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Use Of Psilocybin And Other Classic Psychedelics In Fibromyalgia: A Survey Study

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USE OF PSILOCYBIN AND OTHER CLASSIC PSYCHEDELICS IN FIBROMYALGIA: A SURVEY STUDY

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MEDICAL/CLINICAL PSYCHOLOGY

ABSTRACT

Psilocybin and other classic psychedelics may have potential for treatment of fibromyalgia, a chronic condition characterized by widespread musculoskeletal pain and other symptoms including fatigue, cognitive difficulties, and sleep problems. In this exploratory, descriptive study, an online survey was distributed among individuals with fibromyalgia to gather reports of any changes in pain related to past classic psychedelic use. Sixty-four participants with fibromyalgia completed the study, with most having used psilocybin mushrooms or LSD. In addition to recreational use and other reasons, use of psychedelics for mental health or pain-related reasons was frequently endorsed. Of the participants who reported experiencing any change in pain with past psychedelic use (n = 36), most (n = 32 or 88.9%) described an acute reduction in pain. Many participants (n = 25 or 69.4%) reported lingering improvements in pain lasting one to two days, sometimes up to several weeks or longer, and a subset of participants (n = 11 or 30.6%) noted a decreased need for pain medications following use. Results add to a small but growing body of work suggesting promise for classic psychedelics such as psilocybin for chronic pain.

Keywords: fibromyalgia, chronic pain, psilocybin, classic psychedelic

DEDICATION

I dedicate this work to my godmother.

ACKNOWLEDGMENTS

I would like to acknowledge the support and guidance of my research mentor and committee members, as well as the support from my family, friends, and partner. I would also like to thank each of the individuals who participated in this study, and all of those who assisted with recruitment efforts.

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INTRODUCTION

Fibromyalgia (FM) presents with a range of symptoms including chronic widespread musculoskeletal pain, fatigue, cognitive difficulties, and sleep problems (Wolfe et al., 2010). Affecting up to 6.6% of the general population (Marques et al., 2017) , the syndrome can carry substantial disability and socioeconomic burden (Lacasse et al., 2016). Current standard pharmacologic treatments include serotonin and norepinephrine inhibitors (duloxetine and milnacipran) and the gabapentinoid pregabalin, although these medications are not effective for most individuals (Okifuji et al., 2016; Schmidt-Wilcke & Diers, 2017). Identification of more effective treatments is strongly needed. Classic psychedelics such as psilocybin have potential for treatment of chronic pain conditions like FM (Castellanos et al., 2020; Elman et al., 2022; Whelan & Johnson, 2018). In this introduction, a review of FM characteristics, the current state of treatment, and research on associated mechanisms will first be presented. A summary of psilocybin and its psychopharmacology will follow, with a subsequent discussion of classic psychedelics as potential treatments for pain and FM. An overview of the present study will then be described.

Fibromyalgia

Characteristics

FM is a multi-symptom pain condition affecting about 4 million people in the United States (Walitt et al., 2015). FM often leads to significant impairments in physical abilities and detrimental impacts on psychological and social well-being (Galvez-Sanchez et al., 2019). Characterized primarily by chronic widespread pain, the condition is often accompanied by persistent fatigue, unrefreshing sleep, and cognitive dysfunction (Wolfe et al., 2016). FM pain can encompass both allodynia (pain in response to typically non-painful stimuli, such as touch) and hyperalgesia (augmented pain sensitivity). Mood problems, autonomic disturbances, headaches, abdominal pain, muscle stiffness, and sensory hypersensitivity are also common. Prevalence of FM tends to increase with age (Walitt et al., 2015) and is most commonly diagnosed in middle adulthood.

Women represent approximately 90% of those diagnosed clinically (Yunus, 2002); however, research has shown bias among clinicians towards diagnosing FM in women (Srinivasan et al., 2019; Wolfe et al., 2019) and individuals with greater psychological distress (Wolfe et al., 2019). Many individuals who meet self-report criteria for FM do not have a formal diagnosis from a healthcare provider (Walitt et al., 2015). Among unbiased samples using self-report criteria, women are estimated to represent about 60% of those with FM (Wolfe et al., 2018). Although diagnoses are most frequent among white women, a national survey study of 8446 people yielded no difference in prevalence among non-Hispanic white, non-Hispanic Black, and Hispanic individuals, lower prevalence in Asian Americans, and greater prevalence in individuals identifying as another or more than one race (Walitt et al., 2015).

Diagnosis

There is no biomarker or gold standard for FM diagnosis, and the diagnostic criteria have evolved over the past three decades. Patients often spend years after the onset of symptoms before receiving a diagnosis, with the average time to diagnosis being over six years (Gendelman et al., 2018). The American College of Rheumatology (ACR) published diagnostic criteria in 1990 which required the presence of at least 11 out of a possible 18 tender points, in addition to self-reported widespread chronic pain for at least three months (Wolfe et al., 1990). The tender point exam is conducted by a physician and determines the threshold at which individuals experience pain in response to pressure applied at various sites on the body, using an algometer. The emphasis on a tender point exam was dropped by the ACR in 2010, who then introduced the use of a widespread pain index (WPI) and a symptom severity scale (SSS) (assessing severity of fatigue, cognitive difficulties, and unrefreshing sleep, and the presence of headaches, abdominal pain, and depression). The 2010 criteria also required the absence of another disease or condition that would explain the musculoskeletal pain (Wolfe et al., 2010). Intended primarily for use in research, additional revisions were introduced in 2011 which enabled FM case criteria to be met entirely via self-report (Wolfe et al., 2011).

In 2016, a further revised set of criteria were published, designed for both clinical and research use (Wolfe et al., 2016). The 2016 revisions kept the symptom scores from 2010/2011 but abandoned the exclusionary criterion of having other conditions that may contribute to pain. With that change, a FM diagnosis could be “valid irrespective of other diagnoses” and “does not exclude the presence of other clinically important illnesses” (Wolfe et al., 2016).

There is increasing recognition that FM symptoms exist on a continuum, with the higher end of polysymptomatic distress associated with worsened outcomes. A polysymptomatic distress scale for "fibromyalgianess" can be calculated by summing the WPI and SSS scores of the ACR criteria. This method provides a continuous FM severity scale ranging from 0-31 that can aid with both assessment of symptoms and severity change over time (Wolfe & Rasker, 2021).

Misdiagnosis of FM occurs for a variety of reasons, including but not limited to the lack of an objective diagnostic test. In a 2016 study of national survey data, the majority of those reporting a clinical (physician-based) diagnosis of FM (73%) did not actually meet the study's surrogate criteria for diagnosis (Walitt et al., 2015). Further, many individuals who meet self-report-based diagnostic criteria are not clinically diagnosed. For example, in a 2019 study of over 3000 primary care patients, only one third who met ACR criteria had a clinical diagnosis (Srinivasan et al., 2019). Problems with misdiagnosis were also observed in a 2019 study of approximately 500 rheumatology clinic patients that compared rates of clinician and ACR criteria (Wolfe et al., 2019). Given biases toward diagnosing FM in women and individuals with increased psychological distress, these discrepancies may reflect misinterpretation of patient symptom reports by providers. It is also possible that at the time a clinical diagnosis was made, an individual met ACR criteria, but after receiving treatment their symptoms improved such that the criteria were no longer met (Wolfe & Rasker, 2021). Misdiagnosis may also occur in the early stages of rheumatic diseases (e.g., preclinical rheumatoid arthritis, inflammatory spondylarthritis), prior to the emergence of abnormal laboratory or physical exam findings. Neurological disease, metabolic and endocrine

disorders, gastrointestinal disease, infectious illnesses (e.g., Lyme disease, hepatitis C), and early stages of cancers can also mimic FM (Hauser et al., 2019).

Comorbidities and Overlapping Conditions

Among individuals with FM, rates of comorbid medical and mental health conditions are generally higher than in individuals without fibromyalgia (Walitt et al., 2015). For example, hypertension, myocardial infarction, diabetes, asthma, liver disease, and other medical illnesses occur more than twice as commonly in FM compared to individuals without FM (Walitt et al., 2015). Many chronic pain and fatigue illnesses have overlapping symptoms with FM and are commonly comorbid (e.g., chronic fatigue syndrome/myalgic encephalomyelitis [CFS/ME] (Rusu et al., 2015), irritable bowel syndrome [IBS] (Kleykamp et al., 2021), temporomandibular disorder [TMD] (Kleykamp et al., 2021), chronic migraines and tension-type headaches (Kleykamp et al., 2021), interstitial cystitis (Reed et al., 2012), and vulvodynia (Reed et al., 2012)). About one in five people with FM reported also having CFS/ME in a nationally representative Canadian health survey (Rusu et al., 2015). In a systematic review of comorbid chronic pain conditions in FM, weighted lifetime prevalence rates were estimated at 39% for low back pain, 44% for IBS, 48% for migraine, 56% for chronic tension-type headache, and 57% for TMD among FM patients (Kleykamp et al., 2021).

Psychiatric conditions such as mood and panic disorders also present frequently in FM (Hudson et al., 1992; Kleykamp et al., 2021; Walitt et al., 2015). A systematic review of studies that used structured clinical interviews suggested a point prevalence of 25%, and a life-time prevalence of 65%, of comorbid major depressive disorder (MDD) in FM

(Loge-Hagen et al., 2019). Similar rates were confirmed in a later review (Kleykamp et al., 2021). These rates are higher than those found in the general US adult population (in which 12-month and lifetime prevalence of MDD have been estimated as 10.4% and 20.6%, respectively (Hasin et al., 2018)). Prevalence of depressive symptoms and disorders in FM are comparable, however, to those observed in other chronic pain conditions such as TMD, chronic back pain, neck pain, and abdominal pain (Hooten, 2016). In addition to depression, elevated rates of current comorbid anxiety (30%) and posttraumatic stress disorder (39.1%) have been observed in FM (Kleykamp et al., 2021). Bipolar disorder also may occur more frequently in those with FM. A review including 4 case-control studies reported a pooled odds ratio of 7.55 [95% confidence interval (CI) =3.9-14.62] for bipolar disorder in patients with FM compared to non-FM patients (Kudlow et al., 2015) .

Impact

A number of quality-of-life domains are impacted by FM. In a survey study with 800 patients (Choy et al., 2010), individuals reported moderate to strong impact of FM symptoms on most aspects of their quality of life (including mood, sex life, ability to care for family and children, personal relationships, etc.). Approximately a fifth of patients were unable to work, and a quarter of patients missed substantial time at work due to their symptoms. Individuals with FM often experience feelings of isolation in attempting to manage their symptoms on a day-to-day basis in the context of family, work, and social roles (Galvez-Sanchez et al., 2019). The impact of FM is also compounded by the

uncertainty and stigma of dealing with what many consider an “invisible”, “mysterious”, and “unexplained” illness.

Coping Styles/Beliefs

As in other chronic pain and health conditions, coping styles/beliefs influence the symptom severity, functioning, and quality of life among patients with FM. Increased scores on pain catastrophizing measures have been associated with higher symptom severity, worse functional outcomes, depressive symptoms, greater attention directed towards pain, and disability in FM (Edwards et al., 2006). Exactly what pain catastrophizing represents has been debated, and individuals with chronic pain often describe the term as stigmatizing, given implications of pain being exaggerated, not real, or all in one’s head (Amtmann et al., 2018). Multiple definitions of pain catastrophizing have been proposed, including, most traditionally, patterns of negative thoughts or appraisals related to pain and its current and future impact, accompanied by magnification of and rumination on pain, and a sense of helplessness. Catastrophizing has also been suggested as an emotional regulation strategy that interacts with personality traits and is related to activation of the behavioral inhibition system, leading to increased avoidant behaviors (Petrini & Arendt-Nielsen, 2020). Avoidant coping, including avoidance of activity, is associated with worse function (Galvez-Sanchez et al., 2019). Conversely, increased acceptance of pain (Tangen et al., 2020) and higher perceived self-efficacy (Van Liew et al., 2013) have been correlated with improved mental health, reduced symptom severity, and less FM adverse impact.

Treatment

There is no cure or highly effective treatment for FM. At present, treatment recommendations focus on multidisciplinary approaches combining both pharmacologic and nonpharmacologic methods from a biopsychosocial perspective.

Three medications are approved by the U.S. Food and Drug Administration (FDA) for FM treatment, including duloxetine, milnacipran, and pregabalin. Both duloxetine and milnacipran are serotonin (5-HT) and norepinephrine (NE) reuptake inhibitors (SNRIs). Pregabalin is an anticonvulsant that binds to the alpha2-delta (α2-δ) subunit of voltage-gated calcium channels, modulating release of excitatory neurotransmitters such as glutamate and substance P. These treatments have modest treatment efficacy, with a minority of patients benefiting significantly (Derry et al., 2016; Welsch et al., 2018).

Though only three drugs are approved by the FDA for use in FM, many other medications are prescribed off-label, including the SNRI amitriptyline and other antidepressants, gabapentin (an anticonvulsant drug similar to pregabalin), non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and opioid analgesics. Low dose naltrexone (LDN) has shown promise in small pilot studies for FM pain (Younger & Mackey, 2009; Younger et al., 2013) and has also been prescribed off-label for treatment in FM. As a toll-like receptor 4 (TLR-4) antagonist, LDN is suspected to ameliorate symptoms via microglial modulation and reduction of proinflammatory cytokines (Parkitny & Younger, 2017; Patten et al., 2018). Though LDN may be helpful for some in reducing symptoms of FM, larger clinical trials are still needed. NSAIDs are generally not considered useful for FM symptoms (Derry et al., 2017). Given the significant risks

associated with long-term use and the lack of evidence for benefit in FM, opioids are also not typically recommended (Goldenberg et al., 2016).

In addition to pharmacologic treatment, aerobic exercise, cognitive behavioral therapy (CBT), and multicomponent therapy (combined exercise and psychological therapy) are recommended by multiple guidelines (Ablin et al., 2013). Despite numerous treatments available for FM, their efficacy remains limited, underscoring the need for new and more effective treatments.

Etiological Research

FM's etiology remains unknown. Investigations into pathophysiological causes initially focused on peripheral muscle mechanisms. Etiological research later shifted its focus largely to the central nervous system (CNS). Despite the absence of evidence pointing towards a clear causal mechanism, central sensitization has been hypothesized to drive the persistence of FM pain (Meeus & Nijs, 2007). Psychological factors have also long been considered to play a role in the development, course, and impact of FM. Several hypothesized causes and psychophysiological correlates are presented in this section. Rather than a single causal mechanism, FM likely develops due to numerous, interconnected factors.

Fibromyalgia as a Mental Illness

The extent to which psychological factors are involved has been, and continues to be, controversial. Early reports conceptualized FM (or "fibrositis") as a form of psychoneurosis, a psychosomatic manifestation, or "psychogenic rheumatism" (Boland,

1947; Reynolds, 1978). Others have hypothesized FM as a variant of depression (Alfici et al., 1989), a masked or muted depression, or a somatoform pain disorder. Such explanations have since been rejected (Ahles et al., 1987; Hauser & Fitzcharles, 2018; Hauser & Henningsen, 2014). Though depression and other psychiatric illnesses overlap with FM and are common comorbid conditions, most individuals with FM do not experience simultaneous depression. In sum, despite a great deal of investigation directed towards the topic, there remains no compelling evidence of FM to be a psychiatric disorder.

Hudson and Pope (2004) posited FM as part of a family of affective spectrum disorders, emphasizing the overlap, common comorbidity, and frequent familial aggregation with other disorders involving chronic pain (IBS, headaches, facial pain, etc.), chronic fatigue (CFS/ME), and psychiatric conditions (e.g., major depressive disorder, panic disorder). They suggested that the disorders are all driven at least partially by a shared underlying pathophysiology, given similar beneficial treatment responses from antidepressants. Yunus (2007) suggested central sensitivity (or sensitization) as a uniting factor for FM, CFS/ME, IBS, and other overlapping syndromes, but did not include mood and other psychiatric disorders within this umbrella.

Central Sensitization

Central sensitization is posited as an amplification of nociceptive signaling in the brain and spinal cord, promoting decreased thresholds for pain and heightened response to painful stimuli (Meeus & Nijs, 2007). Quantitative sensory testing (QST) has been used to explore differences in sensory function among FM patients compared to healthy

controls and other clinical populations. Temporal summation and conditioned pain modulation are two methods thought to provide evidence of central sensitization. Temporal summation is a QST paradigm in which noxious stimuli are repeatedly applied, provoking an enhanced perception of pain, a response similar to the wind-up phenomenon observed in animals. Wind-up is an augmented excitatory response that occurs due to abnormal activity of C-fibers in the spinal dorsal horn. Enhanced temporal summation has generally been reported more in individuals with FM than in healthy controls (O'Brien et al., 2018).

Other researchers have posited dysfunction in central pain processing occurring at the supraspinal level. Conditioned pain modulation is measured using a QST paradigm in which a test stimulus (e.g., heat) and a conditioning stimulus (e.g., cold-water immersion) are applied concurrently, which typically lowers perception of pain. This phenomenon is thought to result from inhibitory pain mechanisms. Inhibitor pain mechanisms are monoaminergic pathways that descend from the midbrain to block nociceptive messages in the spinal cord. Conditioned pain modulation is lower among individuals with FM, when compared to healthy controls, suggesting diminished inhibitory processes (Julien et al., 2005; O'Brien et al., 2018).

Neurotransmitter Dysfunction

Abnormalities in neurotransmission underlying endogenous pain facilitative and inhibitory processes have also been observed in FM. Alterations in serotonergic, noradrenergic, and dopaminergic systems likely play a role not only in FM pain but also other symptoms, such as sleep and mood difficulties. Decreased serotonergic and

noradrenergic activity has been suggested, given the reduced levels of norepinephrine and serotonin metabolites found in the cerebral spinal fluid (CSF) of FM patients compared to controls (Russell et al., 1992). The use of SNRIs in FM supports this premise, as they increase levels of both serotonin and norepinephrine (Welsch et al., 2018). Decreased dopaminergic function has also been posited. When compared to healthy controls, FM patients have shown reduced D_2/D_3 receptor availability in some brain regions (Albrecht et al., 2016; Wood et al., 2007) and have demonstrated abnormal dopaminergic responses to painful stimuli (Wood et al., 2007) .

Abnormalities in endogenous opioid activity and differences in levels of excitatory neurotransmitters have also been reported in FM when compared to non-FM patients. High levels of enkephalins have been found in the CSF of individuals with FM (and of individuals with low back pain) compared to controls (Baraniuk et al., 2004). Decreased opioid receptor binding in the brain has also been observed in FM (Harris et al., 2007). Substance P, an excitatory modulator of spinal nociceptive transmission, is elevated in CSF of individuals with FM compared to those without FM (Russell et al., 1994). Further, increased levels of the excitatory neurotransmitter glutamate have been found in the CSF and brains of FM patients (Pyke et al., 2017; Sarchielli et al., 2007). In support of a potential role for glutamate in FM, some patients experience reduced pain following treatment with N-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine (Pastrak et al., 2021).

Stress

FM has been hypothesized as a stress-related disorder (Van Houdenhove & Egle, 2004). A history of physical and psychological stressors has been associated with FM and chronic widespread pain in numerous studies (Kaleycheva et al., 2023; Yavne et al., 2018), and stressful events have been reported to precipitate FM onset by a subset of patients. For example, in a study of 939 patients with FM, 27% of individuals reported one or more precipitating events. Of those that identified a precipitating event, the majority reported physical trauma (e.g., motor vehicle accidents, surgeries, childbirth, etc.), and one fifth identified infectious illnesses (e.g., respiratory infection, Epstein-Barr virus, etc.) as triggering events (Jiao et al., 2015). Elevated rates of PTSD have been reported in individuals with FM (Hauser et al., 2013; Raphael et al., 2006). Evidence for FM as a stress-related disorder further stems from abnormal findings in the stress response system. Lower basal cortisol levels in FM have been observed in some studies (Gonzalez-Vives et al., 2020; Riva et al., 2010), though not all (Tak et al., 2011), and evidence of reduced heart rate variability and increased sympathetic activity in FM has been described (Meeus et al., 2013; Tracy et al., 2016).

Small Fiber Pathology

Another area of FM research concerns small fiber pathology, as several studies have shown that a subset of patients with FM have small fiber neuropathy (Giannoccaro et al., 2014; Oaklander et al., 2013). Skin biopsy results showing reduced intraepidermal nerve fiber density have been observed (Kosmidis et al., 2014) and may be related to

increased FM severity in some patients (Evdokimov et al., 2019). Reduced diameter of dermal C-fibers has also been reported (Doppler et al., 2015).

Genetics

Studies finding strong familial aggregation of FM have lent support to a role for genetics (Arnold et al., 2004). A large-scale genetic study estimated heritability of FM at 13.9%, with higher rates estimated among younger age groups and lower heritability with older age (Dutta et al., 2020). Genetic factors have been proposed to contribute to up to 50% of the risk of developing FM, and epigenetic changes have been hypothesized as mechanisms involved in FM onset (D'Agnelli et al., 2019).

Multiple candidate gene polymorphisms that could influence pain processing have been suggested. For example, FM has been associated with polymorphisms of genes important for serotonergic function, including the 102T/C polymorphism in the serotonin 2A receptor gene (HTR2A), which was associated with FM susceptibility in one study (Lee et al., 2012). Polymorphisms in the serotonin transporter gene (SLC6A4) have also been associated with FM in some studies (D'Agnelli et al., 2019), and have been related to differences in conditioned pain modulation/inhibitory processes (Lindstedt et al., 2011).

Alterations in the trace amine-associated receptor 1 (TAAR1) gene, which could impact pain sensitivity via modulation of dopaminergic receptor activity (Xie & Miller, 2009), have also been associated with FM (Smith et al., 2012). Given the catechol-O-methyltransferase (COMT) gene's role in metabolism of catecholamines, alterations in the COMT gene could impact the modulation of pain perception. Findings related to

COMT gene variants in FM, however, have been inconsistent (Lee et al., 2012). Other potential candidate genes have included the transient receptor potential vanilloid channel 2 gene (TRPV2), the myelin transcription factor 1 like gene (MYT1L), and the neurexin 3 gene (NRXN3) (D'Agnelli et al., 2019). TRPV2 is expressed on dorsal root and trigeminal ganglia neurons and is involved in mechano- and thermosensation (Shibasaki, 2016). MYT1L is involved in neuronal differentiation and has been associated with cognitive disability (D'Agnelli et al., 2019). Changes in NRXN3, a gene involved in cell recognition and adhesion, could be involved in pain by influencing signal transmission in the CNS (Docampo et al., 2014).

Immune Dysregulation

Immune and neuroimmune dysregulation has also been posited as a mechanism for FM. In a positron emission tomography (PET) imaging study using a translocator protein (TSPO) radioligand, increased microglial activation was observed among individuals with FM compared to healthy controls (Albrecht et al., 2019). Differences in peripheral pro-inflammatory (tumor necrosis alpha [TNF-α], interleukin [IL]-6, IL-8) and anti-inflammatory (IL-10) cytokines have also been reported (O'Mahony et al., 2021). Sex hormones are known to be involved in pain processing (Gregus et al., 2021) and sex-specific immune responses may contribute to the increased prevalence of FM among women (Meester et al., 2019).

Psilocybin

Psychedelics refer to psychoactive substances that induce significant perceptual, cognitive, and affective changes during acute drug action. The complex and unique nature of such changes has been compared to that experienced during dreams, extreme states such as psychosis, and religious and spiritual experiences. As a classic psychedelic, psilocybin is thought to elicit such effects primarily via agonistic activity at the serotonin type 2A receptor. Lysergic acid diethylamide (LSD), dimethyltryptamine (DMT) of ayahuasca, and mescaline from the peyote cactus are examples of other classic psychedelics. Classic psychedelics have also been known as hallucinogens (a less favored term given the implication of hallucinations as a principle effect), entheogens (meaning "to generate the divine within", referring to the association with spiritual and religious experiences), and psychotomimetics (referencing the provocation of a psychotic-like state) (Nichols, 2016). Seeking an alternative to psychotomimetic, Humphrey Osmond introduced the term psychedelic (meaning "mind-manifesting") in 1957 (Osmond, 1957).

Natural and Synthetic Sources

Psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine or 3-[2-(dimethylamino)ethyl]-1*H*-indol-4-yl dihydrogen phosphate) and its active metabolite psilocin (4-hydroxy-*N,N*-dimethyltryptamine or 3-[2-(dimethylamino)ethyl]-1*H*-indol-4-ol) are tryptamine alkaloids with structures closely resembling that of serotonin (Fricke et al., 2019). Psilocybin is naturally produced by over 200 species of mushrooms. More than 150 of the fungal species belong to the genus *Psilocybe*, though species from other genera (e.g., *Gymnopilus*, *Panaeolus*, *Pluteous*, *Conocybe*, *Copelandia*, *Inocybe*) also

contain psilocybin. More than half of the known *Psilocybe* mushrooms grow in Central and South America, with some species common to continents across the world (e.g., *P. cubensis*, *P. cyanescens* and *P. semilanceata*) (Guzmán, 2009). Psilocybin and psilocin are biosynthesized from the amino acid tryptophan in a series of steps, a process first described in 1968 (Agurell & Nilsson, 1968), the understanding of which has since been refined (Fricke et al., 2019). Concentration of psilocybin and psilocin typically range from 0.2% to 1% by dry weight (Tyls et al., 2014), varying by mushroom species, size, part (e.g. cap, stem, mycelium), age, and other factors. Fresh or dried mushrooms are typically eaten whole, crushed into a powder, mixed with other foods such as chocolate, or steeped in boiling water or tea for consumption.

Synthetic psilocybin is the predominant form of the substance utilized in clinical research at present. Pure psilocybin appears as a white crystalline powder (Geiger et al., 2018). The Swiss chemist Albert Hofmann and his colleagues first isolated psilocybin and psilocin from *P. mexicana* in the late 1950s (Hofmann & Troxler, 1959). They also were the first to structurally identify and chemically synthesize the compounds. Hofmann's employer, Sandoz pharmaceutical company, produced and sold synthetic psilocybin, marketed as Indocybin, for use in psychedelic-assisted therapy and research during the 1960s (Geiger et al., 2018). Hofman and colleagues' protocol for synthetic production starts with 4-hydroxyindole and later involves phosphorylation of psilocin into psilocybin; several adjustments to the protocol have since been made to increase yield. Most psilocybin used in research currently is created from chemical synthesis. Procedures for in-vitro enzymatic and heterologous in-vivo production (e.g., from yeast (Milne et al., 2020)) have also been published (Fricke et al., 2019).

Pharmacodynamics

Psilocin, the active metabolite of psilocybin, is a partial agonist of the 5-hydroxytrypamine (serotonin) type 2A ($5HT_{2A}$) receptor, an excitatory G-protein coupled receptor widely distributed in the human brain, especially in the cortex (Beliveau et al., 2017). In addition to its strong binding potential for $5HT_{2A}$ receptors, psilocin has strong binding potential for serotonin type -1D, -1B, -1C, -5, -6, and -7 receptors, and moderate binding potential for type -1A and -1B receptors (Geiger et al., 2018). $5HT_{2A}$ receptors are densely expressed in the claustrum and on layer V pyramidal neurons of the prefrontal cortex (PFC) (Nichols et al., 2017). $5HT_{2A}$ receptors are also located on cortical and subcortical inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons and expressed presynaptically on thalamocortical afferents to the PFC (Vollenweider & Preller, 2020). Psilocin also inhibits the serotonin transporter (SERT) and exerts activity at histamine, alpha-2A and -2B, and dopamine-3 (D3) receptors (Geiger et al., 2018).

Psilocin's psychedelic effects primarily derive from its actions at the $5HT_{2A}$ receptor. In animals trained with psilocybin, administration of a selective $5HT_{2A}$ receptor antagonist (M100907) blocks stimulus control (Winter et al., 2007). Further, $5HT_{2A}$ receptor knockout mice given psilocin do not produce the characteristic head twitch response, considered a behavioral proxy for human psychedelic effects (Halberstadt et al., 2011). In humans, pretreatment with the $5HT_{2A/2C}$ receptor antagonist ketanserin or the mixed $5HT_{2A}/D_2$ antagonist risperidone dose-dependently blocks most psilocybin-induced effects (Vollenweider et al., 1998). Further, in a PET study, the intensity of

psychedelic effects was correlated with plasma psilocin levels and $5HT_{2A}$ receptor occupancy (Madsen et al., 2019).

Psilocin modulates neural activity through multiple sites of action and downstream effects. For example, preclinical research has shown that the compound inhibits activity of the dorsal raphe nucleus by $5HT_{1A}$ autoreceptor agonism (Aghajanian & Hailgler, 1975). In the rat, administration of psilocybin increases expression of several immediate early genes associated with synaptic plasticity, particularly in the PFC (Jefsen et al., 2021). In the human brain, neuroimaging research with psilocybin has indicated acute excitatory effects (increased glucose metabolism, blood perfusion) in areas associated with cognition, memory, and emotional processing (PFC regions and medial temporal lobe) (Vollenweider & Preller, 2020). Psilocin leads to region-dependent relative changes in glutamate, specifically increases in the medial PFC and decreases in the hippocampus (Mason et al., 2020). Alterations in functional connectivity have also been observed. Plasma psilocin level and subjective drug intensity have been negatively correlated with acute reductions in brain network integrity (e.g., of the default mode network [DMN]), and enhanced connectivity across networks (Madsen et al., 2021).

Pharmacokinetics

Psilocybin is a prodrug that undergoes first-pass dephosphorylation rapidly after ingestion. Dephosphorylation occurs in the acidic environment of the stomach or by alkaline phosphatase or other nonspecific esterases in the gut, transforming into the active metabolite psilocin (Dinis-Oliveira, 2017). The bioavailability of psilocin is estimated as 50% after oral psilocybin ingestion (Hasler et al., 1997). Psilocin is lipid soluble and able

to cross the blood-brain barrier. It is detectable in plasma within 20-40 minutes. Plasma levels reach peak concentrations at about 80 to 105 minutes, remaining relatively stable for approximately 50 minutes. This plateau is followed by a slower decline ending at about 6 hours (Hasler et al., 1997; Passie et al., 2002). In a clinical study with doses of oral psilocybin ranging from 0.3 to 0.6 mg/kg (Brown et al., 2017), linear pharmacokinetics were observed, and the elimination half-life of psilocin was 3 hours, with a standard deviation [SD] of 1.1. In another study, the half-life of psilocin was approximately 2.7 hours following oral administration of psilocybin doses of 0.224 ± 0.002 mg/kg (10-20 mg) (Hasler et al., 1997). The half-life of psilocin is considerably shorter when psilocybin is administered intravenously (Hasler et al., 1997).

From psilocybin, psilocin is further metabolized via phase-I and phase-II metabolism. The majority (80% or more) of psilocin undergoes phase-II reactions involving glucuronidation by UDP-glucuronosyltransferases (UGTs), particularly UGT1A10 in the small intestine and UGT1A9 in the liver (Manevski et al., 2010). Another portion of psilocin undergoes phase-I reactions involving oxidative metabolism, catalyzed by monoamine oxidase (MAO) or aldehyde dehydrogenase. From an intermediary metabolite, 4-hydroxyindole-3-acetaldehyde (4-HIA), psilocin then transforms into 4-hydroxyindole-3-acetic acid (4-HIAA) or 4-hydroxytryptophole (4-HT) (Hasler et al., 1997; Passie et al., 2002). An alternative, minor oxidative pathway of psilocin has also been suggested, yielding a product with an o-quinone or iminoquinone structure (Dinis-Oliveira, 2017). Most psilocin is renally excreted as a psilocin-O-glucuronide conjugate (Geiger et al., 2018; Grieshaber et al., 2001).

History of Human Use

Psilocybin-containing mushrooms have been used by indigenous peoples for thousands of years as sacred medicine traditions. Pre-Columbian Mesoamerican cultures used such mushrooms in religious and healing ceremonies. Use was common among Aztec, Maya, Totonac, Huastec, and Mazatec peoples (Carod-Artal, 2015). Prehistoric ritual use has also been suggested from art historical evidence in Africa and Europe (Froese et al., 2016).

María Sabina, a Mazatec *curandera*, introduced an American mycologist R. Gordon Wasson to the use of psilocybin-containing mushrooms during a healing ritual in Oaxaca, Mexico in 1955. Wasson later wrote about his experience in a popular *Life* magazine article published in 1957. He also sent samples of mushrooms to Albert Hofmann, whose earlier discovery of LSD had ignited increased scientific attention towards psychedelic substances. The pharmaceutical company Sandoz had begun distributing LSD-25 under the name Delysid to researchers and psychiatrists, noting indications for use in analytical psychotherapy and in research on psychosis (Hofmann, 1980). Following Hofmann and colleagues' isolation of psilocybin/psilocin in the late 1950s (Hofmann & Troxler, 1959), Sandoz began marketing psilocybin as Indocybin with similar indications as Delysid (Geiger et al., 2018).

As the use of psychedelic substances in research and therapeutic practices grew, interest in recreational use also expanded. High profile accounts of psychedelic experiences contributed to their popularity, and the substances became associated with the counter-culture movement. Media reports circulated about dangerous drug effects, including claims of potential for chromosomal damage and insanity, prompting

substantial public backlash. Multiple research experiments were also carried out with controversy and questionable ethics during this time (Carhart-Harris & Goodwin, 2017). Several restrictions on research and manufacture of the drugs were initiated in the mid-1960s, and in 1970 the US Congress passed the Controlled Substances Act, classifying LSD, psilocybin, and other psychedelics as Schedule I drugs. This designation denotes drugs without any accepted medical use or accepted safety in use, and with high potential for abuse ("Controlled Substances Act," 1970). Research of psychedelic substances thus went dormant for decades. Since the early 2000s, however, a renewal of efforts to expand understanding of these substances has gained substantial momentum.

Effects at Typical Dosages

When administered orally in humans the threshold for detection of psychoactive effects is 3 to 5 mg of psilocybin, eliciting slight drowsiness and intensification of mood (Hasler et al., 2004). Doses from 8 to 10 mg or more are considered to elicit psychedelic effects, particularly perceptual distortions (Passie et al., 2002). High doses of ≥ 25 mg are associated with fuller, more profound subjective experiences. Following oral administration of psilocybin, onset of subjective effects is usually between 20 and 40 minutes, peaking after 60 to 90 minutes and remaining relatively stable for another 60 to 120 minutes before wearing off. Total duration of effects is approximately 6 to 8 hours (Hasler et al., 2004; Tyls et al., 2014). When administered intravenously, typical doses in humans are 1-2 mg, onset of effect is rapid (approximately 1-2 minutes), and total duration of effect is about 20 minutes (Tyls et al., 2014). The lethal dose of psilocybin in humans has been estimated as greater than 1000 times the therapeutic dose (Gable, 2004).

Findings from preclinical and clinical research with psilocybin/psilocin suggest low risk for physiological harm and dependence, though repeated dosing results in diminished effects (tolerance) (Gable, 1993, 2004; Johnson et al., 2018). Common acute physiologic effects of psilocybin administration in humans include mild to moderate increases in blood pressure, mild increases in heart rate, nausea, dizziness, pupil dilation, and fatigue. Tremor, hyperreflexia, ataxia, lack of appetite, drowsiness, and vomiting may also occur acutely. Fatigue and decreased energy may last for up to a day following administration (Johnson et al., 2008; Passie et al., 2002; Studerus et al., 2011). Delayed-onset, transient headaches are also commonly reported after psilocybin use, lasting into the day following administration (Johnson et al., 2012).

Moderate to high doses of psilocybin produce an acute altered state of consciousness, which may include significant changes in affect, a sense of euphoria, dream- or trance-like experiences, detachment, and enhanced capacity for introspection. Individuals may experience synesthesia and sensory distortions (e.g., visual alterations in color perception, intensification of visual imagery, illusions), altered experience of time and space, and emotional changes (e.g., intensification of mood, anxiety, panic, or fear, emotional lability). In addition to acute affective and perceptual effects, psilocybin evokes cognitive changes such as broadening of associations, reduction in attention span, more imaginative thought, changes in body image, and alterations in the sense of self, or ego-function (Letheby & Gerrans, 2017; Preller & Vollenweider, 2018; Studerus et al., 2011). Higher doses are more likely to be stimulating and to involve visual distortions, whereas lower doses tend to be mildly sedating and to increase visual acuity (Hasler et al., 2004). Several studies by Griffiths and colleagues suggest that psilocybin elicits dose-

dependent mystical-type experiences, in which individuals perceive a sense of unity (internally and externally), noetic quality, sacredness, ineffability, transcendence of time and space, and positive mood (Barrett & Griffiths, 2018). A recent meta-analysis of studies that administered psilocybin to healthy volunteers also found positive, dose-dependent associations between psilocybin, perceptual changes, and positively experienced ego-dissolution (Hirschfeld & Schmidt, 2021).

Safety

The risks of psilocybin administration in general most often involve adverse psychological effects. Intensely dysphoric and challenging experiences, sometimes referred to as "bad trips", are characterized by overwhelmingly frightening, psychotic-like states, which may include paranoia, confusion, agitation, and extreme anxiety (Johnson et al., 2008). Though these types of reactions are typically transient and responsive to psychotherapeutic support, this type of experience could escalate to potentially dangerous outcomes if an individual is unprepared or in an unsafe environment. Other, relatively rare adverse psychological risks of psilocybin include a prolonged state of psychological distress and/or psychotic reaction, the worsening of a pre-existing psychotic disorder, and persistent visual disturbance effects (Bender & Hellerstein, 2022). Thus, research with psychedelic substances involves considerable attention to preparation and screening of participants and to aspects of the environment.

The nature of subjective experience varies substantially among individuals depending not only on dose, but also on personal expectations or mindset in approaching the experience and on the context, factors known respectively as set and setting. Set

typically encompasses individual factors (e.g., personal attributes, expectations, preparation, personality, mood, etc.), whereas setting refers to aspects of the physical and social environment. For example, in clinical research studies, settings with PET imaging are associated with increased anxiety during the experience (Studerus et al., 2011). In terms of set, baseline states of decreased surrender and increased preoccupation, apprehension, and confusion have been associated with increased likelihood of having a dysphoric experience. Trait levels of absorption, acceptance, and openness positively predict ratings of euphoric and mystical-type experiences (Aday et al., 2021).

Proposed by Johnson and colleagues (2008), safety guidelines serve to minimize physiologic and psychologic risks with use of high doses of psilocybin in clinical research. These guidelines include the following areas, in brief: careful screening of study participants (e.g., exclusion of individuals with hypertension, personal or family history of psychotic disorders, etc.); careful selection of study personnel; a calming, comfortable, and safe physical environment; preparation of participants to thoroughly inform them of psychedelic effects, risks, procedures, etc., and to build rapport and trust with study staff; provision of support during the drug administration session; and post-administration/follow-up support.

Research with Other Conditions

Studies conducted over 50 years ago reported potential benefits of classic psychedelics for patients with conditions such as anxiety (Weston et al., 2020), depressive disorders (Rucker et al., 2016), alcohol dependence (Krebs & Johansen, 2012), and cancer-related distress (Grof et al., 1973). Since the early 2000s, research on

the therapeutic use of psilocybin in both clinical and non-clinical populations has increasingly been underway. Psilocybin has shown promise for reducing anxiety and depression among individuals with terminal illnesses such as advanced-stage cancer (Agin-Liebes et al., 2020; Dos Santos et al., 2019), for individuals with tobacco (Garcia-Romeu et al., 2014; Johnson et al., 2017) and alcohol dependence (Bogenschutz et al., 2015), anxiety (Goldberg et al., 2020), obsessive-compulsive disorder (Moreno et al., 2006), and treatment-resistant depression (Carhart-Harris et al., 2018). A meta-analysis on randomized controlled trials of psilocybin and other classic psychedelic substances reported both acute and long-term mood improvements among individuals with mood disorders (Galvao-Coelho et al., 2021). The mystical-like experiences induced by psilocybin have been associated with clinical response among several populations, e.g., anxiety and depression among late-stage cancer patients (Ross et al., 2016) and tobacco dependence (Garcia-Romeu et al., 2014).

Classic Psychedelics and Pain

Early Clinical Research

Research in the 1960s and 1970s showed promise for clinical applications of classic psychedelics in pain (Fanciullacci et al., 1977; Grof et al., 1973; Kast & Collins, 1964). In a study among 50 hospitalized patients with severe cancer-related, ischemic, or neuropathic pain, Kast and Collins (1964) reported reductions in pain severity ratings and increased pain-free periods after LSD administration when compared to meperidine and dihydromorphinone. Further, in a case series, Grof and colleagues (Grof et al., 1973) discussed benefits of LSD-assisted psychotherapy for 31 cancer patients in lowering pain

severity, pre-occupation with pain and distress, anxiety, and depression. In addition, an early case series of lower-dose LSD for treatment of phantom limb pain reported reduced use of pain medications and lowered pain in 5 of 7 participants (Fanciullacci et al., 1977).

Recent Clinical Research

Relative to depression and other mental health conditions, few recent studies with humans have examined pain (either acute or chronic) in relation to psychedelics, though interest in this area has been surging. In an experimental study on acute pain, researchers examined the effects of very low doses of LSD on pain tolerance among healthy individuals who underwent cold pressor tests (CPTs) 1.5 and 5 hours after treatment administration (Ramaekers et al., 2020). A dose of 20 mcg LSD was associated with increased pain tolerance (immersion time) and reduced ratings of experienced pain and unpleasantness when compared to placebo at both post-treatment timepoints (Ramaekers et al., 2020). In an exploratory, placebo-controlled, crossover study regarding chronic pain (migraine), a low dose of psilocybin (0.143mg/kg) was associated with fewer days with migraine over a 2-week follow-up period (Schindler et al., 2021). Another exploratory, placebo-controlled study utilized a pulse regimen with a low dose of psilocybin for cluster headache (Schindler et al., 2022).

Multiple clinical trials are currently registered involving the use of psilocybin in pain conditions, including phantom limb pain (clinicaltrials.gov; NCT05224336), cancer pain (NCT 06001749, NCT05506982), chronic low back pain (NCT05351541), post-treatment Lyme disease syndrome (NCT05305105), and various headache disorders (cluster headache [NCT02981173], and migraine [NCT04218539]). Several trials are also

underway involving administration of psilocybin among individuals with FM (NCT05128162, NCT05068791, NCT05548075).

Findings from case reports, survey studies, and qualitative work have supported and informed continued research on application of psychedelics in chronic pain. In two cross-sectional retrospective surveys of patients who had used LSD and/or psilocybin for cluster headaches, results showed reduced severity of headaches and longer remission periods. Users also reported psilocybin and LSD to be more effective in preventing cluster headaches than standard pharmacologic treatments (Schindler et al., 2015; Sewell et al., 2006). In a qualitative analysis of online patient support group discussions, psilocybin and LSD were reported as beneficial for the treatment and prevention of cluster headaches and migraines (Andersson et al., 2017). Further, psilocybin combined with mirror therapy led to remission of one patient's phantom limb pain in a case report (Ramachandran et al., 2018). A survey among individuals who microdosed has suggested possible use in shingles, migraine, and other pain-related conditions (Fadiman & Korb, 2019). More recently, a case series described benefit of microdosing for chronic neuropathic pain among three individuals (Lyes et al., 2023), and in another case report, an individual with lupus experienced long-lasting improvement in joint pain following a very high dose of psilocybin mushrooms (Arkfeld et al., 2023).

A qualitative study explored the use of classic psychedelics for past treatment (self-medication) of chronic pain among 11 individuals (Bornemann et al., 2021). When asked for retrospective pain ratings, 9 of the 11 individuals reported acute reductions in pain during their psychedelic experience, whereas two described acute amplifications. The majority of those who reported acute reductions in pain described gradual returns to

baseline pain levels over 2-5 days. Two individuals reported enduring reductions in pain lasting over 6 months following their psychedelic experience (Bornemann et al., 2021).

Another study used an online survey to examine the past use, knowledge, and perceptions of psychedelics among 354 individuals with FM (Glynos et al., 2022). Thirty-six individuals reported having chronic pain at the time they had taken a psychedelic (most commonly LSD and psilocybin mushrooms). The majority experienced either no change in symptoms (50%) or symptom improvement (47.2%). In addition to generally neutral or positive perceptions held towards psychedelics, a potentially powerful role for intention was highlighted. Of the 12 individuals in the study who had taken a psychedelic substance intentionally to treat their pain, 11 reported symptom improvement. Though interpretation of such findings is limited by selection bias and other methodological constraints, the results call for further exploration of psychedelics in relation to chronic pain.

There is not yet any published clinical data specifically on psychedelics and FM. However, headache disorders (migraine, chronic tension-type headaches) are highly comorbid with FM (Kleykamp et al., 2021), and several studies have pointed to bidirectional relationships (Penn et al., 2019) and/or shared pathophysiology of FM and chronic headaches (Sarchielli et al., 2007; Singh et al., 2019). It is therefore reasonable to suspect a potentially beneficial effect of psychedelics on FM.

Possible Mechanisms

5HT$_{2A}$ Agonism

Multiple mechanisms have been proposed supporting possible application of psilocybin and other psychedelics in pain (Castellanos et al., 2020; Elman et al., 2022; Whelan & Johnson, 2018; Zia et al., 2023). As a 5HT$_{2A}$ receptor agonist, psilocybin may influence chronic pain via serotonergic actions and downstream effects. Serotonin is involved in the modulation of pain perception (Cortes-Altamirano et al., 2018), and, as previously described, FM has been associated with decreased serotonergic functioning (Sluka & Clauw, 2016). Polymorphisms of the 5HT$_{2A}$ receptor gene (Bondy et al., 1999) and serotonin transporter gene have been related to FM in some studies (D'Agnelli et al., 2019), and two of the three current FDA-approved medications for FM are serotonin-norepinephrine reuptake inhibitors.

Descending serotonergic pathways in the CNS can either facilitate or inhibit nociception. The nature of influence depends on the receptor types activated, the location of receptors, and nature of the noxious stimulus. Whether 5HT$_{2A}$ receptor activation promotes an anti-nociceptive vs. pro-nociceptive effect remains controversial. Evidence suggests more likely an anti-nociceptive role in the brain, yet both pro- and anti-nociceptive influences of 5HT$_{2A}$ receptor activation have been observed in the spinal cord (Tao et al., 2019).

Preclinical reports of psilocybin and other 5HT$_{2A}$ receptor agonists have suggested applications for pain. For example, a recent study was performed in a rat model of inflammatory (formalin-induced) pain. Compared to saline, a single dose of psilocybin reduced mechanical hypersensitivity in both ipsilateral and contralateral paws for 28 days

(Kolbman et al., 2023). Also, in a central neuropathic pain model of spinal cord injury, the $5HT_{2A}$ agonist TCB-2 [(4-bromo-3,6-dimethoxybenzocyclobuten-1-yl)methylamine hydrobromide] led to decreased thermal hyperalgesia and mechanical allodynia in mice, an effect associated with upregulation of potassium chloride cotransporter 2 (KCC2) (Sanchez-Brualla et al., 2018). In a preclinical model of orofacial inflammatory pain and stress, thermal and mechanical hyperalgesia were reversed following intrathecal administration of a $5HT_{2A}$ or $5HT_{2C}$ receptor agonist (Xue et al., 2020). Antinociceptive effects of spinal $5HT_{2A}$/$5HT_{2C}$ receptor activation have also been observed in other inflammatory (formalin) and neuropathic (chronic constriction injury) pain models in rats (Sasaki et al., 2003). $5HT_{2A}$ receptor activation in the spinal cord has further been associated with reduced allodynia and increased KCC2 expression in a model of knee osteoarthritis in mice following electroacupuncture (Yuan et al., 2022). In contrast, pronociceptive effects of $5HT_{2A/2C}$ agonism have been reported. For example, pretreatment with the $5HT_{2A/2C}$ agonist (2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in the spinal cord augmented pain response behaviors in a peripheral inflammatory pain model (Kjorsvik et al., 2001).

A few studies have suggested that psychedelics may reduce inflammation via $5HT_{2A}$ receptor activation (Flanagan & Nichols, 2018). In an in vitro study, (*R*)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane [(*R*)-DOI] strongly inhibited expression of proinflammatory markers stimulated by tumor necrosis factor alpha (TNF-α) in primary rat aortic smooth muscle cells; this effect was completely blocked after pretreatment with a $5HT_{2A}$ receptor-selective antagonist (Yu et al., 2008). Similar findings have been demonstrated in mice, in which systemic administration of (*R*)-DOI prevented TNF-α-

induced increases in pro-inflammatory markers, such as interleukin (IL)-6, IL-1β, fractalkine, and others, in gut and vasculature tissues (Nau et al., 2013). Inhalation of (*R*)-DOI also blocked the development of airways inflammation, pulmonary eosinophil recruitment, and other features of allergic asthma in a mouse model (Nau et al., 2015).

Psychological Mechanisms

Brouwer and Carhart-Harris propose that the experiences induced by classic psychedelics represent a pivotal mental state, characterized by enhanced cortical plasticity, increased associative learning, and a greater capacity for the development of major, enduring psychological change (Brouwer & Carhart-Harris, 2021). They hypothesize that these states, mediated by $5HT_{2A}$ receptor signaling, serve an adaptive function, or allostatic recalibration, with the constellation of environmental and personal contextual factors (such as set and setting) driving the direction of change (e.g., a path towards symptom improvement or worsening). Carhart-Harris and Friston's relaxed beliefs under psychedelics (REBUS) model can also be considered within this framework. The REBUS model posits that the psychedelic experience promotes the relaxing or loosening of over-weighted priors (i.e., maladaptive habits or biases), enabling significant change in beliefs to occur (Carhart-Harris & Friston, 2019). Psychedelic experiences have been hypothesized to assist in disrupting patterns of rigid thinking common to mood, anxiety, and other mental health conditions in this way.

The concepts described above have transdiagnostic therapeutic implications applicable not only for mental health conditions but also in chronic pain. Given the associations of catastrophizing, magnification, and other patterns of thinking with

worsening of pain (Geisser et al., 1994), it is possible that psychedelics could benefit individuals with chronic pain similarly. Two processes appeared to be linked with experiences of symptom improvement in a qualitative study on self-medicating with psychedelics for chronic pain (Bornemann et al., 2021). One of the processes was described by the authors as *positive reframing*, in which individuals described changes in their perspectives increasingly in directions towards acceptance, empowerment, compassion, and hope, and away from depression and pain catastrophizing. Another process, referred to as *somatic presence*, encompassed increased awareness of the mind-body connection and physical presence, or embodiment. Individuals in the same study often described concurrent engagement in additional practices such as movement or breathwork during their psychedelic experience.

Several of the identified themes overlap substantially with components of acceptance and commitment therapy (ACT). ACT is a type of psychotherapy that employs mindfulness and acceptance strategies to foster psychological flexibility, which represents the capacity to remain in contact with the present, regardless of distressing thoughts, emotions, and sensations, and to engage in choices aligned with one's values. ACT has been shown to improve quality of life and functional impact of FM in several clinical trials (Galvez-Sanchez et al., 2021). Psychological flexibility has also been suggested to mediate psychedelics' effects on mood and anxiety in some studies (Agin-Liebes et al., 2022; Davis et al., 2020). It is possible that the use of psychedelics may contribute to altered perspectives on pain and other related outcomes, such as depression symptoms, in concert with (or potentially instead of) any partial or direct analgesic effects. Increases in factors such as pain acceptance or present-moment awareness

(mindfulness), and reductions in experiential avoidance, for example, could potentially mediate longer-term improvements in functioning, quality of life, and well-being.

Study Overview

Few studies have examined retrospective reports of past use of psychedelics including psilocybin in relation to chronic pain and FM. More research is needed to determine if psychedelics help FM specifically, and whether psilocybin in particular benefits FM. The nature of psilocybin effects on FM pain are also unknown (e.g., whether effects are acute or durable, direction of effects, related factors, etc.). To help address these gaps, and to inform future clinical trials, a questionnaire was distributed online among individuals with FM and past use of psychedelics. The purpose of this study was to assess characteristics of past psychedelic use among individuals with FM, and to explore reported effects on pain. No hypotheses were planned given the exploratory, descriptive nature of this study. The research questions of interest included the following:

1. *How, and with what intentions and expectations, have individuals with FM used classic psychedelics?*
2. *Have individuals with FM experienced changes in pain in relation to classic psychedelics, and if so, which substance(s)?*
3. *How do individuals with FM describe the impact of classic psychedelic use on pain? (e.g., strength, direction, duration of change)*

4. *How do individuals with FM describe the impact of classic psychedelic use on other symptoms of FM?*
5. *What factors are associated with any positive or negative impacts of classic psychedelics on pain in FM?*

METHODS

Design and Ethical Approval

An exploratory, descriptive approach was employed involving the administration of an online survey. The survey was intended for individuals who have used classic psychedelics and who have FM. Nonprobability sampling was used. The survey included both close-ended and open-ended questions to provide sources of both quantitative and qualitative data. The study was approved by the University of Alabama at Birmingham (UAB) Institutional Review Board (IRB-300009401, see Appendix A).

Inclusion and Exclusion Criteria

To be eligible for the study, individuals had to be able to access the survey online, be at least 18 years of age, have a history of chronic pain, and have used a classic psychedelic substance at least once in their lifetime. They were required to view an information page about the study and voluntarily consent to participate. Individuals were excluded from participating if they did not consent to the study, were under age 18, denied a history of chronic pain, or denied past psychedelic use.

Recruitment

Participants were recruited using a combination of email distributions and social media posts from September of 2022 through May of 2023. A brief description of the study and survey link were posted on the UAB Neuroinflammation, Pain, and Fatigue

Lab Twitter and Facebook accounts, shared with relevant Facebook groups, and posted on multiple Reddit threads related to fibromyalgia and/or psychedelics. Individuals who had previously expressed interest in chronic pain and fatigue studies at the UAB Neuroinflammation, Pain, and Fatigue Lab were notified of the study opportunity via an email that included the study link. Information about the study was also distributed to colleagues and several fibromyalgia advocacy organizations to share on their respective social media pages, if desired. A gift card raffle incentive was added to the protocol following IRB approval of this change in December 2022, with the goal of increasing interest in the study. The study information page was updated to include information about this incentive.

Procedures

The survey was created and hosted on Qualtrics (Provo, UT), a secure platform for conducting survey research online. Responses were collected anonymously. The "Prevent Multiple Submissions" setting in Qualtrics was used to decrease the chance that individuals would take the survey more than once. All data collected was stored on secure computers located in Dr. Jarred Younger's research office space at UAB.

Upon clicking the survey link, individuals interested in the study were presented with a study information page. This page described the general purpose of the study and types of questions included, the estimated length of time required to complete the study, the data that would be collected, how it would be stored, and contact information for the principal investigator. Participants were informed that the length of time estimated to complete the survey was 30 minutes on average. At the bottom of this page, individuals

interested in participating were asked to select whether they consented to the study or not. If they selected, “I consent, begin study”, they were directed to the next survey page. The survey remained open throughout the data collection period and was accessed via an anonymous link. To preserve anonymity for participants, no IP addresses or other identifying information were collected, and no contact with the researchers was required to complete the survey.

When they reached the end of the survey, participants were asked whether they wished to enter a random drawing for a $50 online gift card. If they responded “Yes”, they were asked to click on a link which directed them to a separate Qualtrics form to enter their name and email address. No names or email addresses were collected or stored with the survey responses. Following the data collection period, names were randomly drawn and a total of 17 electronic Amazon gift cards were distributed via email.

Questionnaire Development

The survey was developed by multiple research staff by drawing from literature review and review of publicly available surveys related to past use of psychedelics. Quantitative items included multiple choice and yes/no questions, checklist items, and numerical pain rating scales (e.g., current and retrospective 0-10 pain severity ratings). Qualitative data was drawn from full text, open-ended questions (e.g., “please describe how your pain changed in relation to the psychedelic experience”). Questions were developed to minimize task difficulty and only questions relevant to the research questions of interest were included. Conditional and branching logic were utilized for items that may or may not have applied to all participants, and a limited number of long

lists and rating scales were used to minimize increased risk for response order bias. The survey in full is attached in Appendix B.

Additional Survey Details

Survey items were presented to all participants in the same order (they were not randomized or alternated between participants). The final survey contained a total of 90 questions over 40 pages (screens), with an average of two to three questions displayed per screen. Certain questions were conditionally displayed depending on other item responses. For example, individuals who reported never having experienced any change in pain related to the use of a psychedelic were not asked to respond to items 4.10 through 4.49 since they were not applicable. For most questions, participants were required to select a response in order to progress to the following page. Most items included a non-response option of "Prefer not to answer" and/or a "Don't know" option. Participants were able to use a Back button throughout the survey if they needed to review/change previous answers. Incomplete survey responses were recorded automatically after one week.

To aid in spam and fraud detection, the following embedded Qualtrics survey settings were enabled: Prevent multiple submissions, bot detection/reCAPTCHA, security scan monitor, and RelevantID. Survey responses were regularly checked by the author for possible spam throughout the data collection period.

Information Collected

1. FM status and symptom severity: Participants were assessed for the presence of current FM symptoms and severity using the 2016 revisions to the ACR 2011 self-report criteria (Wolfe et al., 2016) embedded within the survey. The WPI (range 0-19) and SSS score (range: 0-12) were summed to form a FM severity scale score (0-31) for each participant, with higher scores reflecting increased symptom severity. An individual met self-report criteria for current FM if the following were met: WPI $\geq$ 7 and SSS $\geq$ 5 OR WPI 4-6 and SSS score $\geq$ 9; generalized pain (presence of pain in at least 4 of 5 regions, not including jaw, chest, and abdominal pain), and the presence of symptoms for at least 3 months.
2. Clinical FM diagnosis: Individuals were asked if they have ever been diagnosed by a medical provider with FM and if so, the year of diagnosis.
3. Other medical conditions: Participants were asked to list any current pain conditions or other medical conditions, including mental health conditions.
4. Demographic information: Demographic items were collected, including age in years, sex assigned at birth, gender identity, racial identity, Hispanic ethnicity status, highest education completed, current occupational status, most recent/current occupation, relationship status, country of residence, and state of residence (if in US).
5. Medication and substance use: Participants were asked to list any current medications, including over-the-counter medications and supplements. Participants were also asked about use of the following substances: alcohol, benzodiazepines, barbiturates, bath salts, CBD or cannabidiol products, cannabis/marijuana, cocaine, heroin, ketamine,

kratom, MDMA, methamphetamine, opioids, stimulants, synthetic marijuana, and nicotine/tobacco use.

6. Current pain intensity and interference: The PEG (Krebs et al., 2009), a shortened version of the Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994), was used to assess current pain intensity and interference. The PEG items ask for 0-10 ratings over the past week of average pain intensity, average pain interference with enjoyment of life, and average pain interference with general activity. The scores were then averaged to obtain an overall PEG score ranging from 0-10.
7. Type and frequency of use of classic psychedelics: Participants were asked whether they had used any classic psychedelic in the past, including psilocybin, psilocybin mushrooms, LSD, DMT, 5-MeO-DMT, mescaline, and ayahuasca. Participants who answered "yes" to that question were asked to indicate frequency of use for each of the classic psychedelics listed from the following options: "never", "once", 2-5 times", "6-10 times", "11-20 times", "21-50 times", "51-100 times", "101-300 times", or "more than 300 times". Participants also had the option to write in other substance names and indicate relative frequency of use.
8. Characteristics of experiences with classic psychedelics: Participants were asked to describe any relevant psychedelic experience(s) with an open-ended question. Participants were also asked about the setting of the experience (e.g., location, number of people they were with at the time, their familiarity with others around them, etc.).
9. Change in pain related to use of classic psychedelics: Change in pain related to use of classic psychedelics was assessed using the following yes/no question: "Have you ever experienced a change in your pain that was related to the use of a psychedelic

substance?" If participants respond with "yes", they were presented with a series of additional items inquiring about the type of change, the psychedelic substance(s) involved, and the duration of change. Retrospective pain ratings using 0 ("no pain") to 10 ("pain as bad as you can imagine") numerical rating scales (NRS) were collected to further explore participants' perceived changes in pain in relation to a past psychedelic experience.

10. Change in other FM-related symptoms: Participants were asked broadly using an open-ended question whether any other symptoms besides pain had changed in relation to their psychedelic use.
11. Negative effects: Participants were asked whether they experienced any negative effects from their psychedelic use and, if so, to provide additional details using free-text. Participants' responses to other open-ended items were also examined for reports of negative effects. Any increases in pain reported were considered negative effects.
12. Reasons for use: Participants were asked about their reasons for using psychedelics with two items. One was a "select all that apply" item, including a list of common reasons drawn from the literature. The second item prompted participants to describe using free text their strongest reasons for psychedelic use.
13. Expectations: Participants who reported any pain changes related to psychedelic use were asked to describe their expectations prior to that occasion of use.

Analyses

Simple descriptive statistics were calculated using Microsoft Excel and IBM SPSS (Version 29), including means, standard deviations, and frequencies, to summarize

all quantitative data. Retrospective pain ratings in relation to classic psychedelic use were graphed for visual representation.

For qualitative data, a conventional content analysis approach was used (Hsieh & Shannon, 2005). All text responses to open-ended survey questions regarding psychedelic use, pain, and other symptoms were read multiple times and coded using NVivo (R1) software. Codes were derived inductively from the data and were developed and revised throughout data familiarization. Codes were then grouped into categories based on relatedness. To aid in presentation of results, quotes were selected from among the survey responses and labeled with a participant identification or ID number, in addition to the substance used, if applicable. Quotes are presented in the results as they were originally written within the survey responses, unless otherwise indicated. Survey items relevant for addressing each research question (RQ) are indicated below.

1. *How, and with what intentions and expectations, have individuals with FM used classic psychedelics?* This question was explored via items related to frequency and type of classic psychedelic(s) used, as well as items assessing reasons for use (#4.7 and #4.28), and expectations (#4.29) related to past use of classic psychedelics.

2. *Have individuals with FM experienced changes in pain in relation to classic psychedelics, and if so, which substance(s)?* This question was answered based on analysis of responses to items #4.9 (“Have you ever experienced a change in your pain that was related to the use of a psychedelic substance?”) and #4.12 (“What psychedelic substance was associated with the change in your pain?”)

3. *How do individuals with FM describe the impact of classic psychedelic use on pain (e.g., strength, direction, duration of change)?* Analyses primarily focused on the free text responses to items #4.17 ("How did your pain changed in relation to the psychedelic experience") and #4.18 ("How long did you experience the change(s) in your pain?"), in addition to reported retrospective pain ratings (#4.27). Responses to item #4.32 were also examined, specifically whether a participant checked the box(s) for "an increase in my pain", "a decrease in my pain", and/or "a change in my perspective on pain" experienced "during" and/or "following" the psychedelic experience(s).

4. *How do individuals with FM describe the impact of classic psychedelic use on other symptoms of FM?* Survey item #4.20 was primarily used to explore this research question. Item #4.20 was open-ended and asked, "Please describe if, and how, any of your other symptoms changed in relation to the psychedelic experience. Please include how long you noticed these changes, if any." A portion of item #4.32 was also used, specifically whether a participant checked the box for any changes in other FM symptoms experienced "during" and/or "following" the psychedelic experience(s).

5. *What factors are associated with any positive or negative impacts of classic psychedelics on pain in FM?* To answer this question, free text responses to item #4.19 were analyzed ("Why do you think there was a change in your pain?"). Other item responses were also examined, including those assessing motivation for use (#4.28),

expectations (#4.29), preparation (#4.34 and #4.35), type (#4.12) and dose (#4.21 and #4.22) of psychedelic substance, setting characteristics (#4.24, #4.25, and #4.26), negative effects (#4.31), changes in perspective on pain/other FM symptoms/mental health/quality of life (#4.27), use of pain treatments (#4.36 and #4.37), other areas of life (such as social activity, physical activity, etc.) (#4.38 and #4.39), and degree of personal meaningfulness, spiritual experience, psychological insight, and/or awe related to the psychedelic experience (#4.40 through #4.47).

RESULTS

Survey Responses

From September of 2022 through May of 2023, the survey received a total of 874 responses (Figure 1). Seventy-eight were identified by Qualtrics as spam and 236 were flagged as likely bots and/or fraudulent. Increased amounts of spam and fraudulent responses were observed during several periods in late 2022 and early 2023. In consideration of suggestions for identifying fraud in anonymous web-based surveys (Dewitt et al., 2018), all survey responses were manually inspected and flagged for possible removal if they demonstrated very short completion times, inconsistent responding, high levels of non-response, low differentiation across grid items, or duplicated or gibberish responses to open-ended items. This process resulted in the removal of an additional 185 responses (170 due to duplicated responding evident across surveys, and 15 due to inconsistent responding).

Fifty-one individuals consented to the study but did not complete the screening questions, and 65 responses were ineligible due to having previously taken the survey. Two respondents were ineligible due to being under the age of eighteen, 23 individuals were ineligible due to no history of chronic pain, and 67 were ineligible due to never having used a classic psychedelic. Sixty-five individuals passed the screening items but discontinued the survey prior to completing it; of those 65, eleven completed at least 50% of the survey items and were included in the analyses. Ninety-one individuals completed the survey in full. Thus, the analysis set included 102 survey responses in total.

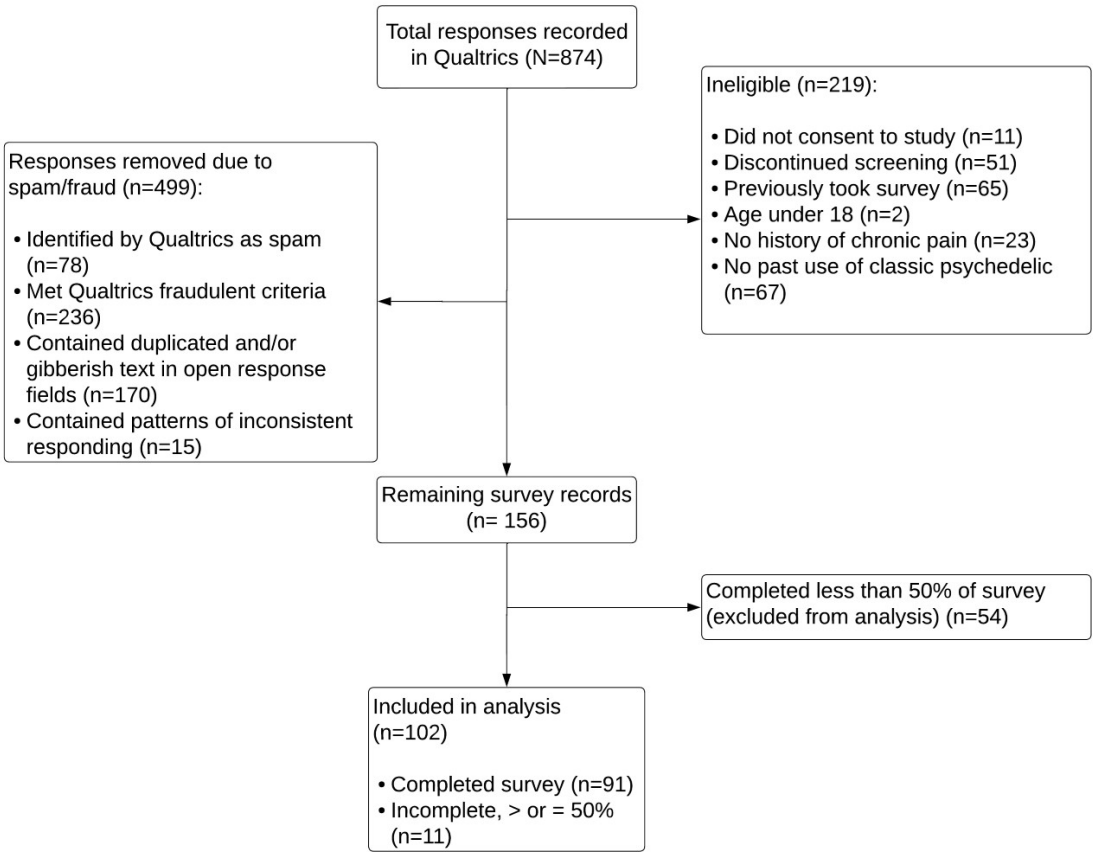

Figure 1. Inclusion and exclusion of participants.

Participant Characteristics

Demographics

Demographic and pain-related characteristics are summarized in Table 1 and Table 2. Because the demographic items were at the end of the survey, this information was not available for the 11 participants who discontinued early (6 of the FM group and 5 of the non-FM group). For the 91 participants who completed the survey, the average age was 44.9 years (SD = 13.9, range = 19-82). More than half the participants reported identifying as women (*n* = 55, or 53.9%). Two participants identified as Black or African

American (2.0%), 72 participants (70.6%) identified as white, and 10 participants (9.8%) identified as multiracial (Native American or Alaska Native and white (n = 4), Black or African American and white (n = 1), Asian and white (n = 2), unspecified (n = 3)). Seven respondents (6.9%) reported Latin, Mexican, or Hispanic ethnicity. Demographic characteristics are shown in Tables 1 and 2 for the total sample and for the participants with FM (n = 64).

More than half of all participants (n = 57 or 55.9%) had obtained at least a bachelor's degree or higher education. About half of the total sample (n = 53 or 52%) reported current employment (including full-time, part-time, and self-employed status), and about one quarter of the sample reported disability (n = 25 or 24.5%). More than two-thirds of the participants lived in the United States (n = 71 or 69.6%), most commonly in the Southern and Western regions.

Table 1. Participant demographic characteristics.

Characteristic	FM (n = 64)		Total (N = 102)	
	n	%	*n*	%
Gender				
Woman	39	60.9	55	53.9
Man	7	10.9	22	21.6
Two-spirit	1	1.6	1	1.0
Genderfluid, nonbinary, or other gender identity	6	9.4	6	5.9
Prefer not to answer	5	7.8	7	6.9
Race				
Black/African American	2	3.1	2	2.0
Multiracial	9	14.1	10	9.8
White	44	68.8	72	70.6
Prefer not to answer	1	1.6	1	1.0
Hispanic [a]	3	4.7	7	6.9
Relationship status				
Single	15	23.4	24	23.5
Married or in committed relationship	38	59.3	59	57.8
Divorced or separated	4	6.3	7	6.9
Widowed	0	0.0	1	1.0
Prefer not to answer	1	1.6	1	1.0
Highest educational level				
High school or GED	1	1.6	2	2.0
Some college	9	14.1	16	15.7
Trade/technical training or associate degree	14	21.9	17	16.7
Bachelor's degree	18	28.1	32	31.4
Graduate degree	16	25.0	25	24.5
Occupational status				
Unemployed	4	6.3	6	5.9
Student	4	6.3	7	6.9
Employed, part-time	11	17.2	16	15.7
Employed, full-time	15	23.4	31	30.4
Self-employed	2	3.1	6	5.9
Homemaker	6	9.4	6	5.9
Disabled	24	37.5	25	24.5
Retired	4	6.3	9	8.8
Location of residence				
Europe	9	14.1	15	14.7
Canada	4	6.3	4	3.9
Central America	0	0.0	1	1.0
United States	45	70.3	71	69.6
Northeast	5	7.8	9	8.8
South	15	23.4	28	27.5
Midwest	8	12.5	10	9.8
West	17	26.6	24	23.5

[a] Reflects the number and percentage of participants answering "yes" to this question.

FM Status

In this study, participants were considered part of the FM group (n = 64 or 62.7%) if they responded "Yes" to ever receiving a clinical diagnosis of FM, or if they met self-report criteria (Wolfe et al., 2016) based on the Widespread Pain Index, Symptom Severity Scale, and duration of pain symptoms. Half (n = 55 or 53.9%) of the total sample (N = 102) reported ever receiving a diagnosis of fibromyalgia by a medical provider. Among these participants, year of FM diagnosis ranged from 1970 to 2022. Nine additional participants met the self-report criteria but denied ever having received a diagnosis from a provider. They were therefore considered part of the FM group for the purposes of this study. No demographic information was available for six of the 64 participants with FM due to early discontinuation of the survey.

Pain-related characteristics are shown in Table 2. Among the participants with FM, the mean number of pain areas endorsed using the Widespread Pain Index (range: 0-19) was 10.9 (SD = 4.6), with the shoulder girdles and neck most reported. The mean FM severity scale score (range 0-31, with higher scores reflecting greater severity) was 19.9 (SD = 6.0) among those with FM, and 16.3 (SD = 7.4) across all participants. The average pain intensity and interference (PEG) score was 6.8 (SD = 1.9) in the FM group.

Table 2. Age and pain characteristics.

Characteristic	FM (n = 64)			Total (N = 102)		
	M	SD	Range	M	SD	Range
Age	45.0	12.6	22-72	44.9	13.9	19-82
Widespread Pain Index	10.9	4.6	0-19	8.2	5.3	0-19
Symptom Severity Scale	9.1	2.2	2-12	8.1	2.8	1-12
FM Severity Scale	19.9	6.0	4-31	16.3	7.4	1-31
Pain Intensity	6.3	1.7	1-10	5.7	2.1	0-10
Pain Interference (enjoyment)	7.1	2.4	0-10	6.3	2.9	0-10
Pain Interference (activity)	6.9	2.3	0-10	6.4	2.7	0-10
PEG Total	6.8	1.9	0.3-10.0	6.1	2.4	0.0-10.0

Note. Age was missing for 11 participants total (6 with FM and 5 without FM).

Other Conditions

Most participants (n = 79, or 77.5%) described the presence of musculoskeletal pain, and a quarter of the sample (n = 21, or 20.6%) reported chronic headache or orofacial pain. Other than fibromyalgia, the most frequently cited pain conditions included arthritis, degenerative disc disease, and migraine. Across the sample, depression and anxiety were the most common mental health diagnoses reported. Further information on pain and mental health conditions is summarized in Tables 3 and 4.

Table 3. Pain types.

Type/Condition	FM (n = 64)		Total (N = 102)	
	n	%	*n*	%
Musculoskeletal	64	100.0	79	77.5
Arthritis	15	23.4	20	19.6
Degenerative disc disease	6	9.4	15	14.7
Ehlers-Danlos syndrome	7	10.9	10	9.8
Visceral	11	17.2	14	13.7
Irritable bowel syndrome	7	10.9	7	6.9
Endometriosis	3	4.7	5	4.9
Neuropathic	9	14.1	21	20.6
Spinal cord injury	2	3.1	5	4.9
Small fiber neuropathy	3	4.7	3	2.9
Chronic headache or orofacial pain	17	26.6	21	20.6
Migraine	12	18.8	13	12.7
Occipital neuralgia	1	1.6	3	2.9
Trigeminal neuralgia	2	3.1	3	2.9
Cluster headache	0	0.0	1	1.0
New daily persistent headache	0	0.0	1	1.0
Post-surgical pain	3	4.7	6	5.9
Cancer pain	2	3.1	4	3.9
Complex regional pain syndrome	3	4.7	4	3.9
Lupus	3	4.7	3	2.9
Sjogren's syndrome	3	4.7	3	2.9
ME/CFS	13	20.3	13	12.7

Table 4. Mental health conditions reported.

Condition	FM (n = 64)		Total (N = 102)	
	n	%	*n*	%
Depression	25	39.1	36	35.3
Anxiety	20	31.3	26	25.5
Stressor/trauma-related disorder	14	21.9	18	17.6
ADD or ADHD	8	12.5	13	12.7

Medication and Substance Use

Most participants reported current use of one or more medications or supplements (Table 5). Among those with FM, vitamins, minerals, and other supplements were most frequently reported (56.3%), followed by antidepressants (45.3%), NSAIDs (25%),

opioids (23.4%), cardiovascular medications (23.4%), gabapentinoids (21.9%), and low-dose naltrexone (20.3%).

Table 5. Medication use.

Medication/supplement use	FM (n = 64)		Total (N = 102)	
	n	%	*n*	%
Supplement use	36	56.3	48	47.1
Antidepressant	29	45.3	39	38.2
Cardiovascular medication	15	23.4	25	24.5
Opioid	15	23.4	24	23.5
Gabapentinoid	14	21.9	19	18.6
NSAID	16	25.0	19	18.6
Gastrointestinal medication	11	17.2	18	17.6
Anxiolytic/sedative/hypnotic	8	12.5	16	15.7
Muscle relaxant	11	17.2	16	15.7
Acetaminophen	10	15.6	13	12.7
Low-dose naltrexone	13	20.3	13	12.7
Thyroid hormone replacement	10	15.6	12	11.8
Antihistamine	9	14.1	10	9.8
Immunosuppressant medication	7	10.9	9	8.8
Migraine medication	3	4.7	5	4.9
None reported	3	4.7	16	15.7

Note. "Supplement use" reflects the use of one or more vitamins, minerals, or other nutritional supplements.

Approximately one-fifth of participants with FM endorsed current nicotine or tobacco use. Most participants (76.6%) reported consuming zero alcohol-containing drinks per week on average. The most frequently used non-psychedelic substances were cannabis and cannabidiol (CBD) products, used regularly (at least once a month) by 40.6% and 26.6% of respondents with FM, respectively. Additional details on non-psychedelic substance use are shown in Table 6.

Table 6. Non-psychedelic substance use.

Substance use	FM (n = 64)		Total (N = 102)	
	n	%	*n*	%
Nicotine/tobacco	15	23.4	26	25.5
Cannabis/marijuana	26	40.6	54	52.9
CBD or cannabidiol products	17	26.6	33	32.4
Benzodiazepines, non-prescribed	1	1.6	5	4.9
Opioids, non-prescribed	3	4.7	7	6.9
Ketamine	4	6.3	5	4.9
MDMA	-	-	1	1.0
Cocaine	-	-	2	2.0
Kratom	3	4.7	6	5.9
Heroin	-	-	2	2.0
None of the above	29	45.3	33	32.4

Note. Participants were asked about regular, current use of any of the substances above, defined as at least once a month.

Knowledge about Classic Psychedelics

Among participants with FM (n = 64), most rated themselves as "moderately knowledgeable" (n = 25 or 39.1%), "slightly knowledgeable" (n = 16 or 25.0%), or "very knowledgeable" (n = 14 or 21.9%) about classic psychedelics (Table 7). Few participants with FM identified as being either "not at all knowledgeable" (n = 4 or 6.3%) or "extremely knowledgeable" (n = 5 or 7.8%) about psychedelics.

Among participants without FM (n = 38), about one third rated themselves as "moderately knowledgeable" (n = 14 or 36.8%) about classic psychedelics and one quarter as "slightly knowledgeable" (n = 10 or 26.3%). None of these participants rated themselves as "not at all knowledgeable", and a relatively greater portion described themselves as "extremely knowledgeable" (n = 8 or 21.1%).

Table 7. Knowledge about psychedelics.

Self-rating	FM (n = 64)	Non-FM (n = 38)	Total (N = 102)
	n (%)	n (%)	n (%)
Not at all knowledgeable	4 (6.3)	0 (0.0)	4 (3.9)
Slightly knowledgeable	16 (25.0)	10 (26.3)	26 (25.5)
Moderately knowledgeable	25 (39.1)	14 (36.8)	39 (38.2)
Very knowledgeable	14 (21.9)	6 (15.8)	20 (19.6)
Extremely knowledgeable	5 (7.8)	8 (21.1)	13 (12.7)

RQ 1: Classic Psychedelic Use Among Individuals with FM

Type and Frequency of Use

Among participants with FM (n = 64), the most frequently used classic psychedelics were psilocybin mushrooms, used at least once by 54 respondents (84.4%), and LSD, used at least once by 46 participants (71.9%). A quarter of the FM sample (16 participants) endorsed past use of mescaline. Less frequently, individuals with FM reported past use of DMT (n = 9 or 14.1%), 5-MeO-DMT (n = 6 or 9.4%), and ayahuasca (n = 6 or 9.4%). Additional types of psychedelic use reported included lysergic acid amide or LSA (n = 2) and the psychedelic phenethylamines 2C-I, 2CB, and 25I-NBOMe or 25-I (n = 1, respectively).

About half of participants with FM (n = 31 or 48.4%) endorsed use of both microdoses and macrodoses. Fifteen participants (23.4%) had used macrodoses only, and ten participants (15.6%) reported use of only microdoses. Eight participants (12.5%) were unsure of the dosage type(s) they had used. The average age of first psychedelic use was 23.9 years (range = 12 - 70, SD = 12.0), and the first substance used was most often either LSD (n = 30) or psilocybin mushrooms (n = 27). The average age of most recent psychedelic use was 36.2 years (range = 15 - 70, SD = 13.6).

Practical Motives

Responses from a combination of close-ended and open-ended items were utilized to examine motives for past psychedelic use. Motives were grouped broadly into four categories: (1) use of psychedelics to self-medicate, (2) use of psychedelics for fun and recreation, (3) use for growth or exploration, and (4) other reasons (Table 8).

Table 8. Reasons for use among participants with FM.

Category	Subcategory	FM (*n* = *64*) *n* (%)
Practical Motives		
Self-medicating	General mental health/well-being	34 (53.1)
	Trauma	23 (35.9)
	Depression	12 (18.8)
	Anxiety	10 (15.6)
	Pain-related	22 (34.4)
	To reduce use of medications	3 (4.7)
Fun/recreation	Fun/recreation	36 (56.3)
Growth/exploration	Personal growth/exploration	29 (45.3)
	Broaden consciousness/perspective	31 (48.4)
	Spiritual reasons	26 (40.6)
Other reasons	Curiosity	32 (50.0)
	Social reasons	18 (28.1)
	As an escape	16 (25.0)
	Feel euphoric or elated	21 (32.8)
	To enhance an activity	14 (21.9)
	To feel more connected to nature	25 (39.1)
Contributing factors		
	Support from providers	6 (9.4)
	Heard about others' experiences	9 (14.1)
Change in reasons over time		6 (9.4)

Self-Medicating

Participants often reported using psychedelics to self-medicate, i.e., to improve one's health or help deal with a certain problem. Self-medicating in general involves use of a medication or substance typically in the absence of a prescription or doctor's recommendation. When asked about their strongest reasons for using psychedelics, participants described wanting to better manage, heal, or cope with a problem, particularly a mental health or pain-related issue. Participants also noted an interest in using psychedelics to reduce their need for prescription medications.

To improve mental health. Thirty-four participants with FM (53.1%) reported using psychedelics to help with their mental health. Managing trauma-related symptoms (n = 23 or 35.9%), depression (n = 12 or 18.8%), and anxiety (n = 10 or 15.6%) were the most frequently mentioned mental health concerns motivating psychedelic use. Four participants (6.3%) discussed using specifically to help with hopelessness and suicidal ideation. For instance, when asked about their motivation for use, one individual who microdosed psilocybin described: "I was suffering from severe depression and I almost committed suicide" (ID79). Others wrote about using psychedelics to support them in processing emotions tied to relationship issues, helping manage premenstrual dysphoric disorder, and managing OCD (n = 1, respectively).

Four participants discussed looking to psychedelics to help deal with the psychological impacts of one or more chronic health conditions. For example, one participant with FM described how she became interested in using psychedelics to cope with the emotional toll of long COVID, writing:

> Since getting Covid-19 again a year ago I have been dealing with worsening health issues, along with increased depression and anxiety from being unable to work. I've been hearing multiple people using Psilocybin and reading multiple articles discussing the benefits of it on mental health so I wanted to see if it would help my mental health while I recover. I've since found it to be helpful with pain which has prompted me to continue use. (ID70)

To help with pain. More than a third of participants with FM (n = 22 or 34.4%) described a pain-related reason as one of their strongest motivations to use psychedelics. Participants expressed interest in treating various types of pain, including pain they attributed to fibromyalgia, ME/CFS, myofascial pain, long COVID, CRPS, migraine, and other conditions. Many of the written responses were similar to that of participant ID82, who simply stated, "I wanted to see if it would help my pain." Some participants described wanting to use psychedelics specifically during periods of increased pain, such as participant ID68, who wrote regarding their psilocybin use, "My pain was off the charts. I was maxed out on prescription meds for the day & needed relief without going to the hospital."

Two participants with FM and other health conditions described how their interest in psychedelic use grew after exhausting the treatment options available to them, with little relief for their pain and other symptoms. One such participant described, "I have tried traditional medicine, alternative therapies, supplements etc without much success. This was a last resort" (ID20).

While most participants primarily sought relief from pain, some described an interest in enhancing their ability to cope with or better understand their pain. For example, one participant was motivated to use psilocybin for "exploration and understanding/working with my pain symptoms" (ID18). Similarly, another participant had wanted to use psilocybin "to have a better understanding of my MECFS and Fibromyalgia" (ID57).

To reduce use of medication. Three participants expressed motivation to use psychedelics to reduce their use of prescribed medications. One participant shared about their interest in growing psilocybin mushrooms for pain management, stating, "I am interested in attempting microdosing in an effort to reduce my medication needs" (ID52). Another participant described the use of a psychedelic to help with withdrawals from a pain medication taper. For one individual, their interest in the use of mushrooms was driven in part by a desire to reduce risk for chemical dependence from opioids:

> As a person in recovery from alcohol misuse & already prescribed the strongest pain medication on the market, I am very mindful of what I put in my body. Mushrooms provide the same, if not better, pain relief as IV morphine without the risk of chemical dependence ... I don't want to keep stacking opiates on top of opiates, even if they are prescribed. (ID68)

Recreation

More than half of participants with FM endorsed past use of psychedelics for fun or recreation (n = 36 or 56.3%). When asked to describe their strongest reasons for

psychedelic use, nearly a third of participants (n = 20 or 31.3%) shared recreational motives, such as "thought it would be fun" (ID45). Several participants specified having used psychedelics for recreation in a social context or when they were younger in age.

Growth/Exploration

When asked to consider general reasons for past psychedelic use from a list of possible options, many participants endorsed past use for the purposes of broadening consciousness or perspective (n = 31 or 48.4%), for personal growth or exploration (n = 29 or 45.3%) and for spiritual reasons (n = 26 or 40.6%). When asked about their motivation for use, one such participant described, "to explore my consciousness, feel more spiritually connected, and to improve my quality of life" (ID57).

Other Reasons

Other reasons endorsed included curiosity, social reasons, as an escape, and to feel euphoric or elated. The use of psychedelics to enhance an activity, such as music, or to feel more connected to nature was also reported.

Contributing Factors

In addition to practical motives, participants described additional factors that contributed to their reasons for use. Participants were encouraged after receiving support from providers and after hearing about others' experiences with psychedelics.

Received support/encouragement from providers. Receiving support from doctors, therapists, or other providers was mentioned by some respondents (n = 6) as a contributing factor to their strongest reasons for use. As one participant described, sometimes support was found unexpectedly: "I decided to discuss it with my doctor and was surprised at how supportive he was. He said he had others in his practice that are microdosing with positive results" (ID20).

Heard about others' positive experiences. When asked about their strongest reasons for use, nine participants in the FM group (14.1%) mentioned having heard about others' positive experiences with psychedelic use. They wrote about having been inspired by positive research findings or experiences shared on social media sites. Others described having been motivated to try psychedelics after talking about them with a friend or family member who themselves had experienced some form of benefit, as the following participant explained, "I was first inspired by the research done at John's [*sic*] Hopkins University by Dr. Roland Griffiths, along with hearing from a close friend of mine who said Psilocybin, along with meditation, probably saved his life" (ID57).

Change in Reasons for Psychedelic Use over Time

Some participants (n = 6) delineated a change in their reasons for psychedelic use over time. They discussed having initially used psychedelics for one reason (often recreationally or out of curiosity), then later having developed different motivations for use, such as for mental health or pain. For example, one participant shared, "When I was

younger it was a recreational thing. I read a lot about people having good results with managing pain and past trauma with Psilocybin. It is the pain and past trauma" (ID41).

Expectations Related to Psychedelic Use

Participants who reported a change in pain following use of a psychedelic were asked to indicate their expectations, if any, regarding their psychedelic use at that time. Of the participants with FM who either responded to this question or who described their expectations elsewhere in the survey (n = 38), most described having either little to no expectations (n = 13), e.g., "none" (ID36) or "I wasn't sure what to expect" (ID64), or positive expectations (n = 13), such as "I only expected to have a fun night" (ID77).

Four individuals described pain-related expectations. Of these four, three expected their pain to be helped in some way, whereas one participant expected increased pain and other unpleasant feelings. Overall, relatively few participants reported having had negative expectations (n = 3).

RQ 2 and RQ 3: Changes in Pain with Classic Psychedelic Use

Participants were asked with a close-ended item whether they had ever experienced a change in pain with use of a psychedelic. In response to this question, about half of the participants with FM (n = 36 or 56.3%) responded "Yes" (Table 9). More than a quarter (n = 17 or 26.6%) had never experienced a change in pain with past use, and 11 participants (17.2%) were unsure.

Table 9. Any change in pain with past psychedelic use.

Have you ever experienced a change in your pain that was related to the use of a psychedelic substance?	FM (n = 64)	Non-FM (n = 38)	Total (N = 102)
	n (%)	n (%)	n (%)
Yes	36 (56.3)	19 (50)	55 (53.9)
No	17 (26.6)	14 (36.8)	31 (30.4)
Don't know	11 (17.2)	5 (13.2)	16 (15.7)

Among the 36 participants who reported a change in pain, the type of substance used was most often psilocybin mushrooms (n = 29 or 80.5%). A smaller number of participants reported a change in pain with use of LSD (n = 6), mescaline (n = 2), and DMT (n = 1). All participants reported oral ingestion. When asked to describe how often they had experienced pain-related changes with psychedelic use, most participants endorsed more than one occasion (once, n = 2; twice, n = 4; three to five times, n = 10; six to ten times, n = 7; more than 10 times, n = 9; unsure of how many times, n = 4).

Of the 36 participants who reported pain changes, most (n = 32 or 88.9%) described an acute reduction in pain lasting at least one hour during the period of drug effects (Table 10). Three participants (8.3%) reported an acute worsening in pain, and one participant reported no acute change. When asked about duration of pain changes, many participants (n = 25 or 69.4%) noted lingering improvements in pain, lasting for one to two days or longer. Retrospective pain ratings were provided from 33 of the 36 participants and are presented in Figures 2, 3, 4, 6, and 7 by corresponding substance/dosage type. Means from the retrospective pain ratings are also shown in Table 11.

Table 10. Direction of pain changes by psychedelic substance.

	Any*	LSD	Psilocybin (micro)	Psilocybin (full)	Mescaline	DMT
	n = 36	*n* = 6	*n* = 9	*n* = 20	*n* = 2	*n* = 1
Increased Pain	4	2	1	1	0	0
During	3	2	0	1	0	0
Following	1	0	1	0	0	0
Decreased Pain	35	5	9	19	2	1
During	32	3	9	18	2	1
Following	25	5	4	14	2	1

Note. "During" refers to acute changes in pain during the active period of psychedelic drug effects. "Following" refers to changes present after that period, of any duration. Five participants reported experiencing both increases and decreases in pain either during or after the acute effects of the drug.

Table 11. Means of retrospective pain ratings by psychedelic substance.

	Average Pain Rating (0-10)				
	Prior to use	During	Immediately After	Short-term	Longer-term
Substance	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*	*M(SD)*
LSD	6.2(2.3)	4.5(3.8)	2.0(1.4)	3.0(2.4)	4.2(2.6)
Mescaline	7.0(4.2)	3.5(5.0)	3.0(2.8)	2.0(1.4)	4.0(1.4)
Psilocybin (micro)	7.3(2.1)	3.3(2.3)	5.0(2.8)	5.4(1.8)	5.9(2.3)
Psilocybin (full)	7.2(1.6)	1.6(2.1)	1.9(2.3)	2.7(2.6)	4.7(2.7)

Note. Total *N* for retrospective pain ratings = 33 *(*LSD, *n* = 6; mescaline, *n* = 2; psilocybin, microdose, *n* = 8; psilocybin, full or macrodoses, *n* = 17). "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer. Pain ratings were not provided from the 1 participant who described a change in pain with the use of DMT.

Pain Changes with Use of Psilocybin Mushrooms

Twenty-nine FM participants reported pain changes with use of psilocybin (nine using microdoses, and 20 using full or macrodoses [low dose, *n* = 2; moderate/medium dose, *n* = 8; high dose, *n* = 6; very high dose, *n* = 1; don't know or unspecified, *n* = 3]).

Of these 29 participants, 27 (93.1%) described reductions in pain, while two (6.9%) described pain amplifications.

Among the nine FM participants who described pain changes with microdosing, four reported regular use for pain relief. Dosage schedules varied from one to five days a week. All nine participants reported acute reductions in pain intensity, lasting up to four to six hours (Figure 2). One of the nine reported experiencing worse pain on the day following use.

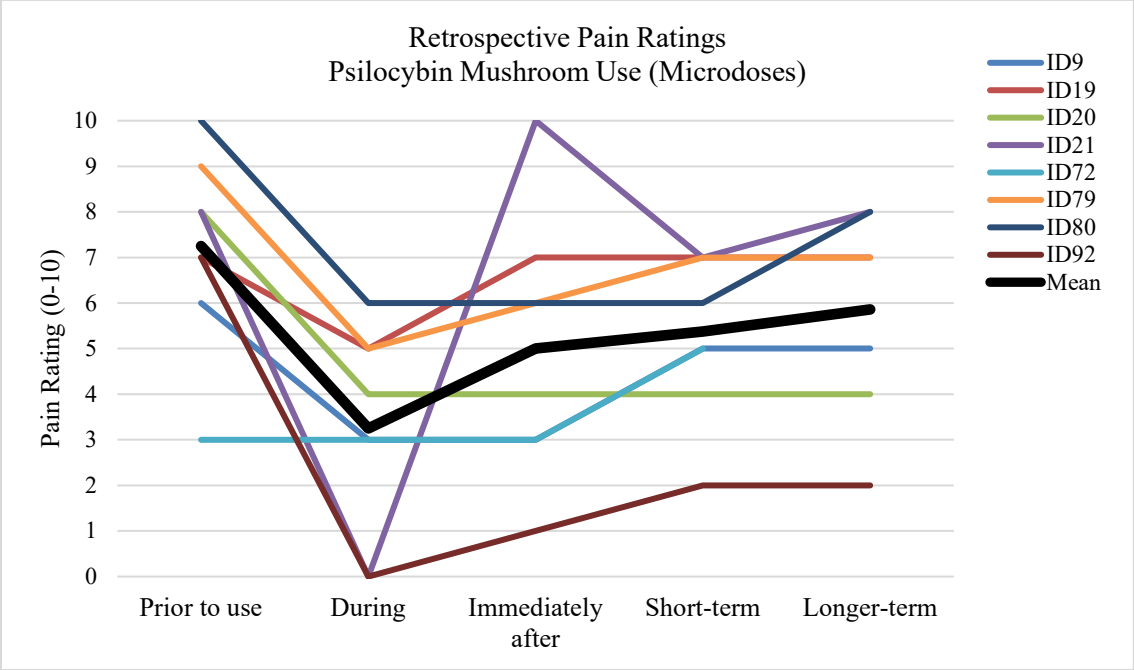

Figure 2. Retrospective pain ratings – Psilocybin microdoses.

Note. Ratings were provided by 8 individuals who reported use of microdoses. The mean ratings for these 8 individuals are displayed by the thicker black line. "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer.

Of the 20 FM participants who endorsed pain changes with use of psilocybin macrodoses (Figures 3 and 4), 18 reported acute pain reduction and one reported pain amplification. One participant reported no acute pain change with use, but a subsequent reduction in pain below their baseline level for up to one week. Thirteen of the 20 participants described enduring periods of pain reduction ranging from one or more days to months after use. Six individuals with FM reported regular use of psilocybin macrodoses (weekly or biweekly) to alleviate pain. Durations of pain reduction and associated psilocybin dosage types are depicted in Figure 5.

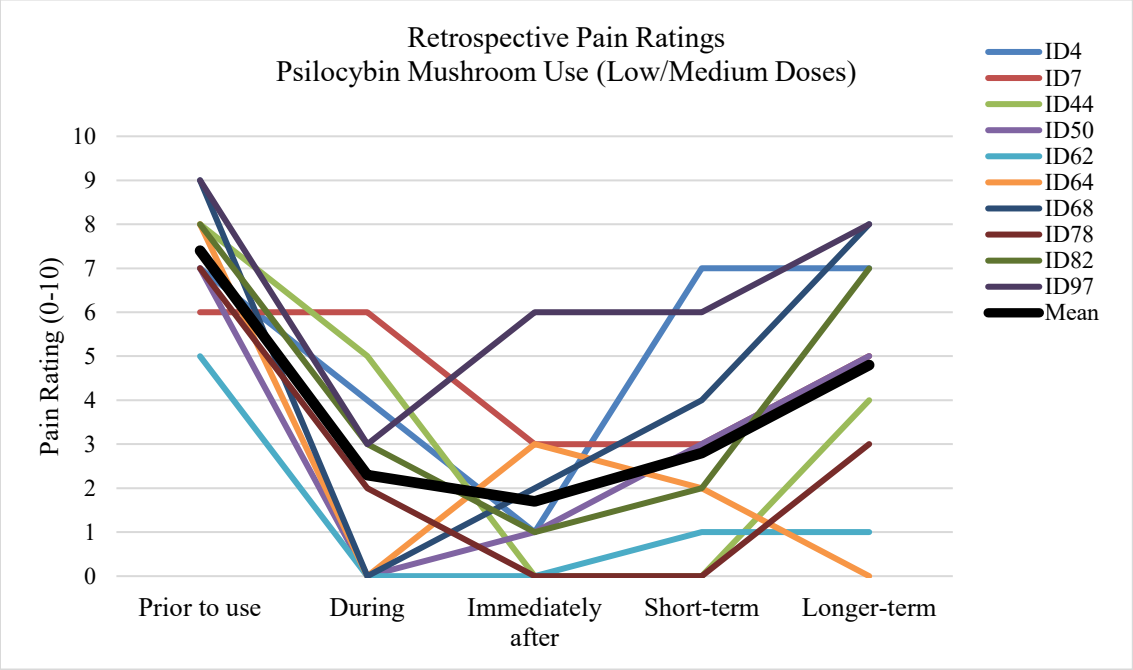

Figure 3. Retrospective pain ratings – Psilocybin low/medium doses.

Note. Ratings were provided by 10 individuals who reported use of low or medium doses. The mean ratings for these 10 individuals are displayed by the thicker black line. "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer.

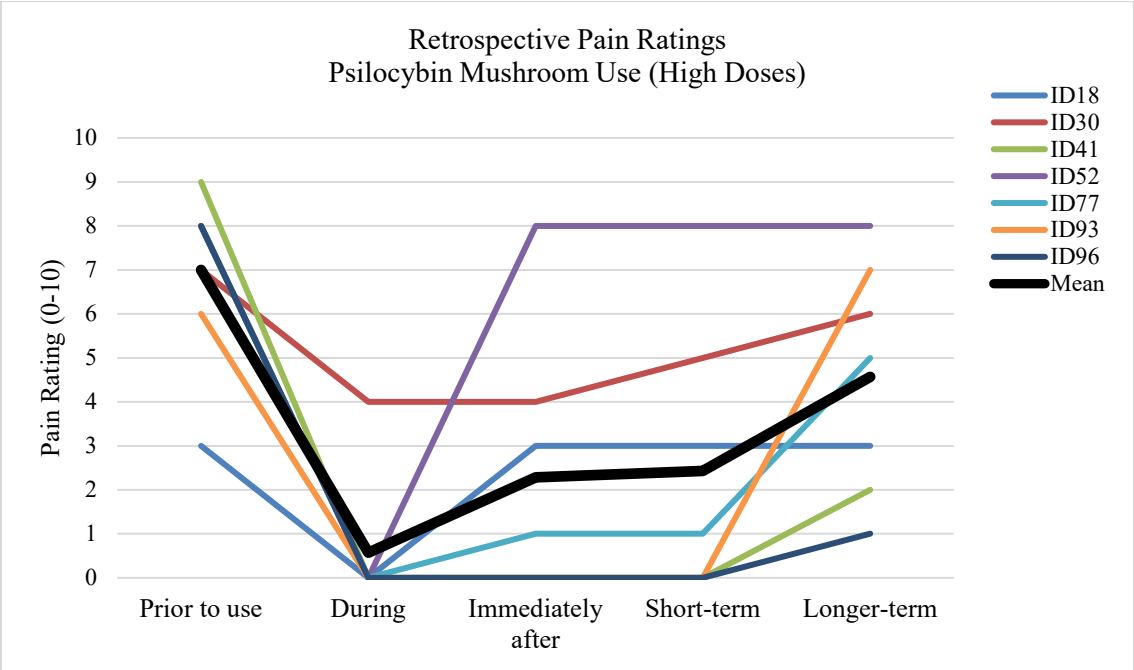

Figure 4. Retrospective pain ratings – Psilocybin high doses.

Note. Ratings were provided by 7 individuals who reported use of high or very high doses. The mean ratings for these 7 individuals are displayed by the thicker black line. "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer.

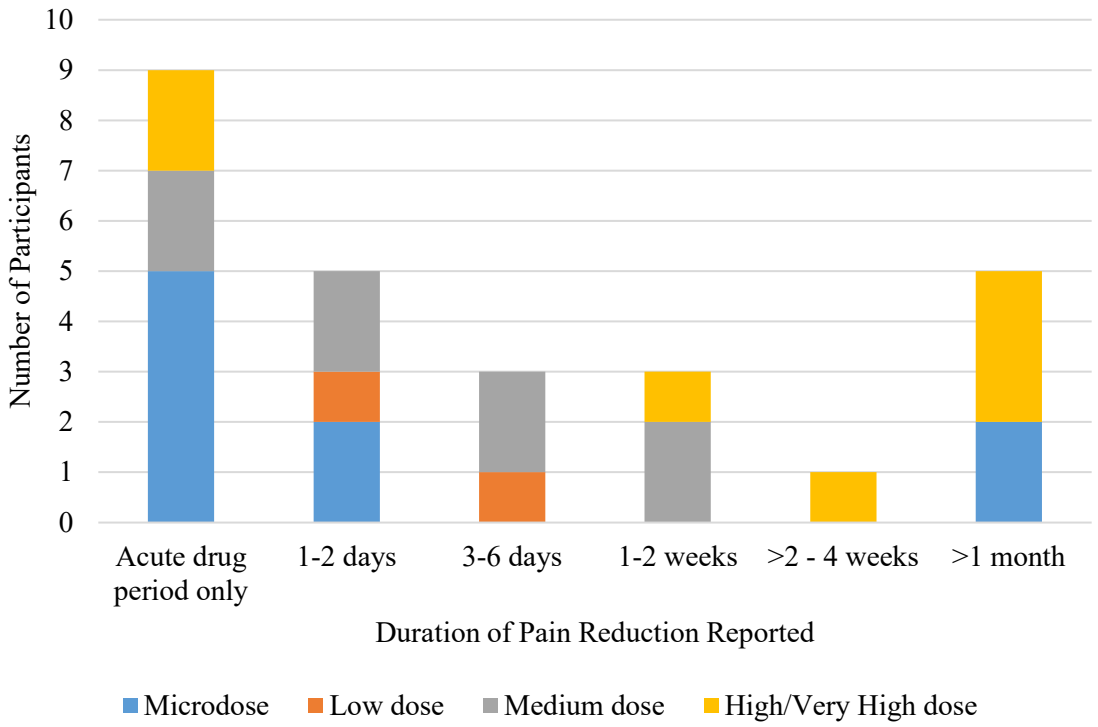

Figure 5. Duration of pain reduction by psilocybin dosage type.

Note. The two individuals who microdosed and reported reductions in pain lasting greater than 1 month did not report dosing schedules.

Pain Changes with Use of LSD

All individuals who endorsed pain change(s) with use of LSD described having taken a medium or moderate dose (n = 6) (Figure 6). Two of the 6 participants reported acute increases in pain. One of the two with pain increases experienced a return to their baseline pain level following the period of acute drug effects. The other participant reported a subsequent reduction (below their baseline pain level) for several weeks. Of the remaining four participants, one reported no acute pain change, and three experienced acute pain reductions. All four described reductions in pain following LSD use, lasting several days, up to a month or longer.

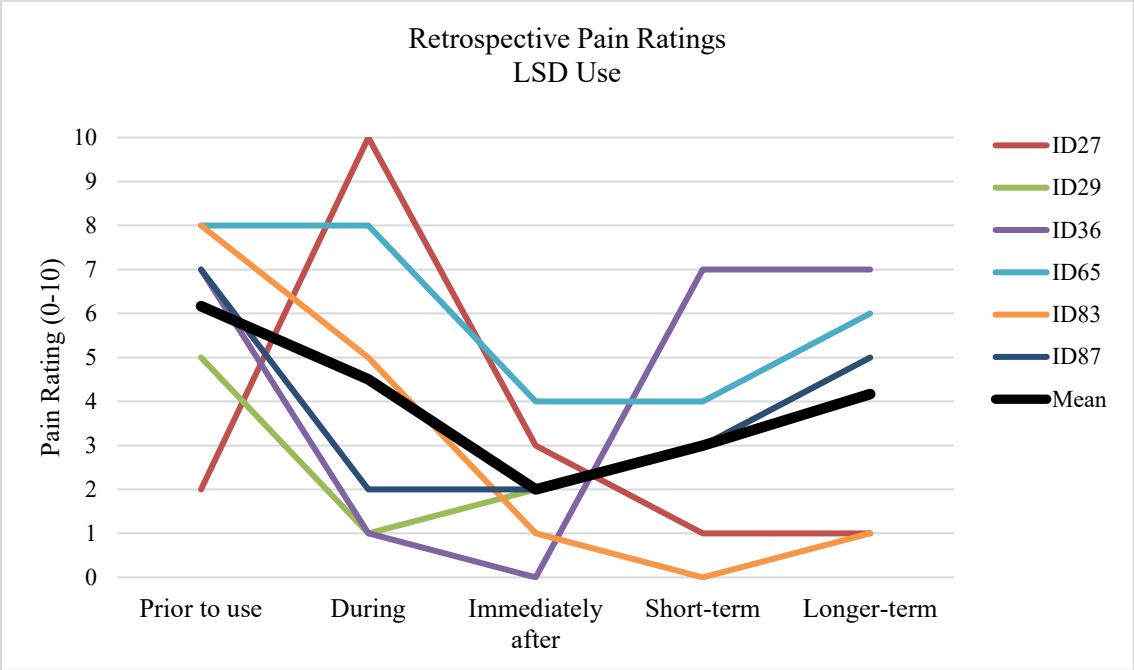

Figure 6. Retrospective pain ratings – LSD.

Note. Ratings were provided by 6 individuals who reported use of LSD. The mean ratings for these 6 individuals are displayed by the thicker black line. "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer.

Pain Changes with Use of Other Classic Psychedelics

One participant reported regular use of DMT for pain, and two participants reported mescaline-related pain changes (Figure 7). For mescaline use, both participants described reductions in pain during the period of acute drug effects and immediately afterwards (ranging from 24 to 36 hours). DMT use was described as helpful for pain by a participant who also reported benefit from psilocybin for pain. DMT dosage information was not provided.

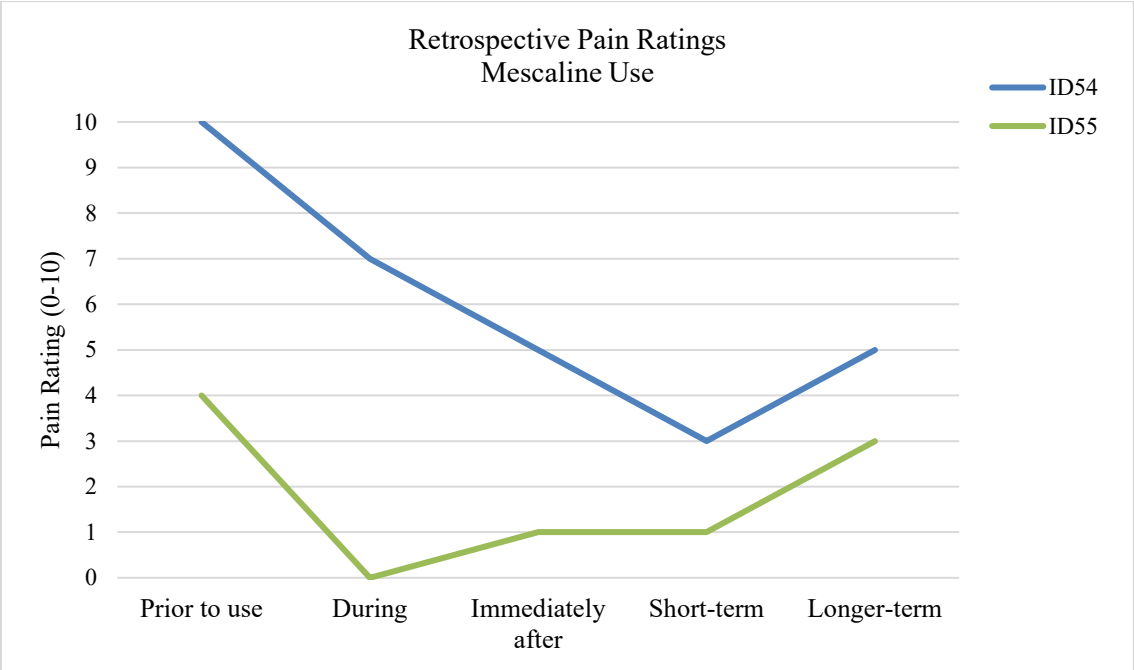

Figure 7. Retrospective pain ratings – Mescaline.

Note. Ratings were provided by 2 individuals who reported use of mescaline. "Immediately after" was specified in the survey as in the 1-2 days following use, "short-term" as within 1 week following use, and "longer-term" as over the next month or longer.

Impact of Psychedelic Use on Pain

Thirty-six participants in the FM group provided written responses regarding the impact of psychedelic use on their pain. Impacts on pain were grouped into two major categories: (1) changes in pain and physical sensations; and (2) changes in an individual's relationship with pain (Table 12).

Table 12. Impact of classic psychedelic use on pain.

Category	Subcategory	Frequency of cases *n* (% of 36)
PAIN AND PHYSICAL SENSATIONS		
During use	Pain reduced	32 (88.9%)
	Pain increased	3 (8.3%)
	Body relaxation	6 (16.7%)
	Feeling of lightness	4 (11.1%)
	Feeling connected to body	2 (5.6%)
	Moving without pain	3 (8.3%)
Following use	Pain reduced	25 (69.4%)
	Pain increased	1 (2.8%)
RELATIONSHIP WITH PAIN		
Change in pain-related distress	Improved coping with pain	5 (13.9%)
	Provided distraction from pain	2 (5.6%)
	Changed perspective on pain	3 (8.3%)
	Control over pain	2 (5.6%)
	Pain as separate from self	1 (2.8%)
Functional improvement		6 (16.7%)
Reduced use of pain medication		11 (30.6%)

Changes in Pain and Physical Sensations

Reduced pain. Thirty-two participants described acute reductions in their pain, or periods of complete pain relief, during psychedelic use. For most of them (n = 23), pain intensity decreased or was dulled. For nine participants, pain went away completely for a

brief period, as one described, “During the experience I didn’t feel pain” (ID7/psilocybin). Another individual wrote that their “pain disappeared from all areas as if it didn’t exist nor ever had for 4 hours” (ID21/psilocybin). Among those whose pain reduced, several (n = 3) likened the effect to decreasing the volume on a dial: “It was like the volume knob was turned down significantly” (ID97/psilocybin).

Twenty-five participants described reductions in their pain that extended past the period of acute drug effects. Over half of this subset of participants (n = 14) reported pain relief enduring from one to five days after psychedelic use. Other periods of pain relief ranged from one to four weeks (n = 6), and up to a month or longer (n = 5). The following participant shared about the change they experienced for several weeks after an experience with psilocybin, “The constant aching/throbbing pain I feel throughout my body subsided to a minimal or nonexistent level following the experience for about 2 weeks. I went from crying in pain every day to almost feeling normal again” (ID77).

Some participants described regular, ongoing use of psychedelics for pain relief (psilocybin microdoses [n = 4], psilocybin macrodoses [n = 6], mescaline [n = 1], and DMT [n = 1]). After years of struggling with FM in addition to functional neurological disorder, regular use of psilocybin macrodoses had helped one person get rid of their pain completely, as they described:

> For a decade my fibromyalgia never let up. Then when I started taking psilocybin it went away 80% of the time after a few weeks. Then after a couple months of weekly psilocybin therapy (3-5 grams) my pain has stopped completely. (ID96)

Increased pain. Three participants described acute increases in pain intensity (two with use of LSD, and one with use of psilocybin). One of these participants shared about a particularly uncomfortable experience, despite having had positive experiences with LSD previously:

> I have used psilocybin and lsd many times in the past and had wonderful experiences and very significant spiritual experiences but this was the first time I used LSD since I developed fibromyalgia and it caused the most intense pain flare up imaginable. It felt like I was being burned alive on my back and neck and the back of my head at the base of my head. I would have given anything for it to stop. (ID27)

This individual considered presenting to the emergency room due to the intensity of their pain. Another participant described tense body aches with acute use of LSD, followed by a pain reduction (below their baseline pain level) for several weeks. In addition to increases in pain reported with use of LSD, one participant reported worsened pain the day after microdosing psilocybin.

Body relaxation. Six participants described feeling physical relaxation and release from tension. For one, a sense of relaxation precipitated the acute disappearance of their pain. They wrote, "As soon as the effects begin and the whole body relaxation starts, my pain immediately vanishes and I overall feel lighter." (ID50/psilocybin)

Feelings of lightness. Pain reduction was accompanied by a sense of lightness for four participants (including the one quoted immediately above). Another participant

described this acutely as a “feeling of weightlessness - as if you're in a pool” (ID70/psilocybin). A different participant shared how “the heaviness of pain had retreated” (ID7) over several days following psilocybin use.

Feeling connected to body. Two participants wrote about feeling more connected to their bodies with psychedelic use. For one, this connection also involved a greater sense of acceptance: “I felt very connected to my body, instead of aware and resistant to its experience” (ID57/psilocybin).

Moving without pain. Three participants described how much they enjoyed getting up to walk or stretch without their usual sensations of pain during the acute period:

> I remember reaching this point where it felt like I could stretch out every muscle in my body, and it felt insanely good that I could move and not wince in pain … I’d been having trouble doing basic things like getting up. When that point came that the pain went away, I remember stretching out my back as much as I could because I actually could do it. It was such a relief to not have that pain that had been gnawing at me for weeks. (ID64/psilocybin)

Changes in Relationship with Pain

In addition to changes in pain itself and other physical sensations, participants described how psychedelics had influenced their relationship with pain. These changes involved coping, distraction, perspective, functional improvement, and use of pain

treatments. Other interesting reports included descriptions related to control over pain and viewing pain as separate from oneself.

Coping with pain. Better pain coping, or management, was described by five participants. One participant described how they experienced benefits in coping for longer than they noticed actual pain reduction. They shared:

> I experience total lack of pain during the trip and up to a day after. For the next 3 to 5 days I experience greatly reduced pain and for the next 2 weeks I experience pain closer to my average but I am able to cope far better than without having taken mushrooms. (ID50)

Psychedelics were helpful for another participant in coping with the despair and isolation their chronic pain had caused:

> I struggle with despair; I used to be very fit and healthy and now I can injure myself so easily I can barely keep up with basic activities of daily living…There's so much that I loved to do…that's just beyond me now. I feel that psychedelics do a great job of helping me manage that despair, and cope with the aloneness/isolation that chronic pain can cause. (ID30)

Perspective on pain. Three participants wrote about changes in their perspective on pain. When discussing an experience with psilocybin, one participant shared, *"*It helped me get a better perspective on how pain was interacting with my life, as well as when my mental state was amplifying pain from a sensation into a cause of suffering*"* (ID18). Also, in results from a close-ended question in the survey, more than half of the

36 participants endorsed having experienced changes in their perspective on pain, during (n = 19 or 52.8%) and/or following (n = 21 or 58.3%) psychedelic use.

Distraction from pain. Two participants described the effect of psychedelic use on their pain as an acute distraction. One of these participants shared that they had been hoping for more of a lasting perspective change (which they did not experience), but that psilocybin "did offer a distracting experience that was pleasant for someone whose life in bed was like groundhog's day everyday" (ID8).

Control over pain. Two participants described an enhanced sense of control over pain. For one, this sense occurred following an emotional interaction with a vision of their younger self and a feeling of release:

> I looked down at my younger self, locked eyes, and told him everything was ok. In that moment I felt love and as if I released something. I then came back to my present and felt as though all of my ability to feel was being shut down limb by limb until I was numb. I felt as though this meant I could control pain. (ID41/psilocybin)

Pain as separate from self. For another participant, in addition to a sense of control, their experience with LSD involved imagery in which pain was depicted as malleable figures, separate from oneself: "Pain spasms were entities that appeared like cartoon figures I could crush like paper and throw it away. I was able to stop them at their entrance and the pain was gone for a day" (ID36).

Functional improvement and mobility. Six participants shared about improvements in physical functioning and mobility. Despite their pain remaining at the same level, one participant noticed increased activity while microdosing psilocybin:

> I have noticed that sometimes I might be in the same amount of pain that I have been in without the psilocybin, but I have also increased what I do during the week. I used to be bed ridden and not be able to wash my hair, but now I can maybe wash my hair once every other week and I am doing daily yoga, where I used to do none. (ID19)

Use of pain treatments. Thirteen participants reported changes in their use of pain treatments following psychedelic use. Eleven of the thirteen reduced their use of analgesic medications, including opioids, gabapentin, muscle relaxants, and others. One participant described not needing as much pain medication as previously following a period of microdosing: "I cut my pain meds completely while using, since I have been unable to locate a reliable source of psilocybin I have started taking pain meds but half as much as before" (ID72). Another participant with a history of long-term opioid analgesic use reported, in relation to microdosing psilocybin, "My pain decreased and allowed me to completely taper off tramadol. I had been on opiates over 10 years and it finally helped me get off of them" (ID19). A couple participants also reported seeking out new pain treatment or management methods following psychedelic use, such as working with a pain psychologist.

Beliefs about Why Pain Changed

When asked why they thought they had experienced a change in their pain, participants suggested possible physiological effects, positive emotional changes, relaxation, and improved coping. Nearly all the responses provided to this question were from individuals who reported positive impacts of psychedelic use on their pain.

Eleven participants said they were unsure why their pain had changed, most of whom went on to contemplate possible reasons. For others, understanding why their pain had changed was not important, as one participant shared, “I have no idea and frankly, I don't care. I just know that I took mushrooms and a little while later, I could live life for a while without pain” (ID76).

Physiological Changes

Twenty-two participants hypothesized about potential physiological effects leading to changes in pain, particularly via the brain or nervous system. Neural rewiring and/or neuroplasticity was mentioned by five individuals, and three participants wondered whether changes in specific neurotransmitters (dopamine or serotonin) could have played a role. One participant pondered whether psychedelics had helped reduce inflammation. The following participant likened the change they imagined within their brain to freeing up space on a computer:

> I figure that my brain learned to send improper signals that there was something wrong with my central nervous system. Which there was nothing wrong in the 8 mri’s that I’ve had of my CNS. I think of psilocybin as clearing the cache on your brain like you would your computer so that it unlearns unhealthy habits that don’t

> serve you properly. Now I'm creating new habits that are healthier and helpful. Some thing [*sic*] that western medicine could not do for me. (ID96)

Reduced Psychological Pain

Three participants discussed their improvements in physical pain as being driven at least in part by reductions in their psychological or emotional pain with use of psychedelics. One participant had described confronting loneliness and trauma during their experience with psilocybin, eventually reaching their inner self and feeling love and joy. When asked why they believed their pain had changed, they wrote, "The psychological pain that affected my nervous system had been relieved" (ID7). Another participant described having "let go" of issues contributing to their pain: "I feel like shrooms allow me to "let go" way more than I'd be able to without them. By that I mean let go of whatever I'm carrying around that's causing physical or emotional pain" (ID64).

Relaxation and Mind-Body Connection

Four participants suggested that psychedelics had helped their pain by promoting relaxation. In the following excerpt, a participant described the changes they noticed with use of psilocybin. In addition to changes in physical and mental relaxation, they note shifts in their perception of pain and the amount of attention directed towards it, comparing the experience to biofeedback:

> I believe that it alters how I perceive pain and makes it less of a priority and less startling to me, therefore lessening my body's reaction over all. It also forces full body relaxation as well as mental relaxation both of which no doubt contribute to

> the dampening effect. It reminds me of the bio-feedback therapy I had been given when I was 17 wherein they had me relax my body fully, make myself completely aware of the pain and then dismiss it as a way of coping. A method that I had found to be very effective. (ID50)

Acceptance

Two participants suggested acceptance of pain as a potential mechanism of change. For one participant, pain did not completely go away but they noticed being better able to cope with it. When asked why their pain had changed, they responded, "Maybe because it's mentally easier to accept my pain? It doesn't make it go away entirely, it just makes it easier to cope with, perhaps?" (ID30)

Awe

One participant connected their experience of surrender and awe with use of mescaline to their reduction in pain, writing, "there's a surrender that happens, a surrender to oneness and I think the mind is so in awe with that it takes away from the physical pain" (ID55/mescaline).

RQ 4: Impact of Psychedelic Use on Other Symptoms

In addition to pain-related changes, 31 participants endorsed changes in their mental health with psychedelic use, and 25 participants reported changes in other FM symptoms, including brain fog, fatigue/energy, and gastrointestinal issues (Table 13).

Table 13. Other changes reported with psychedelic use.

	Frequency of cases
	n (% of 36)
Improved mental health/well-being	31 (86.1)
Relieved depression	13 (36.1)
Lowered anxiety	10 (27.8)
Helped with processing trauma	6 (16.7)
Improved other symptoms of FM	25 (69.4)
Reduced fatigue/energy	6 (16.7)
Reduced brain fog	7 (19.4)
Reduced GI issues	4 (11.1)
Reduced light and/or noise sensitivity	2 (5.6)

Note. Only participants who answered "yes" or "don't know" to whether they experienced a change in pain with use of a psychedelic were presented with questions related to changes in mental health, quality of life, and other symptoms of FM.

Mental Health Symptoms

Depression and Anxiety

Among participants with FM, psychedelic use was associated with reported improvements in depression (n = 13) and anxiety (n = 10). One participant wrote, "In addition to physical pain relief, I experienced a reduction in anxiety and depressive feelings. These effects lasted as long as for [*sic*] the physical pain and helped me manage stress for up to a few days after usage" (ID97/psilocybin). Another participant described effects on anxiety lingering for up to a month:

> Using psychedelics always eases my anxiety disorder and helps me realize that I should only worry about the things that I can control. It sort of resets my brain in a way that allows me to live with minimal to no anxiety for up to a month after each experience. (ID77/psilocybin)

Increases in anxiety were also reported with psychedelic use, as well as symptoms of fear, paranoia, and increased irritability (for details, see below section on Negative Effects).

Trauma

Six participants with pain-related changes reported that psychedelics had helped them with processing trauma. In addition to experiencing substantial relief from pain, one participant reported lasting reductions in depression, anxiety, and trauma symptoms, stating, “I was free from depression for about 3 months and my anxiety didn’t begin to return until 6-8 weeks post experience…I was still aware of the trauma I had been through, but I began processing and accepting it” (ID41/psilocybin). Similarly, psychedelic use helped another participant “move through some emotions” related to PTSD and their role as a caretaker, stating, “I no longer feel like I'm fighting to swim up-stream and have the ability to flow with the current” (ID55/mescaline).

Brain Fog

Seven participants noticed improvements in their cognitive symptoms, or brain fog, after using psychedelics. Having written about their experience with microdosing psilocybin, one participant shared, “I felt like my brain was not as heavy, tense and foggy” (ID92). Another participant, with both FM and ME/CFS, described their surprise at experiencing a clearing in brain fog with psilocybin use, which endured for several months:

> Something that was extraordinary to me was how my usually debilitating brain-fog was GONE. I didn't have problems connecting my thoughts to my speech, which usually disturbs me greatly. I usually have extreme monkey-mind, but I had no issues connecting my thoughts in my head. Word retrieval wasn't an issue. It was the longest I held a conversation without anxiety, an ME/CFS crash, or general brain fog in years. (ID57)

Fatigue/Energy

Reduced fatigue or increased energy was reported by six FM participants who had used psilocybin. Most of these participants reported use of microdoses, though one had experienced fatigue improvement with use of a macrodose. For one of the participants who microdosed, reduced fatigue was accompanied by improved sleep. Increased fatigue was reported by one participant following use of psilocybin (for details, see below section on Negative Effects).

Gastrointestinal Problems

Four participants described improvements in gastrointestinal or digestive issues. After use of a moderate dose of psilocybin, one of the four noted, "My IBS was completely cured for a few days. I had no stomach pain or abdominal pain, nothing upset my stomach, I could eat whatever I wanted and I enjoyed food for the first time in a long time" (ID44). Eight participants reported gastrointestinal upset with psychedelic use (for details, see below section on Negative Effects).

RQ 5: Factors Associated with Positive and Negative Impacts on Pain

Among those who reported pain changes with psychedelic use, most participants described having positive overall experiences with psychedelics. Several participants, however, reported negative experiences or effects from psychedelic use, including increased pain and other unpleasant symptoms.

Negative Effects

Fifteen individuals with FM reported negative effects in relation to their psychedelic use (Table 14). These individuals either responded "yes" to a close-ended item regarding negative effects, or they described negative effects within free-text responses. The most frequently mentioned negative effects were gastrointestinal upset (n = 8) and emotional distress (n = 8). Other symptoms included increased pain, headache/migraine, fatigue, difficulty sleeping, and feeling cold. Most negative effects occurred during the period of acute drug effects, though four individuals reported symptoms occurring one or more days after use.

Gastrointestinal Upset

Gastrointestinal upset was reported by eight participants, seven of whom experienced nausea and/or vomiting during the period of acute drug effects. These participants had either used psilocybin (macrodoses) or LSD.

Table 14. Negative effects reported with psychedelic use.

	Total	Acute	Day or more following use
	n (% of 43)	*n*	*n*
Any negative effects	15 (34.9)	12	4
Pain increase	4 (9.3)	3	1
Headache/migraine	2 (4.7)	1	1
GI upset	8 (18.6)	7	1
Nausea		4	1
Vomiting		3	
Acid reflux			1
Felt cold	2 (4.7)	2	
Fatigue	1 (2.3)		1
Difficulty sleeping	1 (2.3)		1
Emotional distress	8 (18.6)	6	2
Fear		2	
Anxiety		4	
Paranoia		2	
Flashbacks			1
Irritability/sensitivity			1

Note. Some participants reported multiple negative effects.

Distressing Psychological Symptoms

Negative emotional experiences were described by eight participants, ranging from mild anxiety to fear and paranoia. One participant described difficulty with sleep and flashbacks following use of LSD.

Increased Pain

As noted in the results section for RQ 2, four participants reported intensification of pain with psychedelic use. Two of the four experienced acute worsening of pain with LSD. The other two participants had used psilocybin, one of whom described acute body aches during use of an unspecified dose. The other participant reported worse pain the day following microdosing psilocybin, as they described, “The only negative effect is the

day after I am extremely exhausted and pain is worse" (ID21). The participant who experienced a strong pain intensification during use of LSD wrote that in general they had noticed changes to their response to drugs since developing FM. They also had been experiencing a pain flare on the day of their LSD use, as they described:

> I have had many changes to my response to drugs since I developed fibromyalgia…I had previously taken the same batch of the tabs a year or two ago with no effect besides feeling tired more quickly, but that day I was having a "flare up" and went ahead with taking the lsd anyway. (ID27)

Preparation and Additional Characteristics of Psychedelic Use

Preparation

Of the 36 participants with FM who reported a change in pain with use of a psychedelic, about half (n = 17) answered "Yes" when asked whether they prepared in some way prior to their use. Several forms of preparation were described, including self-preparation, preparing the setting, talking with others about their plans to use a psychedelic, and preparing the substance/dose itself. Participants described preparing themselves mentally and physically by reading about what to expect with use of psychedelics (n = 1), dedicating time to the experience (n = 4), setting an intention (n = 4), engaging in a relaxing and/or mindful activity (n = 7), monitoring their mindset (n = 1), and getting enough sleep, staying hydrated, and eating healthily or fasting prior to use (n = 7). Two participants described stopping use of certain medications with known contraindications prior to psychedelic use. Notifying someone about their plans, and/or arranging to have social support available, was described by four individuals.

Setting

Several participants (n = 5) wrote about the importance of having a comfortable setting for the experience. Most participants (n = 31) reported location of use as their home or the home of a friend, partner, or family member. About a third (n = 11) described being alone at the time. Three individuals mentioned having someone present to assist if needed, such as a "sitter", and one participant was with a shaman during their experience. Two individuals reported having integration sessions with a therapist.

Subjective Experience Ratings

Insight. Among the 36 participants with pain changes, twenty-three (63.9%) reported their experience had been psychologically insightful ("extremely insightful" = 11, "moderately insightful" = 7, "mildly insightful" = 9, "not at all insightful" = 4).

Meaning. When asked whether their psychedelic experience had been profound and personally meaningful, eighteen (50%) responded "Yes".

Awe. When asked whether they had experienced awe, wonder, or amazement with use of a psychedelic, 20 (56%) of the 36 participants with pain changes selected from "somewhat" to "completely".

Intensity. Participants rated the intensity of their psychedelic experience as "mildly intense" (n = 8), "moderately intense" (n = 12), "strongly intense" (n = 7), or "overwhelmingly intense" (n = 5).

Spiritual. Participants were asked whether they had a spiritual or mystical experience during their use of psychedelics. About 40% (n = 15) of those who had experienced pain changes responded "Yes" to this item.

Additional Changes Following Psychedelic Use

Behavioral Changes

Several close-ended items assessed whether participants with psychedelic-related pain changes experienced behavior changes following psychedelic use. In response to these items, participants endorsed changes in physical activity/exercise (n = 16), relationships (n = 16), and social activity (n = 13). When these changes were elaborated upon in free-text responses, participants generally described increased physical activity. For example, one participant described how psilocybin had helped them "make a recommitment to practices (meditation, yoga) that are useful for pain management" (ID18). Participants reported that psychedelic use had improved their social functioning and deepened their relationships. It had also prompted two participants to leave unhealthy relationships. Other behavioral changes reported following psychedelic use included reduced alcohol (n = 2) and cannabis use (n = 2).

Quality of Life

More than two-thirds of participants with pain changes (n = 20) answered "Yes" when asked whether they had experienced changes in their quality of life following psychedelic use. Six participants denied experiencing such changes. Among those who provided additional detail, participants' written responses generally indicated perceived improvement in quality of life.

Reset

Eight participants described psychedelics as providing them with a "reset", be it physically, mentally, or both. For example, one participant expressed, "Shrooms kinda give me a small reset in physical and emotional functioning" (ID64).

Practicality, Support, and Access

In addition to reports about psychedelic use and symptom changes, several participants shared concerns about practicality, support, and access to psychedelics. Concerning practicality, four participants reported taking full or macrodoses of psilocybin on a weekly to biweekly basis to help their pain. Though they described several benefits from this pattern of use, a couple of them found the schedule difficult to maintain. The repeated dosing could become impractical, as one participant wrote:

> Despite my success with this treatment, I found it difficult to cope with having a profound psychedelic experience that frequently, especially while trying to care for young children, doing my job, and managing my household. Giving up 6 hours a week or more often is difficult for busy humans. I'm very good at coping

> with pain and pushing through as I've been doing it my whole life and that seems somehow better than mucking around with tripping so much. I still can and will take psychedelics for a break when needed, but it takes a few doses to have effect and things actually get worse after the first dose so I have to set aside time for it all. My kids are getting older now so I might get back to it eventually. (ID4)

For another participant, the use of full doses of psilocybin provided some pain relief, but the effects were not long-lasting enough for them to continue. They noted a desire for more ongoing pain reduction, without interference in functioning, and became interested in trying microdosing for these reasons. Describing their experience with pain and macrodoses, the participant explained:

> I felt that it was short-lived relief. I was concerned about having to ingest too much over time, which leads me to believe that microdosing may be a much better way to go… I liked that it was gone and out of my body soon, too. If so, that would be awesome for the bad days. It meant that 24 hours later, I could go right back to work, driving and be legal and safe. Mj doesn't have that quality, sadly…I think that microdosing is my next experiment with pain. I'm wondering, [*sic*] if I can control pain with small amounts at regular intervals. (ID52)

On the other hand, some participants who had tried micro- or lower doses of psilocybin expressed interest in using higher doses to see if effects may be stronger and more durable for their pain, but they were concerned about doing so without additional support. Several participants also shared about their desire for increased access to psychedelics, more psychedelic research, and decriminalization.

DISCUSSION

This study examined reports of naturalistic psilocybin mushroom and other classic psychedelic use among individuals with FM. In an online survey, a combination of close-ended and open-ended items assessed characteristics of past use and related changes in pain or other symptoms. No hypotheses were established given the descriptive, exploratory nature of the study.

Of the 102 total responses received from individuals with chronic pain and past classic psychedelic use, 64 met self-report criteria for FM or reported an FM diagnosis. Use of psilocybin mushrooms was most often reported, followed by LSD, and over a third of participants with FM described pain-related reasons for use. Over 50% of those with FM (n = 36) reported experiencing any change in pain with psychedelic use. The direction of change was a reduction in pain for most participants (n = 32 or 88.9%), varying in duration from hours to days, and sometimes longer. Improvements in cognitive symptoms, fatigue, and gastrointestinal issues were also reported by a small subset of participants.

Several of the main findings will be discussed below, beginning with the use of psychedelics for the purpose of self-medicating. Reports regarding reductions in pain and other FM symptoms with psychedelic use will then be discussed, followed by potential factors involved in pain-related changes and negative experiences. Finally, a summary of limitations, future directions, and conclusion will be presented.

Self-Medicating with Classic Psychedelics

Self-medicating with psychedelics for mental or physical health issues was frequently reported among FM participants in this study. When asked about their reasons for psychedelic use, about half of the FM participants (n = 34 or 53.1%) endorsed wanting to improve their mental health in some way, and over a third (n = 22 or 34.4%) described pain-related reasons. These results are generally consistent with findings suggesting health-related motives as common among users of psychedelics (Glynos et al., 2023; Mason & Kuypers, 2018; Matzopoulos et al., 2021; Pestana et al., 2021). In a large online survey of U.S. adults (weighted N = 251,297,495), use for general mental health and well-being was reported by nearly two-thirds of individuals that used psilocybin mushrooms (Matzopoulos et al., 2021). In that same survey, nearly a third of those that used psilocybin mushrooms reported doing so to manage a diagnosed mental health condition. Self-medicating for various health reasons is also frequently reported among individuals who microdose psychedelics (Hutten et al., 2019; Lea, Amada, Jungaberle, Schecke, & Klein, 2020; Lea, Amada, Jungaberle, Schecke, et al., 2020; Rootman et al., 2021).

Few prior studies have examined motives for psychedelic use specifically in chronic pain or FM populations. In a survey among individuals with FM by Glynos et al. (2022), fun/recreation and spiritual/psychological/personal exploration were the most frequently reported reasons for psychedelic use. These motives were also frequently endorsed in the present study. Use for self-medicating purposes (i.e., treatment of chronic pain, improving mental health, and managing past trauma) was reported among individuals with FM in the survey by Glynos et al. (2022), though at relatively lower

rates. It is possible that due to differences in recruitment/eligibility, the current study included more individuals who had used psychedelics for pain or mental health reasons. It is also possible that the practice of self-medicating with psychedelics could be gaining popularity among those with FM.

Reductions in Pain with Psychedelic Use

About half of the FM participants in this study endorsed any change in pain with past use of a classic psychedelic. Among that subset of participants, most (88.9%) described an acute reduction in pain. Three individuals reported acute pain increases, and one described worse pain on the day following use. Overall, these results are similar to those by Glynos et al. (2022), in whose survey 50% of respondents with FM endorsed no change in chronic pain symptoms with past psychedelic use, 47.2% reported improved symptoms, and 2.8% indicated worsened symptoms. Results are also consistent with those of Bonnelle et al. (2022), in whose survey most individuals with chronic pain and past psychedelic use described pain reductions in relation to use (67.9% of those who had used microdoses, and 72.4% of those who used macrodoses).

Results further align with those of Bornemann et al. (2021), in whose qualitative study, 9 of 11 individuals with chronic pain reported acute pain reductions with psychedelic use, and 2 of 11 reported acute pain amplifications. Reported durations of analgesic relief ranged from about 3 to 7 days, with pain gradually returning to its baseline level, whereas psychological effects related to pain persisted longer (up to several months or more) (Bornemann et al., 2021). This pattern was similar to that observed in the present study, in which most participants described returns to baseline

pain levels within hours to days of use, but generally more durable changes in emotions and other psychological factors, such as improved mood, reduced anxiety, and improved pain coping.

Microdosing vs. Macrodosing

In this study, some individuals reported reductions in pain with use of microdoses, and others with macrodoses. In general, those who reported changes in pain with use of macrodoses tended to report greater magnitude and longer durations of pain reduction than those who microdosed. A similar trend was described by Cavarra et al. (2023) among a subsample of FM participants with past psychedelic use. In their study, macrodoses or full doses were associated with greater pain relief, relative to both conventional medications/cannabis and microdoses. Though based on subjective, retrospective reporting, data from the present study as well as past findings suggest potential pain-related dosage effects warranting further research.

Dosage effects may also interact with intentions related to pain. Among participants with chronic pain, Bonnelle et al. (2022) examined differences in perceived pain relief between those who had pain management intentions and those who did not. They reported that perceived pain relief with use of macrodoses did not differ by the presence of pain-related intentions. However, in the case of microdosing, participants who had used psychedelics with the intention of managing their pain reported greater pain relief. Also, in the survey by Glynos et al. (2022), nearly all the individuals with FM who reported pain treatment intentions described symptom improvement following psychedelic use (11 out of 12), though specific dosage types were not mentioned. Taken

together, pain-related intentions may influence perceived pain changes with psychedelics and could vary by dosage.

LSD, Mescaline, and DMT

Though most participants in this study who described pain improvement in relation to psychedelics had used psilocybin mushrooms, pain reductions were also described by five participants who had used LSD, two participants who had used mescaline, and one individual who had used DMT. LSD has previously been associated with pain relief in several case series with phantom limb pain (Fanciullacci et al., 1977; Kuromaru et al., 1967), a clinical study in severe pain related to terminal illness (Kast & Collins, 1964), and multiple studies involving cluster headache (Andersson et al., 2017; Di Lorenzo et al., 2016; Schindler et al., 2015; Sewell et al., 2006).

Compared to psilocybin and LSD, mescaline and DMT have been studied considerably less in relation to pain. Some Indigenous peoples have traditionally used peyote to reduce pain during childbirth and to treat pain associated with rheumatism, toothache, burns, and other conditions (Schultes, 1938). Interestingly, in a recent clinical study among participants without any major health conditions, significant increases in plasma oxytocin were observed following administration of mescaline, surpassing those elicited by LSD and psilocybin (Ley et al., 2023). Given oxytocin's potential for reducing pain sensitivity (Goodin et al., 2015; Mekhael et al., 2023), this characteristic of mescaline could be relevant for future investigations into its effects on pain.

A few reports of pain relief from use of DMT have been described in qualitative studies, including one among individuals with cluster headache and migraine (Andersson

et al., 2017), and a naturalistic field study which included an individual with FM (Michael et al., 2023). Also, in a case report involving use of *changa* (a combination of DMT and *Peganum harmala* seeds), an individual with chronic fatigue and FM experienced about 2 weeks of pain relief following several administration sessions (Ona & Troncoso, 2019).

Reductions in Opioid Use

Rates of prescription opioid use among individuals with FM have remained high (Bruce et al., 2021), despite their association with poorer outcomes and multiple clinical guidelines advising against their use (Goldenberg et al., 2016). In this study, several participants reported a reduced need for pain medications, including opioids, following use of psychedelics. It is possible that reductions in pain driven by psychedelics could indirectly reduce reliance on opioid analgesics. Reductions in opioid use following psychedelic use have been previously reported in multiple cross-sectional surveys (Glynos et al., 2023; Lea, Amada, Jungaberle, Schecke, et al., 2020) and a longitudinal survey (Fadiman & Korb, 2019). Reductions in opioid use following psychedelic use have further been reported among individuals with opioid use disorder (OUD) (Argento et al., 2022; Garcia-Romeu et al., 2019). Several clinical trials are currently planned or underway investigating potential application of psilocybin in OUD (NCT04161066; NCT06005662) and in the tapering of long-term opioid therapy for chronic pain (NCT05585229).

Impacts on Other Symptoms in FM

In this study, some participants reported improvements in mental health, quality of life, and other FM symptoms (i.e., cognitive symptoms, fatigue, gastrointestinal issues) following psychedelic use. Improvements in mental health have previously been reported in surveys of individuals who self-medicate with psychedelics (Hutten et al., 2019; Kopra et al., 2023; Mason & Kuypers, 2018; Raison et al., 2022; Rootman et al., 2021). Findings from studies specific to chronic pain and/or FM have also suggested benefits from psychedelic use on mood, well-being, and quality of life (Bonnelle et al., 2022; Bornemann et al., 2021; Glynos et al., 2022). Given that currently available treatments are associated with only modest effects on quality of life in FM (Mascarenhas et al., 2021), such findings warrant further investigation, and could potentially be related to or independent of changes in pain.

Besides changes in mental health and quality of life, benefits in brain fog or thinking difficulties, fatigue/energy, and gastrointestinal symptoms were also described by some participants in this study. Improved cognition and increased energy have been reported in survey studies of microdosing, though there is limited evidence supporting these types of changes in laboratory studies (Polito & Liknaitzky, 2022). In research with psilocybin specifically, a recent scoping review (Bonnieux et al., 2023) suggested acute increases in creativity with microdoses. Conversely, psilocybin macrodoses tended to acutely worsen cognitive performance and creativity, with mostly neutral and occasionally positive effects reported after the acute drug period (Bonnieux et al., 2023).

While acute gastrointestinal upset is a well-known side effect of psilocybin use (Johnson et al., 2008), a few participants in this study described improvements in

gastrointestinal symptoms following use. To this writer's knowledge, no clinical studies have been published as of yet regarding effects of psilocybin on gastrointestinal symptoms or conditions such as IBS.

Potential Factors Involved in Pain-Related Changes

This study was not designed to identify mechanisms or mediators of change in pain with the use of psychedelics, but findings will be discussed to consider several potential factors. In the present study, acute experiences of pain relief included for some participants a sense of increased relaxation, body connection, and movement. More durable changes in relation to pain and psychedelic use involved improved mental health and coping with pain, incorporation of positive behavioral changes, better functioning, and adoption of altered perspectives. Several themes related to changes in pain will be highlighted below, in addition to possible physiologic mechanisms.

Mind-Body Connection

An increased sense of embodiment or physical presence was described by Bornemann et al. (2021) among individuals with chronic pain who had self-medicated with psychedelics. In their study, participants reported greater body connection both acutely and over longer periods, with some also engaging in concurrent mind-body practices during psychedelic use, such as breathwork, visualization, meditation, and movement. Use of similar mind-body practices with psychedelics was described positively by participants in the present study, in addition to a few reports of enhanced sense of connection to the body, and an enjoyment in moving without pain. Interoceptive

awareness has been proposed as a possible mechanism of mind-body therapies in chronic pain (Gnall et al., 2024) and could play a role in pain-related effects of psychedelic experiences. As previously suggested by Bornemann et al. (2021), measures of body awareness or mind-body connection may be useful to include in clinical trials. Of note, however, neither changes in body awareness nor mindfulness were associated with pain relief from psychedelic use in the survey by Bonnelle et al. (2022).

Cognitive and Behavioral Changes

Psychedelic experiences could positively influence pain in FM by assisting with the alteration of pain-related beliefs and promoting increased engagement in more adaptive behaviors. Some participants in this study mentioned positive shifts in their perspective on pain and improved pain coping, which were broadly consistent with the theme of *positive reframing* described by Bornemann et al. (2021). These changes could reflect increased psychological flexibility, which has been proposed to mediate psychedelic effects on anxiety and mood (Agin-Liebes et al., 2022; Davis et al., 2020), and may contribute to improved outcomes in FM (Eastwood & Godfrey, 2023; Vallejo et al., 2021).

Participants also reported engaging in new or previously stopped activities (e.g., exercise) following psychedelic use. Spontaneous health behavior changes have been associated with psychedelics in past studies, and behavior change in relation to addiction is an active area of psychedelic research (Teixeira et al., 2022). Such changes could help indirectly facilitate reductions in chronic pain by improving pain management and quality of life.

Two participants in this study described acute experiences with psychedelics involving an increased sense of control over pain and associated imagery. Psychedelic experiences could elicit similar effects as in guided imagery, which has been associated with increased self-efficacy and functional status in a prior study in FM (Menzies et al., 2006). Increased agency over pain has previously been reported in relation to psychedelic use (Bornemann et al., 2021), and an increased sense of control has been associated with improved functioning in FM (Rubio Fidel et al., 2022).

Possible Physiological Mechanisms

As described earlier in the Introduction section, psilocybin or other classic psychedelics could modulate pain in FM via serotonergic actions. Reduced serotonergic functioning has been associated with FM (Sluka & Clauw, 2016), in addition to polymorphisms of the $5HT_{2A}$ receptor gene (Bondy et al., 1999) and the serotonin transporter gene (D'Agnelli et al., 2019). There is also limited research suggesting that supplementation of 5-HTP benefits pain in FM (Sarzi Puttini & Caruso, 1992).

The role of $5HT_{2A}$ receptor activation in descending pain modulation is unclear, with some studies suggesting facilitative and others inhibitory effects (Tao et al., 2019). In addition to $5HT_{2A}$, psilocybin's active metabolite psilocin binds to other serotonergic receptors, such as the $5HT_{1A}$ receptor, the activation of which has been more frequently associated with analgesic effects in preclinical research (Tao et al., 2019). Other possible physiologic mechanisms could involve dopaminergic actions of psychedelics, changes in neuroplasticity, alterations in connectivity of brain networks, and effects of psychedelics in reducing inflammation (Castellanos et al., 2020; Zia et al., 2023).

Negative Experiences

Though most participants in this study described positive experiences with psychedelics, several negative experiences were reported. Gastrointestinal upset and emotional distress were the most frequently reported negative effects, and pain increases were also described. Acute worsening of pain with psychedelic use has previously been noted among individuals with chronic pain and FM (Bonnelle et al., 2022; Bornemann et al., 2021; Glynos et al., 2022), though at relatively lower rates than neutral or positive effects on pain. Though pain reductions seem to occur more frequently, increases in pain are important to recognize and may be underreported, underscoring the importance of monitoring for such effects in future clinical trials.

It is possible that individual differences, substance/dosage type, or setting characteristics may increase the likelihood of pain amplification for some people. Multiple studies have highlighted dosage, planning/preparation, and other aspects of 'set' and 'setting' as significant contributing factors to whether someone's experience with psychedelics is perceived overall as negative or positive (Bender & Hellerstein, 2022; Johnson et al., 2008). Several participants in this study described having sought information about psychedelics prior to use, and many considered preparation to be important, both for mitigation of negative effects and for improving their overall experience. In a large survey of individuals who had self-treated with psychedelics for a mental health condition or specific worry/concern, increased negative outcomes were associated with LSD use, younger age, and higher intensity of the experience (Kopra et al., 2023). Higher intensity of experience was also associated with more positive

outcomes, along with use of psilocybin mushrooms, treatment of PTSD, and seeking information or advice about psychedelics before use (Kopra et al., 2023).

Limitations

There are several limitations to this study. The use of an online questionnaire inherently limited the sample only to individuals with internet access and a capable device. Though the survey was designed to be anonymous, some individuals may have felt uncomfortable answering sensitive items related to medical history or disclosing past use of classic psychedelic substances given their legal status, which may have made them less likely to complete the survey or provide as much detail, resulting in nonresponse bias. The use of social media groups and forums for recruitment may have further contributed to selection bias, leading to higher inclusion of individuals with positive experiences with, or particularly strong opinions of, psychedelics.

In addition to selection and non-response bias, the survey may have been affected by recall bias, and the accuracy of reported dosage amounts is uncertain. Individuals may have had difficulty remembering aspects of a psychedelic experience, or any related changes in pain, especially if an experience occurred a long time ago. Participants may have also become fatigued or bored over the course of the survey, contributing to early termination, or rushing through items without thinking through their answers. Some participants did not know or remember dosage amounts. Others reported approximate dosages, which may or may not have been accurate.

Finally, the process of coding and qualitative analysis is inherently subjective and influenced by the researcher's assumptions, and potentially, expectations. Results

regarding psychedelics and reported changes are not appropriate for generalizability, nor do they imply causation. This study population was quite heterogenous, with many types of pain conditions reported in addition to FM. Thus, it is unknown whether the types of changes that were described from use of psychedelics were specific to pain in FM. Clinical trials are required to further assess the potential benefit of psilocybin and other psychedelics in FM and other chronic pain conditions.

Future Directions

The present findings lend support to a growing body of work indicating a possible role for psychedelics in chronic pain and FM, though all studies published to date on FM have been based on retrospective reports. There is a need to determine with clinical studies whether psychedelics such as psilocybin are tolerable and safe when administered in FM, and whether they lead to any improvements in pain. Several initial trials are currently underway. If future studies suggest preliminary efficacy, many questions remain surrounding optimal dosage, frequency of doses and treatment protocol, the role of psychotherapy, and the mechanisms involved. Other areas of exploration include the importance of subjective or mystical-type effects to any reported improvements in pain, the degree to which intentions and expectancy play a role in perceived changes, and whether psychedelics may help reduce the need for other pain medications, such as opioid analgesics or gabapentinoids.

Most participants in this study did not use psychedelics in a clinical setting or with psychotherapeutic support, though some mentioned that a supportive individual was either present or available during their experience, and a few mentioned working with a

therapist. It is unknown whether the greatest potential for psychedelics to alleviate pain will be realized by combining psychotherapy with psilocybin or other psychedelics. It is possible that psychotherapy could augment the drug's benefits by enhancing processes such as cognitive reframing and behavioral changes, supporting improved pain management and overall functioning. If so, future questions will concern whether a particular type of psychotherapy (e.g., acceptance and commitment therapy, cognitive behavioral therapy for chronic pain, etc.) confers increased benefit, in addition to method of delivery (e.g., frequency of sessions, modality).

Conclusion

This study used an online survey to explore reports of past classic psychedelic use in relation to changes in pain among individuals with FM. Most participants had used psilocybin mushrooms or LSD. About half of the participants with FM described any change in pain with past psychedelic use, with the direction of change typically being a pain reduction. A small subset of participants also reported a reduced need for opioid analgesics or other pain medications following psychedelic use. This study, in combination with prior research, suggests potential for the application of psilocybin, and possibly other psychedelics, in FM, though evidence at present is weak. Clinical trials are necessary to determine whether psychedelics are helpful for pain or other symptoms in FM.

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APPENDIX A

STUDY IRB APPROVAL FORM

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Hodgin, Kathleen

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

DATE: 27-Jun-2022

RE: IRB-300009401
IRB-300009401-002
Classic Psychedelics in Chronic Pain Survey

The IRB reviewed and approved the Initial Application submitted on 23-Jun-2022 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review: Exempt
Exempt Categories: 2
Determination: Exempt
Approval Date: 27-Jun-2022
Approval Period: No Continuing Review

The following apply to this project related to informed consent and/or assent:

- Waiver of HIPAA

Research Project Title:

USE OF PSILOCYBIN AND OTHER CLASSIC PSYCHEDELICS IN FIBROMYALGIA: A SURVEY STUDY

Student Name:

KATHLEEN HODGIN

Documents Included in Review:

- IRB EPORTFOLIO
- IRB PERSONNEL EFORM

To access stamped consent/assent forms (full and expedited protocols only) and/or other approved documents:
1. Open your protocol in IRAP.
2. On the Submissions page, open the submission corresponding to this approval letter. NOTE: The Determination for the submission will be "Approved."
3. In the list of documents, select and download the desired approved documents. The stamped consent/assent form(s) will be listed with a category of Consent/Assent Document (CF, AF, Info Sheet, Phone Script, etc.)

APPENDIX B

SURVEY

Classic Psychedelics in Chronic Pain Survey

UAB IRB Protocol #: IRB-300009401

SECTION I (Informed Consent)

The purpose of this research is to learn more about how classic psychedelics might interact with chronic widespread pain, such as in fibromyalgia. **We are interested in hearing from individuals who have experienced chronic, widespread pain, and have taken a classic psychedelic (psilocybin mushrooms, LSD, mescaline, peyote or San Pedro cactus, DMT or ayahuasca).** *Please do not count drugs such as cannabis/marijuana, MDMA/ecstasy, MDA, ketamine, PCP, nitrous oxide, or salvia divinorum.*

If you agree to join this research study, you will be presented with questions about your health, pain, substance use, and experience(s) with use of psychedelics. You will be asked about any changes in pain or other symptoms related to past psychedelic experiences. **Participation in this study takes on average 30 minutes.**

If you complete this study, you will have an option to enter into a random drawing for a $50 e-gift card. Your name and email address will be collected on a form that is separate from your survey responses so that they will not be linked in any way.

Your participation in this research is voluntary and you may withdraw from the study at any time. Your responses will be kept confidential. If you complete the written section of the survey, we may quote from your text responses. However, if you provide specific identifying information, we will edit your responses to protect your confidentiality. All data is encrypted and maintained on password-protected servers that only the research team can access.

There is a chance that you may experience emotional distress or discomfort when asked to recall or describe experiences during the survey. You may discontinue this survey at any time.

If you have any questions or concerns about the research, please contact Kathleen Hodgin at psychedelicpainsurvey@gmail.com. If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

If you are not ready to complete the survey now, please return to this page at a time that is convenient for you. During the survey, please do not hit the "back" button on your internet browser as it may erase your answers or prematurely terminate your session. **We recommend using a tablet or computer, rather than a cell phone, to complete this survey if possible. Please try to complete the survey in one sitting.**

By clicking 'I consent, begin the study' you affirm that:

1. You have read the information above
2. You voluntarily agree to participate
3. You are at least 18 years old

○ I consent, begin the study
○ I do not consent, I do not wish to participate

SECTION II (Inclusion/Exclusion Questions)

2.1. Before you proceed, please complete the captcha below:
(Participants will be required to complete a captcha verification to proceed)

2.2. Have you previously taken this survey?
○ Yes
○ No
○ Don't know

2.3. Are you at least 18 years of age or older?
○ Yes
○ No

2.4. Have you ever had chronic pain?
○ Yes
○ No

2.5. Have you ever taken a classic psychedelic substance, such as psilocybin or psilocybin mushrooms, LSD, DMT, 5-MeO-DMT, mescaline, or ayahuasca?

Please do not count drugs that are sometimes labeled psychedelics such as cannabis/marijuana, MDMA/ecstasy, MDA, ketamine, PCP, nitrous oxide, or salvia divinorum.

○ Yes
○ No

If no to any of the above questions, end survey.

SECTION III (Health History and Pain Assessment)

3.1. Have you ever been diagnosed with fibromyalgia by a physician or other medical professional?
○ Yes
○ No
○ Don't know
○ Prefer not to answer

If yes: **3.2. What year were you diagnosed? (Please type your response):** _____

3.3. Have you ever been diagnosed with any other pain conditions?
○ Yes
○ No
○ Don't know
○ Prefer not to answer

If yes: **3.4. What pain conditions?** _____

3.5. Which of the following best describes your pain?
☐ Pain exists throughout the body
☐ Pain is migratory (moves around)
☐ Pain is limited to a specific region of the body
☐ Don't know
☐ Does not apply to me / I do not currently have pain
☐ Prefer not to answer

3.6. Please indicate if you have had pain or tenderness in any of the areas below over the past 7 days (select all that apply).

*Shoulder girdle: muscles over your shoulder blade and collar bone

☐ Shoulder girdle*, Left
☐ Shoulder girdle*, Right
☐ Upper Arm, Left
☐ Upper Arm, Right
☐ Lower Arm, Left
☐ Lower Arm, Right
☐ Hip (buttock, trochanter), Left
☐ Hip (buttock, trochanter), Right
☐ Upper Leg, Left
☐ Upper Leg, Right
☐ Lower Leg, Left
☐ Lower Leg, Right
☐ Jaw, Left
☐ Jaw, Right
☐ Chest
☐ Abdomen
☐ Upper Back
☐ Lower Back
☐ Neck
☐ NO PAIN
☐ Prefer not to answer

If any of the above pain areas are selected:

3.7. How long have you experienced this pain? *(Please type your response in days, months, OR years)*

○ I've experienced this pain for ___ days (please type # of days)
○ I've experienced this pain for ___ months (please type # of months)
○ I've experienced this pain for ___ years (please type # of years)
○ Don't know
○ Prefer not to answer

3.8. Using the following scale, indicate for each item your severity over the past week by selecting the appropriate option.

	No Problem (0)	Slight or mild problems; generally mild or intermittent (1)	Moderate; considerable problems; often present and/or at a moderate level (2)	Severe: continuous, life-disturbing problems (3)	Prefer not to answer
Fatigue	○	○	○	○	○
Trouble thinking or remembering	○	○	○	○	○
Waking up tired (unrefreshed)	○	○	○	○	○

3.9. During the past 6 months have you had any of the following symptoms?

	Yes	No	Prefer not to answer
Pain or cramps in lower abdomen	○	○	○
Depression	○	○	○
Headache	○	○	○

3.10. Do you believe one or more certain events (injury, illness, experience, etc.) was linked to the start of your pain?

○ Yes
○ No
○ Prefer not to answer

3.11. If so, please describe the event(s): _____

3.12. Please rate your pain by selecting the number that best describes your <u>pain on average in</u> the past week.

○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
No Pain										Pain as bad as you can imagine

3.13. What number best describes how, during the past week, pain has interfered with your <u>enjoyment of life</u>?

○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
Does not interfere										Completely interferes

3.14. What number best describes how, during the past week, pain has interfered with your <u>general activity</u>?

○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10
Does not interfere										Completely interferes

3.15. Please list any medical diagnoses or health conditions you currently have, including any current physical and mental health conditions: *If none, please enter "None"*

_____

_____

3.16. What medications do you currently take? (Please list all current medications, including prescribed and over-the-counter, and any supplements/vitamins): *If none, please enter "None"*

_____

_____

3.17. On average per week, how many drinks containing alcohol do you consume?
○ 0
○ 1-2
○ 3-4
○ 5-6
○ 7 or more
○ Prefer not to answer

3.18. Do you use any nicotine or tobacco products?
○ Yes
○ No
○ Prefer not to answer

3.19. Do you use any of the following substances regularly (at least once a month)? (Select all that apply)
☐ Cannabis/marijuana
☐ CBD or cannabidiol products
☐ Benzodiazepines, non-prescribed (e.g., Xanax, Ativan, Klonopin)
☐ Opioids, non-prescribed (e.g., OxyContin, Percocet)
☐ Amphetamines, non-prescribed (e.g., Ritalin, Adderall)
☐ Methamphetamine (crystal meth)
☐ MDMA (ecstasy, molly)
☐ Cocaine
☐ Ketamine
☐ Salvia divinorum (salvia)
☐ PCP (phencyclidine)
☐ Kratom
☐ Heroin
☐ Synthetic cannabinoids (e.g., K2, Spice)
☐ Barbiturates
☐ Synthetic cathinones (e.g., bath salts, Flakka)
☐ Not listed here (Please describe):
☐ **I do not use any of these substances regularly**
☐ Prefer not to answer

3.20. How would you rate your knowledge about classic psychedelics (LSD, psilocybin mushrooms, ayahuasca, mescaline, etc.)?
○ Not at all knowledgeable
○ Slightly knowledgeable
○ Moderately knowledgeable
○ Very knowledgeable
○ Extremely knowledgeable
○ Prefer not to answer

SECTION IV (Psychedelic Use and Relation to Pain)

4.1. On how many separate occasions have you taken one or more of the psychedelic substances below?	Never	Once	2-5 times	6-10 times	11-20 times	21-50 times	51-100 times	101-300 times	More than 300 times
Psilocybin mushrooms	○	○	○	○	○	○	○	○	○
Psilocybin (synthetic)	○	○	○	○	○	○	○	○	○
LSD (acid)	○	○	○	○	○	○	○	○	○
DMT	○	○	○	○	○	○	○	○	○
5-MeO-DMT	○	○	○	○	○	○	○	○	○
Ayahuasca	○	○	○	○	○	○	○	○	○
Mescaline (synthetic, extracted, San Pedro cactus, or Peyote cactus)	○	○	○	○	○	○	○	○	○
Other: _____	○	○	○	○	○	○	○	○	○
Other: _____	○	○	○	○	○	○	○	○	○

4.2. How old were you when you first took a psychedelic substance? _____

4.3. How old were you when you most recently used a psychedelic substance? _____

4.4. What was the first psychedelic substance you ever used?

○ Ayahuasca
○ DMT
○ 5-MeO-DMT
○ LSD (acid)
○ Mescaline (Peyote cactus, San Pedro cactus, extracted, synthetic)
○ Psilocybin mushrooms
○ Psilocybin (synthetic)
○ Other (please describe): _____
○ Don't know
○ Multiple psychedelic substances (please describe): _____

4.5. What psychedelic substance did you most recently use?

○ Ayahuasca
○ DMT
○ 5-MeO-DMT
○ LSD (acid)
○ Mescaline (Peyote cactus, San Pedro cactus, extracted, synthetic)
○ Psilocybin mushrooms
○ Psilocybin (synthetic)
○ Other (please describe): _____
○ Don't know
○ Multiple psychedelic substances (please describe): _____

4.6. What kinds of psychedelic doses have you used?

○ Only full or macrodose(s) (elicits perceptual effects)
○ Only microdose(s) (very low dose, elicits sub-perceptual effects)
○ Both full dose(s) and microdose(s)
○ Don't know
○ Prefer not to answer

4.7. For what reasons have you used psychedelics? (Select all that apply)

☐ For fun/recreation
☐ Curiosity
☐ General mental health and well-being
☐ Personal growth or self-exploration
☐ Spiritual exploration or experience
☐ To enhance an activity (such as listening to music, etc.) (Please describe):_____
☐ Social reasons (part of social context)
☐ To feel more connected to nature
☐ To broaden your consciousness/take a different perspective on the world
☐ To feel euphoric or elated
☐ As an escape

☐ To manage or treat a mental health condition (please describe): _____
☐ To manage or treat a health problem (please describe): _____
☐ To address a specific worry or concern in your life (please describe): _____
☐ To manage past trauma
☐ No reason
☐ Other, please describe: _____
☐ Prefer not to answer

4.8. If desired, please elaborate on your strongest reasons for using psychedelics below:

_____
_____

4.9. Have you ever experienced a change in your pain that was related to the use of a psychedelic substance?
○ Yes
○ No
○ Don't know
○ Prefer not to answer

If no, skip to Section V (Demographics)

4.10. How many times have you experienced a change in your pain that was related to the use of a psychedelic? (Please select the number of separate occasions in which you experienced any change in your pain related to a psychedelic)
○ 1 time
○ 2 times
○ 3-5 times
○ 6-10 times
○ >10 times (please enter approximate number): _____
○ Don't know
○ Prefer not to answer

4.11. For the following questions, please bring to mind the psychedelic experience that was associated with a change in your pain. If you have had multiple, different experiences you wish to describe, there will be an opportunity to do so later in the survey.

4.12. What psychedelic substance was associated with the change in your pain?

○ Ayahuasca
○ DMT
○ 5-MeO-DMT
○ LSD (acid)
○ Mescaline (Peyote cactus, San Pedro cactus, extracted, synthetic)
○ Psilocybin mushrooms
○ Psilocybin (synthetic)
○ Other (please describe): _____
○ Don't know
○ Multiple psychedelic substances (please describe): _____

4.13. Were you using any other substances at the same time? (Select all that apply)

☐ Alcohol
☐ Tobacco or nicotine products
☐ Amphetamines, non-prescribed (e.g., Ritalin, Adderall)
☐ Antidepressants, prescribed OR non-prescribed (e.g., Prozac, Lexapro, Wellbutrin)
☐ Benzodiazepines, non-prescribed (e.g., Xanax, Ativan, Klonopin)
☐ Cannabis/marijuana
☐ CBD or cannabidiol products
☐ Opioids, non-prescribed (e.g., OxyContin, Percocet)
☐ Methamphetamine (crystal meth)
☐ MDMA (ecstasy, molly)
☐ Cocaine
☐ Ketamine
☐ Salvia divinorum (salvia)
☐ PCP (phencyclidine)
☐ Kratom
☐ Heroin
☐ Synthetic cannabinoids (e.g., K2, Spice)
☐ Barbiturates
☐ Synthetic cathinones (e.g., bath salts, Flakka)
☐ Other psychedelics (please describe): _____
☐ Other substances not listed here (please describe):_____
☐ Don't know
☐ **I was not using any other substances at the same time**
☐ Prefer not to answer

4.14. How long ago was the psychedelic experience that was associated with a change in your pain? *(Please type your response in days, months, OR years)*

○ This psychedelic experience was ___ days ago (please type # of days)
○ This psychedelic experience was ___ months ago (please type # of months)
○ This psychedelic experience was ___ years ago (please type # of years)
○ Don't know
○ Prefer not to answer

4.15. How old were you when that psychedelic experience took place? (Please enter your age at the time in years) _____

For the following items, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.16. What was the psychedelic experience like? Please describe in as much detail as possible.

_____
_____
_____
_____

4.17. How did your pain change in relation to the psychedelic experience? Please describe in as much detail as possible.

_____
_____
_____
_____

4.18. How long did you experience the change(s) in your pain? Please be as specific as possible.

_____

4.19. Why do you think there was a change in your pain?

_____
_____
_____
_____

4.20. Please describe if, and how, any of your **other symptoms** changed in relation to the psychedelic experience. Please include how long you experienced these changes, if any.

_____
_____
_____
_____

For the following items, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.21. How would you describe the dose that was related to a change in your pain?
○ Microdose (sub-perceptual effects)
○ Low dose
○ Moderate or medium dose
○ High dose
○ Very high dose
○ Don't know
○ Prefer not to answer

4.22. What was the dose you ingested to the best of your knowledge?
○ The dose was: _____
○ I don't know the dose
○ Prefer not to answer

4.23. How did you consume the psychedelic substance that was related to a change in your pain?
○ Orally (i.e., by swallowing, dissolving in mouth)
○ Smoked or vaporized
○ Nasally (i.e., snorted)
○ Other, please describe: _____
○ Prefer not to answer

4.24. Where were you during the majority of the psychedelic experience? (Select all that apply)
○ At my home
○ At the home of a friend, partner, or family member
○ At a retreat or in a spiritual or religious setting (option to provide more details): _____
○ In a therapeutic setting (option to provide more details): _____
○ At a public event, such as a concert or festival (please describe): _____
○ Outside (please describe): _____
○ Other (please describe): _____
○ Prefer not to answer

4.25. Who was with you for the majority of the experience?
○ I was alone or by myself
○ I was with 1 other person
○ I was with a few other people (2-5 people)
○ I was in a group of about 6-20 people
○ I was in a group of about 21-100 people
○ I was in a crowd of over 100 people
○ Other (please describe): _____
○ Prefer not to answer

4.26. How would you describe the people you were with during that experience? (Select all that apply)

○ This does not apply to me, I was alone
○ I was with one or more people I knew (a friend, spouse, partner, or family member) who were **not** using psychedelics
○ I was with one or more people I knew (a friend, spouse, partner, or family member) who were **also under the influence** of psychedelics and/or another substance
○ Some people I was with were using psychedelics and some were not
○ I was with a therapist or health professional
○ I was with people I did not know/I was with strangers
○ Other, please describe: _____
○ Prefer not to answer

For the following item, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.27. Using the scale below, please select the number that best represents your AVERAGE PAIN LEVEL in relation to your psychedelic experience. If you do not remember, or do not wish to answer this item, please leave it blank and continue to the next item.

Average Pain Level	No Pain 0	1	2	3	4	5	6	7	8	9	Pain as bad as you can imagine 10
PRIOR TO that psychedelic experience	○	○	○	○	○	○	○	○	○	○	○
DURING that psychedelic experience	○	○	○	○	○	○	○	○	○	○	○
IMMEDIATELY AFTER (in the 1-2 days following) that psychedelic experience	○	○	○	○	○	○	○	○	○	○	○
SHORT-TERM (i.e., 1 week) following that psychedelic experience	○	○	○	○	○	○	○	○	○	○	○
LONGER-TERM (i.e., over the next month or longer) following that psychedelic experience	○	○	○	○	○	○	○	○	○	○	○

You are more than half-way done with this survey!

For the following items, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.28. What was your **main reason (or motivation)**, if any, for taking the psychedelic substance at the time?

_____
_____

4.29. What **prior expectations**, if any, did you have about what might occur during or after the experience?

_____
_____

4.30. Did you experience any negative effects from this psychedelic experience?
○ Yes
○ No
○ Don't know
○ Prefer not to answer

For this item, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.31. What **negative effects** did you experience?

_____
_____
_____
_____

For this item, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.32. Did you experience any of the changes below? If so, please indicate whether they occurred during and/or following the experience. (Select all that apply)

	NO	**YES - DURING** the psychedelic experience	**YES- FOLLOWING** the psychedelic experience	**Prefer not to answer**
An increase in my pain	☐	☐	☐	☐
A decrease in my pain	☐	☐	☐	☐
A change in my perspective on pain	☐	☐	☐	☐
A change in other fibromyalgia symptoms, please describe: _____	☐	☐	☐	☐
A change in my mental health	☐	☐	☐	☐
A change in my quality of life	☐	☐	☐	☐
Other, please describe: _____	☐	☐	☐	☐

4.33. Please elaborate on any of the changes you selected above, if not previously described:

_____
_____
_____
_____
_____

For the following items, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.34. Did you prepare in any particular manner for the psychedelic experience?

○ Yes
○ No
○ Don't know
○ Prefer not to answer

4.35. How did you prepare?

_____
_____

4.36. Did anything about your use of treatments for chronic pain change after your psychedelic experience (e.g., did you stop a previous treatment or adopt a new one, did your use of medications change, etc.)?

○ Yes
○ No
○ Don't know
○ Prefer not to answer

4.37. How did your use of treatments change?

_____
_____

4.38. Did you experience any changes in the areas below following the psychedelic experience? (Select all that apply)

☐ Changes in relationships
☐ Changes in work/education
☐ Changes in social activity
☐ Changes in physical activity or exercise
☐ Changes in diet
☐ Changes in alcohol use
☐ Changes in tobacco use
☐ Changes in drug use
☐ None of these changes
☐ Prefer not to answer

4.39. If desired, please elaborate on any changes selected above:

_____
_____

For the following items, please keep in mind the psychedelic experience that was associated with a change in your pain.

4.40. During the psychedelic experience that was related to a change in your pain, would you say that you had a profound, personally meaningful experience?
○ Yes
○ No
○ Prefer not to answer

4.41. How personally meaningful was the experience?
○ No more than routine, everyday experiences
○ Similar to meaningful experiences that occur on average once or more a week
○ Similar to meaningful experiences that occur on average once a month
○ Similar to meaningful experiences that occur on average once a year
○ Similar to meaningful experiences that occur on average once every 5 years
○ Among the 10 most meaningful experiences of my life
○ Among the 5 most meaningful experiences of my life
○ The single most meaningful experience of my life
○ Prefer not to answer

4.42. What was the intensity of this experience?
○ Mildly intense
○ Moderately intense
○ Strongly intense
○ Overwhelmingly intense
○ Prefer not to answer

4.43. During that psychedelic experience, would you say that you had a "spiritual or mystical experience," or a moment of a sudden spiritual awakening or insight?
○ Yes
○ No
○ Prefer not to answer

4.44. Indicate the degree to which the experience was spiritually significant to you.
○ Not at all
○ Slightly
○ Moderately
○ Very much
○ Among the 5 most spiritually significant experiences of my life

4.45. During that psychedelic experience, would you say that you had a psychologically insightful experience?
○ Yes
○ No
○ Prefer not to answer

4.46. How psychologically insightful was the experience?

○ Not at all insightful
○ Mildly insightful
○ Moderately insightful
○ Extremely insightful
○ Prefer not to answer

4.47. During that psychedelic experience, would you say that you felt awe, wonder, or amazement?

○ 1 (Not at all)
○ 2
○ 3
○ 4 (Somewhat)
○ 5
○ 6
○ 7 (Completely)
○ Prefer not to answer

4.48. Do you have any additional psychedelic experiences you would like to describe?

○ Yes
○ No
○ Don't know

If yes or don't know is selected:

4.49. If you have had other experiences with psychedelics that you would like to describe in relation to your pain and/or other symptoms, please do so here.

_____
_____
_____
_____
_____

SECTION V (Demographics)

5.1. What is your age? (please type in years): _____

5.2. What sex were you assigned at birth?
○ Female
○ Intersex
○ Male
○ Prefer not to answer

5.3. Gender identity: (Select all that apply)
☐ Cisgender man
☐ Cisgender woman
☐ Transgender man
☐ Transgender woman
☐ Non-binary
☐ Two-spirit
☐ Agender
☐ Genderfluid
☐ Questioning or unsure
☐ Type your response: _____
☐ Prefer not to answer

5.4. Race: (Select all that apply)
☐ American Indian or Alaska Native
☐ Asian
☐ Black or African American
☐ Native Hawaiian or Pacific Islander
☐ White
☐ Type your response: _____
☐ Prefer not to answer

5.5. Do you identify as Hispanic?
○ Yes
○ No
○ Prefer not to answer

5.6. What is the highest level of education that you have completed?
○ Some high school or less
○ High school diploma or equivalent such as GED
○ Some college, no degree
○ Technical, vocational, or trade training
○ Associate degree (for example: AA, AS)
○ Bachelor's degree (for example: BA, BS)
○ Master's degree (for example: MA, MS)

○ Professional or doctoral degree (for example: MD, JD, PhD, etc.)
○ Prefer not to answer

5.7. What is your current occupational status? (Select all that apply)

☐ Employed full-time
☐ Employed part-time
☐ Homemaker
☐ Disabled
☐ Retired
☐ Student
☐ Unemployed
☐ Not listed (please describe): _____
☐ Prefer not to answer

5.8. What is your current or most recent occupation?

○ Please type your response: _____ ○ Prefer not to answer

5.9. Sexual orientation: (Select all that apply)

☐ Asexual
☐ Bisexual
☐ Gay
☐ Heterosexual (straight)
☐ Lesbian
☐ Pansexual
☐ Questioning or unsure
☐ Type your response: _____
☐ Prefer not to answer

5.10. What is your current relationship status?

☐ Single
☐ In committed relationship
☐ Married or in a civil union
☐ Separated
☐ Divorced
☐ Widowed
☐ Not listed (please describe): _____
☐ Prefer not to answer

5.11. Do you live in the United States?

○ Yes
○ No
○ Prefer not to answer

If yes:
5.12. In which state or territory do you currently live?
(Select from drop-down menu)

If no:
5.13. In what country do you currently live?
(Select from drop-down menu)

5.14. How did you hear about this survey?
☐ Social media
☐ From an organization related to fibromyalgia and/or chronic pain (please specify, if desired): _____
☐ From a friend
☐ From a healthcare provider
☐ UAB website
☐ Not listed (please type your response): _____
☐ Prefer not to answer

5.15. Do you have anything to add that you think would be valuable to know? If so, please describe below. If not, please continue to the end of the survey)
_____
_____