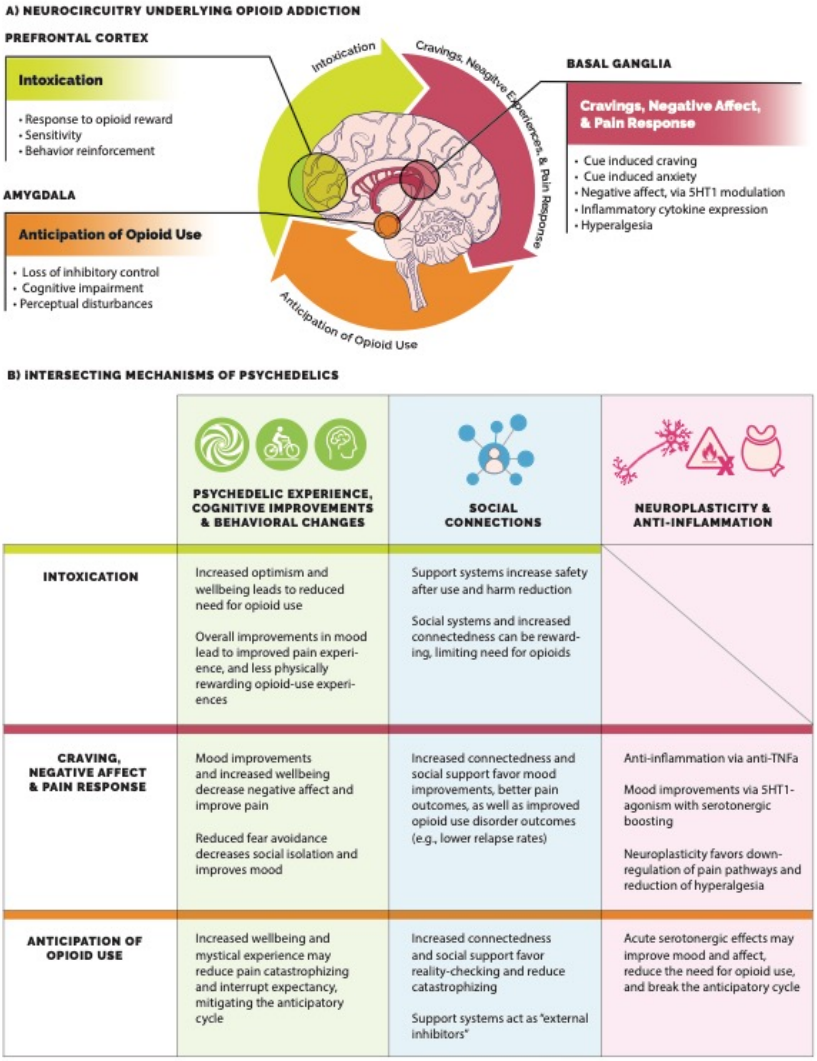
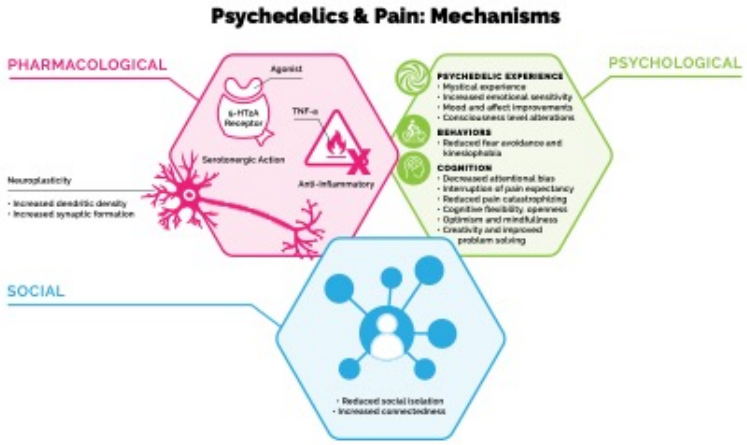
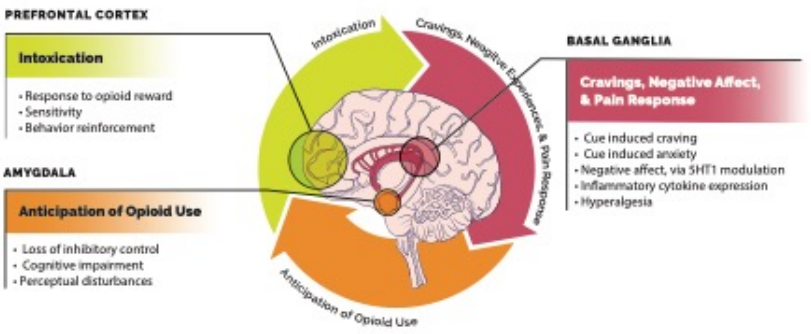


Figure 2. Figure 2A. Overview of neurocircuitry of addiction.**Figure 2B.** Overlap of psychedelic mechanisms as they may theoretically influence specific areas of the neurocircuitry of addiction as relevant to both pain and opioid use disorder.



A) NEUROCIRCUITRY UNDERLYING OPIOID ADDICTION



B) INTERSECTING MECHANISMS OF PSYCHEDELICS

	PSYCHEDELIC EXPERIENCE, COGNITIVE IMPROVEMENTS & BEHAVIORAL CHANGES	SOCIAL CONNECTIONS	NEUROPLASTICITY & ANTI-INFLAMMATION
INTOXICATION	Increased optimism and wellbeing leads to reduced need for opioid use Overall improvements in mood lead to improved pain experience, and less physically rewarding opioid-use experiences	Support systems increase safety after use and harm reduction Social systems and increased connectedness can be rewarding, limiting need for opioids	
CRAVING, NEGATIVE AFFECT & PAIN RESPONSE	Mood improvements and increased wellbeing decrease negative affect and improve pain Reduced fear avoidance decreases social isolation and improves mood	Increased connectedness and social support favor mood improvements, better pain outcomes, as well as improved opioid use disorder outcomes (e.g., lower relapse rates)	Anti-inflammation via anti-TNFa Mood improvements via 5HT1-agonism with serotonergic boosting Neuroplasticity favors down-regulation of pain pathways and reduction of hyperalgesia
ANTICIPATION OF OPIOID USE	Increased wellbeing and mystical experience may reduce pain catastrophizing and interrupt expectancy, mitigating the anticipatory cycle	Increased connectedness and social support favor reality-checking and reduce catastrophizing Support systems act as "external inhibitors"	Acute serotonergic effects may improve mood and affect, reduce the need for opioid use, and break the anticipatory cycle