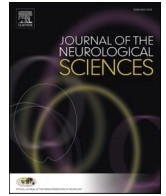




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Psilocybin pulse regimen reduces cluster headache attack frequency in the blinded extension phase of a randomized controlled trial

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ABSTRACT

Background: In a recent randomized, double-blind, placebo-controlled study, we observed a nonsignificant reduction of attack frequency in cluster headache after pulse administration of psilocybin (10 mg/70 kg, 3 doses, 5 days apart each). We carried out a blinded extension phase to consider the safety and efficacy of repeating the pulse regimen.

Methods: Eligible participants returned to receive a psilocybin pulse at least 6 months after their first round of study participation. Participants kept headache diaries starting two weeks before and continuing through eight weeks after the first drug session. Ten participants completed the extension phase and all ten were included in the final analysis.

Results: In the three weeks after the start of the pulse, cluster attack frequency was significantly reduced from baseline [18.4 [95% confidence interval 8.4 to 28.4] to 9.8 [4.3 to 15.2] attacks/week; $p = 0.013$, $d' = 0.97$). A reduction of approximately 50% was seen regardless of individual response to psilocybin in the first round. Psilocybin was well-tolerated without any unexpected or serious adverse events.

Discussion: This study shows a significant reduction in cluster attack frequency in a repeat round of pulse psilocybin administration and suggests that prior response may not predict the effect of repeated treatment. To gauge the full potential of psilocybin as a viable medicine in cluster headache, future work should investigate the safety and therapeutic efficacy in larger, more representative samples over a longer time period, including repeating the treatment.

Clinical Trials Registration: NCT02981173

1. Introduction

Since the serendipitous discovery of therapeutic effects of classic

psychedelic drugs in cluster headache in the 1990s, case reports and survey studies [1–3], and now clinical trials [4,5], have described lasting reductions in attack frequency after consuming a limited number of

Abbreviations: LSD, lysergic acid diethylamide; 5-HT_{2A}, 5-hydroxytryptamine 2 A; BOL or BOL-148, 2-bromo-LSD; VACHS, Veterans Affairs Connecticut Healthcare System; DEA, Drug Enforcement Administration; R1, round one; R2, round two; NRS, numerical rating scale; NSU, Neurobiological Studies Unit; VAS, visual analog scale; 5D-ASC, 5-Dimensional Altered States of Consciousness; OBN, oceanic boundlessness; DED, dread of ego dissolution; VRS, visionary restructuring; AUA, acoustic alterations; VIR, vigilance reduction; AE, adverse event; SD, standard deviation; MAP, mean arterial pressure; PAP, psychedelic-assisted psychotherapy.

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¹ Posthumous (RAS passed away in 2013, but was key to the conception of this study).

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doses. Classic psychedelics include such compounds as psilocybin, lysergic acid diethylamide (LSD), and lysergic acid amide (found in morning glory seeds), which share 5-hydroxytryptamine 2A receptor agonism. The drug class is best known for its ability to acutely alter sensation, perception, and consciousness, although there is evidence that these namesake effects may not be related to the therapeutic effects seen in headache disorders [4,6]. Consistent with this notion, cluster headache patients describe therapeutic effects with low or sub-psychedelic doses [1,2] and furthermore, the non-psychedelic LSD analogue, 2-bromo-LSD (BOL or BOL148) has also been reported to have therapeutic effects in cluster headache [1,7].

We recently reported the results of a randomized, double-blind, placebo-controlled pilot study of psilocybin in cluster headache that utilized a patient-informed pulse, or “busting,” regimen of three low doses of psilocybin (10 mg/70 kg) taken five days apart each [4]. This study showed an approximate 30% reduction in cluster attack frequency that failed to reach statistical significance. The design of the original pilot study included an extension phase to determine the efficacy and safety of a repeated round of treatment (a practice carried out by patients for improved results and/or maintenance of treatment effect [1]). As in the first round of the study, we hypothesized that psilocybin would suppress several measures of cluster headache burden, with primary interest in attack frequency (attacks/week) and demonstrate safety when administered under experimental conditions. This report is the primary analysis of these data and includes some secondary analysis from the original pilot study.

2. Methods

The methods for this study are similar to those described in our pilot psilocybin cluster headache study [4].

2.1. Regulatory approvals and funding

This study was registered on clinicaltrials.gov (NCT02981173) and received approvals from the Human Studies Subcommittee of Veterans Affairs Connecticut Healthcare System (VACHS) and the Human Investigations Committee of Yale University. The study was conducted under an approved Investigational New Drug application (#124,874) with the US Food & Drug Administration and Drug Enforcement Administration (DEA) Schedule 1 registration. Funding for this extension phase came from Ceruvia Lifesciences.

2.2. Psilocybin

Synthetic psilocybin was obtained under DEA Schedule 1 registration from the University of Wisconsin-Madison (author NVC) or Osona Institute. The material was between 98.6% and 100% pure by high performance liquid chromatography. Weight-based doses of psilocybin (10 mg/70 kg [0.143 mg/kg]) were compounded for each participant into blue gelatin capsules by the VACHS Investigational Research Pharmacy. The psilocybin dose was the same as that used in the first round of study participation [4].

2.3. Participants

Participants who previously took part in the cluster headache pilot study (heretofore referred to as round 1 [R1]) were eligible to return for a second round of participation (round 2 [R2]) after at least 6 months from the last test day and if they continued to meet all study criteria (the same criteria as for R1 [4]). Participants were required to be aged 21 to 65 years (inclusive), free from serious medical or psychiatric disease, have cluster headache as defined by the International Classification of Headache Disorders III-beta [8], and have a minimum attack frequency of approximately 1 attack per day. For episodic participants, the typical cluster period was required to last approximately 2 months or more. Use

of psilocybin or other psychedelic compounds in the prior three months was prohibited. Caffeine and nicotine were not restricted. Participants were required to be free from serotonergic antidepressants (e.g., fluoxetine) for at least six weeks. Triptans (e.g., sumatriptan) were permitted, but no more than twice weekly and not within five elimination half-lives of said triptan before each test day, nor within five elimination half-lives (fifteen hours) of psilocin, the active metabolite of psilocybin, after experimental drug administration. Research assistants and the principal investigator evaluated eligibility, obtained informed consent, and enrolled participants. In compliance with the Helsinki Declaration of 1975, as revised in 2000 [9], written informed consent was obtained from every participant who participated in the study. Participants taking part in R2 underwent the same screening and informed consent procedures as they had in R1. All participants were informed that they could decline to participate in the extension study without penalty and were free to withdraw at any time.

2.4. Study design

All participants received psilocybin (10 mg/70 kg) in this extension phase, which took place under an approved enhanced blinding procedure in which psilocybin dose was unknown to participants and research staff. This blinded condition was also reflected in the clinicaltrials.gov registration. Participants completed three dosing sessions, separated by 5 ± 2 days each, during which they received psilocybin at each session. Participants maintained a headache diary starting 2 weeks before and continuing until 8 weeks after the first experimental session. Participants were instructed to document every cluster attack, including date, time of onset, time of offset, and pain intensity (0–10 numerical rating scale [NRS]: 0 = none, 1 = minimal, 5 = moderate, 9 = severe, 10 = worst imaginable). The 14 days prior to the first experimental session (baseline) and the 56 days after the first experimental session (inclusive) were counted in the final analysis.

2.5. Drug administration sessions

Sessions were conducted in the Neurobiological Studies Unit (NSU) at VACHS. Participants typically received the drug capsule between 8:30 AM and 9:30 AM. Vital signs were measured at baseline and throughout experimental sessions. General drug effects (‘overall,’ ‘anxiety/fear,’ ‘sleepiness/sedation,’ ‘nausea,’ ‘joy/intense happiness,’ ‘peace/harmony’) were self-reported on a 0–3 visual analog scale (VAS; 0 = none, 1 = minimal, 2 = moderate, 3 = definite) at baseline and throughout experimental sessions. Psychedelic effects were self-reported at the end of experimental sessions using the validated 5-Dimensional Altered States of Consciousness (5D-ASC) scale, which is a 94-item questionnaire divided into the following subscales: oceanic boundlessness (OBN), dread of ego dissolution (DED), visionary restructuring (VRS), acoustic alterations (AUA), and vigilance reduction (VIR) [10]. Participants marked their 5D-ASC scale responses on a 10 cm VAS. Participants were discharged from the NSU no sooner than 6 h after capsule ingestion and only once acute physiological and neuropsychological drug effects had resolved. Telephone safety follow-up was performed periodically out to 6 months after the last experimental session. After all participants completed study procedures, participants were called and debriefed on drug randomization. Participants were paid US \$50 for screening and US \$100 per experimental session.

2.6. Outcome measures

The same primary outcome as was used in R1 was used in R2—change in weekly attacks compared to baseline in the 3-week period after the start of the pulse regimen. Secondary outcomes included within-subjects comparisons between R1 and R2; separate measures of attack frequency in episodic and chronic participants; changes in attack duration (minutes), pain intensity, and use of abortive

medications; acute changes in vital signs; general drug effects; psychedelic ratings; and adverse events (AEs).

2.7. Statistical analysis

Statistical methods were similar to those used in R1 [4]. Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA). All statistical tests were two-sided with an overall pre-hypothesis threshold of alpha threshold of 0.05. Descriptive statistics included frequencies, percentages, means, and standard deviation (SD). For each diary measure, means and 95% confidence intervals were estimated. Diary measures over 3- or 8-week periods were compared to respective baseline via paired *t*-tests. Changes from baseline were also compared between R2 and R1 via paired *t*-test. There were no missing diary data. Acute effects of drug administration on mean arterial pressure (MAP), heart rate, peripheral oxygenation, and general drug effects measured throughout the session were analyzed using linear mixed models, which included test day and time (throughout experimental session) as within-participants factors, and random participant effects. All multi-way interactions were modeled and the best-fitting variance-covariance structure was based on information criteria. Least-square means were compared post-hoc to determine the nature of significant interactions. Psychedelic effects as measured by the 5D-ASC scale were calculated as a percent of the total possible score (940) [4,6,11,12] and compared using the same mixed models described above for vitals and general drug effects except time was dropped from the model, as the 5D-ASC was only measured once at the end of each session. Potential associations between general drug or psychedelic effects and the change in weekly attacks were assessed using correlation (Spearman) analysis. The numbers of AEs were described as incidences; group comparisons were carried out via Fisher exact test.

3. Results

3.1. Participants

Between January 2020 and April 2022, patients were assessed for extension phase eligibility. In-person study procedures did not take place between April 2020 and October 2020 due to the novel coronavirus (COVID-19) pandemic. Thirteen of the 16 former study participants were considered for the extension phase, ten of whom met eligibility criteria, were enrolled, and were included in the final analysis (Fig. 1). There were 7 males and 3 females (all cisgender) with an average age of 52.3 (SD 8.9; range 35–61) years (Table 1). Four participants had episodic cluster headache and 6 were chronic (no subtype transformations from R1). Half the participants were on a preventive medication, verapamil being the most common. There were no significant changes in subject characteristics between R1 and R2 (data not shown). The average interval between rounds of study participation was 14.4 (11.8) months (range 6.4 to 42.8 months). Given weight-based dosing in this study, the average amount of drug received by participants was 11.8 (2.6) mg.

3.2. Attack frequency

Attack frequency was significantly reduced from baseline (18.4 [95% CI 8.4–28.4] attacks/week) after psilocybin (9.8 [4.3–15.2] attacks/week; $p = 0.013$; $d' = 0.97$; Table 2). Attack frequency reductions approached significance with large effect sizes for both episodic ($p = 0.057$, $d' = 1.51$; Table 3; Fig. 2) and chronic ($p = 0.083$, $d' = 0.88$) participants over 3 weeks (Table 4), and in chronic participants over 8 weeks ($p = 0.094$, $d' = 0.84$; Table 4). Fig. 2 shows the week-by-week number of attacks in episodic and chronic participants. Heterogeneity among participant responses is noted. In seeking to match the primary outcome of a contemporary study [5], attack frequency in chronic

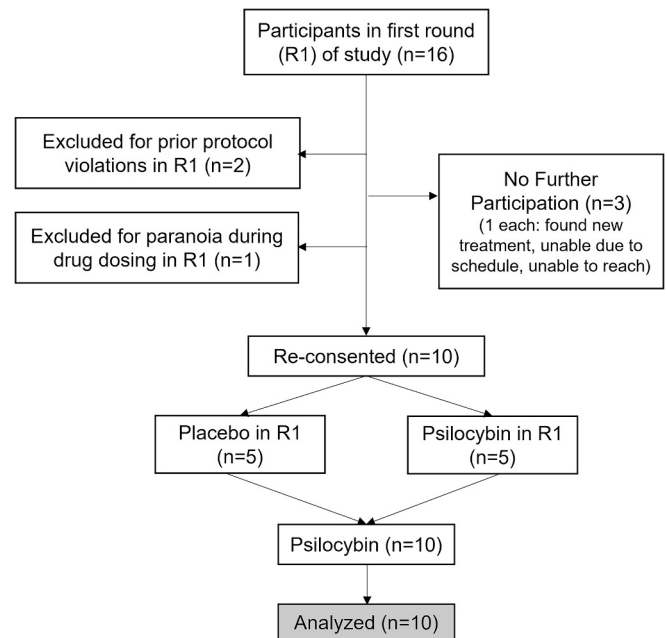


Fig. 1. Participant eligibility, re-consenting, and final analysis numbers for round 2 of study participation.

Table 1
Participant characteristics.

Characteristic	
Sex (biological)	7 male 3 female
Age, mean years (SD)	52.3 (8.9)
Weight, mean kg (SD)	82.4 (18.4)
Cluster headache subtype	4 episodic 6 chronic
Attack side	7 right 3 left
Attack time of day	5 any 3 overnight 2 specific times
Current preventives (some on multiple medications)	5 none 4 verapamil 2 melatonin 1 topiramate 1 gabapentin
Round 1 drug	5 placebo 5 psilocybin
Interval b/w rounds, mean months (SD)	14.4 (11.8)

Table 2
Diary outcomes at baseline and over 3 weeks after start of pulse ($n = 10$).

Cluster attack feature	Baseline	3 weeks	<i>p</i> value	Effect size
Frequency (attacks/week)	18.4 (8.4 to 28.4)	9.8 (4.3 to 15.2)	0.013	0.97
Duration (minutes)	31.3 (16.4 to 46.2)	48.2 (17.9 to 78.5)	0.143	0.51
Pain (0–10)	5.9 (4.7 to 7.1)	5.3 (4.3 to 6.3)	0.013	0.98
Abortive use (days/week)	6.3 (5.7 to 6.9)	4.0 (2.5 to 5.6)	0.001	1.44

participants in the four weeks after psilocybin pulse completion (pulse duration ranging from 7 to 15 days) was reduced from 23.1 (6.2 to 40.1) to 10.9 (4.4 to 17.5) attacks/week ($n = 6$; $p = 0.073$, $d' = 0.93$).

Table 3
Diary outcomes in episodic cluster headache participants ($n = 4$).

Feature	Baseline	Over 3 weeks	p value	Effect size
Frequency (attacks/week)	11.4 (1.3 to 21.5)	4.6 (−0.5 to 9.7)	0.057	1.51
Duration (minutes)	35.5 (−1.7 to 72.7)	66.8 (−12.9 to 146.4)	0.154	0.96
Pain (0–10)	7.0 (6.3 to 7.7)	6.0 (4.8 to 7.1)	0.040	1.73
Abortive use (days/week)	5.7 (4.1 to 7.4)	2.3 (0.8 to 3.8)	0.002	5.21

The baseline attack frequency in R2 (18.4 [8.4 to 28.4] attacks/week) was approximately double that in R1 in these 10 participants (9.6 [5.9 to 13.2] attacks/week; $p = 0.036$). Increases did not differ based on sex, age, headache subtype, R1 drug group, or presence of preventive medication (data not shown). Among the five participants who had received psilocybin in R1, the three who had previously responded below average (< 30% reduction in weekly attacks) now had an average percent frequency reduction in R2 of 49.8%. The other two subjects who responded in R1 had an average percent frequency reduction in R2 of 51.0%. Fig. 3 shows sample participants and their R1 and R2 responses.

3.3. Attack pain severity, duration, and abortive medication use

There were significant reductions from baseline in attack pain severity (−10% on 0–10 numerical rating scale [NRS]; $p = 0.013$) and abortive medication use (−37% days/week; $p = 0.001$; Table 2). Tables 3 and 4 show specific changes in attack duration, pain severity, and abortive medication use in episodic and chronic participants, respectively.

3.4. Consideration of selection bias

In consideration of potential selection bias in the R2 group, characteristics of subjects who took part in both study rounds were compared with those who only took part in R1 (Suppl Table 1). Baseline and post-psilocybin changes in attack frequency, pain severity, duration, and abortive medication use were also compared between groups in the R1 period (Suppl Table 2). No significant differences in either characteristics or response to psilocybin were seen.

3.5. Acute effects of drug administration

3.5.1. Vital signs

An effect of time was observed for MAP on dosing days 1 [$F(10, 288) = 3.93, p < 0.0001$] and 2 [$F(10, 288) = 2.39, p = 0.010$] but not 3 [$F(10, 288) = 1.45, p = 0.158$], however, these times trends did not differ across days (day by time interaction: $F(20, 288) = 0.57, p = 0.933$; Suppl Table 3). Psilocybin increased MAP maximally between 60 and 90 min with an average increase over baseline of 10.0 (1.3) mm Hg. A significant effect of time was found on day 1 for heart rate [$F(10, 288) = 1.91, p = 0.044$] and day 3 for SpO2 [$F(10, 288) = 2.32, p = 0.012$], but there were no significant differences among dosing days (Suppl Table 3).

3.5.2. General drug effects

An effect of time was observed for ‘overall drug effects’ on all three dosing days [Day 1 $F(8, 232) = 36.3$; Day 2 $F(8, 232) = 28.4$; Day 3 $F(8, 232) = 31.5$; all $p < 0.0001$] but these effects did not differ across days (interaction: $F(16, 232) = 1.02, p = 0.440$; Suppl Table 3). Psilocybin induced maximal ‘overall drug effects’ between 90 and 120 min with an average maximum rating of 2.8 (0.08) on a 0–3 NRS. Given that 7 out of 10 participants gave the highest rating for this measure (3; i.e., ceiling effect), an average score was calculated wherein ratings were considered along with duration of effect. This average score for ‘overall drug effects’ did not correlate with changes in attack frequency ($r = -0.190$; $p =$

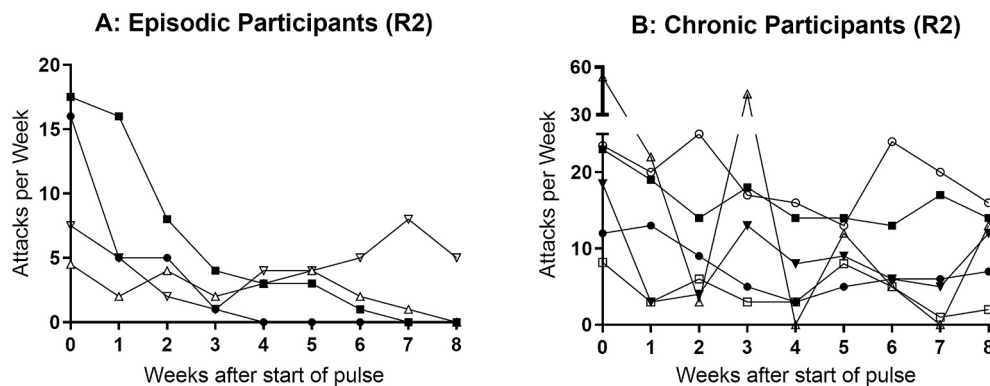


Fig. 2. Weekly attack frequency is shown at baseline and over the 3-week period in individual episodic participants (A; $n = 4$) and over the 8-week period in individual chronic participants (B; $n = 6$). Open symbols denote participants randomized to placebo in R1; closed symbols denote participants randomized to psilocybin in R1.

Table 4
Diary outcomes in chronic cluster headache participants ($n = 6$).

Feature	Baseline	Over 3 weeks	p value	Effect size	Over 8 weeks	p value	Effect size
Frequency (attacks/week)	23.1 (6.2 to 40.1)	13.2 (4.9 to 21.5)	0.083	0.88	10.9 (5.0 to 16.7)	0.094	0.84
Duration (minutes)	28.5 (6.6 to 50.4)	35.8 (−1.5 to 73.2)	0.599	0.22	26.7 (6.1 to 47.2)	0.732	0.15
Pain (0–10)	5.1 (3.3 to 7.0)	4.9 (3.1 to 6.7)	0.138	0.72	4.8 (2.9 to 6.6)	0.118	0.77
Abortive use (days/week)	6.7 (6.0 to 7.3)	5.1 (3.0 to 7.3)	0.067	0.95	5.0 (3.0 to 6.9)	0.031	1.22

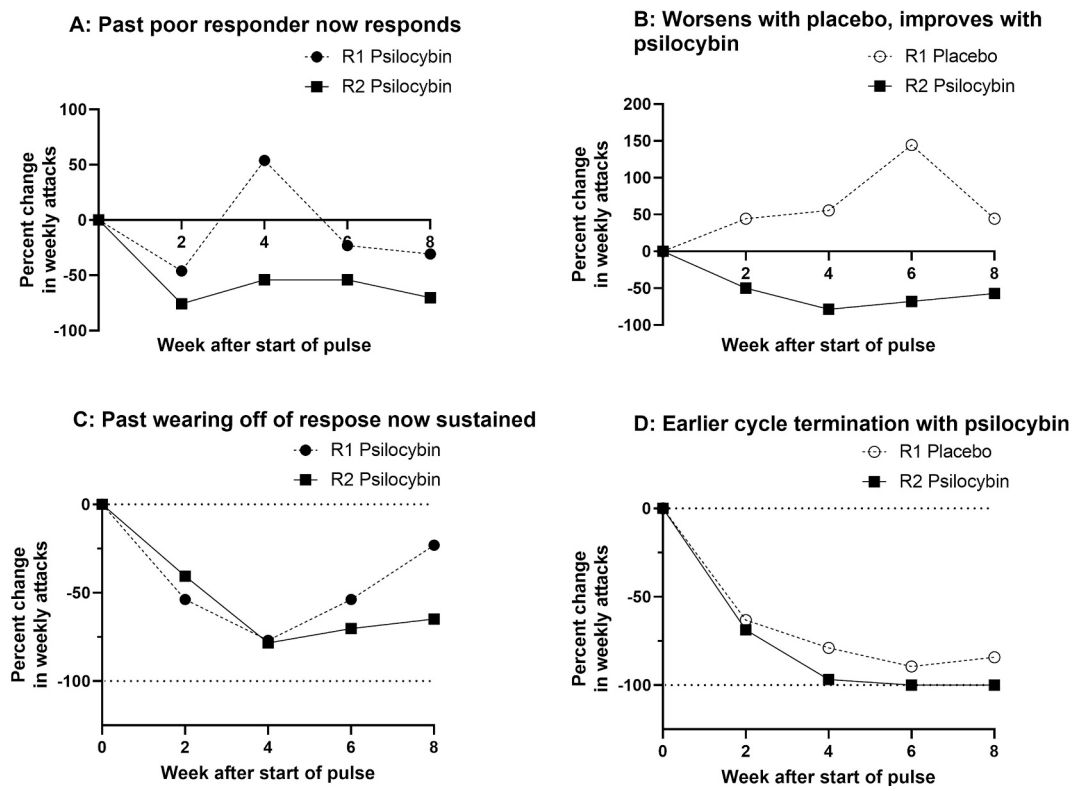


Fig. 3. Sample participant responses to pulse administration in R1 and R2 are shown. Panel A is a chronic participant who overall did not respond to psilocybin in R1 but had a sustained response over the diary period in R2. Panel B shows a chronic participant who had an increase in attack frequency after receiving placebo in R1 and a decrease after psilocybin in R2. Panel C shows a chronic participant whose good response to psilocybin was longer lasting in R2 than in R1. Panel D shows an episodic participant who had reduced burden in but not termination of their cluster cycle in R1 with placebo but had an earlier termination in R2 with psilocybin (dosing in both rounds took place one month into their cycle). Open circle, placebo in R1 (B, D); closed circle, psilocybin in R1 (A, C); closed square, psilocybin in R2 (all participants).

0.600). A significant effect of time was observed for the feelings of ‘sleepiness,’ ‘nausea,’ ‘joy/intense happiness,’ and ‘peace/harmony,’ but not ‘anxiety/fear’ (Suppl Table 3). There were no significant differences in general drug effect among dosing days.

3.5.3. Psychedelic effects

The percent total 5D-ASC scale score averaged over the three test days was 22.6% (13.2% to 32.1%); there was no significant difference among the three dosing days [$F(2, 9) = 2.28, p = 0.158$; Suppl Table 4]. There were also no significant differences in scores among test days for any of the 5 dimensions of the scale (Suppl Table 4). There was an association between percent total 5D-ASC scale score (averaged over the three test days) and the percent change in weekly attacks over the 3-week period after the start of the pulse ($r = -0.638; p = 0.047$). This association was not significant in chronic cluster headache participants over the entire 8-week period ($r = -0.242; p = 0.644$), where, similar to 3 weeks, an approximate 50% reduction in attack frequency was observed. In seeking to match outcomes with a contemporary psilocybin-cluster headache study [5], there was no correlation between percent total 5D-ASC scale score and the percent change in weekly attacks over the 4 weeks after completion of the psilocybin pulse ($r = -0.226; p = 0.667$).

3.6. Adverse events

There were no serious or unexpected AEs from study participation (Table 5). The most frequently reported AEs during dosing sessions were cluster attacks, fatigue, and nausea. The most frequently reported AEs the day after drug dosing were cluster attacks and fatigue. All AEs were self-limiting and in the case of cluster attacks, treated by typical abortive

Table 5

Adverse events during drug dosing and next 24 h.

Adverse	During dosing session	24-h Period after
Cluster attack / cluster pain	7	8
Fatigue	6	5
Nausea	5	–
Drunk feeling	2	–
Anxiety	2	–
Restlessness	2	–
Yawning / sighing	2	–
Lightheadedness	1	–
Dizzy	1	–
Tingling	1	–
Feeling cold	1	–
Muscle tension	1	–
GI upset	1	1
Insomnia	–	3
Headache (general)	–	1
Vivid dream	–	1
None	–	1

means (e.g., high-flow oxygen). There were no significant differences in incidence of AEs between participants who were receiving psilocybin for the first or second time (data not shown). No lasting physical or neuropsychological changes were reported out to 6-month follow-up with participants.

4. Discussion

In this extension phase of a controlled investigation of psilocybin in cluster headache, a patient-informed psilocybin pulse regimen

significantly reduced cluster attack frequency by approximately 50%. This effect was sustained in chronic participants over 8 weeks. Findings support therapeutic efficacy after a second round of treatment and suggest that non-response after a single trial may not predict subsequent poor efficacy. In conventional headache management, there is commonly a delay for the full effect of preventive medications to take effect (e.g., verapamil, galcanezumab [13,14]). Additionally, a conventional transitional treatment—occipital nerve blockade—may be repeated periodically in cluster headache to maintain disease suppression [15]. Therefore, it is not unreasonable to expect that psilocybin may require intermittent pulses for maximum efficacy and/or maintenance of treatment effect.

As in R1, the treatment response in R2 was heterogeneous, suggesting that the magnitude and timeline for response differ among individuals. Furthermore, while 3 weeks was chosen as the timeframe for the primary efficacy outcome based on recent preventive treatment research [16], given that psilocybin is unlike conventional agents and acts more like a transitional treatment, this timepoint may not be sufficient to capture all the drug's therapeutic effects. In a contemporary cluster headache trial with psilocybin, the 4 weeks after completion of the drug pulse compared to the 4 weeks before the start of the pulse was chosen as the measure of efficacy [5]. This study only included chronic cluster headache patients, allowing for long baseline and follow up periods. Given the inclusion of episodic patients in the present study, this was not possible. In our chronic participants, however, an approximate 50% reduction in attack frequency was seen over the 4 weeks after pulse completion, although this reduction failed to reach statistical significance, likely due to the low number of participants in this subgroup ($n = 6$). In addition, half of the chronic participants in this subgroup were receiving their first psilocybin pulse, which, as discussed above, may not be sufficient to assess ultimate response.

It was noted that baseline attack frequency approximately doubled from R1 to R2. The execution of R2 took place just before and then during the early period of the COVID-19 pandemic, which might represent a stressor that could have increased attack frequency. The nasal swabs performed for COVID testing during study screening and prior to each test day also generated extra attacks in some participants. One R2 participant experienced heightened stress in the setting of a sick family member and also had an increase in baseline attack frequency. While varying baselines between study rounds limited within-subjects comparisons, the higher level of disease burden in R2 might have allowed for the observed significant clinical improvement. This threshold effect is also noted in the response of migraine patients to onabotulinum toxin A, with significant differences from placebo being seen in higher frequency episodic patients and chronic patients (i.e., those with more headache days per month at baseline) [17,18].

Unlike R1 and our psilocybin-migraine study [4,6], the changes in cluster attack frequency in R2 were correlated with the intensity of acute psychedelic effects on dosing days. It was noted, however, that this correlation was lost in chronic patients over the entire 8 weeks of the headache diary. Similar to R1, the small number of participants and relatively low 5D-ASC scale scores (from a low dose of psilocybin), make definitive relationships difficult to confirm. It is also noted that cluster headache patients who self-manage their disease often use low or sub-perceptual doses [1,2]. BOL, a minimally psychotropic analogue of LSD, also reduced cluster attack frequency after a 3-dose pulse in an open label study [7]. Together, these findings suggest that the lasting effects of psilocybin in cluster headache are independent from the acute psychedelic experience. This aligns with some studies in mental health [19,20] and contrasts with others [21,22]. The role of the psychedelic experience in the therapeutic effects of psilocybin and other psychedelics remains an active area of debate in the field. Importantly, whereas psychedelic effects are understood to stem from 5-HT_{2A} receptor activation, whether this receptor is also the mediator of therapeutic effects in cluster headache, migraine, or other conditions has not been determined.

Unlike studies in mental health disorders, where psilocybin is typically used as an adjunct to psychotherapy [23], in cluster headache and migraine studies, psilocybin is administered alone without psychotherapy [4,6,24]. This distinction is important, particularly when considering how psilocybin and other psychedelics might be applied as medicines in the future. Whereas financial interests and regulatory bodies are conforming to the model known as psychedelic-assisted psychotherapy (PAP), which includes psychotherapy, guided drug dosing sessions, and curated settings (e.g., music, décor), both anecdotal and controlled evidence suggest that this design is not required for headache disorders. In addition, the clinical application of the PAP model on a large scale (for any condition) faces substantial issues related to cost, quality, and accessibility. Unless disease-specific protocols are recognized early on, challenges with securing study approval, funding, and ultimately clinical approval for psychedelics in cluster headache and other headache disorders are likely to arise.

As in R1, drug administration was well-tolerated and without serious or unexpected adverse events in R2, suggesting that repeating the pulse regimen at least 6 months later is safe. The existing psilocybin clinical trial literature almost exclusively reports on the safety of a single dose, or 2 to 3 doses administered over a week or a month's time [25,26]. Such safety reports do not apply to the practice among cluster headache patients of periodic pulses over the long-term (i.e., years, decades) [1,2]. While the need for repeated (aka booster) treatments is discussed more broadly in the psychedelic literature [26,27], such safety and efficacy studies have not yet been carried out. The present study represents an important first step in bridging the gaps between controlled investigations, patient practices, and anticipated clinical practice. In designing longer-term studies with repeated treatments, it will also be important to make appropriate adjustments for the variety of cluster headache patients, their disease patterns, and their responses to treatment.

While research is still very preliminary, it is tempting to postulate psilocybin's mechanism of action in cluster headache. Among headache disorders, cluster headache and other trigeminal autonomic cephalalgias spotlight several neurobiological systems that might serve as targets for psilocybin and other psychedelics. These systems include neuroendocrine and autonomic function, sleep, and circadian rhythm [28]. The hypothalamus is of particular interest in cluster headache, given activation of this brain region during attacks and during cycles [29]. Both animal [30,31] and human [32] studies have shown acute effects of psilocybin in the region of the hypothalamus. Recently, changes in functional connectivity of the hypothalamus were shown to be associated with reductions in cluster attack burden after psilocybin treatment [5]. Replication of this finding would serve to center on a potential target for psilocybin's clinical effects in cluster headache.

The small sample size is a clear limitation of this study; however, the results serve to provide estimates of effect sizes to be used for designing future larger scale studies. As in R1, participants were not representative of the general cluster headache population (i.e., all Caucasian, more chronic than episodic participants, episodic participants had long cycles). While all participants received psilocybin in R2, an enhanced blinding protocol was in place so that dose was not known, which allowed for some level of blinding. Still, expectation was likely higher in R2, potentially resulting in a more robust response. As in R1, the VIR dimension of the 5D-ASC scale scored highest during psilocybin administration, suggesting that a drug that induces fatigue may serve as an adequate active control agent for the dose of psilocybin used (10 mg/70 kg). The approximate doubling of baseline attack frequency from R1 to R2 limited direct within-subjects comparison but may have also produced a threshold level required for observing significant clinical effects. This situation also highlighted public and personal experiences that might aggravate disease burden. While exceptional events like pandemics may not be avoided, future studies can consider baseline disease burden in the treatment response and will seek to include larger numbers of more representative subjects. The use validated scales of

expectation and blinding success [33,34], and employing an active control agent (such as diphenhydramine used in our most recent migraine study [NCT04218539]) will also serve to address common confounds in psychedelic studies.

Within the limitations of this extension phase study, a patient-informed 3-dose psilocybin pulse significantly reduced cluster attack frequency by approximately 50%. The repeated pulse appeared effective regardless of prior response to psilocybin and was safe and well-tolerated. This study adds to the growing body of literature on psychedelics in cluster headache, although larger, longer-term studies with repeated rounds of administration will be required to gauge the full potential of psilocybin as a safe and effective treatment in cluster headache.

CRedit authorship contribution statement

Emmanuelle A.D. Schindler: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **R. Andrew Sewell:** Methodology, Conceptualization. **Christopher H. Gottschalk:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **L. Taylor Flynn:** Writing – review & editing, Project administration, Investigation, Data curation. **Yutong Zhu:** Writing – review & editing, Project administration, Investigation, Data curation. **Brian P. Pittman:** Writing – review & editing, Validation, Software, Formal analysis. **Nicholas V. Cozzi:** Writing – review & editing, Resources. **Deepak C. D'Souza:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2024.122993>.

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