Neurotherapeutics
https://doi.org/10.1007/s13311-020-00962-y

ORIGINAL ARTICLE

Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin

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Accepted: 27 October 2020

Abstract

While anecdotal evidence suggests that select 5-hydroxytryptamine 2A (5-HT_{2A}) receptor ligands, including psilocybin, may have long-lasting therapeutic effects after limited dosing in headache disorders, controlled investigations are lacking. In an exploratory double-blind, placebo-controlled, cross-over study, adults with migraine received oral placebo and psilocybin (0.143 mg/kg) in 2 test sessions spaced 2 weeks apart. Subjects maintained headache diaries starting 2 weeks before the first session until 2 weeks after the second session. Physiological and psychological drug effects were monitored during sessions and several follow-up contacts with subjects were carried out to assure safety of study procedures. Ten subjects were included in the final analysis. Over the 2-week period measured after single administration, the reduction in weekly migraine days from baseline was significantly greater after psilocybin (mean, − 1.65 (95% CI: − 2.53 to − 0.77) days/week) than after placebo (− 0.15 (− 1.13 to 0.83) days/week; $p = 0.003$, $t(9) = 4.11$). Changes in migraine frequency in the 2 weeks after psilocybin were not correlated with the intensity of acute psychotropic effects during drug administration. Psilocybin was well-tolerated; there were no unexpected or serious adverse events or withdrawals due to adverse events. This exploratory study suggests there is an enduring therapeutic effect in migraine headache after a single administration of psilocybin. The separation of acute psychotropic effects and lasting therapeutic effects is an important finding, urging further investigation into the mechanism underlying the clinical effects of select 5-HT_{2A} receptor compounds in migraine, as well as other neuropsychiatric conditions. Clinicaltrials.gov: NCT03341689

Key Words Migraine · headache · preventive treatment · psilocybin · psychedelics

Introduction

Migraine is one of the most common headache disorders with a prevalence of approximately 15% and is among the top three disabling diseases worldwide [1–3]. A range of treatment options for migraine exists, though limited efficacy and unpleasant side effects may preclude long-term success [4]. Evidence suggesting that select 5-hydroxytryptamine 2A (5-HT_{2A}) receptor agonists, such as psilocybin and lysergic acid diethylamide (LSD), have clinical effects in migraine has existed for over half a century [5–7]. While chemically and pharmacologically similar to other migraine medications (e.g., dihydroergotamine (DHE), methysergide), these particular 5-HT_{2A} agonists are reported to produce long-lasting reductions in headache burden after a single or few oral doses [6, 8–10]. Such a clinical effect is novel and intriguing, though definitive studies are lacking. In the setting of numerous controlled studies with select 5-HT_{2A} agonists in mental health disorders and

R. Andrew Sewell, posthumous (RAS passed away in 2013)

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Published online: 12 November 2020

addiction also suggesting long-lasting therapeutic effects after limited dosing [11–17], the demonstration of such effects in headache disorders would suggest that this unique benefit of the drug class seen among different diseases is effected through a shared neurobiological mechanism(s).

The goal of this exploratory, proof-of-concept study was to investigate the effects of psilocybin in migraine in a double-blind, placebo-controlled, cross-over design. We hypothesized that a single administration of low-dose oral psilocybin in migraine patients would suppress migraine over a 2-week period and be safe in the controlled experimental setting. We were also prepared for unanticipated findings and sought to use all information learned in the design and development of future studies.

Methods

Regulatory Approvals

This exploratory study was registered on clinicaltrials.gov (NCT03341689) 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 with Drug Enforcement Administration (DEA) Schedule 1 registration (author DCD).

Psilocybin

Synthetic psilocybin was prepared under DEA Schedule 1 registration at the University of Wisconsin–Madison (author NVC). Psilocybin was synthesized as described by Shirota et al. [18] with some slight modifications. Chemical analysis to confirm identity and purity included ^{1}H and ^{13}C NMR, HPLC, thermogravimetric analysis, differential scanning calorimetry, and GC-MS. The material was deemed 100% pure by HPLC. Weight-based capsules of psilocybin (0.143 mg/kg) and matching placebo (microcrystalline cellulose, obtained from Fagron, St. Paul, MN) were compounded for each subject into identical blue gelatin capsules by the VACHS Investigational Research Pharmacy.

Subjects and Selection Criteria

Adults (age 21 to 65 years, inclusive), free from serious medical or psychiatric disease, with migraine as defined by the International Classification of Headache Disorders III-beta [19] and with a frequency of migraine attacks of 2 per week or more were eligible to participate in this study. Among the excluded medical conditions were uncontrolled hypertension, coronary artery disease, cardiac arrhythmia, cerebrovascular disease, and serious central or peripheral nervous system or spinal disease (e.g., multiple sclerosis, amyotrophic lateral sclerosis). Psychotic or manic disorders in the subject or a first-degree relative were also exclusionary, as were substance abuse within the past 3 months and any prior serious adverse event with psilocybin, LSD, or related compounds (e.g., mescaline). 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 3 months was prohibited. Alcohol consumption within 1 week of the first experimental test day was prohibited. Caffeine and nicotine were not restricted. Subjects were required to be free from serotonergic antidepressants (e.g., fluoxetine) for at least 6 weeks, serotonergic antiemetics (e.g., ondansetron) for at least 2 weeks, and vasoconstrictive medications (e.g., pseudoephedrine) for at least five elimination half-lives of said medication. 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 each test day.

Recruitment and Screening

Subjects were recruited from the local community, headache centers, online headache websites, and word of mouth. Interested candidates were informed of the study and prescreened over the telephone. If candidates passed the prescreen based on the study criteria, they were 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 migraine and other medical and psychiatric conditions, subjects' physicians were contacted in order to corroborate their migraine diagnosis and inquire about medical, psychiatric, and substance use history; written consent for this physician 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 multistage screening process, study procedures and the physiological and psychological effects of psilocybin were repeatedly reviewed with subjects. Subjects were also quizzed on study procedures, the expected effects of psilocybin, and emergency contacts. In compliance with the Helsinki Declaration of 1975, as revised in 2000 [20], informed consent was obtained from every subject who participated in the study. Furthermore, subjects 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

This was an exploratory double-blind, placebo-controlled, crossover study. Subjects completed 2 experimental sessions, separated by at least 14 days, under a standard approved blinding procedure, in which drug dose and order of administration were unknown to subjects and research staff. The blinded procedure was also reflected in the clinicaltrials.gov registration. In the first experimental session, all subjects received an oral placebo capsule, and in the second experimental session, all subjects received an identically appearing oral psilocybin capsule. In this design, each subject acted as his own control and placebo was given first so that the potential long-term effects of psilocybin, if given first, would not interfere with placebo treatment, if given second.

Assessment of Migraine Burden

Subjects maintained a headache diary starting 2 weeks before the first experimental session until 2 weeks after the second experimental session. Subjects were required to document every headache attack, migraine (with associated migrainous symptoms), or otherwise (without associated migrainous symptoms; not counted as a migraine attack in the analysis). Migraine attack pain and associated symptoms—photophobia (light sensitivity), phonophobia (sound sensitivity), nausea/vomiting—as well as attack-related functional impairment were documented using a 0–3 numerical scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Abortive medications taken and their effects were also recorded in the diary. Only the 14 days prior to the first experimental session (baseline) and the 14 days after each experimental session (drug effect) were counted in the final analysis.

Experimental Sessions

At 8:00 am, subjects reported to the Neurobiological Studies Unit (NSU), an outpatient research facility and the location of neuropsychopharmacologic studies with investigational drugs at VACHS/Yale for > 25 years. Urine drug, urine pregnancy (when applicable), and alcohol breathalyzer tests were done and required to be negative in order to proceed. After a light breakfast, an intravenous line was placed (for potential rescue medication) and baseline measures were collected (see below). Subjects typically ingested the drug capsule between 8:30 am and 9:30 am. Blood pressure, heart rate, and peripheral oxygenation were measured at baseline, every 15 min for the first hour, every 30 min for the second hour, and then every hour thereafter. 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, every 30 min for the first 2 h, and then hourly thereafter. The rating of "overall" drug effect served as a means for subjects to report the integrated sensation that they had received a drug. 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 divided into the following subscales: oceanic boundlessness (OBN), dread of ego dissolution (DED), visionary restructuralization (VRS), acoustic alterations (AUA), and vigilance reduction (VIR) [21]. Subjects were discharged from the NSU no sooner than 6 h after capsule ingestion and not until physiological and psychological drug effects had resolved. Subjects were not allowed to drive themselves after experimental sessions. Emergency contacts, including 24-h/7-day psychiatry services, were provided to all subjects.

Follow-up and Payment

Telephone follow-up was performed by a research team member familiar to the subject the day after and weekly for 2 weeks after each experimental session and then at approximately 2 and 3 months. Subjects were asked about adverse events (AEs), physical health, and psychological health, and any questions they had were answered. After all subjects completed study procedures, subjects were contacted by telephone and told what they had received during experimental sessions. Subjects were paid US $100 per experimental session and US $50 for in-person screening.

Outcome Measures

The primary outcome measure was the change in migraine frequency, measured as the change in weekly migraine days compared to baseline in the 2 weeks after drug administration. Other primary outcome measures included change in weekly migraine attacks, light sensitivity, sound sensitivity, nausea/vomiting, and attack-related functional impairment in the 2 weeks after drug administration. Secondary outcome measures included change in the use of migraine abortives, time to the next migraine attack, acute changes in vital signs, general drug effects, psychotropic ratings, and adverse events. As this study was exploratory, minor changes to outcomes, which did not alter findings or conclusions, were made and are detailed in the Supplemental Methods.

Statistical Analysis

A total of 12 subjects was sought for this exploratory study. For within-subject analyses with a two-tailed $\alpha = 0.05$, 12 subjects would provide 80% statistical power to detect large effects ($d' = 0.9$). Our final sample of $n = 10$ (Fig. 1) provided 80% statistical power to detect large effects ($d' = 1.0$).

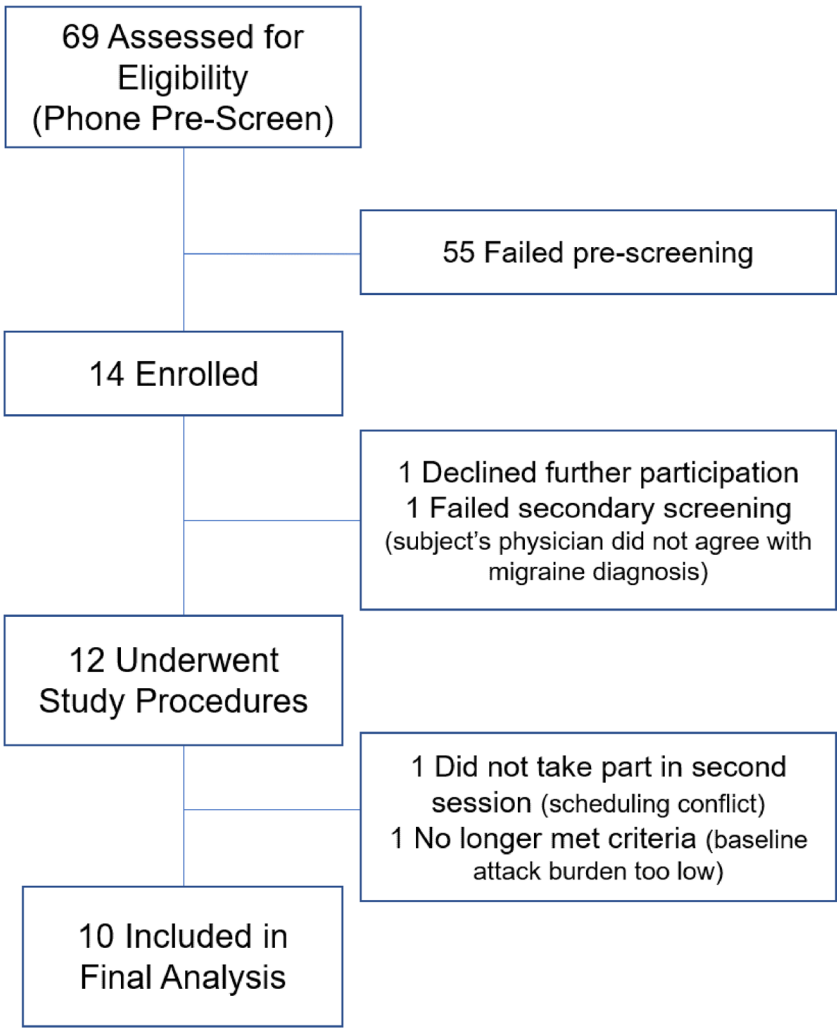

Fig. 1 Subject screening and enrollment

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC) and figures were produced with GraphPad Prism (GraphPad Software Inc., La Jolla, CA). All statistical tests were two-sided with an overall prehypothesis alpha threshold of 0.05. Measures of error are shown as standard error about the mean (SEM) or 95% confidence interval (95% CI). The changes from baseline in migraine burden as measured in the headache diary were calculated as raw values and compared between placebo and psilocybin via paired *t* test. The analysis plan developed by the statistical consult (author BPP) considered alternatives (including analysis of variance), which did not affect the results. The time to the first and second migraine attacks after drug administration was also compared between placebo and psilocybin via paired *t* test. When no migraine attacks occurred for this measure, "15 days" was used as the time to that attack. 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 treatment and time as within-subject effects and random subject effects. 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. Psychotropic effects as measured by the 5D-ASC scale were calculated as a percent of the total possible score [14, 22] and compared using a linear mixed model with treatment and dimension (see scale dimensions) included as within-subject factors and random subject effects. Potential associations between general drug or psychotropic effects and the change in weekly migraine days were assessed using correlation (Spearman) analysis. The numbers of AEs were compared between placebo and psilocybin using Fisher's exact test.

Results

Between November 2017 and December 2019, patients were assessed for study eligibility. A total of 69 candidates was prescreened; 14 underwent secondary screening and 12

underwent study procedures. Ten subjects were included in the final analysis (Fig. 1). Two subjects were excluded from final analysis; 1 was unable to participate in the second experimental session for scheduling conflicts and 1 subject's baseline period did not contain enough migraine attacks for qualification.

Demographics, Migraine Characteristics, and Substance Use (Table 1)

Seven females and 3 males were included in the final analysis. The average age was 40.5 (SEM 4.4) years. Two subjects had previously tried psilocybin (not specifically for migraine treatment). At the time of enrollment, only 1 subject indicated that they were satisfied with their current migraine treatment regimen and all subjects indicated that they would at least consider trying a new migraine treatment if it were available.

Migraine Burden in the 2 Weeks After Drug Administration

Migraine Frequency The change from baseline in weekly migraine days showed a significantly greater reduction after psilocybin (mean, − 1.65 (95% CI: − 2.53 to − 0.77)) than after placebo (− 0.15 (− 1.13 to 0.83); $p = 0.003$, $t(9) = 4.11$; Fig. 2, Table 2). The percentages of subjects who had at least 25%, 50%, and 75% reductions in weekly migraine days were as follows: 80%, 50%, 30% after psilocybin, and 20%, 20%, 0% after placebo, respectively. Psilocybin and placebo significantly differed at the level of at least 25% reduction ($p = 0.023$; Fisher exact).

Other Migraine Outcomes Reductions from baseline were significantly greater after psilocybin compared to placebo in weekly migraine attacks, pain severity, attack-related functional impairment, and weekly migraine abortive days (Table 2). There were no significant differences on migraine attack duration or associated symptom (photophobia, phonophobia, nausea/vomiting) ratings.

Time to Next Migraine Attacks Given that psilocybin is known to acutely induce headache attacks (see AE) [23], the times to both the first and second migraine attack were measured. The time to the first attack was statistically equivocal, but the time to the second attack was significantly greater after psilocybin (10.30 (1.61) days) than after placebo (5.00 (1.13) days; $p = 0.012$, $t(9) = 3.14$; Fig. 3).

Acute Effects of Drug Administration

General Drug Effects During experimental sessions, an interaction between drug and time was observed for "overall drug effects" ($F(8, 142) = 3.74$, $p = 0.0005$), where psilocybin ($F(8, 142) = 11.3$, $p < 0.0001$) but not placebo ($F(8, 142) = 0.57$, $p = 0.80$) elicited "overall drug effects" (Suppl Table). A significant interaction was also observed for the feeling of "peace/harmony," where psilocybin, but not placebo, elicited this feeling. No interactions were observed for other general drug effects. It is noted that only 1 subject remained in the NSU for an additional 60 min following the requisite 6 h after psilocybin administration to allow general drug effects to dissipate. The maximum "overall drug effect" rating during psilocybin exposure did not correlate with the percent change from baseline in weekly migraine days ($r = 0.469$; $p = 0.17$).

Psychedelic Effects Subjects scored the 5D-ASC scale at the end of each experimental session. The percent possible score for the total scale was significantly higher after psilocybin (19.35% (7.55)) as compared to placebo (3.08% (1.80); $p = 0.026$, $t(9) = 2.65$). In the mixed model comparing treatment across individual dimensions, the interaction between treatment and dimension was not significant ($F(4, 81) = 2.22$, $p = 0.07$). The percent total 5D-ASC scale score during psilocybin exposure did not correlate with the percent change from baseline in weekly migraine days ($r = 0.418$; $p = 0.23$).

Adverse Events

There were no serious or unexpected AEs in this study. During experimental sessions, lightheadedness and tension/sore muscles were reported with both placebo and psilocybin administration (Table 3). In the 24 h after experimental sessions, both placebo and psilocybin administration were followed by tension/sore muscles, general headache attack, and migraine attack (Table 3). There were no significant differences between placebo and psilocybin in the incidences of AEs, except that there was a significant drug × time interaction for MAP over the experimental test day ($F(10, 186) = 2.52$, $p = 0.007$; Suppl Table). Post hoc analysis revealed a significant increase in MAP with psilocybin administration starting at 45 min until 4 h after ingestion. The maximum acute increase in MAP over placebo was 12.2 (4.61 to 19.73) mmHg at 1.5 h after ingestion. All AEs were transient and self-limiting (i.e., no rescue medications required), and no subjects withdrew from the study due to an AE. During follow-up with subjects, there were no AEs warranting professional intervention. At 3 months' follow-up, all subjects denied any lasting physical, psychological, or cognitive changes.

Discussion

This exploratory, proof-of-concept, double-blind, placebo-controlled, cross-over investigation showed significant reductions in migraine measures in the 2 weeks assessed after the single administration of a low oral dose of psilocybin. To our

Table 1 Demographics, migraine characteristics, and substance use

Characteristic/behavior/question	Mean (SEM)	Range		
Sex	7 F: 3 M	–		
Age (years)	40.5 (4.4)	23 to 63		
Age of migraine onset (years)	18.7 (2.9)	6 to 35		
Race	Caucasian 100%	–		
Weight (kg)	65.4 (4.9)	47.7 to 95.9		
Body mass index (BMI; kg/m^2)	22.9 (1.6)	18.1 to 32.1		
		Yes	No	Other
Family history of migraine		7	1	2 (unsure)
Migraine attack triggers	Alcohol	9	1	
	Strong smells	8	2	
	Bright/flashing lights	6	4	
	Weather changes	10	0	
	Altitude changes	5	5	
	Travel across time zones	1	9	
	Other	8	2	
	No triggers	0	10	
Have you ever experienced a negative side effect from a medication you took for migraine headache?		9	1	
Are you satisfied with your current medication regimen?		1	6	3 (somewhat)
If there were a new medication available to treat migraine headache, would you try it?		8	0	2 (perhaps)
Current alcohol use		7	3 (quit)	
Past use of controlled substances (for any purpose, excluding alcohol and nicotine)	Psilocybin and related	2	8	
	Cannabinoids	9	1	
	Opioids	6	4	
	Stimulants	6	4	
	Other	5	5	
	None	1	9	
Past alcohol/drug abuse/dependence		1 (remission)	9	

"Psilocybin and related" include psilocybin, lysergic acid diethylamide (LSD), *N,N*-dimethyltryptamine (DMT), and mescaline. "Stimulants" include cocaine, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), and amphetamines. "Other" includes benzodiazepines, barbiturates, and phencyclidine

SEM = standard error about the mean

knowledge, this is the first controlled study of psilocybin in a headache disorder. The findings from this study validate the previous anecdotal reports of therapeutic effects in migraine and complement research in past decades with psilocybin and other select 5-HT$_{2A}$ receptor agonists demonstrating lasting beneficial effects in treating depression [11, 12, 24], anxiety [11, 13, 14], alcohol addiction [16, 25, 26], and cigarette smoking [15, 17].

To our knowledge, the therapeutic effect over 2 weeks after the single administration of an oral agent reported in this study is a novel finding in migraine therapy. This contrasts with existing preventive migraine therapies that necessitate repeated, daily administration (e.g., topiramate) or include treatments that remain in the body long after administration (e.g., anti-calcitonin gene-related peptide or receptor monoclonal antibodies). Lasting clinical effects after relatively limited drug administration are seen with such conventional transitional migraine treatments as corticosteroids, which are administered in oral pulses of various duration, and DHE, which is administered as a thrice daily, 5-day intravenous or subcutaneous injection regimen [27]. It is notable that DHE also has agonist activity at the 5-HT$_{2A}$ receptor, in addition to several other receptors [28]. Whether a shared mechanism of action in migraine exists between psilocybin and DHE or psilocybin and corticosteroids will require further study.

In contrast to some previous psilocybin studies for other neuropsychiatric conditions [11, 17], the current study did not find that psychotropic effects correlated with the migraine

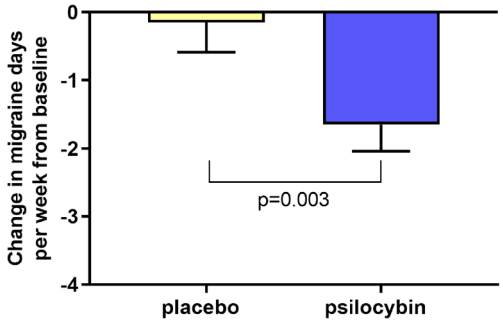

Fig. 2 Change in migraine frequency. The average reduction in weekly migraine days from baseline in the 2 weeks following the single administration of drug was significantly greater after psilocybin than after placebo ($n = 10$, paired t test). Error bars represent standard error about the mean

frequency change over 2 weeks, suggesting that the therapeutic effect of psilocybin in migraine is independent of acute changes in sensation and perception. In fact, subjects in the present study with the highest 5D-ASC scale scores had some of the smallest reductions in migraine burden, fitting with the positive coefficient calculated. These observations are consistent with survey studies reporting that subhallucinogenic doses of psilocybin and LSD provide prophylactic relief in headache disorders [6, 8, 9]. Furthermore, a congener of LSD, 2-bromo-lysergic acid diethylamide (BOL-148 or BOL), which has greatly reduced psychotropic effects, is also reported to have medicinal effects in cluster and other headache disorders [7, 8, 29]. Collectively, these findings suggest dissociation between the acute psychotropic effects and the sustained therapeutic action of psilocybin and other select 5-HT_{2A} receptor compounds in headache disorders. If confirmed, this raises the intriguing possibility that the therapeutic effects of these particular compounds may not require their namesake "psychedelic" effects.

While encouraged by the findings in this exploratory study, before this approach could be used clinically, it is imperative that additional controlled investigations be completed in order to understand psilocybin's full capacity to suppress migraine, as well as its long-term safety and tolerability. To verify the present findings, it will be necessary to replicate the results of this study in a larger sample under a fully randomized design. Studies with a dose range will inform on whether the effects of psilocybin in migraine are dose dependent. Studies investigating repeated administration either in close succession or separated by specified intervals will help illustrate psilocybin's abilities as a transitional and/or preventive treatment. In parallel with clinical investigations, studies determining the mechanisms of psilocybin's effects will inform on the biological target of this agent and potential for drug development, including chemical modifications that can minimize unnecessary effects while maximizing reductions in migraine parameters. For instance, it has been proposed that the immunomodulatory and anti-inflammatory effects common to these select

Table 2 Effects on migraine headache burden 2 weeks after single drug administration

Migraine feature	Measure	Raw values Mean (SEM)			Change from baseline Mean (95% CI)			
		Baseline	Placebo	Psilocybin	Placebo	Psilocybin	p value	Effect size (Cohen)
Migraine day frequency	Days per week	3.35 (0.55)	3.20 (0.56)	1.70 (0.49)	− 0.15 (− 1.13 to 0.83)	− 1.65 (− 2.53 to − 0.77)	0.003	− 1.15
Migraine attack frequency	Attacks per week	2.80 (0.55)	2.67 (0.63)	1.22 (0.30)	− 0.05 (− 0.83 to 0.73)	− 1.40 (− 2.21 to − 0.59)	0.004	− 1.22
Duration	Hours	15.97 (4.19)	13.41 (3.88)	10.13 (4.74)	− 2.87 (− 10.31 to 4.58)	− 6.51 (− 10.97 to − 2.05)	0.21	− 0.46
Pain	Severity (0–3)	2.15 (0.21)	1.99 (0.24)	1.31 (0.23)	− 0.11 (− 0.48 to 0.26)	− 0.70 (− 1.06 to − 0.35)	0.011	− 1.16
Light sensitivity	Severity (0–3)	1.55 (0.26)	1.23 (0.37)	0.81 (0.36)	− 0.18 (− 0.71 to 0.34)	− 0.59 (− 1.24 to 0.06)	0.06	− 0.57
Sound sensitivity	Severity (0–3)	1.21 (0.26)	1.07 (0.55)	0.58 (0.34)	− 0.36 (− 1.11 to 0.40)	− 0.74 (− 1.35 to − 0.14)	0.39	− 0.70
Nausea/vomiting	Severity (0–3)	1.55 (0.28)	0.89 (0.28)	0.75 (0.27)	− 0.64 (− 1.10 to − 0.19)	− 0.66 (− 1.45 to 0.14)	0.96	− 0.02
Functional impairment	Severity (0–3)	1.64 (0.23)	1.23 (0.27)	0.51 (0.19)	− 0.29 (− 0.67 to 0.09)	− 0.96 (− 1.55 to − 0.38)	0.024	− 0.98
Migraine abortive use frequency	Days per week	1.35 (0.27)	1.55 (0.48)	0.70 (0.32)	0.20 (− 0.68 to 1.08)	− 0.65 (− 1.13 to − 0.07)	0.014	− 0.86

SEM = standard error about the mean, CI = confidence interval

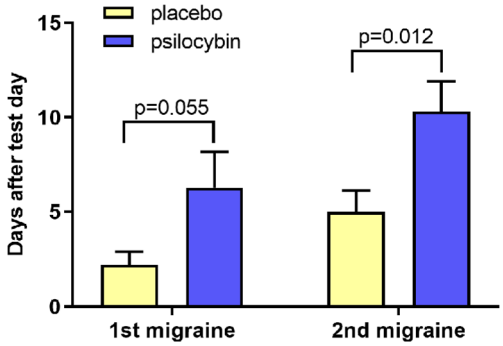

Fig. 3 Time to the next migraine attacks. The average number of days to the first and second migraine attacks after drug administration is shown. The time to the second attack was significantly greater after psilocybin than after placebo ($n = 10$, paired t test). Error bars represent standard error about the mean

5-HT_{2A} receptor compounds involve interactions among serotonin, sigma-1, and toll-like receptors [30], all of which are implicated in migraine, itself a chronic inflammatory condition [31–34]. Neuroendocrine systems and sleep also underlie both migraine pathophysiology and the known actions of 5-HT_{2A} receptor compounds [35–37].

This study has several strengths and limitations. The double-blind, placebo-controlled, cross-over design is a powerful approach. The sample size is small, though appropriate for an exploratory, proof-of-concept investigation. Strong statistical significance and large effect sizes validate the findings in this small sample. All subjects were Caucasian and had relatively high starting headache burden, and while not representative of the general migraine population, it nevertheless allowed for exploring the effects and safety in a proof-of-concept study. We also included subjects meeting criteria for either episodic or chronic migraine in the present study. Subgroup analysis did not reveal significant differences between chronic and episodic subjects ($n = 5$ each; data not shown). There were also no obvious age or sex differences (data not shown), though future, adequately powered studies will be necessary to conclusively determine whether any differences between subgroups exist. The outcome measure of time to next migraine was confounded by ceiling effects, as 2 subjects had only 1 migraine attack and 2 had no migraine attacks in the 2 weeks after psilocybin administration. A longer duration of the headache diary in future studies would help better characterize the headache-free period after drug administration. Validated screens of migraine severity were not employed in this study, though such tools as the Global Assessment of Migraine Severity (GAMS), Migraine Disability Assessment (MIDAS), or Headache Impact Test-6 (HIT-6) could capture this measure, particularly in longer-term studies. Lastly, psilocybin did induce some physiological and psychotropic effects, which might suggest to subjects when they received the drug (i.e., unblinding). "Overall drug effect" and psychedelic effects did not correlate with migraine frequency reduction, however. Furthermore, these same acute drug effects were also reported after placebo administration, indicating some success in the blinding procedure. Future studies using a control agent that has similar acute drug effects to psilocybin, such as niacin, could reduce the risk of unblinding. Quantifiable measures of subject blinding, as well as expectation, were not included in the present study, but should be incorporated into future studies to help determine the impact of these confounds on the results.

In the first controlled investigation of psilocybin in migraine, we have demonstrated migraine-suppressing effects in the 2 weeks measured after the single administration of a low oral dose. The change in migraine frequency

Table 3 Adverse event record

Adverse event	Developed during test day			Developed in the next 24 h		
	Placebo	Psilocybin	p value (Fisher exact)	Placebo	Psilocybin	p value (Fisher exact)
Lightheadedness	1	3	0.58	0	0	1.0
Nausea	0	4	0.09	0	0	1.0
Anxiety	0	3	0.21	0	0	1.0
Tingling/paresthesia	0	1	0.99	0	0	1.0
Cold/shivering	0	1	0.99	0	0	1.0
Dry mouth	0	1	0.99	0	0	1.0
Confusion	1	0	0.99	0	0	1.0
Tension/sore muscles	3	1	0.58	2	2	1.0
Headache attack (general)	0	0	1.0	2	5	0.35
Migraine attack	0	1	0.99	2	2	1.0
IV site induration	0	0	1.0	0	1	0.99

IV = intravenous line

was independent from acute psychotropic effects. This exploratory study supports the viability of psilocybin as an investigational agent in migraine and shows that with careful recruitment, screening, preparatory, monitoring, and follow-up procedures [38], low-dose psilocybin can safely be administered orally to migraine patients in the experimental research setting. This study also represents a new arm in the field of select 5-HT_{2A} receptor compounds, offering a new perspective on the unique abilities of this drug class.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13311-020-00962-y.

Acknowledgments We thank CH-TAC, LLC, and the Schizophrenia Neuropharmacology Research Group at Yale (SNRGY) for their support of this project. This study was conducted with assistance from VACHS. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the Department of Veterans Affairs. The nurses of the NSU where this study was conducted, Ms. Angelina Genovese, Elizabeth O'Donnell, and Margaret Dion-Marovitz, as well as Rachel Galvan, PharmD, of the VACHS Investigational Research Pharmacy, are thanked for their excellent support. A vital force in the foundation of this research was the late Dr. Sewell, who was tragically lost to us in 2013 and whom we honor with the publication of this work.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Compliance with Ethical Standards

This exploratory study was registered on clinicaltrials.gov (NCT03341689) and received approvals from the Human Studies Subcommittee of Veterans Affairs Connecticut Healthcare System (VACHS) and the Human Investigations Committee of Yale University. In compliance with the Helsinki Declaration of 1975, as revised in 2000 [20], informed consent was obtained from every subject who participated in the study.

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Supplemental Table Acute drug effects on experimental test days

Acute effect		**Measure**	**Drug**	**Mean** (SEM; showing only 3 time points)			**ANOVA** (all timepoints)			
				Baseline	2 hours	6 hours	Drug	Time	Drug x time	F, df
Cardiovascular effects	Mean arterial pressure	mmHg	Placebo	87.97 (2.99)	83.13 (4.24)	86.74 (4.30)	0.003	0.46	0.007	2.52, 10
			Psilocybin	84.53 (3.19)	93.17 (4.73)	87.63 (4.22)				
	Heart rate	Beats per minute	Placebo	72.90 (3.82)	68.70 (3.33)	71.89 (3.20)	0.57	0.19	0.35	1.12, 10
			Psilocybin	74.20 (4.26)	69.60 (3.84)	74.8 (2.27)				
	Peripheral oxygenation	SpO2	Placebo	97.78 (0.52)	98.20 (0.42)	98.00 (0.41)	0.71	< 0.0001	0.44	1.0, 10
			Psilocybin	97.90 (0.23)	98.00 (0.52)	97.90 (0.38)				
General drug effects	Overall	VAS (0-3)	Placebo	0.0 (0.0)	0.41 (0.20)	0.0 (0.0)	< 0.0001	< 0.0001	0.0005	3.74, 8
			Psilocybin	0.0 (0.0)	1.97 (0.30)	0.22 (0.13)				
	Sleepiness / Sedation	VAS (0-3)	Placebo	0.75 (0.20)	0.78 (0.22)	0.33 (0.17)	0.64	0.0210	0.14	1.56, 8
			Psilocybin	0.70 (0.23)	1.08 (0.31)	0.27 (0.13)				
	Anxiety / Fear	VAS (0-3)	Placebo	0.27 (0.14)	0.0 (0.0)	0.0 (0.0)	0.11	0.27	0.24	1.33, 8
			Psilocybin	0.16 (0.11)	0.18 (0.11)	0.03 (0.03)				
	Nausea	VAS (0-3)	Placebo	0.31 (0.15)	0.11 (0.11)	0.11 (0.11)	0.0007	0.92	0.15	1.54, 8
			Psilocybin	0.15 (0.15)	0.42 (0.23)	0.20 (0.13)				
	Joy / Intense Happiness	VAS (0-3)	Placebo	0.22 (0.11)	0.70 (0.29)	0.41 (0.23)	0.15	0.018	0.25	1.30, 8
			Psilocybin	0.30 (0.20)	0.87 (0.24)	0.74 (0.26)				
	Peace / Harmony	VAS (0-3)	Placebo	0.69 (0.20)	1.06 (0.28)	0.47 (0.24)	0.99	0.059	0.035	2.15, 8
			Psilocybin	0.36 (0.21)	0.92 (0.24)	1.15 (0.36)				

VAS, visual analog scale; SEM, standard error about the mean; df, degrees of freedom

Supplemental Methods Changes to outcome measures

In this exploratory study, we hypothesized that the single administration of low-dose oral psilocybin (0.143mg/kg) would suppress migraine over a two-week reporting period. At the time the study was conceived, there were no interventions for migraine that could produce lasting effects after a single oral dose or clinical effects that were evident despite the drug or its metabolites being washed out of the body. Therefore, guidance for selecting outcome measures was lacking. The original primary clinical outcome was a change in 'weekly migraine attacks.' However, when starting to follow up with subjects, we noted that several commented specifically on enjoying their *days* without migraine, so 'weekly migraine days' was added as an outcome. This does not alter the findings or conclusion of the study. The original secondary outcome measure of 'time to last attack' was removed, as the definition (i.e., remission) could not be verified in the short 2-week period being investigated. Instead, the 'time to the second migraine attack' was added, as this was a clearly quantifiable measure that also addressed the issue of the first attack potentially being *caused* by drug administration itself. Lastly, in the original design of the study, measures of acute attack pain reduction, associated symptom reduction, and attack-related functional impairment reduction during drug exposure were planned, but these were removed when it was evident that there were simply not enough instances where subjects began experimental sessions with migraine attacks that would have allowed the acute effects of psilocybin to be tested.