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RESEARCH SUBMISSIONS

# Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial

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## Abstract

**Objective:** Using a patient-informed regimen, we conducted an exploratory randomized, double-blind, placebo-controlled study to systematically investigate the effects of psilocybin in cluster headache.

**Background:** Sustained reductions in cluster headache burden after limited quantities of psilocybin-containing mushrooms are anecdotally reported, although to date there are no controlled studies investigating these effects.

**Methods:** Participants were randomized to receive psilocybin (0.143 mg/kg) or placebo (microcrystalline cellulose) in a pulse of three doses, each ~5 days apart. Participants maintained headache diaries starting 2 weeks before and continuing through 8 weeks after the first drug session. A total of 16 participants were randomized to receive experimental drug and 14 were included in the final analysis.

**Results:** In the 3 weeks after the start of the pulse regimen, the change in cluster attack frequency was 0.03 (95% confidence interval [CI] −2.6 to 2.6) attacks/week with placebo (baseline 8.9 [95% CI 3.8 to 14.0]) and −3.2 (95% CI −8.3 to 1.9) attacks/week with psilocybin (baseline 9.6 [95% CI 5.6 to 13.6]; $p = 0.251$). Group difference in change from baseline had a moderate effect size ($d = 0.69$). The effect size was small in episodic participants ($d = 0.35$) but large in chronic participants ($d = 1.25$), which remained over the entire 8-week period measured ($d = 0.81$). Changes in cluster attack frequency were not correlated with the intensity of acute psychotropic effects during

**Abbreviations:** 5D-ASC, 5-Dimensional Altered States of Consciousness; AE, adverse event; BOL or BOL-148, 2-bromo-LSD; CI, confidence interval; LSD, lysergic acid diethylamide; MAP, mean arterial pressure; NS, not significant; NSU, Neurobiological Studies Unit; SD, standard deviation; VACHS, Veterans Affairs Connecticut Healthcare System; VIR, vigilance reduction.

Posthumous (R. Andrew Sewell passed away in 2013).

psilocybin administration. Psilocybin was well-tolerated without any unexpected or serious adverse events.

**Conclusions:** Findings from this initial, exploratory study provide valuable information for the development of larger, more definitive studies. Efficacy outcomes were negative, owing in part to the small number of participants. The separation of acute psychotropic effects and lasting therapeutic effects underscores the need for further investigation into the mechanism(s) of action of psilocybin in headache disorders.

**KEYWORDS**
cluster headache, headache, preventive treatment, psilocybin, psychedelics, transitional treatment

## INTRODUCTION

Cluster headache is a relatively rare headache disorder characterized by distinctive autonomic, circadian, and circannual features. The severity of pain in cluster headache is rated highest among other painful conditions,[1] earning the disorder the pseudonym "suicide headache".[2] This, in addition to deficiencies in clinician knowledge and the limits of conventional treatment, has driven patients to utilize untested agents and practices.[3–5] For over two decades, reports across social media, as well as a few peer-reviewed publications, suggest that psilocybin, lysergic acid diethylamide (LSD), and other indoleamine 5-hydroxytryptamine 2A receptor agonist compounds, also known as psychedelics, may confer therapeutic benefit in cluster headache.[6–9] In contrast to conventional therapies, these compounds are reported to produce lasting reductions in headache burden after a *single* or a few doses.[6–9] In some cases, these brief drug exposures are reported to induce complete disease remission.[6] These sustained effects suggest a yet-unknown mechanism of action that, if verified, would have tremendous value in the understanding and management of cluster headache. In addition, patients who use psychedelic compounds to manage cluster headache often use low or sub-psychedelic doses,[6,7] suggesting a mechanism of action independent from these namesake effects.

One of the more commonly reported regimens used by patients with cluster headache to terminate a cluster period or induce remission is a low dose of psilocybin (between 1 and 2 g dried *Psilocybe cubensis* mushroom, approximately equivalent to 6–12 mg pure psilocybin) taken three times, ~5 days apart each. The goal of this exploratory study was to determine the effects and safety of this patient-informed regimen in cluster headache in a controlled laboratory setting. We hypothesized that relative to placebo, the psilocybin pulse regimen would suppress several measures of cluster headache burden and be safe when administered under experimental conditions. As the first controlled study of psilocybin in cluster headache, we were also prepared for unanticipated findings and sought to use all information learned for the design and development of future studies. This report is the primary analysis of these data and there are no previous publications of these findings.

## MATERIALS AND METHODS

The materials and methods for this study are similar to those described in our published pilot of psilocybin in migraine.[10] They are summarized below with full details available in the Supporting Information.

### Regulatory approvals

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 and Drug Administration and Drug Enforcement Administration Schedule 1 registration.

### Psilocybin

Synthetic psilocybin was obtained under Drug Enforcement Administration Schedule 1 registration from the University of Wisconsin-Madison (N.V.C.) or Usona Institute. The material was between 98.6% and 100% pure by high performance liquid chromatography. Weight-based doses of psilocybin (0.143 mg/kg) and matching placebo (microcrystalline cellulose, obtained from Fagron, St. Paul, MN, USA), were compounded for each participant into identical blue gelatin capsules by the VACHS Investigational Research Pharmacy. The psilocybin dose was chosen as it is 10 mg/70 kg, approximating 1.6 g dried *P. cubensis* (mid-range of what patients typically use).

### Participants

Participants were recruited from the local community, headache centers, online headache websites, and word of mouth. Adults (aged 21–65 years, inclusive), free from serious medical or psychiatric disease, with cluster headache as defined by the *International*

*Classification of Headache Disorders Third Edition* (beta version)[11] were eligible to participate in this study. A minimum attack frequency of ~1 attack/day was required. For episodic participants, the typical cluster period was required to last ~2 months or more. Prior exposure to psilocybin or related compounds was not excluded, although any use in the past 3 months was prohibited. Caffeine and nicotine were not restricted. Participants were required to be free from serotonergic antidepressants (e.g., fluoxetine) for at least 6 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 (15 h) of psilocin, the active metabolite of psilocybin, after experimental drug administration. Research assistants evaluated eligibility, obtained informed consent, and enrolled participants. In compliance with the Helsinki Declaration of 1975, as revised in 2000,[12] written informed consent was obtained from every participant who participated in the study. Furthermore, participants were informed that they could decline to participate in the study without penalty and were free to withdraw from the study at any time.

## Study design

Participants were randomized 1:1 to psilocybin (0.143 mg/kg) or placebo (microcrystalline cellulose) using computer-generated block randomization, stratified by headache subtype (i.e., episodic, chronic). Given the exploratory nature of the study and the lack of available data from which to calculate sample size, a priori statistical power calculation was not conducted. Participants completed three experimental sessions, separated by 5 ± 2 days each, during which they received the same drug at each session. The study took place under an approved enhanced blinding procedure in which drug dose was unknown to participants and research staff. This blinded condition was also reflected in the clinicaltrials.gov registration. Research Pharmacy managed participant randomization and maintained the blind (see Supporting Information). Participants maintained a headache diary starting 2 weeks before until 8 weeks after the first experimental session. Participants documented every cluster attack, including date, time of onset, time of offset, and pain intensity (0–10 numerical scale: 0 = none, 1 = minimal, 5 = moderate, 9 = severe, 10 = worst imaginable). This method of self-reporting attack symptoms in a diary is the "gold standard" in headache research and was also used in the cluster headache preventive trials for galcanezumab and non-invasive vagus nerve stimulation.[13–16] 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.

## Experimental sessions

Sessions were conducted in the Neurobiological Studies Unit (NSU) at VACHS. Participants typically received the drug capsule between 8:30 and 9:30 a.m. 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 (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, dread of ego dissolution, visionary restructuralization, acoustic alterations, and vigilance reduction (VIR).[17] Participants marked their 5D-ASC scale responses on a 10-cm visual analog scale. 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.

## Outcome measures

As this was an exploratory trial, no single primary outcome was defined a priori. Instead, several outcomes were evaluated and interpreted, but emphasis was placed on cluster attack frequency. There were no prior similar studies from which to predict a timeline for therapeutic effects. To capture a clinically relevant duration that would also allow the inclusion of episodic participants, the change in weekly attacks compared to baseline in the 3-week period after the start of the pulse regimen was used as the primary outcome measure. Other primary outcomes included such measures as change in attack duration (min) and pain intensity (0–10 numerical scale) in the 3-week period after start of the pulse. Secondary outcomes included the same clinical outcomes in episodic and chronic participants, extending to 8 weeks in chronic participants, acute changes in vital signs, general drug effects, psychedelic ratings, and adverse events (AEs).

## Statistical analysis

Statistical analyses were performed using Statistical Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA). All statistical tests were two-sided with an overall pre-hypothesis threshold of $p < 0.05$. Analyses were not adjusted for additional variables. Histograms and Q–Q plots confirmed model assumptions. Descriptive statistics included calculations of frequencies, percentages, means, and standard deviation (SD). Diary data were analyzed to show means and 95% confidence intervals (CIs). Headache diary data were calculated for each participant and then averaged across individuals in the group of

interest. The changes from baseline measured in the headache diary were calculated as raw values and compared between placebo and psilocybin via independent *t*-test. Alternative methods of analysis (including analysis of covariance adjusting for baseline) did not affect the results. 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 that included group as a between-participants factor, test day and time (throughout experimental session) as within-participants factors, and random participant effects. All muti-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)[10,18,19] 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. There were some missing data for vital signs, general drug effects, and the 5D-ASC scale. One participant did not partake in their third test day, another's 5D-ASC scale had missing pages, and three participants had isolated missing values for vital signs or general drug effects. The mixed models used to analyze these data used all available data regardless of missing data. Potential associations between general drug or psychotropic effects and the change in weekly attacks were assessed using correlation (Spearman) analysis. The numbers of AEs were compared between placebo and psilocybin using Fisher's exact test.

## RESULTS

Between November 2016 and August 2021, patients were assessed for study eligibility. In-person study procedures did not take place between April 2020 and October 2020 due to the novel coronavirus disease 2019 (COVID-19) pandemic. Recruitment ceased once target randomization was met. There were protocol changes after initiation of the trial, including the inclusion of episodic cluster headache participants and the allowance of triptans (see Supporting Information). A total of 238 candidates were pre-screened; 20 underwent secondary screening and 16 underwent study procedures. In all, 14 participants (six placebo, eight psilocybin) were included in the final analysis (Figure 1). Two participants were excluded from final analysis for protocol violations (use of psilocybin-containing mushrooms in the follow-up period, failure to provide diary after baseline period; see Supporting Information). The decision to drop these subjects'

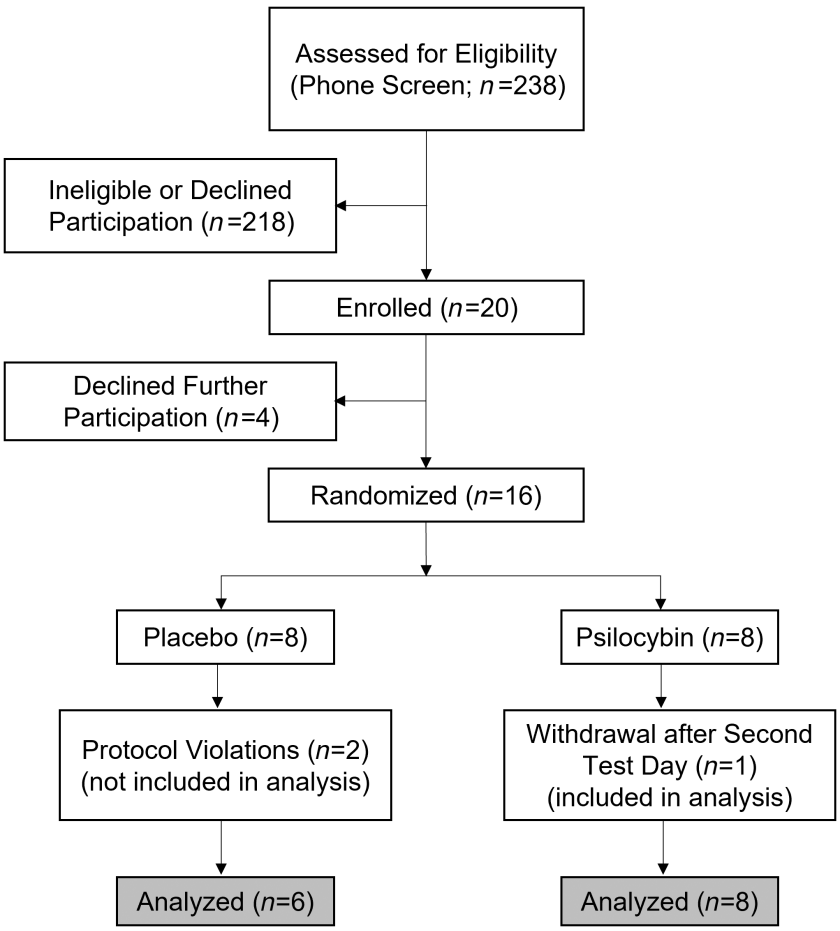


**FIGURE 1** Participant screening, enrollment, randomization, and final analysis numbers.

data was made prior to conducting statistical analysis. Given weight-based dosing in this study, the mean (SD) amount of drug received by participants randomized to receive psilocybin was 10.6 (2.0) mg.

## Participant characteristics

Participant demographics and headache characteristics are detailed in Table 1. There were nine males and five females by biological sex (cisgender) with a mean (SD, range) age of 49.1 (10.7, 27–61) years. Six participants had episodic cluster headache and eight were chronic. Medication and substance use history are detailed in Table 2. No participant was satisfied with their current cluster headache treatment regimen. While five participants had tried psilocybin-containing mushrooms or another psychedelic for recreation (ranging from 2 years to >20 years prior), none had attempted use for the management of cluster headache (a past attempt was not exclusionary).

**TABLE 1** Demographics and cluster headache characteristics

| Characteristic | All participants | Placebo | Psilocybin |
|---|---|---|---|
| Demographics | | | |
| Biological sex (cisgender), male/female, *n* | 9/5 | 5/1 | 4/4 |
| Age, years, mean (SD, range) | 49.1 (10.7, 27–61) | 44.5 (8.6, 35–58) | 52.6 (11.2, 27–61) |
| Race | All Caucasian | All Caucasian | All Caucasian |
| Weight, kg, mean (SD) | 78.9 (17.9) | 85.5 (21.7) | 73.9 (13.8) |
| Body mass index, kg/m$^2$, mean (SD) | 25.5 (4.4) | 26.1 (5.1) | 25.1 (4.1) |
| Attacks (diary baselines) | | | |
| Frequency, *n*/week, mean (SD) | 9.3 (4.6) | 8.9 (4.9) | 9.6 (4.8) |
| Duration, min, mean (SD) | 44.6 (23.7) | 28.7 (13.8) | 56.5 (22.9) |
| Pain intensity score (1–10), mean (SD) | 5.8 (1.7) | 6.1 (2.0) | 5.6 (1.5) |
| Side (locked or predominant), Right/left, *n* | 9/5 | 5/1 | 4/4 |
| Ipsilateral autonomic symptoms, Yes/No, *n* | | | |
| Eye redness and/or tearing | 12/2 | 5/1 | 7/1 |
| Nasal congestion and/or runny nose | 13/1 | 5/1 | 8/0 |
| Eyelid swelling | 8/6 | 2/4 | 6/2 |
| Forehead or facial sweating | 6/8 | 4/2 | 2/6 |
| Forehead or facial flushing | 5/9 | 1/5 | 4/4 |
| Sensation of ear fullness | 4/10 | 1/5 | 3/5 |
| Pupil constriction or eyelid drooping | 9/5 | 3/3 | 6/2 |
| Restlessness or agitation during attacks, Yes/No, *n* | 12/2 | 5/1 | 7/1 |
| Circadian pattern, Yes/No, *n* | 8/6 | 2/4 | 6/2 |
| Attack triggers, Yes/No, *n* | | | |
| Alcohol | 8/6 | 4/2 | 4/4 |
| Strong smells | 5/9 | 2/4 | 3/5 |
| Bright/flashing lights | 2/12 | 1/5 | 1/7 |
| Weather changes | 5/9 | 2/4 | 3/5 |
| Altitude changes | 4/10 | 1/5 | 3/5 |
| Travel across time zones | 1/13 | 0/6 | 1/7 |
| Other | 2/12 | 0/6 | 2/6 |
| No triggers | 5/9 | 2/4 | 3/5 |
| Age of onset, years, mean (SD) | 33.7 (14.4) | 31.2 (10.4) | 35.6 (17.3) |
| Time to correct diagnosis, years, mean (SD, range) | 7.5 (10.3) | 3.3 (2.3, 0.5–6) | 10.7 (12.9, 0.5–38) |
| Family history of cluster, Yes/No, *n* | 1/15 | 0/6 | 1/7 |
| Currently on preventive, Yes/No, *n* (Stable dose and no changes allowed during study. Transitional treatment [e.g., corticosteroid pulse] not permitted.) | 9/5 | 3/3 verapamil, topiramate | 6/2 verapamil, topiramate, gabapentin, melatonin |

**TABLE 2** Medication and substance use

| Question | All participants | Placebo | Psilocybin |
|---|---|---|---|
| Have you ever experienced a negative side-effect from a medication you took for cluster headache? Yes/No, *n* | 12/2 | 4/2 | 8/0 |
| Are you satisfied with your current cluster medication regimen? Yes/Somewhat/No, *n* | 0/6/8 | 0/1/5 | 0/5/3 |
| If there were a new medication available to treat cluster headache, would you try it? Yes/Maybe/No, *n* | 11/3/0 | 4/2/0 | 7/1/0 |
| Current drinker? Yes/Quit/Never, *n* | 8/6/0 | 4/2/0 | 4/4/0 |
| Current smoker? Yes/Quit/Never, *n* | 4/2/8 | 3/0/3 | 1/2/5 |
| Past use of controlled substances for recreation (excluding alcohol and nicotine), Yes/No, *n* | | | |
| Psilocybin and related[a] | 5/9 | 3/3 | 2/6 |
| Cannabinoids | 10/4 | 4/4 | 6/2 |
| Opioids | 0/14 | 0/6 | 0/8 |
| Stimulants[b] | 4/10 | 3/3 | 1/7 |
| Other[c] | 1/13 | 1/5 | 0/8 |
| None | 4/10 | 2/4 | 2/6 |
| Past alcohol/drug abuse/dependence, Yes active/Yes recovered/No, *n* | 0/1/13 | 0/1/5 | 0/0/8 |

[a]Lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), mescaline, etc.

[b]Cocaine, 3,4-methylenedioxy methamphetamine (MDMA, ecstasy), amphetamines, etc.

[c]Ketamine, kratom, nitrous oxide (whippets).

**TABLE 3** Change from baseline over 3 weeks (14 participates)

| | Change from respective baseline, mean (95% CI) | | | |
|---|---|---|---|---|
| Cluster attack feature | Placebo ($n = 6$) | Psilocybin ($n = 8$) | *p* | Effect size |
| Frequency, attacks/week | 0.03 (−2.6 to 2.6) | −3.2 (−8.3 to 1.9) | 0.251 | 0.69 |
| Duration, min | −3.7 (−14.9 to 7.5) | 9.4 (−16.0 to 34.6) | 0.335 | 0.58 |
| Pain intensity score (0–10) | −0.6 (−2.0 to 0.9) | −0.9 (−1.6 to −0.08) | 0.630 | 0.26 |

Abbreviation: CI, confidence interval.

**TABLE 4** Episodic cluster headache: Change from baseline over 3 weeks (six participates)

| | Change from respective baseline, mean (95% CI) | | | |
|---|---|---|---|---|
| Cluster attack feature | Placebo ($n = 3$) | Psilocybin ($n = 3$) | *p* | Effect size |
| Frequency, attacks/week | −1.5 (−7.1 to 4.1) | −3.9 (−27.2 to 19.4) | 0.690 | 0.35 |
| Duration, min | 3.0 (−18.9 to 24.8) | 19.1 (−41.1 to 79.4) | 0.339 | 0.89 |
| Pain intensity score (0–10) | −0.6 (−3.8 to 2.6) | −1.4 (−4.8 to 2.1) | 0.538 | 0.55 |

Abbreviation: CI, confidence interval.

## Attack frequency

Table 3 shows the change from respective baseline in weekly attacks over 3 weeks in all participants. The percentages of all participants who had at least 25%, 50%, 75%, and 100% reductions in weekly attacks were as follows: 33.3% (two of six), 33.3% (two of six), 0% (none of six), 0% (none of six) with placebo and 50% (four of eight), 37.5% (three of eight), 37.5% (three of eight), 0% (none of eight) with psilocybin, respectively (not significant [NS]). Table 4 and Figure 2 show the change from baseline in weekly attacks over 3 weeks for episodic participants. The percentages of episodic participants who had at least 25%, 50%, 75%, and 100% reductions in weekly attacks over 3 weeks were as follows: 66.7% (two of three), 66.7% (two of three), 0% (none of three), 0% (none of three) with placebo and 66.7% (two of three), 66.7% (two of three), 33.3% (one of three), 0% (none of three) with psilocybin, respectively (NS). Table 5 and Figure 2 show the change from baseline in weekly attacks over 3 and 8 weeks for chronic participants. The percentages of chronic participants who had at least 25%, 50%, 75%, and 100% reductions in weekly attacks over 3 weeks were as follows: 0% (none of three), 0% (none of

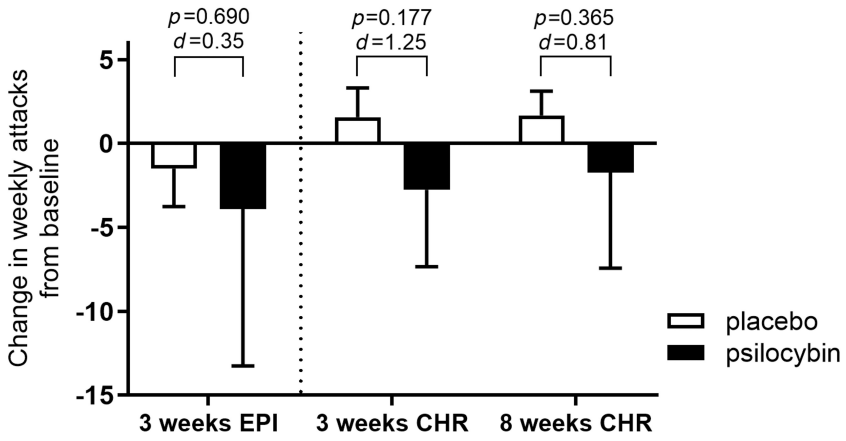


**FIGURE 2** Changes in weekly attacks over the 3-week period after start of pulse regimen is shown for episodic (six) and chronic (eight) participants and over the 8-week period for chronic participants. CHR, chronic; EPI, episodic. The *p* values are from independent *t*-tests.

**TABLE 5** Chronic cluster headache: Change from baseline over 3 and 8 weeks (eight participants)

| | Change from respective baseline (3 weeks), mean (95% CI) | | | | Change from respective baseline (8 weeks), mean (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| Cluster attack feature | Placebo ($n = 3$) | Psilocybin ($n = 5$) | *p* | Effect size | Placebo ($n = 3$) | Psilocybin ($n = 5$) | *p* | Effect size |
| Frequency, attacks/week | 1.6 (−2.8 to 5.9) | −2.8 (−8.4 to 2.9) | 0.177 | 1.25 | 1.7 (−1.9 to 5.3) | −1.7 (−8.8 to 5.4) | 0.365 | 0.81 |
| Duration, min | −10.4 (−31.5 to 10.6) | 3.5 (−39.4 to 46.4) | 0.531 | 0.55 | −12.1 (−24.6 to 0.3) | 5.2 (−39.9 to 50.3) | 0.456 | 0.67 |
| Pain intensity score (0–10) | −0.5 (−5.0 to 4.1) | −0.6 (−1.1 to 0.04) | 0.921 | 0.06 | −1.0 (−6.6 to 4.7) | −0.7 (−1.2 to −0.2) | 0.814 | 0.15 |

Abbreviation: CI, confidence interval.

three), 0% (none of three), 0% (none of three) with placebo and 40% (two of five), 20% (one of five), 20% (one of five), 0% (none of five) with psilocybin, respectively (NS); these same percentages remained over 8 weeks. Figure 3 shows the week-by-week number of attacks in episodic participants out to 3 weeks and chronic participants out to 8 weeks. Heterogeneity among participant responses is noted.

## Attack duration and pain severity

Tables 3–5 show the change in attack duration and pain severity; no significant differences between placebo and psilocybin were found. Of note, baseline attack duration was significantly higher in the group randomized to psilocybin (mean [95% CI] 56.6 [37.4 to 75.7] min) than the group randomized to placebo (mean [95% CI] 28.7 [14.2 to 43.2] min; $p = 0.022$); baseline pain severity was not significantly different between groups (data not shown).

## Acute effects of drug administration

### Vital signs

An interaction between drug and time was observed for MAP on all three test days (Day 1 $F[21,317] = 2.77$, $p < 0.0001$; Day 2 $F[21,317] = 1.77$, $p = 0.021$; Day 3 $F[21,317] = 1.70$, $p = 0.029$) without significant difference among test days ($p = 0.207$; Table S1). Psilocybin increased MAP maximally between 60 and 90 min, with a mean (95% CI) increase over baseline of 8.5 (2.9–14.1) mmHg. No significant drug × time interaction was found for heart rate or oxygen saturation and no significant drug × day interaction was found for any vital sign (Table S1).

### General drug effects

A drug × time interaction was observed for "overall drug effects" on all three test days (Day 1 $F[17,297] = 17.81$; Day 2 $F[17,297] = 21.97$; Day 3 $F[17,297] = 18.05$; all $p < 0.0001$) without significant difference among test days ($p = 0.595$; Table S1). Psilocybin induced maximal "overall drug effects" between 90 and 120 min with a mean (95% CI) increase over baseline of 2.6 (2.2–3.0) on a 0–3 numerical scale. There was no association found between maximal "overall drug effects" (averaged over the 3 test days) and the percent change in weekly attacks over the 3-week period after the start of the pulse ($r = 0.063$; $p = 0.883$). A significant drug × time interaction was observed for the feelings of "sleepiness", "anxiety", "joy/intense happiness", but not "nausea" or "peace/harmony" (Table S1). No significant drug × day interaction was found for any general drug effect (Table S1).

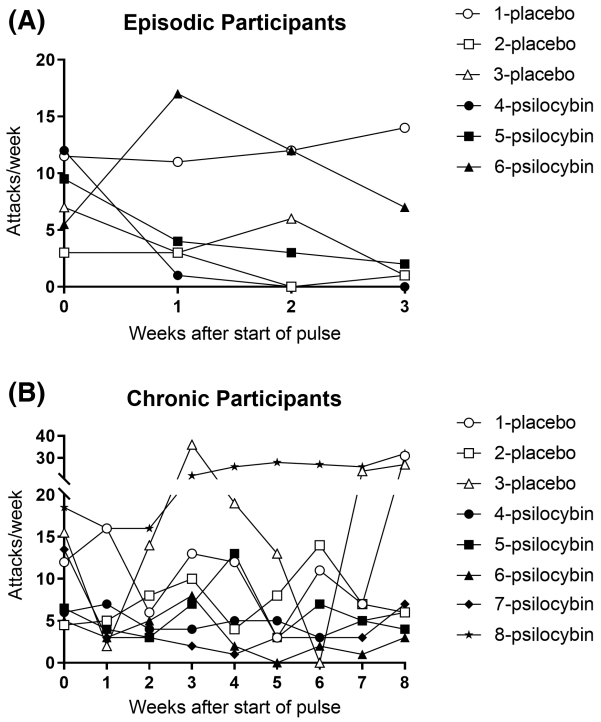


**FIGURE 3** Weekly attack frequency is shown at baseline and over the 3-week period in episodic participants (A; six participates) and over the 8-week period in chronic participants (B; eight participates).

## Psychedelic effects

The percent total 5D-ASC scale score was significantly higher in the psilocybin group ($F[1,11] = 62.93$, $p < 0.0001$; Table S2). There was no significant drug × day interaction ($p = 0.425$, $F[21] = 0.89$). Averaged over the three test days, the mean (95% CI) percent total score was 20.6% (14.8%–26.5%) after psilocybin and 0.9% (0.1%–1.7%) after placebo ($p < 0.0001$, $t[11] = 7.53$). There was no association found between percent total 5D-ASC scale score (averaged over the 3 test days) and the percent change in weekly attacks over the 3-week period after the start of the pulse ($r = 0.527$; $p = 0.224$). Psilocybin exposure resulted in significantly higher percent total scores than placebo in all individual dimensions of the 5D-ASC scale (Table S2). There were no drug × day interactions in any of the individual dimensions, except for acoustic alterations ($p = 0.040$, $F[11] = 4.4$; Table S2), where test day 1 values were significantly higher than test days 2 and 3 (data not shown).

## Adverse events

There were no serious or unexpected AEs from study participation (Table 6). The most frequently reported acute AEs with psilocybin were nausea, anxiety, and fatigue, which were self-limiting. Only the reported incidence of nausea during sessions was significantly higher

**TABLE 6** Adverse events during test days and the day following

| | Developed during test day | | | Developed in the next 24 h | | |
|---|---|---|---|---|---|---|
| **Adverse event, *n*** | **Placebo** | **Psilocybin** | ***p* (Fisher'sexact)** | **Placebo** | **Psilocybin** | ***p* (Fisher's exact)** |
| Lightheadedness | 0 | 2 | 0.473 | 0 | 0 | – |
| Dizzy/spinning | 0 | 2 | 0.473 | 0 | 0 | – |
| Nausea | 0 | 5 | 0.031 | 0 | 0 | – |
| Anxiety | 0 | 3 | 0.209 | 0 | 0 | – |
| Paranoia | 0 | 1 | >0.999 | 0 | 0 | – |
| Fatigue | 1 | 3 | 0.580 | 0 | 4 | 0.085 |
| Insomnia | 0 | 0 | – | 0 | 1 | >0.999 |
| Tingling/paresthesia | 0 | 1 | >0.999 | 0 | 0 | – |
| Shivering | 0 | 1 | >0.999 | 0 | 0 | – |
| Short of breath | 0 | 1 | >0.999 | 0 | 0 | – |
| Restlessness | 0 | 1 | >0.999 | 0 | 0 | – |
| Jaw soreness | 0 | 0 | – | 0 | 1 | >0.999 |
| Ear fullness | 0 | 0 | – | 0 | 1 | >0.999 |
| GI upset | 0 | 2 | 0.473 | 0 | 0 | – |
| Vivid dream | 1 | 0 | 0.429 | 0 | 0 | – |
| Muscle tension | 0 | 1 | >0.999 | 0 | 1 | >0.999 |
| Headache attack (general) | 0 | 2 | 0.473 | 0 | 1 | >0.999 |
| Cluster attack/pain | 3 | 4 | >0.999 | 4 | 5 | >0.999 |

with psilocybin than with placebo ($p = 0.031$). No other AEs were significantly different between psilocybin and placebo. One participant experienced paranoia during their second session, which resolved with staff support, and this participant did not partake in their third session; despite the experience with paranoia, this participant had rapid termination of their cluster cycle and indicated that they would choose to use this method of treatment again. In follow-up with participants 6 months after study participation, no lasting physical or neuropsychological changes were reported.

## DISCUSSION

In this first (to our knowledge) controlled investigation of psilocybin in cluster headache, we used a patient-informed pulse psilocybin regimen of three serial doses administered ~5 days apart each to reduce attack frequency in cluster headache. The reduction seen with psilocybin did not reach statistical significance as compared to placebo, likely owing to the small sample size of this exploratory study. The treatment effect between episodic ($d = 0.35$) and chronic ($d = 1.25$) participants was noted to be different. In this study, drug administration was safe and well-tolerated. Despite the exploratory nature of this study, several important topics related to the study of psilocybin in cluster headache were identified.

Despite efforts to include episodic participants with long cluster periods, the small effect seen in this group may have been confounded by the natural tapering and potential for spontaneous termination of the period. This confound was also raised in the extended portion of the galcanezumab study in episodic cluster headache, where participants receiving the drug had separated from placebo in the earlier 3-week time period.[16] Galcanezumab was also found to have an early effect in chronic participants (weeks 1–2), but it did not separate from placebo over 3 months of monthly treatment.[15] While chronic cluster headache is generally considered more resistant to treatment, non-invasive vagus nerve stimulation has preventive efficacy in patients with both episodic and chronic cluster headache, including in an extension phase out to 8 weeks.[13,14] Just as in the present study, treatment response is heterogenous, with some participants failing to experience a reduction in attack frequency (i.e., non-responders).[13] Ultimately, repeating the present study in a larger sample would help to define the clinical effects in episodic and chronic participants and consider what factors predict treatment response.

Other confounds in the present study include expectation and blinding, which are highly relevant in psychedelic drug studies.[20] No participants in the present study had tried psilocybin or a related compound specifically for cluster headache management and therefore, they did not have personal therapeutic experience from which to derive expectation. However, the general excitement around psychedelics as medicines has circulated in several forms of media, and particularly within the cluster headache community, which might serve to raise expectations for clinical effectiveness. None of the study participants was satisfied with their existing treatment regimen and therefore, hope for an effective treatment may have further raised expectation for success. Alternatively, a history of treatment failure may serve to lower expectations for any new treatment. Future studies should quantify expectation using a validated scale so that it may be used as a covariate measure for analysis.[21] Blinding is similarly vital in designing human research with psilocybin. While the enhanced blinding procedure used in this study did lead some participants to question what they received on experimental test days, more systematic study is necessary. The acute physiological and neuropsychiatric effects of psilocybin certainly have the potential to unblind participants. Similarly, the lack of or minimal acute effects of the placebo agent (microcrystalline cellulose) may produce a nocebo effect, which can limit the full appreciation of preventive efficacy.[22] Though a negative study, these factors remained a concern in its design and execution and will remain so in future studies. The small score on the 5D-ASC scale reported by some participants receiving placebo was mostly related to the VIR dimension, which can reflect fatigue. Interestingly, the VIR dimension also received the highest rating by those administered psilocybin. An active control agent with similar acute effects (e.g., antihistamine, benzodiazepine), but without expected lasting clinical effects, might serve as a better comparator for low-dose psilocybin.

As in our controlled psilocybin-migraine study,[10] the changes in cluster attack frequency in the present study were not correlated with the intensity of acute psychedelic effects on experimental test days, suggesting they may be independent. Additional lines of evidence support this finding. For instance, the minimally psychotropic LSD analog, 2-bromo-LSD (BOL or BOL-148) reduced cluster attack frequency after a three-dose pulse in an open label study.[23] Patients with cluster headache are also reported to use low and subperceptual doses of psychedelic drugs in managing their disease.[6,7] This separation of psychedelic and therapeutic effects in cluster headache (and migraine) is in contrast to reports in mental health disorders.[24,25] However, there are distinctions in the manner of drug administration between these types of studies. In mental health studies, psilocybin is administered as an adjunct to another therapy (e.g., cognitive behavioral therapy), high doses are used (up to 30 mg/kg), and drug sessions are carried out in a manner that centers on the psychedelic experience (e.g., music, décor, monitors present). In our cluster headache and migraine studies, low-dose psilocybin is the only experimental intervention, and it is administered in a neutral clinical setting; participants were informed and prepared for pscychedelic experiences but they were not a focus of the sudy. Going forward, the relevance of the namesake effects of psychedelic drugs in clinical trials should be considered carefully, including such factors as the disorder, drug, dose, setting, concomitant treatments, and the predetermined role of the experience (i.e., highlighted as central vs. described as a side-effect).

That psilocybin and other psychedelics might have therapeutic effects in cluster and other headache disorders should not be a surprise, given that several headache medications have chemical and/or pharmacological overlap with the drug class. Ergotamine and dihydroergotamine are some examples, the latter having

transitional effects (i.e., lasting headache suppression after 5 days of thrice daily dosing)[26,27] similar to those described with psychedelics. Methysergide, which was derived from LSD, was used as a prophylactic agent in cluster headache with good success before its removal from the market for the 5-$HT_{2B}$ receptor-mediated development of tissue fibrosis.[28] Tryptamines like psilocybin have lower 5-$HT_{2B}$ receptor affinity, although there are additional factors related to safety, tolerability, and long-term efficacy that should be considered. Patients who self-medicate with psilocybin-containing mushrooms or related substances report the need to repeat treatments at varying intervals, from every few weeks to once or twice annually.[6] Cases of complete remission after a single treatment (single dose or one pulse) with psychedelics exist but are rare.[6] Loss of efficacy of psychedelic treatment is reported by others.[5] The present study was not designed to consider long-term disease management, and while participants who still qualified after at least 6 months were invited to undergo a second drug pulse (procedures ongoing and results to be reported in a future publication), even this will be insufficient to fully characterize the effects and safety of psilocybin as a durable treatment in cluster headache.

This study was also not designed to investigate the mechanism of action of psilocybin in cluster headache, although some systems may be considered for further study. One system that makes cluster headache stand out among headache disorders is circadian and circannual rhythm.[29] Psilocybin, LSD, and mescaline have acute secretory effects on pineal tissue (the site of melatonin production),[30,31] and in an early study, LSD shifted the circadian cycle of crickets the day following administration.[32] Both LSD and BOL reduced the amount of rapid eye movement (REM) sleep in rats,[33,34] and a few uncontrolled studies in humans report differing effects on REM sleep and sleep quality with single dose LSD.[35–37] In the present study, participants opted to partake in an actigraphy procedure wherein the rest-activity cycle was measured before, during, and after drug treatment (procedures ongoing and results to be reported in a future publication).

The hypothalamus has been identified as a key structure in cluster headache.[38] Animal studies show acute effects of psychedelics on hypothalamic tissue,[39,40] although lasting effects after single or limited dosing have not been explored. In humans, oral psilocybin acutely reduces cerebral blood flow in the hypothalamus, which was discussed as a potential source of acute pain relief in cluster headache.[41] Whether psilocybin leads to more lasting changes in this or other relevant brain regions in conjunction with a reduced headache burden has yet to be reported, although one group is active in this area (NCT04280055).

This study has several strengths and limitations. The randomized, double-blind, placebo-controlled design is a robust design for assessing outcomes. The dose (0.143 mg/kg) and regimen investigated were based on practices reported by patients, considering over two decades of experience managing their disease.[6] The study's sample size is small, although as an initial exploratory study it is appropriate for collecting preliminary data to generate effect sizes that could be used to power larger more definitive studies. The final sample of participants was not representative of the general cluster headache population given that all were Caucasian, there were more chronic than episodic participants, and episodic participants had long cycles (necessary for the time required for study procedures). Past psychedelic exposure was permitted in this study, which is atypical for many drug studies, although also served as a form of safety pre-screening, as a history of intolerability to the drug class was exclusionary. As discussed above, expectation and blinding were not formally assessed, and the placebo agent used did not optimally blind participants. In addition, only one dose of psilocybin (~10 mg) was investigated, although the doses actually used by patients with cluster headache (in the form of *P. cubensis*) range from 0.6–38 mg.[6] Lastly, the fixed design of the present study did not allow for dose or regimen adjustments during the pulse, which are commonly practiced by patients with cluster headache.[42] Whether some participants respond to a higher dose and/or more drug administration days than those studied here needs to be investigated. Despite these limitations, the findings still serve to gain knowledge about the effects and safety of psilocybin that until now has been through self-report and uncontrolled survey analysis only.[6,7]

## CONCLUSION

In the first controlled investigation of psilocybin in cluster headache, we report on the effects of a patient-informed three-dose pulse regimen. Despite a moderate effect size, efficacy outcomes were negative. Future investigations will need to be carried out in larger, more representative samples and with designs that offer improved blinding and seek to understand dose-dependent effects. Interestingly, changes in attack frequency were not correlated with the acute psychedelic effects during drug administration. This separation is noted in other headache reports and urges the contemplation of the neurobiological mechanisms that may serve as a source for psilocybin's lasting clinical effects in headache disorders.

### AUTHOR CONTRIBUTIONS

*Study concept and design*: Emmanuelle A. D. Schindler, R. Andrew Sewell, Christopher H. Gottschalk, Deepak C. D'Souza. *Acquisition of data*: Emmanuelle A. D. Schindler, Christina Luddy, L. Taylor Flynn, Yutong Zhu, Hayley Lindsey, Nicholas V. Cozzi. *Analysis and interpretation of data*: Emmanuelle A. D. Schindler, Brian P. Pittman, Deepak C. D'Souza. *Drafting of the manuscript*: Emmanuelle A. D. Schindler, Christopher H. Gottschalk, Deepak C. D'Souza. *Revising it for intellectual content*: Emmanuelle A. D. Schindler, Christopher H. Gottschalk, Christina Luddy, L. Taylor Flynn, Yutong Zhu, Hayley Lindsey, Brian P. Pittman, Nicholas V. Cozzi, Deepak C. D'Souza. *Final approval of the completed manuscript*: Emmanuelle A. D. Schindler, Christopher H. Gottschalk, Christina Luddy, L. Taylor Flynn, Yutong Zhu, Hayley Lindsey, Brian P. Pittman, Nicholas V. Cozzi, Deepak C. D'Souza.

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Heffter Research Institute; Ceruvia Lifesciences.

## CONFLICT OF INTEREST

Schindler: has received research grant support administered through Yale University from Heffter Research Institute, Ceruvia Lifescences, and Wallace Research Foundation. She serves on the Scientific Advisory Board of Ceruvia Lifesciences and Clusterbusters. She is listed as an inventor on patent US20210236523A1. Cozzi: has received personal fees administered through Yale University. D'Souza: has received research grant support administered through Yale University from Heffter Research Institute, Ceruvia Lifescences, Wallace Research Foundation, NIDA, NIMH, NCATS, Takeda, Biogen, and Boehringer Ingelheim. He serves on the Scientific Advisory Board of Ceruvia Lifesciences and the Physicians Advisory Board of the Connecticut Medical Marijuana Program. He serves as a Consultant for Abide Therapeutics, Jazz Pharmaceuticals, and Biohaven. He is listed as an inventor on patent US20210236523A1. Gottschalk: has served on the Scientific Advisory Board for Alder (now Lundbeck) Biopharmaceuticals, Amgen/Novartis, Biohaven, Theranica, and Eli Lilly. He is a past member of Speaker's Bureaus for Amgen/Novartis, Biohaven, and Allergan. He has served as a Consultant for Eli Lilly and Spherix Global Insights and is a Trustee of the Headache Cooperative of New England (HCNE). Sewell, Luddy, Flynn, Zhu, Lindsey, and Pittman have no conflicts to disclose.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## Supplemental Table 1: Vital signs and general drug effects on experimental test days

| **Acute effect** | | **Measure** | **Drug** | **Mean** (95% CI; showing only 3 time points) (Averaged over three test days) | | | **ANOVA** (all timepoints) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Baseline | 1.5 hours | 6 hours | Drug | Time | Drug x time F, df | Day | Drug x day F, df |
| Cardiovascular effects | Mean arterial pressure | mmHg | Placebo | 89.5 (82.2 to 96.7) | 81.1 (74.3 to 87.9) | 82.3 (73.4 to 91.2) | 0.038 | 0.0001 | <0.0001 4.48, 371 | 0.783 | 0.207 1.58, 371 |
| | | | Psilocybin | 89.2 (82.0 to 96.5) | 96.7 (91.4 to 102.0) | 86.0 (79.2 to 92.9) | | | | | |
| | Heart rate | Beats per minute | Placebo | 66.5 (60.8 to 72.2) | 62.6 (60.3 to 64.9) | 63.7 (60.9 to 66.5) | 0.201 | 0.609 | 0.078 1.7, 371 | 0.822 | 0.559 0.58, 371 |
| | | | Psilocybin | 73.4 (69.5 to 77.2) | 72.2 (61.3 to 83.2) | 72.3 (68.0 to 76.7) | | | | | |
| | Peripheral oxygenation | SpO2 (%) | Placebo | 98.1 (97.6 to 98.6) | 97.9 (97.7 to 98.1) | 98.1 (97.5 to 98.8) | 0.887 | 0.040 | 0.068 1.75, 372 | 0.010 | 0.430 0.82, 372 |
| | | | Psilocybin | 97.3 (96.1 to 98.6) | 98.4 (97.1 to 99.7) | 97.9 (96.2 to 99.7) | | | | | |
| General drug effects | Overall | VAS (0-3) | Placebo | 0.02 (0.02 to 0.02) | 0.14 (-0.03 to 0.31) | 0.02 (0.02 to 0.02) | <0.0001 | <0.0001 | <0.0001 47.42, 297 | 0.637 | 0.595 0.52, 297 |
| | | | Psilocybin | 0.01 (0.01 to 0.01) | 2.6 (2.2 to 3.0) | 0.07 (0.0) | | | | | |
| | Sleepiness / Sedation | VAS (0-3) | Placebo | 0.45 (0.23 to 0.67) | 0.68 (-0.05 to 1.41) | 0.23 (-0.04 to 0.51) | 0.012 | <0.0001 | <0.0001 4.2, 297 | 0.895 | 0.283 1.27, 297 |
| | | | Psilocybin | 0.23 (0.11 to 0.36) | 1.61 (0.77 to 2.45) | 0.39 (0.30 to 0.48) | | | | | |
| | Anxiety / Fear | VAS (0-3) | Placebo | 0.10 (-0.10 to 0.30) | 0.04 (-0.05 to 0.13) | 0.02 (0.02 to 0.02) | 0.002 | 0.0002 | 0.002 3.22, 296 | 0.573 | 0.642 0.44, 296 |
| | | | Psilocybin | 0.72 (0.41 to 1.03) | 0.62 (-0.09 to 1.33) | 0.02 (-0.02 to 0.06) | | | | | |
| | Nausea | VAS (0-3) | Placebo | 0.02 (0.02 to 0.02) | 0.02 (0.02 to 0.02) | 0.02 (0.02 to 0.02) | 0.046 | 0.194 | 0.442 0.99, 297 | 0.978 | 0.983 0.02, 297 |
| | | | Psilocybin | 0.03 (-0.02 to 0.08) | 0.56 (0.11 to 1.01) | 0.08 (0.04 to 0.12) | | | | | |
| | Joy / Intense Happiness | VAS (0-3) | Placebo | 0.46 (0.18 to 0.73) | 0.48 (0.07 to 0.88) | 0.44 (0.28 to 0.60) | 0.042 | 0.0001 | <0.0001 4.6, 296 | 0.551 | 0.934 0.07, 296 |
| | | | Psilocybin | 0.82 (0.68 to 0.96) | 1.51 (1.04 to 1.98) | 1.14 (0.81 to 1.47) | | | | | |
| | Peace / Harmony | VAS (0-3) | Placebo | 0.78 (0.29 to 1.26) | 0.94 (0.15 to 1.72) | 0.70 (0.44 to 0.96) | 0.344 | 0.014 | 0.153 1.51, 297 | 0.169 | 0.156 1.87, 297 |
| | | | Psilocybin | 1.03 (0.97 to 1.10) | 1.35 (0.67 to 2.03) | 1.20 (1.11 to 1.29) | | | | | |

VAS, visual analog scale; 95% CI, 95% confidence interval; df, degrees of freedom

## Supplemental Table 2: Percent possible 5D-ASC scale score

| **5D-ASC scale component** | **Measure** (percent total possible score) | **Placebo** | **Psilocybin** | **ANOVA** (all timepoints) | | | |
|---|---|---|---|---|---|---|---|
| | | Mean (95% CI; average over 3 test days) | | Drug | Day | Drug x day | F, df |
| Total | 0-100 | 0.9 (0.1 to 1.7) | 20.6 (14.8 to 26.5) | <0.0001 | 0.340 | 0.425 | 0.89, 21 |
| OBN | 0-100 | 0.4 (0.09 to 0.9) | 22.3 (10.0 to 34.7) | 0.002 | 0.397 | 0.420 | 0.91, 21 |
| DED | 0-100 | 0.2 (-0.3 to 0.7) | 15.2 (6.4 to 24.0) | 0.003 | 0.182 | 0.180 | 1.86, 21 |
| VRS | 0-100 | 0.3 (-0.3 to 0.9) | 28.1 (12.6 to 43.6) | 0.002 | 0.556 | 0.559 | 0.60, 21 |
| AUA | 0-100 | 0.2 (-0.3 to 0.7) | 4.7 (0.7 to 8.7) | 0.017 | 0.037 | 0.040 | 4.4, 11 |
| VIR | 0-100 | 5.2 (-0.4 to 10.9) | 37.3 (18.0 to 56.5) | 0.004 | 0.734 | 0.896 | 0.11, 21 |

OBN, oceanic boundlessness; DED, dread of ego dissolution; VRS, visionary restructuralization; AUA, acoustic alterations; VIR, vigilance reduction; 95% CI, 95% confidence interval; df, degrees of freedom

**Supplementary Material**

## Materials and Methods (full details)

### Regulatory approvals

This exploratory 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.

### Psilocybin

Synthetic psilocybin was obtained under DEA Schedule 1 registration from the University of Wisconsin-Madison (author NVC) or Usona Institute. The material was between 98.6% and 100% pure by high performance liquid chromatography. Weight-based doses of psilocybin (0.143 mg/kg) and matching placebo (microcrystalline cellulose, obtained from Fagron, St. Paul, MN), were compounded for each participant into identical blue gelatin capsules by the VACHS Investigational Research Pharmacy. The psilocybin dose was chosen as it is 10 mg/70 kg, approximating 1.6 grams dried *P. cubensis* (mid-range of what patients typically use).

### Participants and selection criteria

Adults (age 21 to 65 years, inclusive), free from serious medical or psychiatric disease, with cluster headache as defined by the International Classification of Headache Disorders III-beta (11) were eligible to participate in this study. To ensure proper interpretation of the study

intervention, a minimum attack frequency of approximately 1 attack per day was required. For episodic participants, the typical cluster period was required to last approximately 2 months or more and study participation could only take place when at least 6 weeks of the active bout (cluster period) was anticipated to remain. Certain comorbid medical conditions were excluded, including uncontrolled hypertension, coronary artery disease, cardiac dysrhythmia, cerebrovascular disease, and serious central or peripheral nervous system or spinal disease (e.g., multiple sclerosis, amyotrophic lateral sclerosis). Psychotic or manic disorders, substance abuse within the past three months, and any prior serious adverse event with psilocybin, LSD, or related compounds (e.g., mescaline) were exclusionary. Prior exposure to psilocybin or related compounds through recreational or medicinal use or through participation in other research studies was not excluded, although any use in the past three months was prohibited. Alcohol consumption within one week of the first experimental test day 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, serotonergic antiemetics (e.g., ondansetron) for at least two weeks, and vasoconstrictive medications (e.g., pseudoephedrine) for at least five elimination half-lives of said medication. Criteria were updated to allow abortive treatments beyond high-flow oxygen alone, which is challenging to obtain for many patients (3, 12). 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. Cluster headache preventive medications (i.e., verapamil) were permitted, so long as the participant was on a stable a dose (i.e., steady attack burden) and no changes were made during the study.

Transitional treatments (i.e., corticosteroids) were not permitted during the study, as their therapeutic effects would interfere with assessing experimental drug effects.

## Recruitment and screening

Participants were recruited from the local community, headache centers, online headache websites, and word of mouth. Interested candidates were pre-screened over the telephone and, if they met basic study criteria, were then invited for a full evaluation to assess eligibility. This included a medical history, physical examination, laboratory tests (hematology, chemistry, liver and thyroid studies, urinalysis, urine toxicology, urine pregnancy, electrocardiogram), structured mental health interview, personality assessment, and verbal intelligence quotient test. In addition to research staff taking detailed histories to verify the diagnosis of cluster headache and other medical and psychiatric conditions, participants' clinicians were contacted in order to corroborate their cluster headache diagnosis and inquire about medical, psychiatric, and substance use history; written consent for this clinician contact was required for study participation. Written consent was also obtained to speak with a family member or friend in order to exclude any additional safety concerns for study participation. During the multi-stage screening process, study procedures and the acute physiological and neuropsychological effects of psilocybin were repeatedly reviewed with participants. Participants were also quizzed on study procedures, the expected effects of psilocybin, and emergency contacts. Research assistants evaluated eligibility, obtained informed consent, and enrolled participants. In compliance with the Helsinki Declaration of 1975, as revised in 2000 (13), written informed consent was obtained from every participant who participated in the study. Furthermore, participants were informed that they could decline to participate in the study without penalty and

were free to withdraw from the study at any time. The sources of study funding were also disclosed to all participants.

## Study design

In this exploratory randomized, double-blind, placebo-controlled study, participants were randomized 1:1 to psilocybin (0.143 mg/kg) or placebo (microcrystalline cellulose) using computer-generated block randomization, stratified by headache subtype (i.e., episodic, chronic). Given the exploratory nature of the study and the lack of available data from which to calculate sample size, *a priori* statistical power calculation was not conducted. Participants completed three experimental sessions, separated by 5 ± 2 days each, receiving the same drug at each session. The study took place under an approved enhanced blinding procedure in which drug dose was unknown to participants and research staff. This blinded condition was also reflected in the clinicaltrials.gov registration. Fully revealing the enhanced blinding procedure here could compromise future attempts to use it. Interested parties may contact the corresponding author for further details about the enhanced blinding procedure. Research Pharmacy managed participant randomization and maintained the blind. Experimental drug was compounded into identical size 1 capsules that were opaque so as to obscure the contents. Psilocybin capsules were backfilled with placebo (microcrystalline cellulose) so that any difference in weight of the capsules was indistinguishable. Research Pharmacy delivered experimental drug to the lab at the time of administration in a bottle whose label was devoid of assignment. Participants maintained a headache diary starting 2 weeks before until 8 weeks after the first experimental session. Participants documented every cluster attack, including date, time of onset, time of offset, and pain intensity [0-10 numerical scale: 0 = none, 1 = minimal, 5 = moderate, 9 = severe, 10 = worst

imaginable]. The abortive treatments taken and their effects were also recorded in the diary. This method of self-reporting attack symptoms in a diary is the gold standard in headache research and was also used in the cluster headache preventive trials for galcanezumab and non-invasive vagus nerve stimulation. 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.

Experimental sessions

Sessions were conducted in the Neurobiological Studies Unit (NSU) at VACHS. Participants reported to the NSU at 8:00 AM; standard urine drug, urine pregnancy (when applicable), and alcohol breathalyzer tests were required to be negative to proceed. A standard light breakfast was offered, an intravenous line was placed, and baseline measures (described below) were collected. Participants typically received the drug capsule between 8:30 AM and 9:30 AM. High-flow oxygen with a non-rebreather mask (standard acute abortive therapy for cluster attacks) was made available to participants throughout the session. Blood pressure, heart rate, and peripheral oxygenation 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 restructuralization (VRS), acoustic alterations (AUA), and vigilance reduction (VIR) (14). Participants marked their 5D-ASC scale responses on a 10 cm VAS. Participants were

discharged from the NSU no sooner than 6 hours after capsule ingestion and only once acute physiological and neuropsychological drug effects had resolved. Participants were not allowed to drive themselves after experimental sessions. Emergency contacts, including 24-hour / 7-day psychiatry services, were provided to all participants.

### Follow-up and payment

Telephone safety follow-up was performed by a research team member familiar to the participant the day after each experimental session and weekly for two weeks and at 2, 3, and 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.

### Outcome measures

As this was an exploratory trial, no single primary outcome was defined *a priori*. Instead, several outcomes were evaluated and interpreted, but emphasis was placed on cluster attack frequency. There were no prior similar studies from which to predict a timeline for therapeutic effects, and existing studies with conventional treatments had a range of outcome timepoints. In order to capture a clinically relevant duration that would also allow the inclusion of episodic participants, the change in weekly attacks compared to baseline in the 3-week period after the start of the pulse regimen was used as the primary outcome measure. Other primary outcomes included such measures as change in attack duration (minutes) and pain intensity (0-10 numerical scale) in the 3-week period after start of the pulse. Secondary outcomes included the same clinical outcomes

in episodic and chronic participants, extending to 8 weeks in chronic participants, acute changes in vital signs, general drug effects, psychedelic ratings, and adverse events (AEs).

**Results (full detail of protocol changes and excluded subjects)**

Between November 2016 and August 2021, patients were assessed for study eligibility. In-person study procedures did not take place between April 2020 and October 2020 due to the novel coronavirus (COVID-19) pandemic. Recruitment ceased once target randomization was met. There were four protocol changes after initiation of the trial: (1) In June 2017 episodic participants were included in addition to chronic cluster headache; (2) in December 2018 abortive treatments beyond high-flow oxygen were allowed, including triptans for which the use limits were set; (3) in January 2020 participants were permitted to return for a second round of participation; (4) in April 2020 the option to receive fixed dose drug administration was included (though this was never actually carried out). A total of 238 candidates was pre-screened; 20 underwent secondary screening and 16 underwent study procedures. Fourteen participants (6 placebo, 8 psilocybin) were included in the final analysis (Figure 1). Two participants were excluded from final analysis for protocol violations. One participant began to use psilocybin-containing mushrooms on their own shortly after the dosing sessions completed, while they were still in cycle and the headache diary was still being kept. Another participant failed to provide a diary after the baseline period. In both cases, the effects of the experimental intervention would be uninterpretable. The decision to drop these participants' data was made prior to conducting statistical analysis. Given weight-based dosing in this study, the average amount of drug received by participants randomized to receive psilocybin was 10.6 (SD 2.0) mg.