Journal of Pain Research

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REVIEW

Scoping Review: The Role of Psychedelics in the Management of Chronic Pain

Christopher L Robinson[1,*], Alexandra CG Fonseca[2,*], Efemena M Diejomaoh[3,*], Ryan S D'Souza[4], Michael E Schatman[5,6,*], Vwaire Orhurhu[7,8,*], Trent Emerick[9,*]

[1]Beth Israel Deaconess Medical Center, Department of Anesthesiology, Critical Care, and Pain Medicine, Harvard Medical School, Boston, MA, USA; [2]Department of Anesthesiology, Perioperative & Pain Medicine, Harvard Medical School, Brigham & Women's Hospital, Boston, MA, USA; [3]Department of Psychiatry & Behavioral Science, Meharry Medical College, Nashville, TN, USA; [4]Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Rochester, Rochester, MN, USA; [5]Department of Anesthesiology, Perioperative Care, and Pain Medicine, NYU Grossman School of Medicine, New York, NY, USA; [6]Department of Population Health-Division of Medical Ethics, NYU Grossman School of Medicine, New York, NY, USA; [7]University of Pittsburgh Medical Center, Susquehanna, Williamsport, PA, USA; [8]MVM Health, East Stroudsburg, PA, USA; [9]University of Pittsburgh Medical Center, Department of Anesthesiology and Perioperative Medicine, Chronic Pain Division, Pittsburgh, PA, USA

*These authors contributed equally to this work

Correspondence: Vwaire Orhurhu, University of Pittsburgh Medical Center, Susquehanna, Williamsport, PA, USA, Email vwo569@mail.harvard.edu

Introduction: Amid a lack of effective chronic pain treatments, psychedelics have gained attention as a potential solution, although their Schedule 1 classification poses challenges. Psychedelics, such as lysergic acid diethylamide (LSD) and psilocybin, have gained popularity as alternatives and adjuncts for chronic pain treatment. Studies suggest that they may modulate pain processing through agonism primarily at the serotonin receptor, 5-HT_{2A}. One of the first of its nature, we present an artificial intelligence (AI)-powered scoping review primarily focusing on evaluating psychedelics for chronic pain conditions such as cluster headache, phantom limb pain, and fibromyalgia.

Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, we used an AI-powered comprehensive search strategy utilizing the ChatGPT4.0 Bing chat to search Medline, Embase, Cochrane, and Google Scholar for articles addressing chronic pain. The query was performed on June 1, 2023, focusing on psychedelics for chronic, non-cancer pain including headache disorders. Inclusion criteria were English-only, peer-reviewed articles involving human participants >18 years, focusing on chronic pain conditions (eg, phantom limb pain and cluster headache), using LSD, 2.5-dimethoxy-4-bromophenethylamine (2C-B), N, N-dimethyltryptamine (DMT), psilocybin, or mescaline. Exclusion criteria were reviews, editorials, and opinion articles and studies focusing on tetrahydrocannabinol/cannabis and/or ketamine.

Results: A total of 186 unique database entries were retrieved, of which nine studies were included in the scoping review. These included four case reports/series, an open-label study, a cohort study, two online surveys, and a randomized, double-blind, placebo-controlled trial. They comprised three studies addressing phantom limb pain, four addressing cluster headaches, and two addressing fibromyalgia, spinal cord injury, complex regional pain syndrome, and lumbar radiculopathy.

Conclusion: Psychedelics may have potential in alleviating pain symptoms secondary to a multitude of chronic pain conditions. However, further randomized, double-blind, placebo-controlled trials are needed to further explore and evaluate the role of psychedelics in chronic, non-cancer pain.

Keywords: psilocybin, mescaline, lysergic acid diethylamide, headache, phantom limb pain, scoping review

Introduction

Chronic pain, defined as pain that persists for >3 months or reoccurs, is one of the leading causes of disability in the United States, affecting between 50 and 100 million people and costing annually nearly $600 billion in healthcare bills and lost economic activity alone.[1–3] Moreover, with what initially appeared to be a solution to chronic pain in the 1990s, the prescription opioid epidemic wreaked havoc on the lives of those who were affected and reportedly killed many in the United States, although there are no reliable data that allow for accurate assessment of the death toll. Furthermore, the economic cost alone attributable to the opioid epidemic was estimated at $1.5 trillion, although there are no reliable data indicating the extent to which this figure

Received: 18 September 2023
Accepted: 27 February 2024
Published: 11 March 2024

pertains to prescription vs illicit opioids.[4] The COVID-19 pandemic was found to have increased the monthly opioid overdose death rate by 45%, with illicit fentanyl and its analogues now resulting in a true epidemic.[5]

With the recent rise in the popularity of use in the treatment of chronic pain conditions, psychedelics have been considered a potential adjuvant oral pain medication or perhaps even a primary treatment for a wide variety of pain conditions given the scarcity of novel chronic pain medications.[6–9] Despite the stigma and obstacles associated with psychedelics as well as their Schedule 1 drug classification (drugs with no currently accepted medical use and a high potential for abuse) by the Controlled Substances Act, preliminary research is beginning to emerge for their use in chronic pain, though to date, there have not been sufficiently powered double-blinded, placebo-controlled, randomized clinical trials evaluating their efficacy.[10–21] Though the mechanism is not entirely understood, psychedelics, focusing primarily on the classic hallucinogens lysergic acid diethylamide (LSD) and psilocybin, function by activation of the serotonin-2A (5-HT_{2A}) receptor as antagonism of the receptor blocks the psychedelic effects.[22,23] Furthermore, 5-HT_{2A} is involved in both centrally and peripherally mediated pain as sensory nerve fibers transmitting nociceptive signals project onto the dorsal horn.[23] Activation of 5-HT_{2A} via injection of serotonin (5-HT) into the spinal cord results in anti-nociceptive effects by potentially interfering with pain signaling.[23–25] Additionally, the effect of psychedelics on pain is based on the chronicity of pain.[23] For chronic pain, early data suggest that descending 5-HT pathways have an anti-nociceptive effect which can be increased with activation.[23]

The psychedelic LSD was the first to be synthesized in 1938, although the physiological (hallucinogenic) effects remained unknown until 1943.[26] It functions by activating the serotonergic receptors (5-HT, mainly 5-HT_{2A}) with additional action on adrenergic and dopaminergic receptors, with the psychedelic effect becoming apparent with doses as low at 20 micrograms. Onset of action occurs in as little as 30 minutes and lasts for up to 9 hours.[23,27] Psilocybin, commonly referred to as magic mushrooms, is converted into the active compound psilocin, which is an agonist at the 5-HT receptors, with a high affinity for 5-HT_{2A} and a low affinity for 5-HT_{1A}.[26,28] Psychedelic effects are experienced with oral consumption of 4–10 g, occur within 10 minutes, and last up to 6 hours.[26,27]

Since 5-HT receptors are involved in the pain processing pathway such that their activation results in the inhibition of pain, the use of psychedelics as partial agonists in these same receptors may modulate how pain is processed.[23] When 5-HT is injected into the spinal cord in murine models, the resulting effects are anti-nociceptive with reduced hyperalgesia.[25] However, the effects of 5-HT activation are dependent on the specific characteristics of the pain, such as whether it is acute or chronic, and the location of activation, whether peripheral (pro-inflammatory) or central (anti-nociceptive).[25,27,29] Due to the partial agonist properties of psychedelics on the 5-HT receptor, they may induce anti-nociceptive properties immediately, while also offering long-term effects by acting peripherally and possibly reducing the inflammatory response.[30–33] However, the exact mechanism for how psychedelics may influence pain remains largely unknown, and clinical studies on the use of psychedelics for the treatment of pain remain sparse.[10–12,15–20]

Although the general term "chronic pain" will be utilized throughout this discussion, the most common causes of such pain are lower back pain, headache disorders, fibromyalgia, and neuropathic pain, and thus, the aim of this scoping review is to systematically assess the literature on the use of psychedelics for these pain conditions.[1,34–36]

Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed for this scoping review (PICO strategy in Appendix and Figure 1).[37,38] The Harvard Countway Librarian, Corey J. Purcell, was consulted and assisted in the database queries. The following databases were used for this search: Medline, Embase, Cochrane, and Google Scholar. The time frame of the search was from the database inception to June 1, 2023.

The search strategy was developed by two authors (CP and CR) and Microsoft's ChatGPT4.0 Bing chatbot, and the terms "chronic pain" and "headache" were deliberately used given the scarcity of clinical research focusing on chronic pain and psychedelics. ChatGPT4.0 Bing chatbot was used to convert the Medline search strategy for queries for Embase, Cochrane, and Google Scholar and was used to refine the search. The strategy was reviewed by all authors and was amended appropriately. To address the chronic pain conditions most often encountered by physicians, we focused

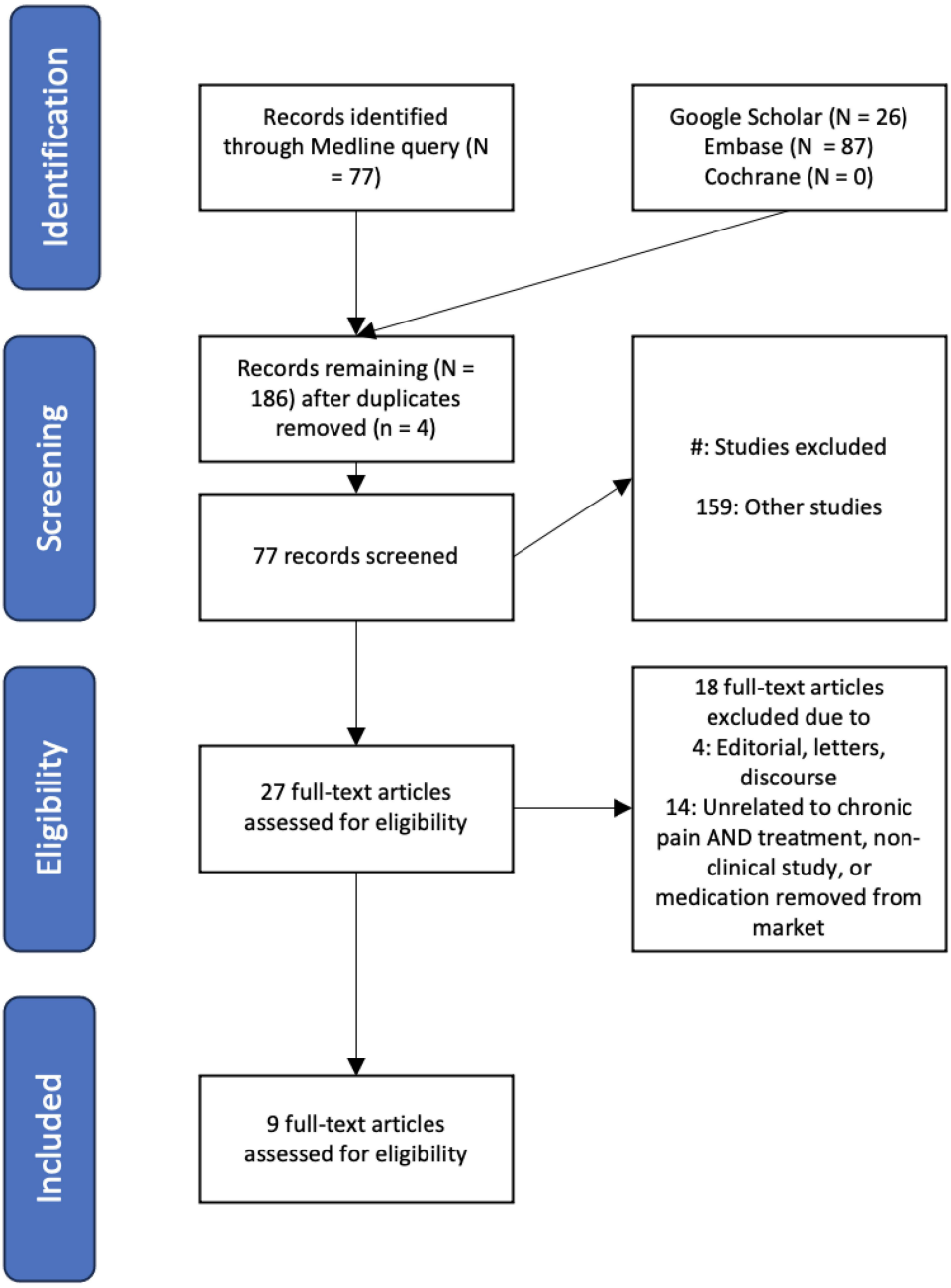

Figure 1 Flowchart overview of the scoping review analysis. Adapted from Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7). Creative Commons.[38]

our search on chronic, noncancer pain including headache disorders. The articles were required to focus on chronic pain specifically, as opposed to acute pain. Data were extracted by a single author (CR), and the scoping review was further evaluated by another author (AF). In the case of a disagreement, a third author (ED) was consulted. Critical appraisal of individual sources of evidence is optional in the PRISMA Extension for Scoping Reviews (PRISMA-ScR) check- list and was omitted for this review.[37]

The query was performed in July 2023 for Medline using the following search strategy: (Hallucinogens[mesh] OR Psychedelic[tiab] OR Psilocybin[mesh] OR Mescaline[mesh] or Lysergic Acid Diethylamide[mesh]) AND (Chronic Pain[mesh] OR Headache[mesh] or Phantom Limb Pain[mesh]).[39] Phantom Limb Pain (PLP) and Headache were

included as mesh terms, as the initial studies focused on these two conditions (search strategies for Embase, Cochrane, and Google Scholar are located in the Appendix).[18–20]

Inclusion Criteria

Inclusion criteria for the eligible studies that were analyzed for this scoping review were the following: 1. Title, article, and abstract must be published in English. 2. Article must be published in a peer-reviewed academic journal. 3. Human studies only and participants must be >18 years of age. 4. Focus on chronic pain diagnoses including headache disorders such as migraine, cluster headache, and tension headache. 5. Published since 1960, given that the research for the first clinical paper on pain and psychedelics was published in 1964. 6. Eligible studies included surveys, case reports, case series, open-label studies, and randomized LSD, 2.5-dimethoxy-4-bromophenethylamine (2C-B), N, N-dimethyltryptamine (DMT), psilocybin, and mescaline.[19] The class of psychedelics is broad and ever-growing, and the list of included psychedelics is not exhaustive. For this review, we focused on inclusion of a subset of psychedelics commonly encountered or described in the peer-reviewed literature with nine studies being eligible (Table 1).

Table 1 Studies Examining the Role of Psychedelics for the Management of Chronic Pain Conditions

Author (Year)	Study Type	Groups Studied and Intervention	Results	Conclusions
Kuromaru et al (1967)[19]	Case series	8 patients with PLP were given 1–3 doses of 50 micrograms of LSD.	No quantitative analysis was performed, but 7 out of 8 patients had resolution of some PLPS.	LSD aids in the abatement of PLPS.
Fanciullacci et al (1974)[18]	Open-label study	5 patients with PLP (3 hospitalized and 4 outpatient) were treated with a placebo daily for a week, followed by 25 micrograms daily of LSD for a week, then 50 micrograms for two weeks, and finally followed with placebo for four weeks.	No quantitative analysis was performed, but 5 out of the 7 patients had pain relief with a reduction in analgesic intake.	LSD reduces pain in PLP and reduction analgesic intake.
Ramachandran et al (2018)[17]	Case Report	Single patient with PLP following an amputation was successfully treated with mirror-visual-feedback.	Pain relief was achieved to a similar extent when comparing it to the phantom limb massage When psilocybin was administered in conjunction with MVF, the pain relief was amplified resulting in momentary, total pain relief; furthermore, there was a decrease in paroxysmal episodes.	The addition of psychedelics as adjuncts has the potential to dramatically improve the efficacy of current pain treatments.
Sewell et al (2006)[20]	Comparative study	53 patients who had consumed psilocybin and/or LSD treat their cluster headache were interviewed.	22 of 26 psilocybin users reported that it aborted attacks, while 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination. Of the psilocybin and LSD users, 18 of 19 and 4 of 5, respectively, reported remission period extension.	First paper to demonstrate the use of sub-hallucinogenic doses, for the treatment of psychedelics for cluster headaches.
Karst et al (2010)[16]	Open, non-randomized case series	5 patients with cluster headache were administered oral 30 micrograms/kg/day 2-bromo-LSD, for a dose every 5 days for a total of 3 doses.	One patient had resolution of her cluster headaches for > 6 months; two had significant reduction in attack frequency, remission for 1 month, and converted to episodic cluster headache; one patient had a significant reduction in attack frequency, but remission lasted < 1 month and she stopped taking acute headache management medications. Finally, the last patient had a profound reduction in pain unfortunately did not experience pain reduction but experienced a reduction in attack intensity.	Non-hallucinogenic, 2-bromo-LSD may have potential in treating cluster headaches.

(*Continued*)

Table 1 (Continued).

Author (Year)	Study Type	Groups Studied and Intervention	Results	Conclusions
Schindler et al (2015)[15]	Online survey	Survey was performed on 496 participants from the Clusterbuster.org website inquiring about the efficacy of indoleamine hallucinogens, and comparing them to standard of treatment.	IH were similar in efficacy if not better, and participants deemed IH able to abort a cluster headache and result in higher rates of remission from chronic cluster headaches.	IH are perceived to aid in aborting cluster headaches.
Schindler et al (2022)[12]	Randomized double-blind, placebo-controlled study	A total of 30 participants were randomized to receive either psilocybin (n = 16, 0.143 mg psilocybin/kg body weight) or placebo (n = 14) in 3 separate doses 5 days apart.	The change in cluster attack frequency was 3.2 (95% confidence interval [CI] −8.3 to 1.9) attacks/week with psilocybin compared to 0.03 attacks/week with the placebo (95% CI −2.6 to 2.6).	Psilocybin administration had no serious adverse or unexpected effects and was well tolerated.
Glynos et al (2023)[10,11]	Cross-sectional survey	A total of 354 patients with fibromyalgia were anonymously surveyed online to assess the understanding and perception of psychedelics and the interest in the use of psychedelics for fibromyalgia.	Only 29.9% of participants had reported use of a psychedelic with 59.4%, 36.8%, and < 3% having a neutral, positive, or negative perception, respectively, on the impact of health and pain. Twelve participants report intentional use for treating chronic pain with 11 noting improvement in pain symptoms.	Participants believed that psychedelics could hold promise for their pain and would be willing to participate in a clinical trial to assess this.
Lyes et al (2023)[10]	Case series	Three patients microdosed with psilocybin-containing mushrooms. The patients with chronic pain/neurological disorders were a 37-year-old male with spinal cord injury resulting in neuropathic pain, 69-year-old female with complex regional pain syndrome, and 40-year-old female with lumbar radiculopathy/neuropathic pain. Patient initiated dosing regimens varied from consuming 250, 500, or 750–1000 mg of psilocybin-containing mushrooms daily. to 1000 mg mushroom chocolate bar every 2 months.	Patients experienced up 80–100% pain relief lasting anywhere from 3–4 hours to 2–4 weeks.	This case series details the experience of these patients including the side effect and high percentage of pain relief though conclusions are limited.

Abbreviations: IH, indoleamine hallucinogens; LSD, lysergic acid diethylamide; MVF, mirror-visual-feedback; PLP, phantom limb pain; PLPS, phantom limb pain syndrome.

Exclusion Criteria

Exclusion criteria included the following: 1. Articles written in languages other than English. 2. Non-peer reviewed publications or articles not found in the aforementioned databases. 3. Studies of individuals who are ≤18 years of age. 4. Acute pain, cancer pain, or other headache disorders with the exception of those aforementioned. 5. Articles published prior to 1960. 6. Others: review, editorial, and opinion papers. 7. Articles discussing tetrahydrocannabinol/cannabis or ketamine.

Results

Phantom Limb Pain (PLP)

The first non-cancer pain study to be performed using psychedelics is a case series published in 1967 on 8 patients with phantom limb pain/sensation (PLPS) using a small dose (50 micrograms) of LSD, repeated up to 3 times.[19] The doses were given at varying times following amputation, ranging from 30 minutes to several months.[19] The participants included 1 patient with brachial plexus injury, 1 with hemiplegia, and 6 patients with a limb amputation immediately preceding treatment.[19] Although no quantitative analysis was performed, 7 of 8 patients reported some degree of resolution of their PLPS, with some ultimately reporting experiencing a return of their pain.[19] Notably, these patients initially experienced a sensation of elongation of the phantom limb (a reversal of the telescoping phenomenon) and ultimately also regained normal sensation in the proximal limb above the level of amputation.[19] At 1–2 hours, the stump felt lighter, with replacement of the PLPS with pruritus.[19] At

hours 2–3, the PLPS was less obvious, but patients did experience a sensation of shortening of the limb. In general, the patients reported disappearance of PLPS at 3–4 hours.[19]

A second study was performed almost 10 years later in 7 patients with PLP (5 males and 2 females, ranging in age from 25 to 78).[18] These 7 patients (3 inpatients and 4 outpatients) were treated with a placebo daily for one week, followed by administration of 25 micrograms daily of LSD for a week, followed by 50 micrograms for 2 weeks, and finally a placebo for an additional 4 weeks. Five of the 7 patients reported pain relief during the 8-week observation period with a reduction in analgesic agent intake.[18]

Approximately 45 years later, a patient with phantom-limb pain following an amputation was successfully treated with mirror-visual-feedback (MVF), a technique in which a mirror is placed in the midsagittal plane, allowing the patient to watch the reflection of the non-amputated limb, mimicking the movement of the amputated limb.[14,17] The pain relief achieved was similar in extent to phantom limb massage.[17] When psilocybin was administered in conjunction with MVF, the pain relief was amplified, resulting in momentary total pain relief and a decrease in paroxysmal episodes.[17]

Cluster Headache

The use of psychedelics for the management of chronic pain caused by cluster headaches was explored in a survey study that included 53 patients who had used psilocybin and/or LSD to treat their cluster headaches.[20] Of these users, 22 of 26 psilocybin users reported that it aborted headache episodes, while 25 of 48 psilocybin users and 7 of 8 LSD users reported cluster period termination.[20] Of the psilocybin and LSD users, 18 of 19 and 4 of 5, respectively, reported remission period extension.[20] This study was the first of its kind to explore the use of sub-hallucinogenic doses of psychedelics for the treatment of cluster headaches.[20]

Given that the promising results of psychedelics in treating cluster headache are limited by the hallucinogenic properties and the Schedule I controlled drug classification, a modified form of LSD was developed.[16] Alteration of the LSD compound's chemical structure (hydrogenation of the double bond in the D ring and substitution with a bromine group at the R2) results in the loss of its hallucinogenic properties.[16,40] Using this saturated and brominated version, 2-bromo-LSD, which had been previously tested in vascular headaches, an open, nonrandomized case series was performed.[16] Patients were administered orally 30 micrograms/kg/body weight of 2-bromo-LSD once every 5 days for a total of 3 doses to 5 patients (1 with episodic and 4 with chronic) cluster headaches who were resistant to conservative and/or invasive management.[16,41] One patient reported resolution of her cluster headaches for >6 months, and 2 reported significant reduction in episode frequency, remission for 1 month, and converted to episodic cluster headaches.[16] One patient reported a significant reduction in headache frequency with remission lasting <1 month but was able to discontinue acute headache management medications.[16] Finally, while the final patient reported a profound reduction in pain acutely, the patient unfortunately did not experience long-term pain reduction, although reported a reduction in attack intensity.[16]

A second survey was performed on 496 participants from the Clusterbuster.org website, an online forum in which members discuss the use of psychedelics in the treatment of cluster headaches.[15] Given that cluster headaches occur more frequently in males than females, the population distribution represented in this study has a male predominance, with participants being 73.8% male and 26.2% female.[15] Participants reported that the indoleamine hallucinogens psilocybin, LSD (double amide form), and the singular amide form, lysergic acid amide, were similar in efficacy if not better than conventional treatments.[15] Similarly, participants also reported that these compounds are able to abort a cluster headache and lead to remission from chronic cluster headaches.[15] Of note, sub-hallucinogenic doses administered at longer intervals were found to be more efficacious than higher and more regularly administered doses.[15]

In the first randomized, double-blinded, placebo-controlled study of psilocybin, its clinical efficacy was evaluated for its use in cluster headaches.[12] A total of 30 participants were randomized to receive either psilocybin (n = 16, 0.143 mg psilocybin/kg body weight) or placebo (n = 14) in 3 separate doses 5 days apart.[12] To set a baseline, the patients documented their headaches 2 weeks prior to the initial dose and for 8 weeks following the initial dose.[12] The reduction in cluster attack frequency was 3.2 attacks/week (95% confidence interval [CI] −8.3 to 1.9) in the active drug treatment group compared to 0.03 attacks/week in the placebo group (95% CI −2.6 to 2.6).[12] Of note, the changes in cluster attack frequency had no correlation with the intensity of acute hallucinogenic effects.[12] Moreover, psilocybin administration reportedly resulted in no serious adverse or unexpected effects and was well tolerated.[12]

Fibromyalgia

Given the limited number of studies on chronic pain, a cross-sectional, anonymous online survey was performed to assess the understanding and perception of psychedelics as well as interest in the use of psychedelics for fibromyalgia.[11] Of the 354 participants surveyed, 29.9% had reported use of a psychedelic with 59.4%, 36.8%, and <3% having a neutral, positive, or negative perceptions, respectively, on their impact of health and pain.[11] Interestingly, 12 participants reported intentional use for treating chronic pain, with 11 noting improvement in pain symptoms.[11] Most notably, participants believed that psychedelics could hold promise for managing their pain and that they would be willing to participate in a clinical trial to assess this possibility.[11]

Neuropathic Pain

The most recent case series on psychedelics being used for the treatment of chronic pain included 3 patients and attempted to characterize the onset and duration of psilocybin microdosing for various chronic pain disorders.[10] These 3 patients were described as such: a 37-year-old male with spinal cord injury resulting in neuropathic pain, a 69-year-old female with complex regional pain syndrome, and a 40-year-old female with lumbar radiculopathy/neuropathic pain.[10] Patient-initiated dosing regimens varied from consuming 250, 500, or 750–1000 mg of psilocybin-containing mushrooms daily to consuming a 1000 mg mushroom chocolate bar every 2 months.[10] Patients reported up to 80–100% pain relief lasting anywhere from 3–4 hours to 2–4 weeks.[10] This case series details the experience of these patients, including the side effects and high percentage of pain relief achieved, although conclusions are quite limited based on this study alone.[10]

Discussion

As chronic pain conditions lead to significant disability and economic losses, more progress is needed in establishing safe, effective, and non-invasive treatments. The 1990s were significant for the rise of prescription opioid medication use in an effort to improve the lives and function of patients suffering from chronic pain. However, prescription opioid use has been limited by concerns for Opioid Use Disorder, lack of long-term therapeutic benefit, as well as the downstream concerns. Though psychedelics are not addictive and have their side effects that occur mainly with overdose (harm to self/others, hallucinations, neurotoxicity, and hypertension), the risks are reduced significantly with the sub-hallucinogenic doses which many of the studies used.[42] Our extensive literature review highlights much of the currently existing data that suggest a possible role of psychedelics in treating chronic pain conditions.

Psychedelics are a largely unexplored alternative avenue for possible development as a pain medication. Despite several surveys suggesting that psychedelics may offer pain relief, conclusions drawn from these types of survey studies need to be made cautiously due to the potential bias of subjects.[11,15,20] The case reports, case series, and open-label studies focusing on psychedelics hint at some activity in reducing pain, but without an adequate and proper control, no strong interpretation can be made.[10,16–20] Furthermore, their use is limited by the lack of sufficiently powered double-blinded randomized clinical trials, and publication bias given that only articles in English were evaluated. In the first randomized, double-blinded, placebo-controlled study of psilocybin there was a trend towards significance, although due to the limited number of participants, there was no statistical significance in using psilocybin for the treatment of cluster headaches.[12] Interestingly, these studies observed extended pain relief even after psychedelic administration has ceased. This observation may be due to their activity at the 5-HT receptor providing not only immediate, short-term pain relief by acting centrally on the nervous system, but additionally, long-term pain reduction by acting peripherally, potentially reducing inflammation.[23] Further trials utilizing the sub-hallucinogenic doses of these agents are needed as higher doses would limit the wide applicability of psychedelics.

The use of psychedelics for the management of mental health disorders has had a renewed interest with research demonstrating beneficial effects on anxiety and depression to post-traumatic disorder.[43–45] Moreover, there is an association with mental health disorders and chronic pain with studies reporting up to 75% of patients with chronic pain having co-morbid mental health disorders and increased improvement of chronic pain with concomitant treatment of mental health disorders.[46,47] Though speculative at the moment given the limited data between mental health, chronic pain, and psychedelics, future research should consider the effect that psychedelics may have on patients with both chronic pain and mental health disorders.

Conclusion

Despite new developments in therapeutic devices and minimally invasive procedures for chronic pain, pharmacotherapeutic options currently utilized remain more limited than pharmaceutical companies would lead patients and physicians to believe. Psychedelics, such as LSD and psilocybin, may offer a potential alternative option for those patients suffering from chronic pain if used under the appropriate clinical guidance and environment. Their use is limited by their classification as a Schedule I substance, along with heroin, which severely limits use both in research and for patient care and affects their perception and acceptance by the public, regulators and healthcare providers. In the face of this classification, there has been a recent boom in interest in psychedelics. These studies demonstrate the interest patients have in exploring psychedelics as a viable alternative treatment, as well as calling into question whether the stigma surrounding these substances will remain a significant barrier to their use.

Acknowledgment

Michael E Schatman, Vwaire Orhurhu, and Trent Emerick are co-senior authors for this study. We would like to thank Harvard Medical School Countway Librarian, Corey J. Purcell, BA MLIS, for his assistance in designing the initial search strategy for PubMed. The final acknowledgment goes to a special woman who believed when no one else would. Through her sweat and tears, the world is better off. May your sacrifice never be in vain, as we are here to treat pain.

Disclosure

Dr Christopher Robinson reports personal fees from TrueLearn, Doc2Doc, Augmend Health, outside the submitted work. Dr Michael Schatman is a research consultant for Modoscript, scientific steering committee for Collegium Pharma, and advisory committee for Syneos Health, outside the submitted work. Dr Trent Emerick reports stock/equity for Vanish Therapeutics, Inc, outside the submitted work. The authors report no other conflicts of interest in this work.

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