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ORIGINAL ARTICLE

Potential analgesic effects of psychedelics on select chronic pain conditions: A survey study

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Abstract

Background: Chronic pain is a major cause of suffering and disability and is often associated with psychiatric complications. Current treatments carry the risk of severe side effects and may lead to limited or no relief at all in a relevant portion of this patient population. Preliminary evidence suggests that classical psychedelics (e.g. LSD and psilocybin) may have analgesic effects in healthy volunteers, and in certain chronic pain conditions and observational studies reveal that they are used in naturalistic settings as a means to manage pain.

Methods: In order to gain insight on the effectiveness of such compounds in chronic pain conditions, we set up a survey addressed to chronic pain patients inquiring about psychedelic use and the relief levels achieved with both conventional treatments, full psychedelic doses and microdoses. We analysed data related to five conditions selected based on diagnostic homogeneity within each of them: fibromyalgia, arthritis, migraine, tension-type headache and sciatica.

Results: Except for sciatica, volunteers reported that psychedelics led to better pain relief compared to conventional medication in all examined conditions. More specifically, full doses performed better than conventional medication. Microdoses led to significantly better relief compared to conventional medication in migraines and achieved comparable relief in the remaining three categories. Implications for future research are discussed.

Conclusions: Full doses and microdoses may hold value in the treatment of some specific chronic pain conditions.

Significance: Psychedelic substances are receiving increasing attention from the scientific literature because of evidence showing beneficial effects on several measures related to mental health in clinical samples and healthy volunteers samples. Previous evidence suggests that people suffering from chronic pain are using psychedelics to seek relief and the present paper presents the results of a survey study investigating their use and analgesic effects among individuals suffering from fibromyalgia, arthritis, migraine, tension-type headache and sciatica.

1 | INTRODUCTION

Improving treatment outcomes for people living with chronic pain (PLCP) patients represents a pressing challenge. CP is a leading cause of disability (Burke et al., 2015), it affects about 20% of the population (Goldberg & McGee, 2011), impacts psychological well-being while decreasing social functioning (Dueñas et al., 2016) and productivity (Cohen et al., 2021). Furthermore, CP is associated with the onset or exacerbation of psychiatric symptoms such as depression (Cohen et al., 2021), anxiety (Dueñas et al., 2016) and substance use problems (Voon et al., 2017).

Recommended pharmacological therapies include non-steroidal anti-inflammatory drugs (NSAIDs) (Yekkirala et al., 2017), opioids, anticonvulsants and antidepressants (Edinoff et al., 2022). While these have some degree of success in achieving relief, a significant portion of patients does not benefit from them (Johannes et al., 2010). Opioids in particular cause several unwanted effects, can be highly addictive (Coussens et al., 2019), are associated with a greater frequency of (serious) adverse events (Els et al., 2017) and may lead to opioid-induced hyperalgesia (i.e. increased sensitivity to pain) https://www.zotero.org/google-docs/?tmAnSp (Nijs et al., 2014). Psychological therapies also seem to contribute to better pain management (Hann & McCracken, 2014; Hoffman et al., 2007). However, the magnitude of their effect is small to medium compared to no treatment and smaller or non-significant when compared to other interventions, such as active controls (e.g. physical therapy, education, medical regimes), or different forms of 'treatment as usual' (Williams et al., 2020; Hann & McCracken, 2014).

Alternative or complementary treatments are often sought and classic psychedelic drugs have recently gained the PLCP's attention as shown by the numerous articles, posts and discussions published on online fora (e.g. Andersson et al., 2017; Soussan & Kjellgren, 2016). Classic psychedelics are a class of psychoactive compounds that produce profound alterations to perception, cognition and emotion through agonism of serotonergic receptors (de Vos et al., 2021). Their use pattern is classically categorized into full dose use, in which doses large enough to generate such alterations are taken, and microdosing, in which doses small enough not to generate perceivable alterations of consciousness (microdoses) are taken repeatedly over the course of several days or weeks (Kuypers et al., 2019). Research to test their analgesic effects began before the *war on drugs* era (Reiff et al., 2020) and evidence of their efficacy was gathered in neuropathic, ischemic or cancer-related pain https://www.zotero.org/google-docs/?KCQPdx (Grof et al., 1973; Kast & Collins, 1963), life-threatening illnesses (Kast, 1967) and phantom limb pain (Fanciullacci et al., 1977). More recent retrospective studies have revealed that individuals suffering from cluster headache who have used psychedelics report improvements even when using low, non-hallucinogenic doses (Schindler et al., 2015; Sewell et al., 2006). Furthermore, a recent randomized controlled trial with healthy volunteers showed that a non-hallucinogenic dose of LSD can improve pain tolerance and ratings of unpleasantness to an extent comparable to oxycodone or morphine (Ramaekers et al., 2021). The responsible mechanisms are still unclear but a reasonable hypothesis points to the psychedelic-induced activation of serotonin receptors (5-HT_{2A}), which may upregulate genes that promote neuroplasticity and suppress inflammatory factors (Castellanos et al., 2020; de Vos et al., 2021). This may help to compensate for the malfunction of the descending inhibitory 5-HT pathways, a supposed cause of hyperalgesia and allodynia in chronic pain and a contributing factor in increasing inflammatory pain (Castellanos et al., 2020). A recent review focussing on the potential mechanisms supporting the pain regulating effects of psychedelics pointed to the fact that psilocin (an active metabolite of psilocybin) binds to several 5-HT receptors and evidence exists of a potential role of both 5-HT2A and 5-HT3 in nociception (Zia et al., 2023). Furthermore, the reduction in 5-HT2A receptor number caused by the use of such compounds may also have contributed to decreased signalling in pathways responsible for nociception (Zia et al., 2023). The authors also add that 5-HT2A agonists may promote the internalization of such receptors potentially resulting in less perceived pain (Zia et al., 2023).

To summarize, while classic psychedelics seem to have potential in the management of CP, their actual effectiveness and mechanisms are still unclear. To better understand the perceived analgesic effects that psychedelics have on CP patients who self-medicate, an online survey (Bonnelle et al., 2022) was set up. Results suggested that psychedelic use led to pain relief, that full doses appeared to work better than microdoses, and that these changes were unrelated to the mood improvement that these substances typically induce nor to the degree in which participants considered themselves advocates for psychedelic use (Bonnelle et al., 2022). The present paper focuses on results concerning specific CP conditions selected based on homogeneity within each individual survey category: fibromyalgia (FM), arthritis, migraine, tension-type headache (TTH) and sciatica (See Supplemental material 1 for a description of the conditions).

2 | METHODS

2.1 | Participants

The sample was recruited via an online survey that was disseminated through the Beckley Foundation website

and social media platforms from August 2020 to July 2021 (Bonnelle et al., 2022). The advertisement was addressed to individuals who had microdosed and had been or were currently suffering from chronic pain. Eligible participants were at least 18 years of age, have already had experience with psychedelics and were suffering or had suffered from CP. Once informed about the study, respondents were presented with the consent form. The Ethics Review Committee of Psychology and Neuroscience at Maastricht University (NL) approved the protocol (ERCPN-226_101_08_2020) and the survey was presented via Qualtrics.

2.2 | Test battery

The test battery included a questionnaire inquiring about demographic information, history of psychedelic use, pain complaints, reported pain relief from conventional medication and cannabis, and reported pain relief from psychedelic use.

2.3 | Demographic information

Respondents' age group, sex and work status (i.e. full-time, part-time, unemployed, unemployed due to pain, home duties, on leave due to pain, studying, other) were gathered.

2.4 | History of psychedelic use

Participants indicated whether they had experience with psychedelics and, if they had, what compound they were most experienced with (LSD/1p-LSD, psilocybin-containing truffles or mushrooms, DMT, ayahuasca, 5-MeO-DMT, mescaline or other). Finally, they indicated the frequency and duration of their psychedelic use for both microdoses and full doses.

2.5 | Pain complaints

Respondents indicated current or past painful complaints requiring pain management interventions. Complaints were grouped as follows: musculoskeletal, inflammatory, neuropathic, headache and orofacial, pain caused by cancer, visceral or other type. Participants could enter multiple conditions and pain severity was then recorded on a Visual Analogue Scale (VAS) ranging from 0 to 10 while pain frequency was recorded on a 4-point Likert scale ranging from 'all the time' to 'less than once a week'. Respondents who indicated no present or past complaints were redirected to the survey end page.

This paper will present the data obtained regarding a subset of such complaints (for the full list, refer to Supplementary material 2). The selection was based on presumed diagnostic homogeneity within the indicated category (i.e. while the 'back pain' complaint may potentially include very diverse conditions, the 'migraine' one may include a more homogeneous subsample of patients). Based on this criterion, results from the following conditions were analysed: FM, arthritis, migraine, TTH and sciatica.

2.6 | Reported effectiveness of conventional medication and cannabis

The survey required participants to indicate which conventional medication they used most often from a predefined list including drugs both acute (i.e. over-the-counter pain relievers/NSAIDS, opioids) and preventive drugs (i.e. antidepressants, anticonvulsants), as well as cannabis which seems to have both prophylactic and abortive effects (Okusanya et al., 2022). Given that cannabis is gaining increasing acceptance as an effective pain management treatment and the fact that several countries are now allowing its prescription, it was included in this category (Häuser et al., 2018). Participants also rated the extent of pain relief they got from such medication on a VAS ranging from 0 (no pain relief) to 10 (complete relief).

2.7 | Reported effectiveness of psychedelics in pain relief

Respondents reported the degree of relief they obtained from microdoses and full doses on a VAS ranging from 0 (no pain relief) to 10 (complete relief), whether they used psychedelics to intentionally obtain pain relief and how long the potential benefits lasted on a multiple choice question which presented the following options: benefit on dosing day only, on dosing day and the following day, on dosing day plus 2–3 days after, on dosing day and for more than 3 days after.

2.8 | Mood and expectation

Since mood and treatment expectations are considered important factors influencing pain perception (Hall et al., 2011), the survey required participants to report whether they experienced changes in mood as a consequence of psychedelic use and whether they used them to intentionally treat pain.

2.9 | Statistical analysis

Data were analysed in SPSS (version 26.0.0.0). Frequencies were computed for the following variables: gender, age, work status, number of concurrent pain complaints, most often used conventional medication and psychedelic compound.

Pain relief scores after conventional medication, microdosing and full doses were not normally distributed according to the Kolmogorov-Smirnov and Shapiro–Wilk tests. The Kruskal–Wallis tests were used to test for differences in pain relief obtained by the different classes of conventional medication across conditions. Related samples Friedman's two-way ANOVA was used to compare pain relief scores between treatment types (conventional medication, microdoses and full doses). Contrasts were carried out via the Wilcoxon signed ranks test, and the Bonferroni correction for multiple comparisons was performed. Effect sizes (Kendall's W for Friedman's ANOVAs and η^2 for Kruskall–Wallis) and *p*-values were reported and the latter tested against a Bonferroni-corrected α level. To determine whether changes in mood were associated with reductions in pain, Pearson's correlation analyses were run between mood change ratings and relief ratings. To determine whether expectations played a role in determining relief scores, Mann–Whitney U tests were run comparing the degree of relief obtained by participants who reported taking psychedelics to intentionally self-treat pain and those who did not.

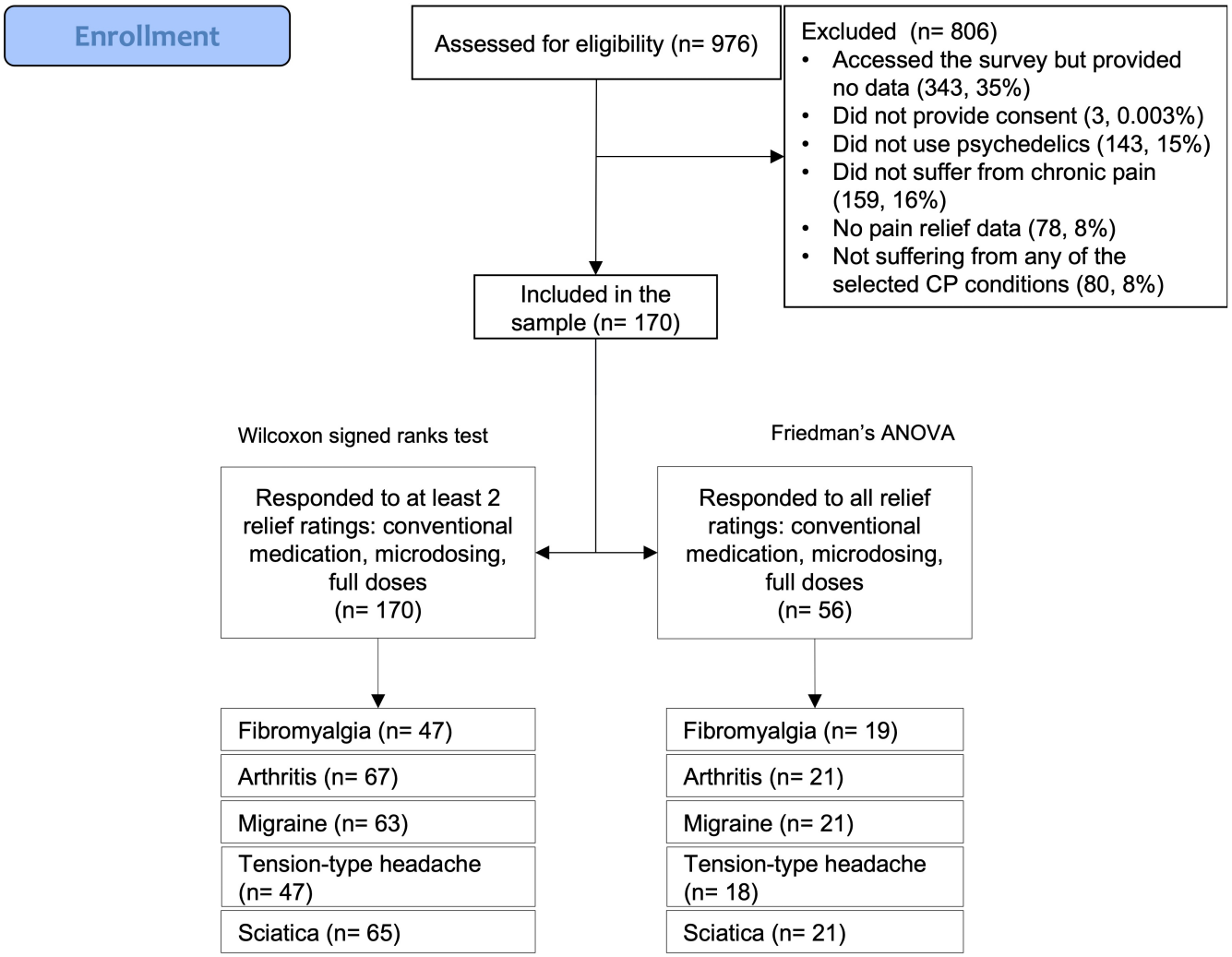

FIGURE 1 Enrolment flowchart detailing how many participants fulfilled inclusion criteria, provided pain relief data and suffered from at least one of the selected CP conditions. Friedman's ANOVA was run including participants who provided all three relief measures (i.e. conventional medication, microdosing and full doses) while contrasts between each treatment pair were run via Wilcoxon signed ranks test considering the whole responder sample (i.e. including participants who provided relief data for at least two substance categories).

3 | RESULTS

3.1 | Demographics

Data on this sample were published in another paper (Bonnelle et al., 2022) and are briefly summarized here. Out of 976 respondents, 170 completed the survey and met the inclusion criteria (Figure 1). Respondents who did not consent to participate, were younger than 18 years of age, did not provide relief data or were not suffering from one of the selected CP conditions were excluded. There were 93 females and 70 males (7 preferred not to say). The majority (33%) fell into the 31–40 age range ($n = 56$), followed by the 18–30 ($n = 40$; 24%), 41–50 ($n = 29$; 17%), 51–60 ($n = 24$; 14%) and finally 61–70 ($n = 21$; 13%). Thirty-five (21%) declared to be unemployed due to pain and 2 (1%) of them being on leave from work because of pain. The average number of concurrent pain complaints was 5 0.88 (SD = 4 0.23).

3.2 | Fibromyalgia

3.2.1 | Demographics

Of the 170 participants, 47 (18.8%; 34 females and 11 males, 2 preferred not to say) participants reported to be suffering from FM. The majority (38.3%) fell into the 31–40 age range ($n = 18$), followed by the 18–30 ($n = 12$; 25.5%), 41–50 ($n = 9$; 19.1%), 51–60 ($n = 7$; 14.9%) and finally 61–70 ($n = 1$; 2.1%). Seventeen participants (34.7%) declared to be unemployed due to pain and 2 (4.1%) of being on leave from work because of pain. The average number of concurrent pain complaints was 8.55 (SD = 5.18).

3.2.2 | Pain relief with conventional medication

Regarding the most used conventional medications, five participants in this subsample reported the use of over-the-counter (OTC)/NSAIDs medication (mean relief = 4.4; $SD = 2.32$), 16 reported use of opioids (mean relief = 5.38; SD = 2.71), 11 of cannabis (mean relief = 6.18; SD = 1.4), 10 of other medications (mean relief = 5.3; SD = 1.89). The latter category included amitriptyline ($n = 1$), anticonvulsants ($n = 3$), ketamine (n = 2), serotonin–norepinephrine reuptake inhibitors (SNRIs) ($n = 2$), codeine/paracetamol ($n = 1$), one participant did not specify. Seven participants did not respond. No significant differences were found in obtained relief between conventional treatments ($H(3) = 2.66$, $p = 0.447$, $\eta^2 = 0.11$).

3.2.3 | Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n = 26$), followed by LSD ($n = 15$), DMT ($n = 1$) and other ($n = 1$). In the other category, one participant indicated LSD and mescaline ($n = 1$; Figure 2a). Four participants flagged the other category but in the free-text field, they indicated compounds that are not considered classical psychedelics (MDMA and ketamine ($n = 1$), ketamine ($n = 2$), THC ($n = 1$)) and were therefore excluded from subsequent analyses investigating relief. Most participants in the FM subsample made alternate use of microdoses and full doses ($n = 39$; 83%) as opposed to just microdoses ($n = 7$; 14.9%) or full doses ($n = 1$; 2.1%).

A significant effect of treatment type ($F_r(2) = 19.042$, $p < 0.001$) with a medium effect size (W = 0.5) was found. Pairwise comparisons were conducted including data from participants who completed at least two of the three relief measures (i.e. relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test with a Bonferroni-adjusted α level. Results showed a significantly greater relief from full doses (M = 8.25) compared to both conventional medication (M = 5.32; $p < 0.001$) and microdoses (M = 6.51; $p < 0.001$) (Figure 3a). Considering this subsample, 68.4% ($n = 13$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 31.6% ($n = 6$) reported a benefit on the dosing day only, 21.1% ($n = 4$) also on the following day, 21.1% ($n = 4$) on the following 2–3 days, and 26.3% ($n = 5$) reported benefits beyond the third day. In terms of benefit duration for low doses, 52.6% ($n = 10$) reported a benefit on the dosing day only, 31.6% (n = 6) also on the following day, 10.5% (n = 2) on the following 2–3 days and 5.3% (n = 1) reported benefits beyond the third day. Pearson correlation analyses revealed no significant association between pain relief and mood change scores for full doses (r = 0.025; $p = 0.919$) and microdoses (r = 0.180, $p = 0.461$).

3.3 | Arthritis

3.3.1 | Demographics

Of the 170 participants, 67 (26.8%; 37 females, 29 males, 1 preferred not to say) participants reported suffering from arthritis. The majority (28.4%) fell into the 31–40 age range (n = 19), followed by the 61–70 range ($n = 15$; 22,4%), 41–50 ($n = 14$; 20.8%), 51–60 ($n = 12$; 17.9%) and

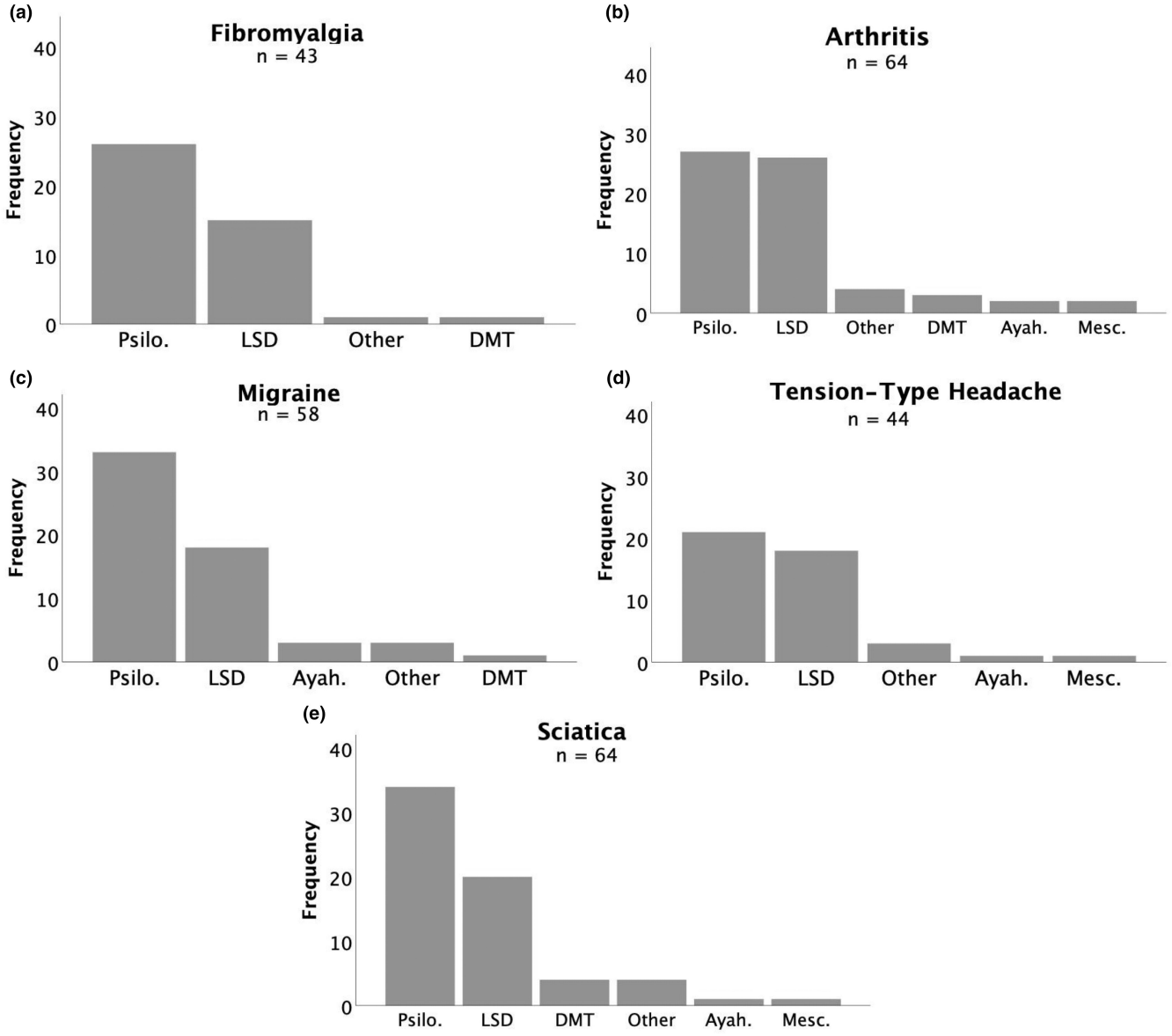

FIGURE 2 Frequencies of most used psychedelics in each condition and sample sizes: (a) fibromyalgia, (b) arthritis, (c) migraine, (d) tension-type headache and (e) sciatica. Psilo. = psilocybin, LSD = lysergic acid diethylamide, Ayah. = ayahuasca, DMT = N,N-dimethyltryptamine, Mesc. = mescaline.

finally 18–30 ($n = 7$; 10.5%). Sixteen participants (23.9%) declared to be unemployed due to pain and 2 (4.1%) of being on leave from work because of pain. The average number of concurrent pain complaints was 6.93 (SD = 4.95).

3.3.2 | Pain relief with conventional medication

Regarding the most used conventional medications, 14 participants in this subsample reported the use of OTC/NSAIDs (mean relief = 4.79; SD = 2.19), 22 of opioids (mean relief = 6.14; SD = 2.36), 16 of cannabis (mean relief = 6.56; SD = 1.71) and four of other medications (mean relief = 5.75; SD = 2.5). The latter category included anticonvulsants ($n = 2$), hydroxychloroquine ($n = 1$) and SSRIs ($n = 1$). Eleven participants did not respond. No significant differences in obtained relief between conventional treatments were found ($H(3) = 8.08$, $p = 0.044$, $\eta^2 = 0.098$).

3.3.3 | Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n = 27$), followed by LSD ($n = 26$), other ($n = 4$), DMT

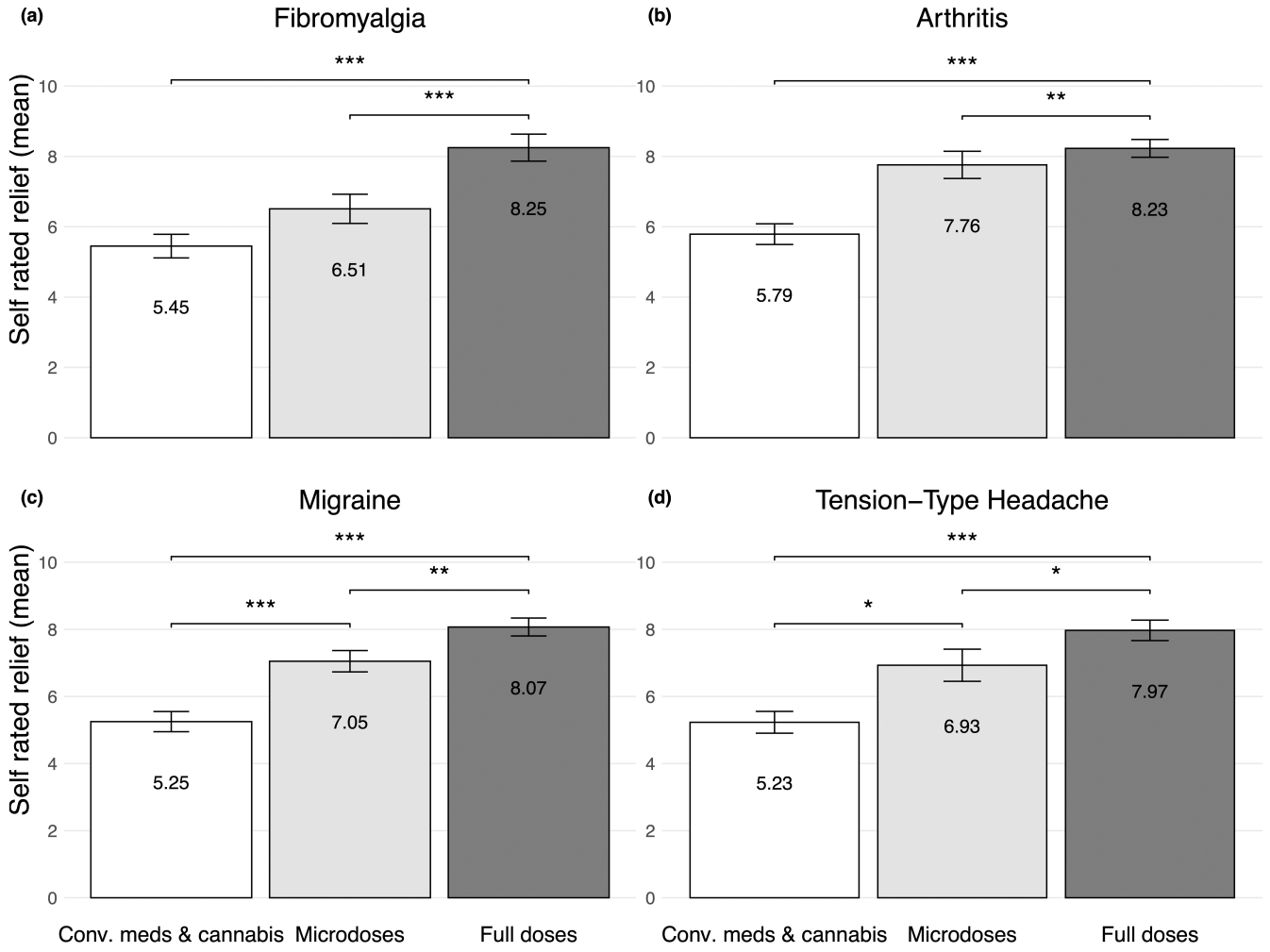

FIGURE 3 Mean self-rated relief from conventional medication plus cannabis, microdoses and full doses for each condition, sample sizes and 95% confidence intervals. Statistically significant differences between groups are denoted by ** (<0.005) and * (<0.01). (a) fibromyalgia, (b) arthritis, (c) Migraine, (d) tension-type headache.

($n=3$), ayahuasca ($n=2$) and mescaline ($n=2$; Figure 2b). In the other category, participants indicated the following substances respectively: LSD and psilocybin ($n=3$), LSD and mescaline ($n=1$). Four participants flagged the other category but in the free-text field, they indicated compounds that are not considered classical psychedelics (ketamine ($n=1$), methamphetamine ($n=1$), THC ($n=1$)) and were therefore excluded from subsequent analyses investigating relief. Most participants in the Arthritis subsample made alternate use of microdoses and full doses ($n=49$; 73.1%) as opposed to only microdoses ($n=4$; 6%) or only full doses ($n=13$; 19.4%).

A significant effect of Treatment Type ($F_r(2)=12.873$, $p=0.002$) with a medium effect size ($W=0.31$) was found. Pairwise comparisons were conducted including data from participants who completed at least two of the three relief measures (i.e. relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni-adjusted α level. Results showed a significantly greater relief from full doses ($M=8.23$) compared to both conventional medication ($M=5.79$; $p<0.001$) and microdoses ($M=7.76$; $p<0.001$) (Figure 3b). Considering this subsample, 52.4% ($n=11$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 33.3% ($n=7$) reported a benefit on the dosing day only, 14.3% ($n=3$) also on the following day, 23.8% ($n=5$) on the following 2–3 days and 28.6% ($n=6$) reported benefits beyond the third day. In terms of benefit duration for low doses, 33.3% ($n=7$) reported a benefit on the dosing day only, 33.3% ($n=7$) also on the following day, 9.5% ($n=2$) on the following 2–3 days and 23.8% ($n=5$) reported benefits beyond the third day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r=-0.083$; $p=0.693$) and microdoses ($r=0.194$, $p=0.353$).

3.4 | Migraine

3.4.1 | Demographics

Of the 170 participants, 63 (25.2%; 42 females, 19 males, 2 preferred not to say) participants reported suffering from migraine. The majority (36.5%) fell into the 31–40 age range ($n = 23$), followed by the 18–30 range ($n = 16$; 25.4%), 41–50 ($n = 14$; 22.2%), 51–60 ($n = 5$; 7.9%) and finally 18–30 ($n = 5$; 7.9%). Eleven participants (17.5%) declared to be unemployed due to pain and 1 (1.6%) of being on leave from work because of pain. The average number of concurrent pain complaints was 6.63 (SD = 4.87).

3.4.2 | Pain relief with conventional medication

Regarding the most used conventional medications, 15 participants in this subsample reported the use of OTC/NSAIDs (mean relief = 4.13; SD = 1.85), 16 of opioids (mean relief = 5.50; SD = 2.42), 13 of cannabis (mean relief = 6.23; SD = 1.96) and nine of other medications (mean relief = 5.22; SD = 2.11). The latter category included anticonvulsants ($n = 2$), triptans ($n = 4$) and kratom ($n = 1$). Two participants did not specify. Ten participants did not respond. No significant differences in obtained relief between conventional treatments were found ($H(3) = 6.72$, $p = 0.081$, $\eta^2 = 0.063$).

3.4.3 | Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n = 33$), followed by LSD ($n = 18$), ayahuasca ($n = 3$), other ($n = 3$) and DMT ($n = 1$). In the other category, participants indicated the following substances respectively: LSD and mescaline ($n = 1$), cannabis and psilocybin ($n = 1$), LSD and psilocybin ($n = 1$; Figure 2c). Two participants flagged the other category, but in the free-text field they indicated compounds that are not considered classical psychedelics [THC ($n = 1$), MDMA and ketamine ($n = 1$)], and were therefore excluded from subsequent analyses investigating relief. Three participants did not respond. Most participants in the Migraine subsample made alternate use of microdoses and full doses ($n = 42$; 66.7%) as opposed to just microdoses ($n = 15$; 23.8%) and full doses ($n = 3$; 4.8%).

A significant effect of Treatment Type ($F_r(2) = 19.973$, $p < 0.001$) with a medium effect size (W = 0.48) was found. Pairwise comparisons were conducted including data from participants who completed at least two of the three relief measures (i.e. relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni-adjusted α level. Results showed a significantly greater relief from full doses (M = 8.07) compared to both conventional medication (M = 5.25; $p < 0.001$) and microdoses (M = 7.05; $p < 0.001$). Microdoses also lead to significantly greater relief compared to conventional medication ($p < 0.005$) (Figure 3c). Considering this subsample, 61.9% ($n = 13$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 19% ($n = 4$) reported a benefit on the dosing day only, 19% ($n = 4$) also on the following day, 33.3% ($n = 7$) on the following 2–3 days and 28.6% ($n = 6$) reported benefits beyond the third day. In terms of benefit duration for low doses, 33.3% ($n = 7$) reported a benefit on the dosing day only, 28.6% ($n = 6$) also on the following day, 33.3% ($n = 7$) on the following 2–3 days and 4.8% ($n = 1$) reported benefits beyond the third day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r = 0.041$; $p = 0.859$) and microdoses ($r = -0.066$, $p = 0.777$).

3.5 | Tension-type headache

3.5.1 | Demographics

Of the 170 participants, 47 (18.8%; 31 females, 14 males, 2 preferred not to say) participants reported suffering from TTH. The majority (34%) fell into the 31–40 age range ($n = 16$), followed by the 41–50 range ($n = 14$; 29.8%), 18–30 ($n = 12$; 25.5%), 51–60 ($n = 3$; 6.4%) and finally 61–70 ($n = 2$; 4.3%). Twelve participants (25.5%) declared to be unemployed due to pain. The average number of concurrent pain complaints was 8.08 (SD = 5.22).

3.5.2 | Pain relief with conventional medication

Regarding the most used conventional medications, 13 participants in this subsample reported the use of opioids (mean relief = 5.54; SD = 1.81), 11 of OTC/NSAIDs (mean relief = 4.09; SD = 1.7), eight of cannabis (mean relief = 6.38; SD = 1.51) and seven of other medications (mean relief = 5.14; SD = 2.8). The latter category included anticonvulsants ($n = 2$), SNRIs ($n = 2$), ketamine ($n = 1$), kratom ($n = 1$) and benzodiazepines ($n = 1$). Eight participants did not specify.

No significant differences in relief between conventional treatments were found ($H(3) = 6.950$, $p = 0.074$, $\eta^2 = 0.092$).

3.5.3 | Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n = 21$), followed by LSD ($n = 18$), other ($n = 3$), ayahuasca ($n = 1$) and mescaline ($n = 1$). In the other category, three participants indicated the following substances respectively: LSD and psilocybin ($n = 1$), LSD and mescaline ($n = 2$; Figure 2d). Two participants flagged the other category, but in the free-text field they indicated compounds that are not considered classical psychedelics [MDMA and ketamine ($n = 1$), and ketamine ($n = 1$)], and were therefore excluded from subsequent analyses investigating relief. One participant did not respond. Most participants in the subsample made alternate use of microdoses and full doses ($n = 37$; 78.7%) as opposed to microdoses ($n = 6$; 12.8%) and full doses ($n = 3$; 6.4%).

A significant effect of treatment ($F_r(2) = 13.16$, $p < 0.005$) with a small effect size ($W = 0.13$) was found. Pairwise comparisons were conducted including data from participants who completed at least two of the three relief measures (i.e. relief from conventional medication, microdosing and full doses) via a Wilcoxon signed ranks test (Figure 3a) with a Bonferroni-adjusted α level. Results showed a significantly greater relief from full doses ($M = 7.97$) compared to conventional medication ($M = 5.23$; $p < 0.001$)—and also revealed a significant difference in relief obtained with full doses compared to microdoses ($M = 6.93$; $p < 0.01$) and with microdoses compared with conventional medication ($p < 0.01$) (Figure 3d). Considering this subsample, 66.7% ($n = 12$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 22.2% ($n = 4$) reported a benefit on the dosing day only, 11.1% ($n = 2$) also on the following day, 33.3% ($n = 6$) on the following 2–3 days and 33.3% ($n = 6$) reported benefits beyond the third day. In terms of benefit duration for low doses, 27.8% ($n = 5$) reported a benefit on the dosing day only, 27.8% ($n = 5$) also on the following day, 27.8% ($n = 5$) on the following 2–3 days and 16.7% ($n = 3$) reported benefits beyond the third day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r = 0.105$; $p = 0.677$) and microdoses ($r = 0.467$, $p = 0.051$).

3.6 | Sciatica

3.6.1 | Demographics

Of the 170 participants, 65 (26%; 36 females, 26 males, 3 preferred not to say) participants reported suffering from sciatica. The majority (26.2%) fell into the 31–40 age range ($n = 17$), followed by 41–50 ($n = 16$; 24.6%), 18–30 ($n = 12$; 18.5%), 51–60 ($n = 12$; 18.5%) and finally 61–70 ($n = 8$; 12.3%). Twenty participants (31.3%) declared to be unemployed due to pain and 1 (1.6%) of being on leave from work because of pain. The average number of concurrent pain complaints was 7.9 ($SD = 5.14$).

3.6.2 | Pain relief with conventional medication

Regarding the most used conventional medications, 16 participants in this subsample reported the use of opioids (mean relief = 5.81; $SD = 2.11$), 15 of cannabis (mean relief = 6.67; $SD = 1.95$), 11 of OTC/NSAIDs (mean relief = 4.91; $SD = 2.26$) and 10 of other medications (mean relief = 5.30; $SD = 2.18$). The latter category included anticonvulsants ($n = 5$), ketamine ($n = 2$), tricyclic antidepressants ($n = 1$) and SNRIs ($n = 1$). One participant did not specify. Thirteen participants did not respond. No significant differences in relief between conventional treatments were found ($H(3) = 5.795$, $p = 0.122$, $\eta^2 = 0.046$).

3.6.3 | Pain relief with psychedelics compared to conventional medication

Psilocybin was the most used psychedelic in this subsample ($n = 34$), followed by LSD ($n = 20$), DMT ($n = 4$), other ($n = 4$), ayahuasca ($n = 1$) and mescaline ($n = 1$). In the other category, four participants indicated the following substances: LSD and psilocybin ($n = 2$), LSD and mescaline ($n = 1$), and psilocybin and cannabis oil ($n = 1$; Figure 2e). One participant flagged the other category but indicated compounds that are not considered classical psychedelics (MDMA and ketamine) in the free-text field, so this response was therefore excluded from subsequent analyses investigating relief. One participant did not respond. Most participants in the subsample made alternate use of microdoses and full doses ($n = 49$; 75.4%) as opposed to just microdoses ($n = 10$; 15.4%) and full doses ($n = 6$; 9.2%). While there were differences in the mean degree of relief obtained with full doses ($M = 8.05$), microdoses ($M = 7.05$) and conventional medication ($M = 7$), analyses did not reveal a significant main effect of Treatment Type on the degree of relief ($F_r(2) = 5.4$, $p = 0.067$). Considering this subsample, 42.9% ($n = 9$) of patients reported making use of psychedelics with the intention of reducing pain. In terms of benefit duration for full doses, 33.3% ($n = 7$) reported a benefit on the dosing day only, 9.5% ($n = 2$) also on the

following day, 23.8% ($n = 5$) on the following 2–3 days and 33.3% ($n = 7$) reported benefits beyond the third day. In terms of benefit duration for low doses, 38.1% ($n = 8$) reported a benefit on the dosing day only, 33.3% ($n = 7$) also on the following day, 9.5% ($n = 2$) on the following 2–3 days and 19% ($n = 4$) reported benefits beyond the third day. Pearson correlation analyses revealed no significant association between relief and mood change scores for full doses ($r = 0.352$; $p = 0.117$) and microdoses ($r = -0.039$, $p = 0.867$).

3.7 | Expectations

Comparisons between individuals who intentionally took psychedelics to self-treat CP and those who did not report such intention across conditions resulted in a non-significant difference in both participants making use of microdoses ($U = 882$; $z = -0.98$, $p = 0.328$) and full doses ($U = 1455$; $z = -0.98$; $p = 0.325$).

4 | DISCUSSION

The aim of the present study was to investigate the perceived analgesic effects that psychedelics may have on selected CP conditions—namely FM, arthritis, migraine, TTH and sciatica—when used in naturalistic settings. This is the first study to investigate the effect of the use of both psychedelic microdoses and full doses in specific pain conditions and to compare their effects with those of conventional medications. Findings demonstrated reduced self-rated pain scores when self-administering psychedelics compared to conventional pharmacological pain treatments. This was true for all selected pain conditions except for those suffering from sciatica.

Participants suffering from migraine seemed to get better relief from microdosing compared to conventional medication and better relief from full doses compared to microdoses. This finding is consistent with an exploratory controlled study which suggested that psilocybin may be able to reduce migraine frequency even at sub or mildly hallucinogenic doses (Andersson et al., 2017; Schindler et al., 2021). The same response pattern was observed in participants with TTH.

Participants suffering from FM and arthritis reported that full doses led to better relief than both microdoses and conventional medication while no significant difference was observed between microdoses and conventional medication. No controlled study has yet investigated the effect of psychedelics on FM, but the present results are in line with another survey study that found that among 12 FM sufferers, 11 reported improvement in symptoms after psychedelic use (Glynos et al., 2022). This is the first study to report a perceived analgesic effect of psychedelics on arthritis pain, although their potential value in treating autoimmune diseases has already been proposed (Flanagan & Nichols, 2018). According to survey participants suffering from FM and arthritis, full doses led to greater improvements compared to the other conventional treatments and microdoses, which suggests that this use type may have therapeutic value. This may be especially true if considering that full doses are usually taken sporadically in contrast to most conventional abortive pain medications such as NSAIDs or opioids and that several respondents reported a benefit duration that extended beyond the day of administration of both full doses and microdoses. In other words, psychedelics may be useful both to treat pain acutely and to use as a prophylactic agent as observed in migraine patients (Schindler et al., 2021). Still, in order to conclude that they have a preventive effect on paroxysmal pain disorders, future research should compare the pain baseline episode frequency with the post-treatment frequency (e.g. number of pain days per month). Furthermore, current treatment options often carry unwanted side effects that range from gastrointestinal ulcers and higher risk of cardiovascular diseases caused by NSAIDs (Edinoff et al., 2022) to addiction, hyperalgesia, constipation, dizziness, drowsiness, fatigue, hot flushes, diaphoresis, nausea, vomiting and pruritus caused by opioids (Edinoff et al., 2022).

Interestingly, participants also reported that microdosing was as effective as (FM, and arthritis) or more effective (migraine and TTH) than conventional treatments. It is unclear whether this effect is achieved through a common biological (e.g. the anti-inflammatory action, increased neuroplasticity (Castellanos et al., 2020; de Vos et al., 2021) causal pathway. Earlier research found that mood (Griffiths et al., 2016) and expectation (Kirsch, 2018) may play a role in determining the perceived intensity of pain. This relationship was not observed in the present study, suggesting that the perceived analgesic effects of psychedelics may not be entirely explained by psychological factors. There may still be other psychological factors that mediate or moderate the relationship (e.g. psychological flexibility and personality profile).

Future research should aim at replicating such findings in a controlled setting and at disentangling the possible causal factors involved while considering the safety, effects of dose, type of psychedelic, frequency of administration and potency. Furthermore, new research should investigate each condition separately and disentangle the acute analgesic effects from the preventive effects. Another interesting way to further the understanding of the potential effects of serotonergic psychedelics would entail to test different conditions that however share the

same causal pathways (e.g. nociplastic pain) regardless of the location of pain itself. While the search for better avenues to manage CP should still aim at producing greater and more stable degrees of relief (Finnerup et al., 2015), results of the current survey suggest that patients may be able to achieve comparable levels of efficacy through substances that carry a potentially better side-effect profile (Kuypers, 2020).

The effect of psychedelics on pain related to sciatica was statistically non-significant. This result may indicate that these substances hold promise only for certain kinds of pain conditions, presumably those in which the inflammatory and/or psychosomatic components play a more prominent role. Also, sciatica is caused by a well-understood structural pathology and, as may be the case with psychedelic-assisted psychotherapy (Cavarra et al., 2022), the greater benefit may be achieved by pairing psychedelics with already established treatments (e.g. physical therapy). Further research is needed to better understand the mechanisms that may account for pain relief.

In line with Bonnelle et al., 2022, no association between measures of mood and pain relief in both microdoses and full doses was found suggesting that the perceived analgesic effect of psychedelics may be supported by different mechanisms.

The present results are in line with what was suggested by early research in the field (Fanciullacci et al., 1977; Grof et al., 1973; Kast, 1967; Kast & Collins, 1963), recent experimental studies on healthy volunteers (Ramaekers et al., 2021), survey studies focussing on headache disorders (Schindler et al., 2015, 2021), recent reviews (Castellanos et al., 2020; Elman et al., 2022) and they expand on previous reports suggesting that psychedelics administered in full doses and microdoses may have the potential to help in the management of CP (Bonnelle et al., 2022).

5 | LIMITATIONS

The current study suffers from several limitations. First of all, this is a naturalistic survey study and as such it provides purely retrospective self-ratings from a self-selected sample of individuals who self-administer psychedelics. This design carries the risk of obtaining biased data and the generalizability of the produced results is only limited. It provides limited information to disentangle the role that different mechanisms play to achieve these perceived analgesic effects. While subjective reports on pain relief are still a valuable source of information given the nature of pain itself, in order to draw conclusions on the effects that psychedelics may have in this area, controlled studies are needed. Second, while there is consensus around the hypothesis that set and setting are important determinants of the outcomes of psychedelic use (Kettner et al., 2021), the survey did not inquire about the context of the administration nor other potentially relevant individual variables (e.g. personality traits) that may have served as mediators of the effects. Third, not all pain complaints had the same degree of homogeneity within the same category. As an example, this survey did not differentiate between different forms of arthritis (e.g. osteoarthritis vs. rheumatoid arthritis) that have different etiopathogeneses. Fourth, the survey did not inquire about doses or dosing schedules in the case of microdosing, which may limit the generalizability of the results. On the other hand, most psychedelic users in naturalistic settings are usually unaware of the dose they are taking, therefore subjective effects were preferred as indicators of the dose range. Fifth, the study does not allow to properly distinguish the effects of psychedelics on paroxysmal pain from those of persisting pain, two categories of conditions that require different clinical management. Also, relevant especially for migraine and TTH, a measure of the frequency of attacks in the attacks per week or per month timescale was not included. Sixth, medications were not presented in separate lists based on them being abortives or preventives, so this may not appropriately capture the effects of preventives like antidepressants that are not supposed to bring acute relief in case of a pain episode. Seventh, albeit participants had the opportunity to enter conventional medications other than those listed, gabapentinoids were not included in the medications list. Considering that they are the first-line treatment for sciatica prevention, analyses may not have been able to capture the comparison of obtained relief between such drug categories and psychedelics. Finally, the sample size for each condition was limited.

6 | CONCLUSIONS

In conclusion, the present study suggests that psychedelics may hold value in the treatment of certain CP conditions. More specifically, participants reported that full doses seem to achieve better perceived results in pain relief than microdosing while microdosing's effectiveness seems comparable to that of conventional medication according to survey participants. Future research should focus on building clinical studies that would allow for controlling doses, dosing schedules and the monitoring of both biological and psychological measures to paint a clearer picture of the causal mechanisms that may lead to analgesic effects.

AUTHOR CONTRIBUTIONS

AF initiated the study. NLM and VB designed the survey with input from KPCK and JGR. VB, WJS and MC carried out data analyses. MC wrote the first draft and all authors discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

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