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Short communication

Prevalence and associations of classic psychedelic-related seizures in a population-based sample☆

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ABSTRACT

Objectives: Previous studies have reported links between classic psychedelic use and seizures, but little remains known about prevalence and potential risk factors of classic psychedelic-related seizures.
Methods: Using a sample representative of the US adult population with regard to sex, age, and ethnicity (N = 2822), this study examined the prevalence and potential risk factors of classic psychedelic-related seizures, in a subsample of respondents who reported lifetime classic psychedelic use (n = 613).
Results: Among those who reported lifetime classic psychedelic use, 1.5 % reported classic psychedelic-related seizures, a statistic that comports with the prevalence of epilepsy in the US population. Among those who reported seizures while using a classic psychedelic, almost half reported co-use of antidepressants, mood stabilizers, or opioid replacement therapies at the time of the seizures. Notably, classic psychedelic-related seizures were more commonly reported in certain respondents, especially those with a personal or family history of epilepsy.
Conclusions: These results suggest that classic psychedelic use could increase the risk of seizures in certain populations, particularly those with a personal or family history of epilepsy.

1. Introduction

Classic psychedelics include psilocybin, N,N-dimethyltryptamine (DMT), the DMT-containing concoction ayahuasca, lysergic acid diethylamide (LSD), mescaline, and the mescaline-containing cacti peyote and San Pedro (Sexton et al., 2020). These psychoactive compounds, which exert effects through agonist activity at the serotonin 2A receptor, have recently received renewed scientific attention (Nutt and Carhart-Harris, 2021). The clinical research to date has been limited in the number of studies and the size of samples (Goldberg et al., 2020), but the evidence suggests that classic psychedelics, delivered in conjunction with therapy, may be particularly effective in the treatment of internalizing disorders (Nutt and Carhart-Harris, 2021). For example, a recent double-blind randomized, controlled trial found that psilocybin-assisted therapy was at least as effective as an active control condition (escitalopram) in reducing depressive symptoms among patients with moderate-to-severe major depressive disorder (Carhart-Harris et al., 2021). The side effects reported in modern-era clinical trials have mostly been mild and transient in nature (Andersen et al., 2021), but important questions remain about potential risks associated

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with classic psychedelic use (Anderson et al., 2020), especially when such substances are taken outside of tightly controlled clinical trials.

One concern is that classic psychedelic use may cause seizures. For example, one study reviewed single-substance exposures of LSD or psilocybin reported to poison control centers in the United States between 2000 and 2016. There were 190 instance (2.0 % of total reports) of seizures related to LSD or psilocybin use, but it is not known whether the seizures were caused directly by these classic psychedelics, drug-drug interactions, or third factors (Leonard et al., 2018). Another study analyzed online reports and found that co-use of lithium and classic psychedelics was associated with seizures (Nayak et al., 2021; see also Fisher and Ungerleider, 1967). However, neither of the studies investigated other potential risk factors (e.g., family history of epilepsy), which may be important to understand in risk assessments of classic psychedelics.

Using data on lifetime classic psychedelic users ($n = 613$) from a sample representative of the United States adult population with regard to sex, age, and ethnicity ($N = 2822$), we aimed to investigate the prevalence and associations of classic psychedelic-related seizures. These data will provide for a more comprehensive understanding of the risk profile of classic psychedelics, which can inform exclusionary criteria as clinical research on these substances continues to grow.

2. Material and methods

2.1. Participants and Procedure

The participants were current residents of the United States of America who were 18 years or older. The sample ($N = 2822$) was recruited in October 2021 on Prolific Academic (https://app.prolific.co), which is an online platform designed specifically to allow researchers to recruit study participants (Peer et al., 2017). Prolific Academic offers a representativeness function that uses proportionate stratification on three census-matched factors (sex, age, and ethnicity) to reflect the demographic distribution of the US adult population. This function was used in this study.

The participants recruited on Prolific Academic were directed to a survey (see Supplemental Material for survey items) hosted on Qualtrics (https://www.qualtrics.com). Those respondents who reported having used a classic psychedelic at least once ($n = 613$) were included in the analyses for this study. Study completion resulted in $2.20 payment. Study procedures were determined to be exempt from review by the Institutional Review Board at the University of Wisconsin – Madison.

2.2. Lifetime classic psychedelic use

All respondents were asked to report lifetime substance use, including which, if any, of the following classic psychedelics they had ever used: psilocybin, DMT, ayahuasca, LSD, mescaline, peyote, or San Pedro (see Supplemental Table 1 for reported use of classic psychedelics by substance type).

2.3. Classic psychedelic-related seizures

Respondents who reported lifetime classic psychedelic use ($n = 613$) were asked to report whether they had ever experienced seizures while using a classic psychedelic. Respondents who reported seizures while using a classic psychedelic ($n = 9$) were asked to report whether they had been using any medications at the time of the seizures (multiple-choice). Medication categories included: tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), St John's Wort, or any other medications with serotonin activity (recoded as antidepressants); haloperidol or any other antipsychotic medications (recoded as antipsychotics); lithium or any other mood stabilizers (recoded as mood stabilizers); and methadone or buprenorphine/suboxone (recoded as opioid replacement therapies). These specific medications were assessed because these medications are commonly prescribed in the treatment of mental health conditions and because trials of classic psychedelics frequently exclude from participation individuals who use these compounds (e.g., ClinicalTrials.gov Identifier: NCT02037126), which is consistent with contemporary guidelines (Johnson et al., 2008). While there is ongoing research on drug-drug interactions between classic psychedelics and opioid replacement therapies (ClinicalTrials.gov Identifier: NCT04161066), there have also been rare reports of withdrawal seizures in opioid dependence syndrome (Khanra et al., 2015), which further motivated the assessment of opioid replacement therapies in the current study. Respondents were also asked to report whether they had a current or past history of epilepsy and whether they had first or second-degree relatives with epilepsy.

2.4. Statistical analyses

Fisher's exact tests was used to examine the relationships between classic psychedelic-related seizures and potential risk factors.

3. Results

Table 1 presents the percentage of respondents who reported having had seizures while using a classic psychedelic. As demonstrated in the table, among those who reported lifetime classic psychedelic use, 1.5% reported seizures while using a classic psychedelic. And among those who reported seizures while using a classic psychedelic, almost half reported co-use of antidepressants, mood stabilizers, or opioid replacement therapies at the time of the seizures. Notably, when evaluated by individual medication type, co-use of lithium and SNRIs during the classic psychedelic-related seizures were each reported by two respondents while co-use of tricyclic antidepressants, medications with serotonin activity, mood stabilizers, and methadone or buprenorphine/suboxone were each reported once (see Supplemental Table 2).

Table 2 presents potential risk factors associated with classic psychedelic-related seizures. As demonstrated in the table, classic psychedelic-related seizures were more common among those with a personal or family history of epilepsy, even when excluding respondents who had seizures concurrent with medication use from the analysis (see Supplemental Table 3). When excluding respondents with a personal history of epilepsy from the analysis, classic psychedelic-related seizures were still more common among those with a family history of epilepsy (see Supplemental Table 4).

4. Discussion

The present study investigated the prevalence and potential risk

Table 1
Prevalence of seizures while using a classic psychedelic.

	Classic psychedelic-related seizures	
	(%)	(*n*)
Yes	1.5	9
No	98.5	604
Reported co-use of medications at the time of the seizures		
	(%)	(*n*)
At least one of the medications below reported	44.6	4
Antidepressants	33.3	3
Antipsychotics	0	0
Mood stabilizers	33.3	3
Opioid replacement therapies	11.1	1

All percentages were rounded to the nearest 0.1%. (*n*) refers to the counts of respondents in each row. Note: reported medication was "check-all-that-apply" multiple-choice and results show how many respondents selected each specific option.

Table 2
Classic psychedelic-related seizures and potential risk factors.

	Classic psychedelic-related seizures		
	No	Yes	*p*
Family epilepsy history			< 0.001
Yes	38	7	
No	566	2	
Personal epilepsy history			< 0.001
Yes	15	5	
No	589	4	

Fisher's exact test was used to examine the relationships between classic psychedelic-related seizures and potential risk factors.

factors of classic psychedelic-related seizures in a sample representative of the US adult population with regard to sex, age and ethnicity. The results suggest that, consistent with prior findings (Leonard et al., 2018), the incidence of classic psychedelic-related seizures in the general population may be low (1.5 %) and comparable to the prevalence of epilepsy in the US population (1.2 %; Zack and Kobau, 2017). However, there are factors associated with a higher likelihood of classic psychedelic-related seizures that deserve more consideration.

The association between lithium co-use and classic psychedelic-related seizures previously reported by Nayak and colleagues (2021) was partially replicated in this study, but we also showed that classic psychedelic-related seizures were more common among respondents with a personal or family history of epilepsy. The significant association with family history of epilepsy remained when those who had a personal history of epilepsy were excluded from the analysis, which suggests that there could be a genetic component that predisposes people with a family history of epilepsy to have classic psychedelic-related seizures (note: two respondents with classic psychedelic-related seizures had neither personal nor family history of epilepsy). It might therefore be appropriate to screen out individuals with a personal or family history of epilepsy from clinical trials (see Johnson et al., 2008 for contemporary screening guidelines), at least until research has further investigated this topic.

While classic psychedelic-related seizures might be related to drug-drug interactions (see Nayak et al., 2021 for mechanistic conjectures) or genetic predispositions to epilepsy, it is also possible that such seizures could be provoked by mental or emotional processes during the acute effects. Previous research suggests that non-epileptic seizures can be triggered by experiencing stressful events (Popkirov et al., 2019), which might occur during the acute effects of classic psychedelics. It is therefore possible that at least some classic psychedelic-related seizures could be caused by psychological rather than pharmacological or genetic factors. Future research should seek to determine the relative contributions of different factors (e.g., pharmacological, genetic, psychological) on classic psychedelic-related seizures.

There are several limitations to consider when interpreting the results. First, the respondents were not asked whether the classic psychedelic-related seizures were associated with any specific classic psychedelic or dosing parameters, which is information that could have been used to identify potential pharmacological risk factors and more clearly estimate dose-dependent effects. It would also have been useful to know about any potential co-use of other drugs (e.g., alcohol, cannabis, or tobacco) prior to the seizure. Second, respondents were not asked to report other physical or mental health conditions known to increase the risk of seizures (e.g., depression; Yang et al., 2021). The relationships reported in this study may therefore have been confounded by variables that were not included in the survey. It is also possible that respondents who reported mood stabilizer use may have used certain mood stabilizers that are also used to treat epileptic seizures (e.g., valproate). However, we only distinguished between lithium and other "mood stabilizers." This association could therefore be due to confounding by indication, where the respondent who reported mood stabilizer use at the time of the classic psychedelic-related seizures was taking these medications (i.e., other "mood stabilizers") to treat epileptic seizures and may have therefore been at elevated risk for seizures regardless of classic psychedelic use. Third, respondents were not asked to describe the subjective experience of classic psychedelic-related seizures. Previous studies have used qualitative interviews with those diagnosed with epileptic and non-epileptic seizures to give insight into the lived experiences of individuals with these diagnoses (McEwan et al., 2004; Rawlings and Reuber, 2016). Such research methods could also be utilized to provide a richer understanding of the experiences of those who have had classic psychedelic-related seizures, as well as their family members who may have also been affected. Fourth, the number of lifetime classic psychedelic users ($n = 613$) and the prevalence of classic psychedelic-related seizures ($n = 9$) was small, which in all likelihood limited power to detect less robust associations. Future studies should employ larger, representative samples to enable more rigorous statistical testing.

5. Conclusions

In conclusion, the results in this study suggest that classic psychedelic use may increase the risk of seizures in certain populations, especially those with a personal or family history of epilepsy. This risk may also be elevated when classic psychedelics are used concurrently with certain widely-prescribed medications. These findings could have real-world implications both for informing exclusion criteria in classic psychedelic trials and for educating individuals who use classic psychedelics outside of research settings. Future research is warranted to further elucidate these relationships, particularly in exploring the relative risk of different classic psychedelics, as well as potential interactions between these and specific prescribed medications.

CRediT authorship contribution statement

OS conceptualized and designed the study, with input from SG and PSH. OS analyzed the data and wrote the manuscript, with comments from SG, PSH, RC, and WO.

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Ethical approval

All procedures performed involving human participants were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was determined to be exempt from review by the Internal Review Board (IRB) at UW-Madison.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

PSH is on the scientific advisory board of Bright Minds Biosciences Ltd., Eleusis Benefit Corporation, and Reset Pharmaceuticals Inc. OS and RC are co-founders of Eudelics AB.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109586.

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