Title

Lysergic acid diethylamide (LSD) and Psilocybin for the Management of Patients with Persistent Pain: A Potential Role?

Authors

Dr Andy Whelan, FRCA, MBCHB [1]

Professor Mark I. Johnson, PhD [2]

Affiliations

1. Leeds Teaching Hospitals NHS Trust

2. Centre for Pain Research, Leeds Beckett University

Address for correspondence

Professor Mark I. Johnson

Centre for Pain Research, School of Clinical and Applied Sciences, Leeds Beckett University

City Campus, Leeds LS1 3HE, United Kingdom

Telephone:

e-mail: m.johnson@leedsbeckett.ac.uk

e-mail: drawhelan@doctors.org.uk

Article Type: Review

Running header: LSD and Psilocybin for Pain?

FUNDING: None

ETHICAL APPROVAL: N/A

COMPETING INTERESTS: None declared

ACKNOWLEDGEMENTS: None

ACCESSING RESEARCH MATERIALS: Underlying research materials related to our paper (for example data, samples or models) can be accessed by contacting Professor Mark I. Johnson

Word Count: 5078

SHORT ABSTRACT (120 words)

Recently, there has been interest in lysergic acid diethylamide (LSD) and psilocybin for depression, anxiety and fear of death in terminal illness. The aim of this review is to discuss the potential use of LSD and psilocybin for patients with persistent pain. Lysergic acid diethylamide and psilocybin are 5-hydroxytryptamine receptor agonists and may interact with nociceptive and anti-nociceptive processing. Tentative evidence from a systematic review suggests that LSD (7 studies, 323 participants) and psilocybin (3 studies, 92 participants) may be beneficial for depression and anxiety associated with distress in life-threatening diseases. Lysergic acid diethylamide and psilocybin are generally safe if administered by a health care professional, although further investigations are needed to assess their utility for patients with persistent pain, especially associated with terminal illness.

LONG ABSTRACT

Chronic pain is a global health care problem and management using mainstay analgesic drugs has proven problematic. Recently, positive outcomes of small scale randomised controlled clinical trials has reawakened interest in the use of psychedelics for depression and anxiety related to fear of death in terminal illness. The aim of this review is to discuss the potential use of lysergic acid diethylamide (LSD) and psilocybin for patients with persistent pain. Research evidence suggests that LSD and psilocybin interact with physiological processes associated with pain, providing a scientific rationale for analgesic effects. Lysergic acid diethylamide and the active ingredient of psilocybin (psilocin) are 5-hydroxytryptamine (5-HT) receptor agonists with a high affinity for 5-HT_2 receptors. 5-hydroxytryptamine acts in the spinal cord and brainstem to inhibit onward transmission of nociceptive information and 5-HT acts in the cerebrum to influence emotional, motivational, and cognitive appraisal systems involved in pain perception. Lysergic acid diethylamide and psilocybin influence processing in the default mode network in the brain. Pain disrupts activity in the default mode network, and therefore LSD and psilocybin may alleviate adverse intrusive cognitions and reverse the breakdown of the normal self. Tentative evidence from a systematic review suggests that LSD (7 studies, 323 participants) and psilocybin (3 studies, 92 participants) may be beneficial for depression and anxiety associated with distress in life-threatening diseases. However, there is an absence of clinical trials on the efficacy of LSD and psilocybin for pain per se. LSD and psilocybin are generally safe if administered under the supervision of a health care professional. Our review suggests there is a need for further investigation of derivatives of LSD and psilocybin to determine their suitability for patients with persistent pain, especially associated with terminal illness, in the presence and absence of neuropsychiatric ailments.

KEYWORDS

Pain, Analgesia, Lysergic acid diethylamide (LSD), Psilocybin, Psilocin, End-of-life care

Introduction

There is an age-old tradition of using fungi and plants to produce psychedelic effects in religious ceremonies and ritual healing. Isolation of substances from fungi and plants led to the development of a range of psychedelic drugs including lysergic acid diethylamide (LSD, made from ergotamine, found in the fungus ergot), psilocybin (found in *Psilocybe* mushrooms), dimethyltryptamine (found in various trees and shrubs including *Acacia* species, *Mimosa tenuiflora, and Psychotria viridis*) and mescaline (found in the peyote cactus *Lophophora williamsii*). Psychedelic drugs (classical hallucinogens) cause visual, auditory, tactile and olfactory hallucinations and/or an altered sense of reality through perceptual anomalies of sensation, cognition, and affect. Drugs that produce a sense of detachment from the surrounding environment and/or a state of delirium (e.g. ketamine, dextromethorphan, phencyclidine, nitrous oxide, belladonna) may also produce hallucinations and/or perceptual anomalies. However, these drugs are not considered psychedelic hallucinogens in the 'classical' sense.

Originally, psychedelic drugs were used to assist explorations of 'inner experience' during psychotherapy. Clinical research in the 1950s and 1960s suggested that psychedelic drugs were of therapeutic promise for distress secondary to terminal cancer and for addiction [1]. However, medical use declined due to prohibition resulting from their use as recreational drugs as part of the counter culture [2]. Recently, there has been a resurgence of interest in the therapeutic use of psychedelic drugs in neuropsychiatry due to positive outcomes of small scale randomised controlled clinical trials [3-6]. This has prompted calls for serious consideration of psychedelics such as LSD and psilocybin as viable treatment for depression and anxiety related to fear of death in terminal illness [1, 7, 8]. In the United Kingdom, LSD and psilocybin are currently classified as schedule one drugs under the Misuse of Drugs Regulations 2001 [9].

To date, the use of psychedelic drugs for the management of pain and associated symptoms has received little attention. The aim of this review was to evaluate the potential use of lysergic acid diethylamide (LSD) and psilocybin for patients with persistent pain.

Lysergic acid diethylamide (LSD)

Pharmacology

In 1938, the Swiss chemist Albert Hofmann was trying to synthesize a respiratory and circulatory stimulant from ergotamine, a chemical from the fungus ergot (*Claviceps purpurea*)[2]. Hoffman

produced a series of lysergic acid derivatives and named the twenty-fifth compound lysergic acid diethylamide-25 (LSD-25). Hoffman abandoned testing with LSD-25 because it caused restlessness in the experimental animals. In 1943, Hoffman synthesized LSD-25 again and found that it produced psychedelic experiences when self-administered. Sandoz distributed LSD under the trade-name Delysid as an investigational drug for psychiatric research and a commercial medication for LSD-assisted psychotherapy for the treatment of alcoholism, neurosis, and psychosomatic disorders. In the 1950s, the Central Intelligence Agency in the United States explored the use of LSD for mind control and chemical warfare. Increasing recreational use and its influence on youth culture in the 1960s led to the prohibition of LSD in the United States. Consequently, global psychedelic research became dormant for several decades.

Lysergic acid diethylamide is 9,10-didehydro-N,N-diethyl-6-methylergoline-8β-carboxamide (IUPAC name) with a molecular formula of $C_{20}H_{25}N_3O$ (non-proprietary name is lysergide) [10]. The abbreviation LSD was derived from the German name LysergSäureDiethylamid. Lysergic acid diethylamide is part of a family of indole alkyl amines that includes other psychedelic substances with substituted tryptamines such as N,N-dimethyltryptamine (DMT) and psilocin. Lysergic acid diethylamide is a 5-hydroxytryptamine (5-HT, serotonin) receptor agonist that passes through the blood brain barrier. Lysergic acid diethylamide has a high affinity for 5-HT_{2A} and 5-HT_{2C} receptor subtypes. Functionally, 5-HT_2 receptors are G-protein coupled, with 5-HT_{2A} and 5-HT_{2C} subtypes having a widespread distribution in the central nervous system and involved in the regulation of mood, anxiety, cognition, psychosis, sleep-wakefulness and eating.

Recently, findings from human studies have demonstrated the importance of 5-HT_{2A} receptors in eliciting psychedelic effects. The 5-HT_{2A} receptor antagonist Ketanserin blocks LSD-induced hypnogenic changes in various states of consciousness including dreaming, cognitive bizarreness, attributing relevance to meaningless stimuli, primary process thinking in imagery and emotionality, connectedness, meaningfulness and tracking of tonal structure in music [11-14]. Imaging studies suggest that 5-HT_{2A} agonists produce acute psychedelic experiences via excitation of regions of the brain involved in emotion, cognition, memory and self-awareness including the medial and lateral frontal cortex and the medial temporal lobe [15]. 5-HT_{2A} agonists also inhibit activity in the default mode network which is a collection of brain regions active during wakeful rest when an individual's mind is not focused on the outside world but thinking about themselves, others, the past, or future (i.e. when the mind is 'wandering')[16].

Therapeutic use

The threshold dose of LSD to initiate psychedelic effects is between 20 and 30 µg p.o. (1-15 µg/kg body weight) with a moderate recreational dose typically 75-150 µg p.o. Physiological and psychological effects of LSD occur 30-45 minutes after ingestions and persist for 6 to 9 hours. There are no active metabolites following metabolism of LSD. Elimination is via the kidney. Plasma elimination half-life is 3 to 4 hours in man. Oral doses of LSD <100 µg produce vivid psychosensory effects, including increased sensory perception, illusionary changes of perceived objects, synesthesia, and enhanced mental imagery. Mood is intensified and thoughts accelerated and broadened in scope, including new associations and modified interpretation and meanings of relationships and objects. Typically, hypermnesia strengthens and ego weakens. The general state of consciousness can be compared to a daydream, but with pronounced affectivity and enhanced production of inner stimuli [17].

The use of LSD in clinical practice requires expertise and patient cooperation because treatment response can be variable and unpredictable. LSD has been used to assist psychotherapy for a wide variety of psychiatric conditions, severe anxiety disorder (including existential distress in life-threatening diseases), post-traumatic stress disorder, and drug dependencies (including tobacco and alcohol)[18-20]. When administered in structured therapeutic settings LSD can generate experiences that enhance self-realization which can alter an individual's understanding of maladaptive cognitions and behaviours and promote an acceptance of behaviour change. LSD also enhances suggestibility that can enhance this effect. There has been renewed interest in the use of LSD (and psilocybin) to alleviate fear and distress associated with impending death in end-stage diseases for individuals who are refractory to conventional anxiolytics [21-23]. In this context, psychedelics are used to induce transcendental experiences that may offer insights, symbolism and meaning to dying including, for some people, comfort associated with an enhanced realization of continuity in an after-life [22-24]. Lysergic acid diethylamide has also been used by individuals to enhance creativity in art, literature and the sciences [25].

The safety profile of serotonergic psychedelics are good when administered in carefully controlled clinical settings. They have very low physiological toxicities, with no evidence of resulting organ damage or neuropsychological deficits even at very high doses [26-28]. Contra-indications are due to hazards resulting from hyperactivity and excitement and include individuals with cardiovascular

disease, pregnancy, epilepsy, and psychosis. There is minimal physical dependence or compulsive drug-seeking behaviour when compared with other drugs of abuse such as cannabis, cocaine, methamphetamine, and opioids. There is no physical withdrawal syndrome but tolerance develops due to down-regulation of 5-HT receptors. There is cross-tolerance with other psychedelic agents including psilocybin and mescaline. Mortality rates with psychedelics are difficult to calculate as they are extremely rare (less than 1 in a million) (https://erowid.org/chemicals/lsd/lsd_death.shtml) with no reports of lethality directly associated with LSD, although acute delusional and paranoid states, prolonged psychosis, suicide, self-injury, fatal accidents and homicide have occurred whilst people are in LSD states. Adverse reactions include anxiety, paranoia, and delusions. Dysphoria ('bad trips') occur in approximately 20% of drug exposures during recreational use. A major concern are hazards due to potential erratic behaviour associated with the psychedelic experience. Safeguards against these risks include the exclusion of volunteers with personal or family history of psychotic disorders or other severe psychiatric disorders, establishing trust and rapport between session monitors and volunteer before the session, careful volunteer preparation, a safe physical session environment, and interpersonal support from at least two study monitors during the session [29]. Larsen reviewed case material in the Danish State Archives of 151 of 154 psychiatric patients treated with LSD in the 1960s and subsequently received financial compensation in the 1980s for LSD-inflicted harm [30, 31]. These patients experienced severe LSD-associated side effects that persisted for many years including flashbacks.

Clinical Efficacy

Clinical trials with small sample sizes provide initial evidence for efficacy of LSD for depression and anxiety related to terminal cancer and for addiction [32, 33]. A systematic review by Reiche *et al.* [34] of 11 clinical trials (445 participants) provided tentative evidence to support the use of LSD (7 studies, 323 participants) and psilocybin (3 studies, 92 participants) to alleviate depression and anxiety associated with existential distress in life-threatening diseases. Side effects were minimal when there was adherence to safety guidelines [29]. Included in the review was a small randomized placebo-controlled crossover study by Gasser *et al.* [5] in which 12 patients with anxiety associated with life-threatening diseases received either high-dose LSD (200 µg) or low-dose LSD (20 µg) followed by an open-label crossover to 200 µg. Reductions in trait anxiety were present at 2-month follow-up and sustained for 12-months post-treatment in 10 participants, with associated improvements in quality of life [35]. There were no prolonged adverse reactions. Krebs et *al.,* [36]

conducted a systematic review with meta-analysis of six trials (536 participants) and found that LSD (210–800 μg) reduced the likelihood of alcohol misuse compared with placebo.

Psilocybin and psilocin

Pharmacology

Albert Hofmann also isolated psilocybin from the mushroom *Psilocybe Mexicana* (one of over 200 species of psilocybin 'magic mushrooms'). Psilocybin is 4-phosphoryloxy-N,N-dimethyltryptamine (IUPAC name) with a molecular formula of $C_{12}H_{17}N_2O_4P$ [10]. Psilocybin is a tryptamine alkaloid. When ingested orally is mostly dephosphorylated in the liver into the active agent psilocin, which has a half-life between one and three hours. Psilocybin and psilocin pass through the blood brain barrier. Psilocin is a full or partial agonist for 5-HT receptors with a high affinity for 5-HT_{2B} and 5-HT_{2C}, and a lower affinity for 5-HT_{2A} receptors. Actions via 5-HT_{2A} and 5-HT_{2C} receptors are similar to those described for LSD. 5-HT_{2B} receptors are strongly expressed in the liver, kidney, heart and stomach but have a sparse distribution in the central nervous system were they are involved in the regulation of mood, anxiety, sleep-wakefulness and migraine. Psychedelic actions are via similar brain regions as LSD. Psilocybin decreases activity in the default mode network (e.g. posterior cingulate cortex and medial prefrontal cortex), the thalamus and the anterior cingulate cortex [37].

Therapeutic Use

Psilocybin is approximately 100 times less potent than LSD. The threshold dose of psilocybin to initiate psychedelic effects is between 4 and 10 mg p.o. (50 and 300 μg/kg body weight) with recreational dosage typically between 10 and 50 mg p.o. (approximately 10–50 g fresh mushrooms, 1-5 g dried mushrooms, plasma concentration approximately 8 μg/L). Physiological and psychological effects occur within 10 to 40 minutes and persist up to 6 hours depending on dose. A medium dosage of psilocybin (12–20 mg p.o.) may alter consciousness accompanied by heightened affect and introspection, and hypnagogic experiences that include illusions, synesthesia, and distortions in the sense of time. Indications and clinical considerations for psilocybin are identical to those previously discussed for LSD including anxiety disorders, post-traumatic stress disorder, and drug dependency [18-20].

Adverse reactions following administration of psilocybin include hypertension, nausea, panic attacks and exacerbation of pre-existing psychosis. Eleven percent of respondents to an online survey study of 1993 recreational psilocybin users reported risk of physical harm to self or others during their

worst 'bad trip' after consuming psilocybin mushrooms, with 2.7% reporting that they received medical attention [38]. Three participants reported the onset of enduring psychotic symptoms and three participants reported suicide attempts. There was a positive correlation between difficulty of experience and higher dose. Two large retrospective population studies, each over 130,000 U.S. adults, failed to find any evidence of lifetime use of serotonergic psychedelics and mental health problems [39, 40]. There was lower likelihood of inpatient mental health treatment and a reduced incidence of suicidal behaviour following use of psychedelics [39, 41]. Evidence from administration of carefully controlled doses of psilocybin in laboratory studies and clinical trials suggests that the incidence of psychological distress and/or risky behaviour is extremely low when there is careful screening, preparation, monitoring, drug-related adverse effects are managed at the time of drug administration and follow-up of participants occurs [1]. A small proportion of people are sensitive to psilocybin and a small proportion of people require high doses to achieve psychedelic effects. There are no known reports of direct lethality associated with psilocybin and no withdrawal syndrome following chronic use. Down-regulation of 5-HT receptors results in tolerance and cross-tolerance with mescaline and LSD.

Clinical Efficacy

The findings of clinical trials with small sample sizes provide tentative evidence for efficacy of psilocybin for depression and anxiety, alcohol and tobacco dependence, and obsessive-compulsive disorder. The systematic review by Reiche *et al.* [34] included three studies (92 participants) that suggested that psilocybin alleviates depression and anxiety associated with life-threatening diseases. Griffiths *et al.* [6] conducted a double blind randomised controlled crossover trial of 51 cancer patients with life-threatening diagnoses. They found that high-dose psilocybin (22 or 30 mg/70 kg) alleviated depressed mood and anxiety, and increased quality of life, life meaning, and optimism at 6-month follow-up compared with very low dose (1 or 3 mg/70 kg). Ross *et al*. [42] conducted a double blind, placebo-controlled, crossover trial whereby 29 patients with cancer-related anxiety and depression received single-dose psilocybin (0.3 mg/kg) with psychotherapy or niacin (Vitamin B3) with psychotherapy. They found that psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects that persisted to the 6.5-month follow-up in approximately 60-80% of participants with improved attitudes towards death. Grob *et al*. [24] found a reduction in anxiety relating to advanced stage cancer at 1 and 3 months after treatment with psilocybin and an improvement of mood that persisted for 6 months.

Cahart-Harris *et al*. [43] conducted an open-label feasibility trial of 12 patients with moderate-to-severe, unipolar, treatment-resistant major depression who received 10 mg p.o. psilocybin and 25 mg p.o. seven days later in a supportive setting. The onset of psychedelic effects occurred within 30-60 min after dosing, peaked at 2-3 hours and disappeared by 6 hours, with no serious, but some transient adverse effects (i.e. anxiety in all patients, confusion/thought disorders in nine patients, nausea in four patients, and headache in four patients). High-dose psilocybin improved depressive symptoms at 1 week and 3 months with sustained improvements in anxiety and anhedonia. Cahart-Harris *et al*. [44] followed this up by reporting the findings of an open-label clinical trial of 19 patients with treatment-resistant depression who had their functional brain activity measured using fMRI before and after psilocybin (10 mg followed by 25 mg, one-week apart). They found that the single high dose of psilocybin combined with psychotherapy to patients with treatment-resistant depression patients caused 100% improvement at 1 week and 47% at 5 weeks.

There is very limited clinical trial data reviewing the use of psychedelics in the treatment of addiction. A meta-analysis of controlled trials has demonstrated a consistent and clinically significant beneficial effect of high-dose LSD [18]. Bogenschutz *et al*. [45] conducted an open label single-group study of ten alcohol-dependent participants who received one or two sessions of oral psilocybin in addition to motivational enhancement therapy. They found that abstinence increased for up to 36 weeks and that an increased psilocybin effect predicted decreases in drinking, craving and increases in abstinence self-efficacy.

Johnson *et al*. [46] conducted an open-label pilot study of 15 psychiatrically healthy nicotine-dependent smokers who received moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin within a structured 15-week smoking cessation treatment protocol and found that 12 participants seven-day point prevalence abstinence at 6-month follow-up. The same investigators reported long-term follow-up data from this open-label pilot study and found that 10 participants were tobacco smoking abstinent at 12-month follow-up and nine participants were smoking abstinent at 16 months [47]. Moreno *et al*. [48] conducted a double-blind study in which nine participants with obsessive-compulsive disorder received increasing single-dose exposures of psilocybin with a one week washout (100 µg/kg), medium (200 µg/kg), and high (300 µg/kg) with an additional very low dose (25 µg/kg) administered randomly any time after the first dose. They found reductions in symptoms in all subjects in at least one of the testing sessions but there was no statistically significant effect of dose.

Lysergic Acid Diethylamide, Psilocybin and Pain

The pharmacological mechanism of action of psychedelics is complex and comprehensive review is beyond the scope of this article. Evidence suggests that LSD having an affinity for 5-HT, dopamine (D2) and trace amine-associated receptors (TAAR1). Psilocybin and psilocin have affinity for 5-HT receptors but not D2 receptors (see [49-51] for comprehensive reviews). Psychedelics may alleviate pain from actions producing psychedelic effects that indirectly affect an individual's final experience of pain and/or actions with physiological systems directly involved in pain and its modulation.

Psychedelic Experience and Pain

The traditional view that pain is a faithful representation of activation of nociceptors and transmission through nociceptive pathways is outdated. Contemporary perspectives suggest that pain is a perceptual experience inferred from bodily sate (i.e., embodied) and socio-environmental context (i.e., embedded in the environment in which pain is experienced). An individual's experience of pain is influenced by a wide variety of sensory, affective, cognitive, social, and bodily cues interpreted within current and evolutionary contexts [52-55]. Pain is defensive, promoting actions that attempt to reduce the impact of threat on the integrity of the body. Pain involves inferences associated with rationalizing complex, uncertain environments and is defined by the boundaries of actions available to the person. The ability to detect physiological state through interoceptive awareness diminishes when pain becomes chronic [56, 57].

Psychedelic drugs produce acute psychedelic experiences by influencing activity in brain regions involved in processes that regulate emotion, cognition, memory and self-awareness. These brain regions are also associated with processes leading to perceptual experience of 'embodied' and 'embedded' pain [15]. Brain imaging studies have found that the thalamus, anterior cingulate cortex, posterior insula and medial and lateral frontal cortices become active in response to transient noxious stimuli [58], although these regions also become active to non-noxious auditory, visual, mechanical and thermal stimuli [59]. The right anterior insula cortex is as an integration hub for autonomic, immune, hormonal, and cardiovascular systems creating a 'metacognitive map' of active processes such as pain, touch, and temperature, and subjective and emotional feelings [60, 61]. The left anterior insular region and the fronto-parietal region contributes to a sense of 'body ownership' and the temporo-parietal regions to a sense of peripersonal space [62]. These regions are

interconnected with the anterior cingulate cortex forming an emotional-motivational appraisal system associated with pain [63]. There is a shift of activity from the posterior to anterior insula with the development of persistent pain reflecting the transition from nociception to emotional responses associated with pain [64].

Evidence also suggests that chronic pain impairs resting state activity in the brain by disrupting processing in the default mode network contributing to intrusive cognition and a breakdown of the normal self [65-67]. Mindfulness training alleviates chronic pain and improves quality of life by developing interoceptive attention to bodily sensations [68]. Psychedelic agents act at regions modulated during mindfulness including the medial prefrontal cortex, posterior cingulate cortex and posterior insula of the default mode network [69-71]. Evidence that 5-HT_{2A} agonists inhibit activity in the default mode network and connector hubs, such as the thalamus and anterior cingulate cortex [16], may provide opportunities to influence activity in brain regions implicated in chronic pain.

5-HT Receptor Binding, Pain and its Modulation

Psychedelics have complex receptor interactions with the serotonergic, dopaminergic, and glutamatergic systems [51, 72]. Lysergic acid diethylamide and psilocybin principally mediate effects through activation of 5-HT_{2A} and 5-HT_{2C} receptors in the central nervous system [73]. These receptors are involved in peripheral and centrally mediated pain processes and in the regulation of mood, anxiety, and cognition. 5-HT_{2A} and 5-HT_7 receptors are involved in anti-nociceptive actions of the rostral ventromedial medulla of the descending pain inhibitory pathways that inhibit onward transmission of nociceptive information in the spinal cord (i.e. by 'closing the pain gate')[74]. Injection of 5-HT into the spinal cord region has anti-nociceptive effects [75]. Drugs that elevate 5-HT levels such as selective serotonin reuptake inhibitors (SSRIs), are indicated for neuropathic pain, musculoskeletal pain and fibromyalgia [76, 77], although evidence about clinical efficacy is inconclusive [78-80]. However, the role of 5-HT in pain processing is bi-directional [81]. For example, persistent pain arising from nerve injury is driven by augmented 5-HT circuitry in the central nervous system and pro-nociceptive actions of 5-HT on central 5-HT_3 receptors. In the periphery, 5-HT_{2A} agonists are pro-nociceptive increasing the effect PGE_2 and noradrenaline [82] and producing thermal hyperalgesia [83].

Evidence from in-vivo electrophysiology in rats suggests that LSD has partial agonist actions at 5-HT_{2A} receptors and full antagonistic action at 5-HT_{1A} in the dorsal raphe, a structure known to be involved

in actions of descending pain inhibitory processes [72]. Descending pain inhibitory pathways are rich in opioid receptors and activation of mu opioid receptors generates analgesia by inhibiting onward transmission of nociceptive information at various levels in the central nervous system. Mu opioid receptors are distributed in mesolimbic regions including the ventral tegmental area and striatum and these classical dopaminergic regions are associated the sense of reward associated with natural behaviors and drugs [84-86]. At higher doses, LSD modulates activity in the ventral tegmental area of the mesolimbic reward system through activation of D2, TAAR1 and 5-HT_{2A}. Mesolimbic circuits modulate nociceptive processes in animal models of neuropathic pain [87] and generate the sense of reward associated with relief of pain [88-90]. However, the reciprocal relationship between 5-HT, opioids, dopamine and noradrenaline is complex with wide spread interconnectivity and bidirectional pro-nociceptive and anti-nociceptive effects [74]. At present, there is an absence of studies investigating the how psychedelics may influence processing of nociceptive information in these brain regions.

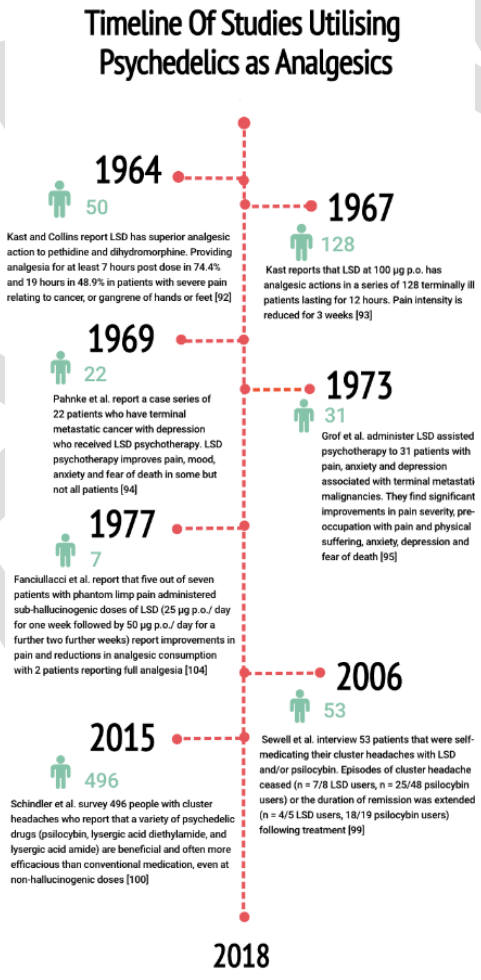
Lysergic acid diethylamide, Psilocybin and Inflammation

Recently, Nichols *et al*. [10, 73] have suggested that psychedelic substances may have potential as therapeutic agents for inflammatory diseases including rheumatoid arthritis via peripheral actions at 5-HT_{2A} receptors. Psychedelic substances instigate signal transduction processes via activation of 5-HT_{2A} receptors at peripheral sites resulting in activation of protein-kinase C, which in turn regulates signal transduction processes associated with the transcription of pro-inflammatory genes mediated via tissue necrosis factor. Tissue necrosis factor is implicated in a wide variety of inflammatory, infectious and malignant conditions and anti-TNF antibodies have been used to manage inflammatory conditions including rheumatoid arthritis [91]. There is a need for further research.

Clinical Research on Lysergic acid diethylamide and Psilocybin to Alleviate Pain

There is a paucity of clinical trials to assess whether LSD or psilocybin have analgesic properties. Evidence to date is from small-scale case series in patients with terminal illness, migraine or cluster headache (Figure 1). One of the first documented human clinical trials assessing the analgesic effects of LSD was in 1964 when Kast and Collins [92] administered a single-dose of dihydromorphone HCl (2mg) and pethidine (meperidine HCl 100mg) in a randomised sequence with a six-hour interval to 50 patients with pain related to cancer or gangrene of hands or feet. Patients who were still experiencing pain six hours after the administration of the second analgesic drug were administered a single dose of LSD (100 µg p.o.). Data presented in the report were difficult to interpret although it

appeared that 48.9% of the patients receiving LSD experienced no pain for at least 19 hours post dose. Kast and Collins concluded that LSD provided a longer and more effective analgesic action than pethidine and dihydromorphone, and that many patients were able to discuss their death freely and displayed “a peculiar disregard for the gravity of their situation” p291 [92]. In 1967, Kast [93] reported that LSD (100 µg p.o.) had analgesic actions in a series of 128 terminally ill patients, commencing at two to three hours after administration and lasting for 12 hours. In 1969, Pahnke *et al*. [94] reported the findings of a case series of 22 patients that had terminal metastatic cancer with depression and received LSD psychotherapy. Pahnke *et al*. claimed that LSD psychotherapy improved pain, mood, anxiety and fear of death, with no adverse effects some but not all patients, although there was no quantitative nor qualitative data provided in the report. In 1973, Grof *et al*. [95] administered LSD assisted psychotherapy for 31 patients with pain, anxiety and depression associated with terminal metastatic malignancies and found significant improvements in pain severity, pre-occupation with pain and physical suffering, anxiety, depression and fear of death.



[Insert Figure 1 here – Timeline of Studies Utilising Psychedelics as Analgesics]

Lysergic acid diethylamide and psilocybin derivatives are structurally related to drugs used to manage migraine and have been used as a potential prophylactic treatment for migraines and vascular headaches since the 1960s [96, 97](for review see [98]). At present, there is an absence of controlled clinical trial evidence to judge clinical efficacy, although internet surveys have found that patients report benefits from using LSD and psilocybin for treatment resistant cluster headaches. Sewell *et al*. [99] interviewed 53 patients that were self-medicating at LSD and/or psilocybin-containing mushrooms and found that episodes of cluster headache ceased (n = 7/8 LSD users, n = 25/48 psilocybin users) or the duration of remission was extended (n = 4/5 LSD users, 18/19 psilocybin users) following treatment. Sewell *et al*. concluded that LSD or psilocybin were better than standard drugs at instigating and extending remission. In 2015, Schindler *et al.,* [100] surveyed 496 people recruited from cluster headache websites and headache clinics who reported that variety of psychedelic drugs (psilocybin, lysergic acid diethylamide, and lysergic acid amide) were beneficial and often more efficacious than conventional medication, even at non-hallucinogenic doses. Karst *et al*. [101] conducted an open label, non-randomized case series of five patients with treatment resistant cluster headache who received a non-hallucinogenic analogue of LSD (i.e. 2-bromo-lysergic acid diethylamide (BOL-148)) that had been synthesised to combat the potentially undesirable hallucinogenic properties of LSD. Three single doses of BOL-148 given over 10 days reduced the frequency and intensity of cluster headache with remission extending for many months or longer. BOL-148 binds to 5-HT_{2A} receptors but has lower efficacy than LSD generating less inhibitory activity of neurons in brain structures [102]. Karst *et al*. [101] suggested that the alleviation of cluster headache by BOL-148 (and by inference LSD and psilocybin) was associated with 5-HT receptor-mediated vasoconstriction rather than psychedelic effects mediated via 5-HT_{1A} and 5-HT_{2A} receptors. Interestingly, a double-blind study by Johnson *et al*. [103] demonstrated that psilocybin causes transient headache in a dose-dependent manner in healthy individuals, although the duration of headaches were always less than 24 hours and the severity of headaches was not disabling.

In 1977, Fanciullacci *et al*. [104] reported that five out of seven patients with phantom limp pain who were administered sub-hallucinogenic doses of LSD (25 µg p.o./ day for one week followed by 50 µg p.o./ day for a further two further weeks) reported improvement in pain and reductions in analgesic consumption. We have been unable to find any other reports of the use of LSD or psilocybin for pain.

Conclusion and the Future

Chronic pain and its management pose a global healthcare problem. With current mainstay drugs, such as opioids, proving problematic there is a need to explore novel pharmacological therapies. Our review suggests there is insufficient evidence to determine whether LSD and psilocybin may be of benefit for patients with persistent pain in the presence and absence of neuropsychiatric ailments. Our review offers indirect evidence that psychedelic drugs such as LSD and psilocybin may interact with endogenous systems in the brainstem and spinal cord that utilise 5-HT such as those involved with inhibition of onward transmission of nociceptive information. Lysergic acid diethylamide and psilocybin influence activity in the same regions of the cerebrum associated with pain as an 'embodied' and 'embedded' perceptual experience, including emotional, motivational, and cognitive appraisal systems. Lysergic acid diethylamide and psilocybin interact with brain regions associated with the default mode network that generates a resting conscious state of awareness. Pain disrupts activity in the default mode network so it seems plausible that LSD and psilocybin may alleviate intrusive cognition and the breakdown of normal-self associated with persistent pain.

The role of a psychedelic experiences in analgesic outcome is unknown although anti-depressant and anxiolytic effects have been shown to occur at sub-hallucinogenic doses. The potential anti-inflammatory properties of LSD and psilocybin may also prove beneficial. There is an absence of clinical trials on the clinical efficacy of LSD and psilocybin for pain, although evidence from uncontrolled case series is promising for alleviating pain, anxiety and depression in terminal illness, migraine and cluster headache. Lysergic acid diethylamide and psilocybin appear to be generally safe if administered under the supervision of a health care professional and do not appear to lead to physiological dependence. Our review suggests a need to assess the utility of derivatives of LSD and psilocybin for patients with persistent pain, especially associated with terminal illness, in the presence and absence of neuropsychiatric ailments.

Future Perspective

Psychedelics appear to have potential to alter management in multiple areas of medicine, yet progress in this field has been dormant due in part to restrictions on the use of the agents in research and clinical practice. The medical community remains reluctant to explore the clinical utility of psychedelics due to safety and abuse concerns. Evidence suggests that these substances are safe and non-addictive for selected patients if administered under carefully controlled clinical conditions. Psychiatry, addiction, pain and end-of-life care are notoriously challenging to effectively treat and

carry costly socioeconomic burdens. Psilocybin and LSD are relatively inexpensive to produce and cost would decline as demand for therapeutic use increases. Presently, evidence for the use of psychedelics in pain management and end-of-life care is limited to pilot studies and uncontrolled case series and there is a need for methodologically robust randomised controlled clinical trials to evaluate the effectiveness.

Our review has revealed an absence of studies from basic sciences assessing the analgesic properties of psychedelic agents using animal models of nociception that record electrophysiological and behavioural outcomes as proxy measures of pain. Systematic investigation of the direct and indirect actions of psychedelics on nociceptive processing at hallucinogenic and sub-hallucinogen doses would inform the potential of these agents for use in the management of pain in a variety of circumstances including at the end-of-life and medical conditions such as neuropathic pain and potentially complex acute pain.

Practice Points

- Worldwide interest in the potential therapeutic value of psychedelics is increasing in many areas of science and healthcare.
- Evidence tentatively suggests benefits in addiction, treatment-resistant depression, terminal-illness related anxiety, obsessive-compulsive disorder, cluster headaches and pain.
- Psychedelics may alleviate pain indirectly through the action a psychedelic experience has on an individual's metacognitive interpretation of the pain.
- Psychedelics may act on the brain modulate similar pathways to mindfulness.
- Psychedelics may alleviate pain directly through 5-HT_{2A} receptor binding at the rostral ventromedial medulla with enhancement of descending pain inhibitory pathways.
- There have been no trials assessing the effectiveness of psychedelics in the management of acute or chronic pain since 1977.
- There are reports that self-medication with psychedelics is superior to current medications in the treatment of cluster headaches and a small case series demonstrated 2-bromo-lysergic acid diethylamide (BOL) improved cluster headache symptoms and frequency of attacks.
- Small studies without controls suggest potential benefit for malignant and neuropathic pain.

References

1. Johnson MW, Griffiths RR. Potential Therapeutic Effects of Psilocybin. *Neurotherapeutics* 14(3), 734-740 (2017).
2. Liester MB. A review of lysergic acid diethylamide (LSD) in the treatment of addictions: historical perspectives and future prospects. *Curr. Drug Abuse Rev.* 7(3), 146-156 (2014).

* Includes a comprehensive historical overview from discovery, use as a research tool, prohibition, and re-awkakening as a therapeutic agent

3. Sanches RF, De Lima Osorio F, Dos Santos RG *et al*. Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study. *J. Clin. Psychopharmacol.* 36(1), 77-81 (2016).
4. Osorio Fde L, Sanches RF, Macedo LR *et al*. Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Rev. Bras. Psiquiatr.* 37(1), 13-20 (2015).
5. Gasser P, Holstein D, Michel Y *et al*. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J. Nerv. Ment. Dis.* 202(7), 513-520 (2014).
6. 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.* 30(12), 1181-1197 (2016).

*Randomized, double-blind, cross-over trial investigating effects of psilocybin in 51 patients depression and/or anxiety associated with life-threatening cancer

7. Sellers EM. Psilocybin: Good Trip or Bad Trip. *Clin. Pharmacol. Ther.* 102(4), 580-584 (2017).
8. Bogenschutz MP. It's time to take psilocybin seriously as a possible treatment for substance use disorders. *Am. J. Drug Alcohol Abuse* 43(1), 4-6 (2017).
9. U.K. Home Office. Guidance. List of most commonly encountered drugs currently controlled under the misuse of drugs legislation (2017). Available at: https://www.gov.uk/government/publications/controlled-drugs-list--2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation
10. Nichols DE, Johnson MW, Nichols CD. Psychedelics as Medicines: An Emerging New Paradigm. *Clin. Pharmacol. Ther.* 101(2), 209-219 (2017).
11. Preller KH, Herdener M, Pokorny T *et al*. The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Curr. Biol.* 27(3), 451-457 (2017).
12. Kraehenmann R, Pokorny D, Vollenweider L *et al*. Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. *Psychopharmacology (Berl)* 234(13), 2031-2046 (2017).
13. Kraehenmann R, Pokorny D, Aicher H *et al*. LSD Increases Primary Process Thinking via Serotonin 2A Receptor Activation. *Front. Pharmacol.* 8 814 (2017).
14. Barrett FS, Preller KH, Herdener M, Janata P, Vollenweider FX. Serotonin 2A Receptor Signaling Underlies LSD-induced Alteration of the Neural Response to Dynamic Changes in Music. *Cereb. Cortex* 1-12 (2017).
15. Dos Santos RG, Osorio FL, Crippa JaS, Hallak JEC. Classical hallucinogens and neuroimaging: A systematic review of human studies: Hallucinogens and neuroimaging. *Neurosci. Biobehav. Rev.* 71 715-728 (2016).

*Comprehensive review of the effects of classical hallucinogens in brain regions

16. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences* 1124 1-38 (2008).
17. Hintzen A, Passie T. *The Pharmacology of LSD*. Oxford University Press, Oxford. (2010).
18. Bogenschutz MP, Johnson MW. Classic hallucinogens in the treatment of addictions. *Prog Neuropsychopharmacol Biol. Psychiatry* 64 250-258 (2016).

19. Grof S. *LSD Psychotherapy*. Multidisciplinary Association for Psychedelic Studies, Ben Lomond, CA. (2008).
20. Das S, Barnwal P, Ramasamy A, Sen S, Mondal S. Lysergic acid diethylamide: a drug of 'use'? *Ther. Adv. Psychopharmacol.* 6(3), 214-228 (2016).
*Comprehensive review of receptor pharmacology, mechanism of action, potential therapeutic benefits and adverse effects of LSD.
21. Richards WA. Mystical and archetypal experiences of terminal patients in DPT-assisted psychotherapy. *J. Relig. Health* 17(2), 117-126 (1978).
22. Sessa B. Can psychedelic drugs play a role in palliative care? *Eur. J. Palliative Care* 15 234-237 (2008).
23. Dutta V. Repression of death consciousness and the psychedelic trip. *J. Cancer Res. Ther.* 8(3), 336-342 (2012).
24. Grob CS, Danforth AL, Chopra GS *et al*. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psychiatry* 68(1), 71-78 (2011).
25. Sessa B. Is it time to revisit the role of psychedelic drugs in enhancing human creativity? *J Psychopharmacol.* 22(8), 821-827 (2008).
26. Gable RS. Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am. J. Drug Alcohol Abuse* 19(3), 263-281 (1993).
27. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl)* 172(2), 145-156 (2004).
28. Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. *J. Nerv. Ment. Dis.* 172(10), 577-595 (1984).
29. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J. Psychopharmacol.* 22(6), 603-620 (2008).
** Comprehensive review of safety issues
30. Larsen JK. Neurotoxicity and LSD treatment: a follow-up study of 151 patients in Denmark. *Hist. Psychiatry* 27(2), 172-189 (2016).
31. Larsen JK. LSD treatment in Scandinavia: emphasizing indications and short-term treatment outcomes of 151 patients in Denmark. *Nord. J. Psychiatry* 71(7), 489-495 (2017).
32. Liechti ME. Modern Clinical Research on LSD. *Neuropsychopharmacology* 42(11), 2114-2127 (2017).
33. Carhart-Harris RL, Goodwin GM. The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. *Neuropsychopharmacology* 42(11), 2105-2113 (2017).
34. Reiche S, Hermle L, Gutwinski S, Jungaberle H, Gasser P, Majic 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* 81 1-10 (2017).
** Systematic review of psychedelic drugs for symptoms of existential distress in life-threatening diseases
35. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *J. Psychopharmacol.* 29(1), 57-68 (2015).
36. Krebs TS, Johansen PO. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. *J. Psychopharmacol.* 26(7), 994-1002 (2012).
**Meta-analysis to evaluate clinical efficacy of LSD for treatment of alcoholism
37. 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.* 109(6), 2138-2143 (2012).

38. Carbonaro TM, Bradstreet MP, Barrett FS *et al*. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences*. J. Psychopharmacol.* 30(12), 1268-1278 (2016).
39. Johansen PO, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study*. J. Psychopharmacol.* 29(3), 270-279 (2015).
40. Krebs TS, Johansen PO. Psychedelics and mental health: a population study*. PLoS One* 8(8), e63972 (2013).
41. Hendricks PS, Johnson MW, Griffiths RR. Psilocybin, psychological distress, and suicidality*. J. Psychopharmacol.* 29(9), 1041-1043 (2015).
42. Ross S, Bossis A, Guss J *et al*. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial*. J. Psychopharmacol.* 30(12), 1165-1180 (2016).
43. Carhart-Harris RL, Bolstridge M, Rucker J *et al*. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 3(7), 619-627 (2016).
44. Carhart-Harris RL, Roseman L, Bolstridge M *et al*. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms*. Sci. Rep.* 7(1), 13187 (2017).
45. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study*. J. Psychopharmacol.* 29(3), 289-299 (2015).
46. 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.* 28(11), 983-992 (2014).
47. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation*. Am. J. Drug Alcohol Abuse* 43(1), 55-60 (2017).
48. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder*. J.Clin. Psychiatry* 67(11), 1735-1740 (2006).
49. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin*. Addict. Biol.* 7(4), 357-364 (2002).
50. Kyzar EJ, Nichols CD, Gainetdinov RR, Nichols DE, Kalueff AV. Psychedelic Drugs in Biomedicine*. Trends Pharmacol. Sci.* 38(11), 992-1005 (2017).

**Comprehensive review of preclinical and clinical data on for addiction, depression, anxiiety and other conditions

51. De Gregorio D, Comai S, Posa L, Gobbi G. d-Lysergic Acid Diethylamide (LSD) as a Model of Psychosis: Mechanism of Action and Pharmacology*. Int. J. Mol. Sci.* 17(11), (2016).
52. Tabor A, Keogh E, Eccleston C. Embodied pain-negotiating the boundaries of possible action*. Pain* 158(6), 1007-1011 (2017).
53. Anchisi D, Zanon M. A Bayesian Perspective on Sensory and Cognitive Integration in Pain Perception and Placebo Analgesia*. PLoS One* 10(2), (2015).
54. Nicholas MK, Ashton-James C. Embodied pain: grasping a thorny problem? *Pain* 158(6), 993-994 (2017).
55. Di Lernia D, Serino S, Cipresso P, Riva G. Ghosts in the Machine. Interoceptive Modeling for Chronic Pain Treatment*. Front. Neurosci.* 10 (2016).
56. Duschek S, Montoro CI, Reyes Del Paso GA. Diminished interoceptive awareness in fibromyalgia syndrome*. Behavioral Med.* 43(2), 100-107 (2017).
57. Di Lernia D, Serino S, Riva G. Pain in the body. Altered interoception in chronic pain conditions: A systematic review*. Neurosci. Biobehav. Rev.* 71 328-341 (2016).

58. Jensen KB, Regenbogen C, Ohse MC, Frasnelli J, Freiherr J, Lundstrom JN. Brain activations during pain: a neuroimaging meta-analysis of patients with pain and healthy controls. *Pain* 157(6), 1279-1286 (2016).
59. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix". *Neuroimage* 54(3), 2237-2249 (2011).
60. Adolfi F, Couto B, Richter F *et al*. Convergence of interoception, emotion, and social cognition: A twofold fMRI meta-analysis and lesion approach. *Cortex* 88 124-142 (2017).
61. Craig AD. Significance of the insula for the evolution of human awareness of feelings from the body. *Annals New York Acad. Sci.* 1225 72-82 (2011).
62. Grivaz P, Blanke O, Serino A. Common and distinct brain regions processing multisensory bodily signals for peripersonal space and body ownership. *Neuroimage* 147 602-618 (2017).
63. Craig AD. How do you feel-now? The anterior insula and human awareness. *Nat. Rev. Neurosci.* 10(1), 59-70 (2009).
64. Hashmi JA, Baliki MN, Huang L *et al*. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. *Brain* 136, 2751-2768 (2013).
65. Baliki MN, Baria AT, Apkarian AV. The cortical rhythms of chronic back pain. *J. Neurosci.* 31(39), 13981-13990 (2011).
66. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: chronic pain hurts the brain, disrupting the default-mode network dynamics. *J. Neurosci.* 28(6), 1398-1403 (2008).
67. Baliki MN, Mansour AR, Baria AT, Apkarian AV. Functional reorganization of the default mode network across chronic pain conditions. *PLoS One* 9(9), e106133 (2014).
68. Zeidan F, Vago DR. Mindfulness meditation-based pain relief: a mechanistic account. *Annals New York Acad.Sci.* 1373(1), 114-127 (2016).
69. Allen M, Dietz M, Blair KS *et al*. Cognitive-affective neural plasticity following active-controlled mindfulness intervention. *J. Neurosci* 32(44), 15601-15610 (2012).
70. Brewer JA, Garrison KA. The posterior cingulate cortex as a plausible mechanistic target of meditation: findings from neuroimaging. *Annals New York Acad. Sci.* 1307 19-27 (2014).
71. Farb NA, Segal ZV, Anderson AK. Mindfulness meditation training alters cortical representations of interoceptive attention. *Soc Cogn Affect. Neurosci.* 8(1), 15-26 (2013).
72. De Gregorio D, Posa L, Ochoa-Sanchez R *et al*. The hallucinogen d-lysergic diethylamide (LSD) decreases dopamine firing activity through 5-HT1A, D2 and TAAR1 receptors. *Pharmacol. Res.* 113, 81-91 (2016).
73. Nichols DE. Psychedelics. *Pharmacol. Rev.* 68(2), 264-355 (2016).
74. Bannister K, Dickenson AH. What the brain tells the spinal cord. *Pain* 157(10), 2148-2151 (2016).
75. Viguier F, Michot B, Hamon M, Bourgoin S. Multiple roles of serotonin in pain control mechanisms--implications of 5-HT(7) and other 5-HT receptor types. *Eur. J. Pharmacol.* 716(1-3), 8-16 (2013).
76. Dworkin RH, O'connor AB, Audette J *et al*. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin. Proc.* 85(3 Suppl), S3-14 (2010).
77. Yancey J, Hydrick EN. Selective Serotonin Reuptake Inhibitors for Fibromyalgia. *American Family Physician* 94(7), 548-549 (2016).
78. Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for neuropathic pain in adults. *Cochrane Database Syst. Rev.* (7), CD011789 (2015).
79. Cording M, Derry S, Phillips T, Moore RA, Wiffen PJ. Milnacipran for pain in fibromyalgia in adults. *Cochrane Database Syst. Rev.* (10), CD008244 (2015).
80. Walitt B, Urrutia G, Nishishinya MB, Cantrell SE, Hauser W. Selective serotonin reuptake inhibitors for fibromyalgia syndrome. *Cochrane Database Syst. Rev.* (6), CD011735 (2015).

81. Bardin L. The complex role of serotonin and 5-HT receptors in chronic pain. *Behav. Pharmacol.* 22(5-6), 390-404 (2011).
82. Abbott FV, Hong Y, Blier P. Activation of 5-HT2A receptors potentiates pain produced by inflammatory mediators. *Neuropharmacology* 35(1), 99-110 (1996).
83. Tokunaga A, Saika M, Senba E. 5-HT2A receptor subtype is involved in the thermal hyperalgesic mechanism of serotonin in the periphery. *Pain* 76(3), 349-355 (1998).
84. Fields H. State-dependent opioid control of pain. *Nat. Rev. Neurosci.* 5(7), 565-575 (2004).
85. Fields HL, Margolis EB. Understanding opioid reward. *Trends Neurosci.* 38(4), 217-225 (2015).
86. Fields HL. Understanding how opioids contribute to reward and analgesia. *Region. Anesth. Pain Med.* 32(3), 242-246 (2007).
87. Zhang H, Qian YL, Li C *et al*. Brain-Derived Neurotrophic Factor in the Mesolimbic Reward Circuitry Mediates Nociception in Chronic Neuropathic Pain. *Biol. Psychiatry* 82(8), 608-618 (2017).
88. Wood PB. Mesolimbic dopaminergic mechanisms and pain control. *Pain* 120(3), 230-234 (2006).
89. Navratilova E, Xie JY, Okun A *et al*. Pain relief produces negative reinforcement through activation of mesolimbic reward-valuation circuitry. *Proc. Natl. Acad. Sci.* 109(50), 20709-20713 (2012).
90. Mitsi V, Zachariou V. Modulation of pain, nociception, and analgesia by the brain reward center. *Neuroscience* 338 81-92 (2016).
91. Bradley JR. TNF-mediated inflammatory disease. *J. Pathology* 214(2), 149-160 (2008).
92. Kast EC, Collins VJ. Study of Lysergic Acid Diethylamide as an Analgesic Agent. *Anesth. Analg.* 43 285-291 (1964).
93. Kast E. Attenuation of anticipation: a therapeutic use of lysergic acid diethylamide. *Psychiatr. Quarterly* 41(4), 646-657 (1967).
94. Pahnke WN, Kurland AA, Goodman LE, Richards WA. LSD-assisted psychotherapy with terminal cancer patients. *Curr. Psychiatr. Ther.* 9 144-152 (1969).
95. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. *Int. Pharmacopsychiatry* 8(3), 129-144 (1973).
96. Sicuteri F. Prophylactic Treatment of Migraine by Means of Lysergic Acid Derivatives. *Triangle* 6 116-125 (1963).
97. Crowther DL. The Prophylactic Effect of 1-Methyl-D-Lysergic Acid Butanolamide (Methysergide) in the Treatment of Vascular Headache. A Clinical Study. *Med. Exp. Int. J. Exp. Med.* 10 137-143 (1964).
98. Sewell RA. Unauthroised Research on Cluster Headache. *Winter Solstice* 16(4), 117-125 (2008).
99. Sewell RA, Halpern JH, Pope HG, Jr. Response of cluster headache to psilocybin and LSD. *Neurology* 66(12), 1920-1922 (2006).
100. 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* 47(5), 372-381 (2015).
101. 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* 30(9), 1140-1144 (2010).
102. Aghajanian GK. LSD and 2-bromo-LSD: comparison on effects on serotonergic neurones and on neurones in two serotonergic projection areas, the ventral lateral geniculate and amygdala. *Neuropharmacology* 15(9), 521-528 (1976).

103. Johnson MW, Sewell RA, Griffiths RR. Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers*. Drug Alcohol. Depend.* 123(1-3), 132-140 (2012).
104. Fanciullacci M, Bene ED, Franchi G, Sicuteri F. Brief report: Phantom limp pain: sub-hallucinogenic treatment with lysergic acid diethylamide (LSD-25)*. Headache* 17(3), 118-119 (1977).