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Could Psychedelics Treat Neuropathic Chronic Pain?

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Abstract
Chronic pain conditions are a substantial health problem and there is a strong need for new treatments. We hypothesise that classical psychedelics such as psilocybin may be one such treatment for chronic pain states. We introduce the pharmacology of psychedelics and existing data on their use in humans, including side effects, safety and abuse liability. We systematically review and explore the existing data on the use of psychedelics to treat pain, predominantly chronic and neuropathic in type. A discussion of the psychological and psychiatric aspects of chronic pain and the effects of psychedelics on these aspects follows, culminating in an integrated hypothesis that psychedelics effect high level priors that compound chronic pain, alongside putative direct nociceptive effects. Finally, we propose a clinical trial to test our primary hypothesis.

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Introduction
Chronic & Neuropathic Pain

Chronic pain is a challenge to patients and clinicians. Pain serves as a signal for imminent or existing tissue damage, and is usually a normal, adaptive response. However, maladaptation within pain pathways can result in hypersensitivity, spontaneous sensations of pain in the absence of stimuli, allodynia, and hyperalgesia [1]. Where pain becomes a chronic and disabling experience anxiety and depression states often develop, compounding the original problem [2].

Pain that persists beyond a period of three months is chronic in nature (as defined for Post-Herpetic Neuralgia) and is mediated by variable elements of both central and peripheral sensitization [3]. Peripheral sensitization involves inflammatory processes at the site of trauma, recruitment of nerve fibres and amplification in the dorsal horn of the spinal cord [4]. Central sensitisation is defined as an increase in excitability of central neurons such that normal inputs produce amplified pain responses [5]. It is mediated by synaptic and circuit plasticity and is a form of learning in which pain processing in the central nervous system is altered in an enduring way [6].

Examples of chronic pain include cancer pain, postherpetic neuralgia, chronic low back pain, migraine and fibromyalgia. Chronic pain often results from (and exists alongside) significant physical disability, for example diabetic neuropathy and osteoarthritis [7]. Chronic pain is a significant public health problem. The economic cost of chronic pain is estimated to be about €200 billion per year in Europe and $150 billion per year in the United States (US) [8] up to £635 billion. Chronic pain affects more people and costs more to society than cancer, diabetes and heart disease combined [9]. The prevalence of all chronic pain within the general adult population of Europe is said to be between 25-35% [10]. Of those in chronic pain around 20% can be subclassified as having chronic neuropathic pain [11].

Neuropathic pain is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [12]. Chronic pain of neuropathic origin is often more severe and is associated with greater negative impact on sleep, psychological performance and daily functioning [13].

First line treatments for neuropathic chronic pain are antidepressants, including tricyclic antidepressants (TCAs) and serotonin noradrenaline reuptake inhibitors (SNRIs), as well as calcium channel α-δ ligands (gabapentin and pregabalin) and topical lidocaine [14,15]. Pharmacotherapy trials for neuropathic pain report very few patients achieving pain remission [16] and less than half of those treated with current best therapies, including tricyclic antidepressants and SNRIs, report more than a 30% reduction in symptoms [15,17, and 18]. Opioid analgesics are second line treatments because of their side effect profile and a high abuse potential, a problem shared by gabapentin and pregabalin [19,20]. Opioids typically do not provide clinically significant relief from chronic pain symptoms [21] and chronic opioid exposure can result in hyperalgesia [22].

Analgesics typically modulate peripheral and subcortical nociceptive pathways. These include targeting inflammatory mechanisms (paracetamol, NSAIDs), ‘defunctionalisation’ of peripheral nerve fibres (capsaicin), descending mu opioid pain modulation (opiates), and nerve conduction (lignocaine, gabapentin, pregabalin, anti-epileptics). Antidepressants, especially tricyclic antidepressants, may represent the most efficacious of established treatments [23]. This is partially explained by their concomitant effect on depression [14], a common comorbidity of chronic pain. While antidepressants appear to have a peripheral effect, they are thought to principally act on central components of pain processing [24], such that targeting central pain processing is a viable route of intervention.

Chronic pain states are complex sensory and emotional experiences that are context dependent, shifting according to psychosocial state [25].
There are both emotional and attentional influences on the modulation of pain perception [26-29]. Clinically, central pain processing is modulated by psychological and psychiatric dysfunction [30]. In line with this, psychotherapy, particularly cognitive behavioural therapy (CBT), provides a modest but clear benefit [31] in the treatment of neuropathic pain.

Current treatment options are limited in efficacy, with only a minority of patients experiencing pain relief, often only partial. Moreover, current pharmacological treatments have a side effect profile, often compounded by polypharmacy, that lead many to discontinue treatment [14]. Thus, there is a significant need for novel treatments.

**Introduction to Classical Psychedelics**

Classical psychedelics are a group of serotonergic agonists that includes psilocybin, d-lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and mescaline. Human administration produces multi-faceted altered states of subjective experience including changes to perception, mood, fluidity of thought and feeling, intensified emotions and, at higher doses, a dissolving of the sense of self and hallucinations [32,33]. They act primarily through the 5HT2A receptor, which is critical to their effects, and other 5HT receptors, including 5HT2C and 5HT1A [34]. Activation of these receptors leads to global increases in functional cortical connectivity [35] and decreased blood flow and functional connectivity in and to regional networks [36,37].

The 5HT2A receptor is implicated in pain processing [38], for example in migraines [39]. It should be noted that activation is generally proalgesic. Centrally there is 5HT2AR distribution and psilocybin binding in central components of the pain matrix, including the Anterior Cingulate Cortex (ACC) [40]. The ACC modulates descending pain control mechanisms, including the periaqueductal grey and dorsal raphe [41]. In chronic pain states 5HT2ARs in the descending pathways also affect pain states [42]. Psychedelics may directly agonise the 5HT2AR, cause temporary down-regulation of the 5HT2AR, or neuroplastic changes. This may underpin early, and or, long lasting changes to pain processing, respectively. Psychedelics lead to plastic changes via increases in BDNF, neurtogenisis, synaptogenesis and spinogenesis [43], potentially altering centrally sensitized pain states. 5-HT2A receptors may also be a promising peripheral target for relieving chronic pain [44]. 5HT2A receptors are expressed in peripheral Mast and Schwann cells and in the dorsal horn of the spinal cord. More detailed exploration of putative nociceptive mechanisms of psychedelics for pain falls out of the remit of this paper and can be found in Castellanos JP, et al. (2020) [45].

**Safety and Abuse Potential of Psychedelics**

Psychedelics appear physiologically and psychologically safe during their acute phase when used in modern clinical settings. There have been no serious adverse events in modern trials studying psilocybin in humans [46-50]. Adverse effects include transient nausea, headaches and at times extreme anxiety and fear (more common at higher doses). Psychedelics including LSD and psilocybin have mild, transient physiological effects [50,51]. Studies looking at ayahuasca have recorded no adverse effects except for vomiting - seen in about 50% of patients [52,53]. Long-term effects are less clear although measures of safety remained high for psilocybin in depressed and healthy humans at 6 months [54,55].

In population studies use of psychedelics is not associated with increased incidence of mental health problems [56]. In the largest randomised controlled trial of psilocybin in humans to date there were no significant changes to participants on a range of cognitive and emotional processing paradigms and no adverse events that led to withdrawal from the study [57]. Classical psychedelics do not appear to create drug dependence or addiction [58,59]. Hallucinogen Persisting Perception Disorder (HPPD) is one complication and features a wide range of persistent subjective effects long after the drug has left the body [60]. HPPD is uncommon in recreational usage and is rare in controlled therapeutic settings.

**Systematic Review**

A small historical literature documents the experimental use of classical psychedelics to treat pain conditions that were in large part neuropathic in origin. This systematic review aims to collate and synthesise historical studies using classical psychedelics to treat pain in humans. We attempt a synthesis of evidence to draw some hypotheses about how psychedelic drugs may modify the effects and perception of chronic pain states in order to make a case for investigation of this area with patient acceptability work and pilot clinical trials.

**Methods**

A search was conducted looking for studies that met the criteria of having used or observed the use of classical psychedelics to treat pain in humans. The MEDLINE database was searched between 1st October 2019 and 30th October 2019 using the following terms: (LSD, lysergic acid diethylamide, psychedelic, psilocybin) AND (pain). The 'Multidisciplinary Association for Psychedelic Studies' (MAPS) Psychedelic Bibliography was searched manually between 1st October and 30th October 2019, using the title search term 'Pain' to find titles containing this term. This database contains a complete list of psychedelic research between 1931 and 1995 [61]. These search methods identified 1107 articles. Titles and abstracts were screened between 1st October 2019 and 30th October 2019 to look for studies that used or observed the use of classical psychedelics to treat pain in humans. English language articles or English language versions of articles were considered.

1107 articles were forthcoming using these search methods of which 7 studies used or observed the use of classical psychedelics to treat pain in humans. After removal of duplicates 4 studies remained and were included in this systematic review. These papers' bibliographies and the bibliographies of commentary and opinion articles produced by the same searches were screened manually by title and then by abstract. This was done between 1st October and 30th October 2019 and between May 1st and May 31st 2020. These additional sources yielded 8 more papers. Of the 1115 articles identified by these methods, after duplicate removal, there remained 1112 articles that were screened, of which 1100 were excluded based on selection criteria (Table 1). 12 full-text articles remain included in this systematic review (Table 2).

**The Use of Psychedelics to Treat Pain in Humans: Description of Studies**

**Historical Research: 1964-1977**

An open label study from 1964 reported that administration of LSD in gravelly ill patients induced a longer and more potent analgesia than either pethidine or dihydromorphinone [62]. LSD was delivered open-label to 50 patients when two prior double blinded administrations of pethidine or dihydromorphinone had proven ineffective. A pain scoring system of mild (0), moderate (1), severe (2) or very severe (3)
was used, a synthesis of the statement of the patient and observations by the clinician and surrounding staff. Patients who received LSD reported the largest mean number of twenty-minute-long pain-free periods (95.6 compared with 5.7 and 8.4 respectively). However, it is unclear if this is due to the effects of LSD lasting much longer than the other drugs, or a strong expectancy effect. LSD did produce the lowest number of patients who suffered with no periods of protracted pain relief as compared to those who received opiate medications alone (25.6% compared with 85.1% and 76.6% respectively). LSD’s increased efficacy may have resulted from summative effects with the previously administered opiates. Most patients were suffering from cancer pain, one from “herpes zoster with burn”, likely to be post-herpetic neuralgia. We infer that many patients had chronic pain, however this is not explicitly stated.

The adverse effects mentioned included “psychotic reactions insufficient to require termination” as well as 3 cases of nausea & vomiting during LSD administration. The nature of the “psychotic reactions” was not detailed but may reflect the hallucinations typical during the acute effects of these drugs. While there was no reported follow-up on patients in the 1964 study, the author stated in a later editorial that they reported pain free periods of up to two weeks [63]. Kast E (1966) [64], also mentions another study on at least 9 patients that used LSD as a pre-anesthetic agent in which “When LSD was used as a pre-anesthetic, no analgesics were needed after surgery for up to 36 hours”. However, no data was published to support either of these claims.

Kast E (1966) [64], Kast E (1966) [65], published two studies describing the administration of LSD to patients with painful and terminal conditions, mostly cancer. LSD was given at a single dose of 100mcg. In the first of these 80 patients were treated [64]. A pain scoring system of mild (0), moderate (1), severe (2) or intolerable (3) (as assessed by the patient) was used. Although graphically documented, no numerical data was presented and no statistical analysis undertaken on the effects of LSD on pain. The graph shows pain scores dropping off during the acute effects and then returning towards a baseline over 3 weeks (Figure 1). In this study chlorpromazine was used to terminate the effects and was used in 70 patients within 12 hours due to “fear, panic, or the desire to rest” - 90% of which were due to “frightening imagery”. Other adverse effects were not reported. 10% of participants were reluctant to repeat the experience.

In the second study, 128 were treated [65]. These included 44 with metastatic carcinoma of the breast; 48 with metastatic carcinoma of the cervix; 18 with carcinomatosis; and 18 with cancer of the digestive tract. In this study, no responses to LSD warranted termination and psychotherapeutic techniques such as encouraging “surrender” to the experience were sufficient to moderate patients’ reactions. This study was graphically documented with no raw data on the effects of LSD on pain and used the same classifications of mild (0), moderate (1), severe (2) or intolerable (3). A drop in average pain is described 2-3 hours after administration with relief lasting 12 hours and reduced intensity lasting for 3 weeks. 7 patients had panic and 42 had mild anxiety reactions, and an unspecified number had disturbing hallucinations. No “adverse medical reactions” occurred.
No explanation was given for either dose or the number of sessions. 14 of 22 patients reported an improvement in a global figure integrating a range of measures including pain severity and depression symptoms. Alleviation of pain symptoms lasted up to 2 months. 8 cases reported no change. Grof S, et al. (1973) [67], administered 60 patients with 2-500μg LSD and 60-105mg Dipropyltryptamine (DPT). 44 patients received LSD, 19 received DPT, and 3 received both drugs. Systematic rating was only carried out for 31 patients who received LSD. Again, no explanation was given for the dramatic range in dosage, or why nearly half the total sample size was excluded from comparison. 9 of 31 patients reported dramatic improvements in pain severity, depression, anxiety, and fear of death. 13 reported moderate improvements, 7 patients reported no change, and 2 patients reported feeling worse than before treatment. Both Pahnke WN, et al. (1969) [66], and Grof S, et al. (1973) [67], reported no clinical adverse effects.

In 1977 Fanciullacci M, et al. (1977) [68], reported seven patients with phantom limb pain treated with a sub-psychoactive dose of oral LSD (25mcg for the first 7 days, 50mcg for the subsequent 14 days). The trial was a cross-over design with placebo, LSD then placebo given sequentially. Based on daily “questioning” of an undisclosed nature two patients were reported as having “striking” reduction in pain symptoms and eventually required no other analgesia; three had “moderate” reduction in pain and a 50% reduction in analgesic use. In two patients LSD was ineffective and analgesic use was unchanged [68]. Placebo was given before LSD and had no effect on pain scores. Pain scores dropped whilst LSD was administered, however they remained low after the drug was switched for a placebo. This could be interpreted as the sustained effect of the LSD for 3-4 weeks after administration; however, blinding was not mentioned and placebo might account for the sustained changes. This very small study requires replication with larger numbers to verify the results seen.

Contemporary research: 2006-present

In a survey of 496 cluster headache sufferers 80 patients were reported to have used psychedelics for prevention and 23 for abortion of attacks [69]. Use of psilocybin-containing mushrooms was reported by the authors to be as effective as high flow oxygen for the abortion of acute attacks and more effective than either oral or intranasal administration of triptans – though less effective than subcutaneous triptans. Abortive doses of psilocybin mushrooms ranged from 0.1 to 5g. Psilocybin, LSD and 2-bromo-LSD were reported to be equally effective as preventative treatments for cluster headaches, and more effective than prednisolone and verapamil. Preventative doses ranged between 0.1 and 6g for psilocybin mushrooms and 100-300ug for LSD. For prevention they were used every few weeks to twice yearly. The complete preventative efficacy for the psychedelic drugs was approximately 40%, greater than that seen with the other conventional medicines [70-72]. Non-psychedelic indoleamines, such as methysergide and melatonin, were less effective than prednisolone and verapamil. Almost no adverse effects related to classical psychedelics were reported by participants, only headache in one user due to LSD.

These results were echoed in a qualitative thematic analysis of user reports undertaken by Andersson M, et al. (2017) [73]. This study reported improvements in cluster headaches and migraine with LSD and psilocybin treatment. Doses ranged from 0.25-3g for psilocybin mushrooms, and 5-150ug for LSD. Daily micro dosing was reported to prevent attacks. No adverse effects were reported. Unfortunately, the sample size was not described. In addition, due to the qualitative nature of the reports, effective comparison between cases is challenging. Overall, though, the data corroborates existing figures to suggest that both LSD and psilocybin might be effective tools for reducing both headache frequency, and severity.

Following selection by means of a standardized questionnaire, 53 participants who used LSD and psilocybin to abort and prevent cluster headaches were interviewed over email or telephone [70]. It was shown that psilocybin aborted attacks in 22/26 users and that LSD and psilocybin terminated cluster periods, in which frequent numbers of attacks occur together, in the majority of reporting patients (25/48 and 7/8, respectively). They also extended remission from attacks in 18/19 and 4/5 users respectively. In 22/43 users sub-psychoactive doses of these compounds were found to decrease the frequency or intensity of attacks, or to offer complete termination of attacks. All three of these studies likely suffered from recall bias and selection bias, where those for whom these drugs worked well were more likely to participate and recall effective use. In Schindler EA, et al. (2015) [69], survey participants were not asked about side effects and in all three studies no adverse effects were reported.

An open, non-randomized case series with 5 sufferers of cluster headache likewise noted significant improvements with the use of a non-psychoactive analogue of LSD (2-bromo-lysergic acid diethylamide) [71]. Here, the administration of three separate doses over 10 days was associated with changes including improvements in the frequency and severity of attacks, the termination of cluster cycles, changes from chronic to episodic cluster headaches, and remissions extending for many months.

One double-blind, placebo-controlled study trialling psychedelics to treat anxiety in patients with advanced stage cancer failed to find robust reductions in pain perception or lessened need for narcotic pain medication [72]. This may be because the focus of the study and researchers was not on pain, and existential distress and measures of anxiety and depression, rather than pain, were the primary outcomes measured. Two weeks after experimental treatment sessions several subjects reported decreased pain while others did not. No numerical data on pain scores was reported.

Discussion

The historical literature found by this systematic review has focussed on headaches - including cluster headaches and migraines - and neuropathic pain in the form of cancer and phantom limb pain.
These studies are of varying quality. The headache papers are all observational survey studies that use the retrospective self-report of participants [69-71, and 73]. By contrast almost all neuropathic pain investigations were uncontrolled and open-label studies with limited numbers of participants [64-68, and 74]. A double-blind, placebo-controlled study [72] measured pain as a secondary outcome. The authors of this study noted that experimentation investigating pain with higher doses of psilocybin than those given (0.2mg/kg or 14mg in a 70kg person) would be justified. In the modern studies using classical psychedelics in terminal patients who would have had chronic pain conditions, measures of pain were either not conducted or not reported [72, and 75-77]. This may be because the primary focus of these studies was on end-of-life anxiety and depression.

Administration of psychedelics like psilocybin to patients with chronic pain risks exacerbating pain or causing other complications. It may be significant that no increases in pain or significant adverse effects were reported in those recent studies looking at use of psilocybin and LSD in those with terminal diseases and cancer [72, and 75-77]. As detailed, no mention of a complication or exacerbation of pain was mentioned in the historical literature reviewed above. However, safety in this patient population needs to be demonstrated, including specific measures of pain outcomes and adverse side-effects.

In the order of 300 patients with cancer pain appear to have been treated with psychedelics in studies that looked at pain as an outcome. These studies contain generally positive subjective reports of their effects on pain. 15 patients have been treated with psychedelics for phantom limb pain. There has been anecdotal corroboration that psychedelics may be useful for phantom limb pain. A recent case report by Ramachandran V, et al. (2018) [78], described that psilocybin use in combination with a mirror-visual feedback technique produced a 50% pain reduction and elimination of paroxysmal pain for 2 weeks.

All studies report no or few side effects, however several do not appear to ask specifically about them. Raw or analysed data is often not presented, especially with the older studies. The studies report a range of efficacies of psychedelics for pain during and after the administration of the drug. In practical terms the acute subjective effects of psychedelics make their administration at suprathreshold doses in a continuous way inappropriate to treat continuous pain. However an ongoing and enduring effect on pain following administration might be of value.

While no conclusions about safety and efficacy can be drawn from these studies, they suggest classical psychedelics may be effective treatments for chronic and neuropathic pain, especially phantom limb and cancer pain. Given the huge unmet clinical and socioeconomic need for new treatments this literature encourages further investigation of classical psychedelics for these indications. This should take the form of a survey of chronic pain patients’ attitudes on the use of psychedelic therapy. In a small pilot study is warranted that tests safety and preliminary efficacy. Modern techniques, validated measures, pain as the primary measure and follow up over an extended period of at least a year would all facilitate more robust conclusions than can be managed here.

One additional paper, not included in our systematic review, merits discussion. In 1979, Richards published a paper that, rather than a distinct study, appears to be a summary of a number of trials undertaken at Johns Hopkins in the 1960s. We expect the numbers reported to overlap with others discussed above, including Pahnke WN, et al. (1969) [66], study. However, it likely contains indistinguishable original material. Richards reports that 91 patients with terminal cancer were treated; 50 received LSD, 40 received DPT, and one received psilocybin. DPT is a non-classical psychedelic substance whose effects are likely mediated by the serotonin 2a receptor [79]. Both LSD and DPT reportedly elicited profound reductions in pain intensity, fear of pain (and death), psychological factors associated with pain aggravation. LSD elicited stronger responses in each category. Richards describes that “some patients appeared to manifest impressive decreases in the intensity of physical pain… for days or even weeks afterwards… [whilst others] reported no noteworthy difference”. No data on the reported changes in pain was provided. The article emphasises a complex interplay between the physical and the psychological in the reduction of pain. Indeed, Richards reports that the therapeutic context is essential for experiencing significant reductions in pain and concluded that alongside “pharmacological factors” psychedelic therapy was “reducing the psychological factors that may aggravate pain”.

**Potential Psychological and Psychiatric Mechanisms of Action of Psychedelics for the Treatment of Chronic Pain**

The psychological and psychiatric aspects of pain: The Gate Control Theory of Pain [80] gave credence to the idea that pain arises from a complex interplay between ‘bottom up’ physical stimulation and ‘top down’ psychological modulation. This model holds that peripheral pain transmission is modulated by a neurological ‘gating’ mechanism in the spinal dorsal horns, whereby afferent nociceptive and non-nociceptive inputs compete with one another for transmission to higher brain centres under the influence of a centrally mediated descending modulation from those higher centres [81]. The clinical impact of this understanding was that psychological factors could now be seen as moderating components of pain processing, not just a consequence of them. Put another way, the perception of pain is not just an objective representation of physical tissue damage, but a complex process influenced by ‘the interaction between cognitive, emotional, socio-cultural and physical factors’ [82].

Evolutionarily, such ‘top down modulation’ is useful in situations where pain must be ignored to achieve certain goals or where situations demand a rapid response to perceived threats. However, it also infers the possibility of an inverse state, where an individual is chronically alert to (and sensitive to) pain stimuli. This in itself may become functionally disadvantageous [81], as occurs in many cases of chronic pain. The intensity of chronic pain states show significant associations between psychological factors, lending more evidence to a complex relationship [82]. Such factors include anger, anxiety [83], the patient’s perceived self-efficacy at coping [84] and their beliefs and cognitions about pain [85]. This is particularly true for negative psychological functions including negative social cognitions and self-statements and self-blame.

A recent systematic study concluded that personal and psychological factors, such as pain ‘catastrophizing’ and comorbid depression and anxiety are among the most important predictors for persistent neuropathic pain [86].

A person’s propensity to develop chronic pain can be predicted by the extent to which an individual fears pain, develops anxiety about pain, and ‘catastrophizes’ this pain [87]. Together, these characteristics are termed Sensitivity to Pain Traumatisation (SPT), and refer to “the anxiety-related cognitive, emotional, and behavioural reactions to pain that resemble the features of a traumatic stress reaction” [87]. In short, SPT represents a predisposing factor to certain maladaptive expressions of and relationships with pain which may also perpetuate the problem after it has developed.
Catastrophizing refers to a tendency to focus on or exaggerate the negative aspects of pain, and it is associated with increased pain and decreased functional outcomes even when depression is controlled for [88]. It is associated with increased pain, physical disability and interference with daily functioning, and long-term improvements in these domains. A longitudinal study on 250 patients with chronic musculoskeletal pain determined that improvements in pain catastrophizing, as well as in depression and anxiety, resulted in significant reductions of pain intensity, interference with daily living, and disability [89]. Similarly, a recent longitudinal study of 538 patients with neuropathic pain has confirmed these findings and has shown that decreases in catastrophizing early in treatment predict subsequent improvements in pain outcomes and vice versa. This suggests a causal role for catastrophizing in the perception of pain, and suggests that the psychological process of catastrophizing may be a viable treatment target [88].

In neuropathic pain, SPT and other psychological states may impact on pain severity and interfere with daily living. Catastrophizing may be the most significant maladaptive coping strategy. It encompasses three thought processes: rumination, magnification, and helplessness. Burton AK, et al. (1995) [90], showed that catastrophizing accounts for 47% of the variance in predicting the likelihood of developing chronic pain in patients who have suffered an episode of acute pain. Poulin PA, et al. (2016) [91], has suggested that rumination promotes symptom hypervigilance, magnification encourages avoidance, and helplessness begets inaction. This culminates in increased pain severity, psychological distress and impaired activity in a number of neuropathic pain disorders [27, 91, and 92]. In contrast, mindfulness – considered the converse of catastrophizing – has been shown to moderate the relationships between catastrophizing, pain intensity and pain interference [90]. Research suggests that mindfulness is composed of five core facets: observation (1) and description (2) of one’s experience; a non-judgemental (3) approach towards one’s thoughts or emotions; awareness (4) of unpleasant inner phenomena, and non-reactivity (5) to these [93]. In terms of pain, this approach acknowledges and accepts pain, thereby buffering against catastrophizing. Mindfulness inversely predicts pain intensity and depression, positively predicts quality of life [91] and improves the psychological aspects of living with chronic pain [94].

Other psychological factors putatively play a role in an individual’s relationship with pain. For example, Vassend O, et al. (2013) [95], suggest personality traits have modest but significant associations with pain phenotypes. Neuroticism and Extraversion may predispose an individual to a greater sensitivity to pain [95]. Neuroticism’s relationship with pain hypervigilance appears to be mediated by pain catastrophizing [96-98]. The personality trait of Openness, on the other hand, may be inversely associated with pain; low levels of Openness have been linked with the “dysfunctional” subtype of chronic pain patients [99] and with the perception that pain would be an enduring aspect of patients’ lives [100] (although others have failed to replicate this finding [101]). Notably, antidepressants have been shown to increase scores of Openness, Extraversion and Conscientiousness while decreasing scores of Neuroticism [102].

Pain and psychiatric conditions, specifically depression and anxiety, are common and often mutually exacerbating comorbidities [103]. Neuropathic pain, especially, is associated with more severe mood disturbances [82]. Longitudinal studies on the relationship between pain and depression and anxiety demonstrate a bidirectional, and reciprocal relationship [104-107]. Pain is a risk factor for the development of depression and anxiety, and this risk is modulated by pain location, intensity and the presence of previous subthreshold affective symptoms [108]. Likewise, patients with depression and anxiety suffer greater pain severity and more pain locations than patients with pain but no psychiatric comorbidities. This relationship is greatest for those with chronic depression and anxiety symptoms, and remission of depression and anxiety is associated with significant decreases in pain [109]. One longitudinal study found that of the psychological and psychiatric factors that interact with pain outcomes, improvements in depression produced the largest benefits to pain intensity, its interference with daily living, and disability, followed by catastrophizing, and then anxiety [89].

In short, there are a number of psychological and psychiatric states that can influence pain perception. Negative psychological and psychiatric states like catastrophizing, depression, and anxiety exacerbate pain and increase resultant dysfunction. Meanwhile positive coping mechanisms like mindfulness improve pain and modulate negative influences [91]. Targeting these factors may, therefore, be effective at controlling chronic pain.

Here we summarise evidence that psychedelics might modify psychological and psychiatric factors that influence chronic pain states, first focusing attention on the psychological and then on the psychiatric. Finally we present a brief hypothesis integrating current theory of psychedelic mechanisms with the psychological and psychiatric elements of chronic pain.

Psychological effects of psychedelics: A double blind study in psychiatrically well humans has shown psilocybin increases the personality domain of Openness [47] with persistent effects for at least 12 months. A similar double blind study showed that in combination with spiritual practice, higher doses of psilocybin increased levels of prosocial behaviors, attitudes and positive psychological functions at 6 months, including interpersonal closeness, life meaning, purpose, gratitude, forgiveness and coping abilities [55]. Moreover, a recent study in treatment-resistant depression patients showed that psilocybin is able to reduce pessimistic bias about future events and improve the accuracy of patients’ predictions about the future, leading to improvements in depressive symptoms [110]. Additionally, psilocybin administration results in changes to personality domains that resemble those observed with antidepressant treatment: decreases in Neuroticism, and increases in Extraversion and Openness, with these changes non-significantly associating with improvements in depressive symptoms [111].

LSD likewise appears to have at least sub-acute effects on mood and cognition, with healthy subjects demonstrating increases in optimism and trait Openness even 2 weeks after administration [112]. Notably, the degree of change in trait Openness is positively associated with the degree by which brain connectivity becomes disordered during the psychedelic experience, a relationship which was positively enhanced by the degree of “ego-dissolution” the subject reports [113]. Other long-lasting psychological effects of single-dose LSD have been reported to include increased subjective positive attitudes about life and/or self, positive mood changes, altruistic/positive social effects, positive behavioral changes, and well-being/life satisfaction [114].

Likewise, ayahuasca produces a number of documented psychological changes [115]. A longitudinal, year-long observational study of ayahuasca users and controls found decreased scores of psychopathology, and significant improvements in neuropsychological function, life attitude, and psychosocial well-being in ayahuasca users [116]. Ayahuasca use is associated with lower scores in the "Harm
Avoidance” personality trait [116-119], which is characterised by excessive worry, fear, shyness, fatigue and weakness. Notably, Harm Avoidance is positively associated with Neuroticism and Extraversion and inversely associated with Openness [120], traits which themselves predispose to [95] or protect from [99] chronic pain, respectively.

Ayahuasca intake in healthy volunteers also produces increases in the “non-judging” and “non-reacting” subscale of the Five Facets Mindfulness Questionnaire and increases in the “decentering” component of mindfulness, defined as “the capacity to observe one’s thoughts and emotions in a detached manner, and to reduce automatic negative judgmental attitudes and inner reactivity” [121,122]. It also leads to improved scores on the “self-compassion” questionnaire [122]. Notably, measures of non-judging remain elevated even at 2 weeks (last follow-up). Moreover, these improvements in mindfulness correlate with neurometabolic and connectivity changes in certain brain regions [122]. A more recent study on ayahuasca users has likewise noted acute improvements in life satisfaction and mindfulness (observe, non-judge, non-react), as well as sustained improvements in convergent thinking, depression and stress that correlate to the level of ego-dissolution experienced [123].

**Psychiatric effects of psychedelics:** In addition to inducing psychological changes in users, psychedelics also appear to produce psychiatric changes in depression, anxiety and substance abuse disorders [124]. For example, single-dose administration of LSD in a randomised control trial has been shown to reduce anxiety scores in patients with life-threatening diseases [76]. Analysis of historical evidence for LSD prior to prohibition, while plagued with methodological shortcomings, reveals clinician-judged improvements in 79.2% (range 40-95%) of patients treated for unipolar depression [125]. To date, 7 clinical trials investigating the use of psychedelics in the treatment of symptoms of distress in life-threatening illnesses have been published [126]; these highlight the potential utility of psychedelics in reducing anxiety, depression, pain, fear of death, feelings of isolation and improving introspection and quality of life.

Like LSD, psilocybin also demonstrates possible beneficial effects on psychiatric and substance abuse disorders [48,50, and 127]. A number of studies have suggested beneficial effects of psilocybin on anxiety and depression in patients with terminal illness [72, and 75-77]. This includes a double-blinded, placebo-controlled randomised control trial demonstrating that psilocybin reduces anxiety scores up to 3 months after administration, and depression scores up to 6 months after [72].

In line with findings from LSD and psilocybin, ayahuasca use is associated with improvements in mood and anxiety [128], as well as substance-use disorders [117, and 130-132]. In treatment-resistant major depression, single-dose ayahuasca administration is associated with significant antidepressant and anxiolytic effects up to 21 days after administration in urban patients with treatment resistant depression. Vomiting was the only reported adverse effect of ayahuasca administration, and was not considered a severe discomfort by patients [133]. Likewise, another prospective study showed first-time ayahuasca users exhibit improvements in the intensity of minor psychiatric symptoms (e.g., anxiety, depression, irritation, somatic symptoms, fatigue) following first ayahuasca use [134] when compared to controls. Cross-sectional studies note ayahuasca users demonstrate improved scores in measures of anxiety, body dysmorphism, and attention deficit disorder than non-ayahuasca using controls [135]. In a cross-sectional study without controls, Halpern et al. reported that ayahuasca users of the Daime church exhibited lower scores for symptoms of somatization, anxiety, depression, hostility, phobia, paranoid ideation, and psychoticism than a normative sample [132]. This group also showed no evidence of clinically significant anxiety (0/32) and one case of depression (1/32) as measured by the Hamilton Depression Rating Scale. The Structured Clinical Interview for DSM-IV Disorder (SCID) further revealed several cases of psychiatric disease in partial to full remission (major depression, simple phobia, post-traumatic stress disorder, panic disorder, a case of bipolar disorder with panic disorder and bulimia nervosa).

These findings suggest a possible beneficial effect of ayahuasca use that may be relevant to the psychiatric compounders of pain. However, much of the evidence comes from cross-sectional, observational designs without clear controls, and often in religious jungle communities that by their nature present confounders when compared with urban use. Additionally, these studies may suffer from a selection bias, in that most evidence comes from experienced ayahuasca users, who by definition have derived enough benefit from ayahuasca to continue using it and who are motivated to prove its use is beneficial.

Taken together, and in the context of the historical literature reviewed we posit that psychedelics might be useful to treat chronic pain and that this may be due to their putative antidepressant, anxiolytic [125,136], mindfulness-enhancing and personality altering effects [47,122].

**An integrated hypothesis of the psychological mechanism of psychedelics’ effects on chronic pain:** Besides putative direct effects on the nociceptive pathways via 5HT2AR, see Castellanos JP, et al. (2020) [45], psychedelics may affect high level priors that compound neuropathic chronic pain. Current theory suggests psychedelics relax high-level priors or ‘beliefs’ by means of 5-HT2AR activation [137]. 5HT2AR activation causes a period of cortical plasticity [138,139] and a period of disruption at neuronal, functional and network levels [140,141]. This disruption includes that of high-level cortical functions that may underpin so-called ‘priors’ such as expectations and beliefs [141,142]. This provides a window of opportunity that if utilised could aid revision of harmful beliefs when administered in a psychotherapeutic setting.

This disruption reflects disintegration and desegregation of the function of resting-state brain networks, a phenomena which correlates with the subjective experience of ego-dissolution produced by classical psychedelics [35,143-146]. This element of mystical experience appears to be important in the therapeutic potential of psychedelic experience [147], and may be of relevance in treatment of chronic pain. In the context of pain 5HT2AR action may allow reorganisation of entrenched and maladaptive patterns of habitual thinking and psychological phenomena that compound chronic pain such as catastrophizing, low openness, depression and anxiety [148,149].

**Conclusion**

As outlined in this paper there is a great imperative for new treatments for chronic and neuropathic pain. Here we propose the use of classical psychedelics as treatments for chronic pain states. There is a small historical data set of studies investigating the use of classical psychedelics to treat pain. We hypothesise that the beneficial effects described may result from 5HT2AR dependent reorganisation of ‘high-level’ priors that contribute to and underpin chronic pain states. Psychedelics may also have direct effects on components of the pain matrix, central sensitization, descending modulatory pathways, the dorsal horn and peripheral sites via the 5HT2AR receptor. Both old and new, the existing studies are of limited quality (Table 3) and yet
they encourage further investigation. Robust evidence obtained in the context of the rigorous modern clinical trials is lacking, in part, due to the historical, cultural and legislative barriers. Despite this and given the dearth of effective pharmacotherapies for and substantial disease burden of chronic pain, an investigation of safety and efficacy for this indication appears justified. A suitable starting point is a survey of chronic pain patients regarding possible use of psychedelic therapy, followed by a small pilot study designed to test safety and offer a first indication of efficacy in this largely unexplored patient group.

Declarations

No funding was received to assist with the preparation of this manuscript.

Conflicts of Interest

The authors declare they have no conflicts of interest.

References


Table 3: Risk of bias assessed using the cochrane risk of bias in non-randomized studies of interventions (ROBIN-I) tool [146].

<table>
<thead>
<tr>
<th>Study</th>
<th>Confounding</th>
<th>Selection of participants into the study</th>
<th>Classification of intervention groups</th>
<th>Deviations from intended interventions</th>
<th>Missing data</th>
<th>Measurement of outcomes</th>
<th>Selection of the reported results</th>
<th>Overall possibility of bias</th>
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