Longitudinal associations between psychedelic use and psychotic symptoms in the United States and United Kingdom

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Ethics approval and consent to participate

Study procedures were determined to be exempt from review by the Institutional Review Board at the University of Wisconsin – Madison. 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. Informed consent was obtained digitally from all individual participants included in the study.

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Competing interests

PSH has been in paid advisory relationships with the following organizations regarding the development of psychedelics and related compounds: Bright Minds Biosciences Ltd., Eleusis Benefit Corporation, Journey Colab Corporation, Reset Pharmaceuticals Inc., and Silo Pharma. OS was a co-founder of Eudelics AB. Alexander Lebedev is a co-founder of Katharsis Journeys.

Availability of data and materials

The data and R syntax are available at https://osf.io/v78kj/

Abstract

It has long been speculated that psychedelic use could provoke the onset of psychosis, but there is little evidence to support this conjecture. Using a longitudinal research design with samples representative of the US and UK adult populations with regard to sex, age, and ethnicity (n = 9732), we investigated associations between psychedelic use and change in number of psychotic symptoms during the two-month study period. In covariate-adjusted regression models, psychedelic use during the study period was not associated with a change in number of psychotic symptoms unless it interacted with a personal or family history of bipolar disorder, in which case the number of symptoms increased, or with a personal (but not family) history of psychotic disorders, in which case the number of symptoms decreased. Taken together, these findings indicate that psychedelic use may affect psychotic symptoms in individuals with a personal or family history of certain disorders characterized by psychotic symptomatology.

Keywords: adverse effects; bipolar; psychedelics; psychotic symptoms; schizophrenia

Psychedelics (i.e., lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), and mescaline; Nichols et al., 2022) are psychoactive substances that can produce profound effects on perception, cognition, and emotions during drug action (Nichols, 2016). Over the last twenty years, there has been a resurgence of clinical research on psychedelic therapy (Nutt & Carhart-Harris, 2021) and a growing body of research is now highlighting its possible efficacy in treating a broad range of mental health conditions, such as end-of-life anxiety (Griffiths et al., 2016), depression (Carhart-Harris et al., 2021; Davis et al., 2021; Goodwin et al., 2022; Palhano-Fontes et al., 2019; Sloshower et al., 2023; von Rotz et al., 2023), and alcohol use disorder (Bogenschutz et al., 2015; Bogenschutz et al., 2022). Currently, over one hundred clinical trials are exploring psychedelic therapy for various mental and medical conditions (Kurtz et al., 2022).

This resurgence has been accompanied by a popular shift in perception of psychedelics (Yaden et al., 2022) and an increased use of these drugs outside of clinical settings (Livne et al., 2022), where risks may be elevated (Carbonaro et al., 2016; Evans et al., 2023; Simonsson, Hendricks, et al., 2023). One much-debated risk that has been associated with psychedelic use is the provocation, or exacerbation, of psychosis (Strassman, 1984), which is a term that refers to the manifestation of one or more psychotic symptoms, namely delusions or hallucinations (without insight into their pathological nature), or a combination of both (Lieberman & First, 2018).

Despite the historical association between psychedelics and psychosis (Friesen, 2022; Nichols & Walter, 2021), the available evidence on whether their use could provoke a transition to psychosis is far from conclusive (Fiorentini et al., 2021). For example, in a study using data from a representative sample of the US population, Krebs & Johansen (2013) found no association between lifetime use of psychedelics and non-affective psychosis when controlling for a range of potential confounders. In fact, lifetime use of psychedelics was

associated with lower odds of reporting one of the six psychotic symptoms evaluated (i.e., "felt force taking over mind"). Another recent study found that psychedelic use was not associated with psychosis-like symptoms when controlling for potential confounders (Lebedev et al., 2021). In contrast, Kuzenko et al. (2011) found that cumulated lifetime psychedelic use (five or more times) was associated with greater likelihood of lifetime experience of (two or more) psychotic symptoms. However, there are some important limitations that should be taken into consideration when interpreting this result, including the retrospective study design that limits the possibility to draw any conclusions on a temporal relationship between lifetime psychedelic use and psychotic symptoms and the lack of an accurate measurement of chronic cannabis use, which presents a large potential confound in outcomes, as it has been associated with transition to psychosis (Kraan et al., 2016; Vallersnes et al., 2016).

Notably, however, evidence from other epidemiological studies and also case reports suggests that the risk of suffering a psychedelic-related psychotic episode could depend on a variety of factors and that individuals with a personal or family history of bipolar or psychotic disorders may be especially vulnerable (Bosch et al., 2022; Dos Santos et al., 2017; Lebedev et al., 2021; Schlag et al., 2022; Simonsson, Goldberg, et al., 2023). For instance, in a recent cross-sectional study, lifetime use of psychedelics interacted with family history of psychotic or bipolar disorders such that psychotic symptoms were higher among those who reported lifetime psychedelic use and a family history of psychotic or bipolar disorders (Simonsson, Goldberg, et al., 2023). Similarly, among case re- ports of psychotic or manic episodes related to psychedelic use, many have concerned individuals with a personal or family history of psy- chotic or bipolar disorders (Barber et al., 2022; Dos Santos et al., 2017; Gard et al., 2021; Halim et al., 2023).

Motivated by the concern that the ingestion of a psychedelic might provoke a psychosis or manic episode, the leading safety guidelines on clinical trials involving psychedelics recommend that participants with a personal or family history of psychotic or bipolar disorders be excluded from participation (Johnson et al., 2008). However, recent clinical research on psychedelic-assisted therapy for treatment resistant bipolar II depression showed no increases in mania or hypomania (S. Aaronson et al., 2023; S. T. Aaronson et al., 2023), suggesting it may be a safe treatment for depression in this population. Although no such efforts have yet been made to investigate psychedelic therapy in individuals with bipolar I disorder or psychotic disorders, low-dose psychedelic-assisted therapy has been proposed as a potential treatment for the negative symptoms of schizophrenia (Wolf et al., 2022). Considering the inconclusive evidence on the association between psychosis and psychedelics, there is a need to better understand the risks associated with psychedelics, especially for individuals in these vulnerable populations.

Using a longitudinal research design with samples representative of the US and UK adult populations with regard to sex, age, and ethnicity (n = 9732), the present study aims to 1) investigate the relationship between naturalistic psychedelic use during a two-month study period and change in number of psychotic symptoms, and 2) the potential interactions between psychedelic use and a personal and/or family history of bipolar disorders or psychotic disorders.

Methods

Participants and procedure

The respondents were recruited through Prolific Academic (https://prolific.com), which is a platform that facilitates the recruitment of study participants for researchers, in August 2022. The platform offers representative samples of two national populations – the United States

and the United Kingdom – that are stratified on three census-matched factors: sex (Male, Female), age (18-27, 28-37, 38-47, 48-57, 58+), and ethnicity (White, Mixed, Asian, Black, Other). Previous research suggests that Prolific Academic provides high-quality data, relative to other recruitment platforms (Peer et al., 2017; Peer et al., 2022).

In this study, we used Prolific Academic's representativeness function to recruit US (n = 4867) and UK (n = 4865) residents who were 18 years or older. Participants were invited to complete two surveys: one at baseline (T_1) and one approximately two months later at follow-up (T_2) (henceforth referred to as the 'study period'). Completion of each survey resulted in a £0.9 payment.

Study procedures were determined to be exempt from review by the Institutional Review Board at the University of Wisconsin – Madison.

In this survey study, we used a longitudinal research design to test whether participants who reported having used psychedelics during the study period reported a change in the number of psychotic symptoms they experienced in the week before completing the surveys, in comparison to those who did not.

Materials

Psychedelic use

At T_1, all respondents were asked to report (yes, no) which, if any, of the following psychedelics they had used in the past two months: psilocybin, ayahuasca, DMT, LSD, mescaline, peyote, or San Pedro. At T_2, respondents were also asked to report which, if any, of the psychedelics they had used during the study period.

Demographics and other substance use

At T_1, all respondents were asked to report their age in years, gender identity, educational attainment, religious belief, and political affiliation. At T_2 respondents were asked to report (yes, no) past two month use of alcohol, nicotine products (e.g., cigarettes, e-cigarettes, cigarillos, little cigars, smokeless tobacco), cannabis products (e.g., weed, tetrahydrocannabinol (THC), cannabidiol (CBD), hemp oil), 3,4-methylenedioxymethamphetamine (MDMA), major stimulants (e.g., cocaine, methamphetamine), illicit narcotic analgesics/opioids (e.g., morphine, heroin, oxycodone), illicit benzodiazepines and barbiturates (e.g., Diazepam [Valium], Alprazolam [Xanax]), inhalants (poppers, whip-its, nitrous oxide, glue), and other substances.

Bipolar disorders I or II, or psychotic disorders

At T_1, all respondents were asked to report (yes, no) present or past histories of bipolar disorders (e.g., type I or II) and/or psychotic disorders (e.g., schizophrenia) as well as first or second-degree relatives (yes, no) with a present or past histories of bipolar disorders and/or psychotic disorders.

Psychotic Symptoms

All respondents completed the psychotic ideation subscale of the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (Zimmerman & Mattia, 2001) at T_1 and T_2. The PDSQ is a 125-item self-report measure to screen for psychiatric diagnoses. Respondents dichotomously report symptoms (yes, no) across 15 symptom domains, including psychosis. The PDSQ shows evidence of good internal consistency, test-retest reliability, convergent and discriminant validity, adequate sensitivity and specificity (Sheeran & Zimmerman, 2004; Zimmerman & Chelminski, 2006a, 2006b; Zimmerman et al., 2004; Zimmerman & Sheeran, 2003). The psychotic ideation subscale used in this study asks respondents to report (yes, no)

psychotic symptoms during the past two weeks based on 6 items: hallucinations, general delusions, paranoia (2 items), control by external force, and special powers or abilities. In our study, we adjusted the questions by reducing the period from two weeks to one in order to increase the likelihood that the psychedelic use would precede the psychotic symptoms. Internal consistency in the present sample was acceptable (Cronbach's alpha = .63 at T_1 and .66 at T_2). The total score was calculated by summing across items with highest score being 6 and lowest score being 0. Change in number of psychotic symptoms at T_2 was calculated by subtracting the total score at T_1 from the total score at T_2.

Statistical Analyses

We used multiple linear regression to test whether there were significant differences in changes in the number of psychotic symptoms between the two groups (i.e., those who reported psychedelic use during the study period versus those who did not). We also used four separate multiple linear regression analyses to test whether there were interactions between psychedelic use during the study period and 1) a personal history of bipolar disorders, 2) a family history of bipolar disorders, 3) a personal history of psychotic disorders, and 4) a family history of psychotic disorders. All analyses included control variables that broadly match those used in a previous longitudinal study on naturalistic psychedelic use (Forstmann et al., 2020): age, gender identity, educational attainment, religious belief, political affiliation, past two month use of alcohol, nicotine products (e.g., cigarettes, e-cigarettes, cigarillos, little cigars, smokeless tobacco), cannabis products (e.g., weed, THC, CBD, hemp oil), MDMA, major stimulants (e.g., cocaine, methamphetamine), illicit narcotic analgesics/opioids (e.g., morphine, heroin, oxycodone), illicit benzodiazepines and barbiturates (e.g., Diazepam [Valium], Alprazolam [Xanax]), inhalants (poppers, whip-

its, nitrous oxide, glue), and other substances at T_2, as well as psychedelic use in the past two months at T_1, consistent with a number of prior studies (e.g., Simonsson, Osika, et al., 2023). In this study, we addressed the issues of missing data using Multivariate Imputation by Chained Equations (MICE) (van Buuren & Groothuis-Oudshoorn, 2011). We used the mice package version 3.15.0 in R Studio (https://cran.r-project.org/web/packages/mice/index.html) to impute the missing data twenty times by means of random forest imputations. General practice is to perform the imputations ten times (van Buuren & Groothuis-Oudshoorn, 2011) but we imputed the values twenty times to stabilize imputations. We subsequently replaced imputed values on hierarchical variables (i.e., variables that should have missing values by design) before we ran analyses on the data. Models were run across imputations and pooled according to Rubin's (1976) rules using the 'with' and 'pool' functions in the 'mice' package (van Buuren & Groothuis-Oudshoorn, 2011) in R Studio. All descriptive statistics demonstrate non-imputed (i.e. observed) values only.

Results

Out of the 9,732 participants completed the survey at T_1, 7,667 individuals completed the survey at T_2, reflecting a retention rate of 79%. Among these, 100 respondents reported psychedelic use during the study period (henceforth referred to as 'psychedelic users'), constituting 1.3% of those who completed the survey at T_2.

Table 1 shows sample characteristics at T_1. Respondents who used a psychedelic during the study period reported significantly higher rates of personal and family histories of bipolar disorders as well as family histories of psychotic disorders (see Supplemental Table 1 for statistics on psychiatric history). Notably, three out of six items related to past-week psychotic symptoms were significantly more common among psychedelic users than among

non-users at T_1 (see Supplemental Tables 2 and 3 for descriptive statistics of past-week psychotic symptoms at T_1 and T_2).

Table 1. Sample characteristics at T_1

	Non-users (n=9,632)	Users (n=100)	*p*
Country			<.001
United States	50.0%	76.0%	
United Kingdom	50.0%	24.0%	
Age			<.001
18-27	20.5%	24.0%	
28-37	22.1%	35.0%	
38-47	18.5%	24.0%	
48-57	15.7%	15.0%	
58+	23.2%	2.0%	
Gender identity			<.001
Male	47.6%	63.0%	
Female	50.9%	33.0%	
Other	1.5%	4.0%	
Educational attainment			.302
Less than bachelor's degree	43.3%	37.0%	
Bachelor's degree or higher	56.8%	63.0%	
Religious belief			<.001
Not at all religious	55.8%	75.0%	
A little religious	19.0%	13.0%	
Quite religious	11.7%	6.0%	
Moderately religious	8.6%	4.0%	
Very religious	5.0%	2.0%	
Political affiliation			<.001
Democratic Party	34.7%	59.0%	
Republican Party	15.1%	17.0%	
Remain side of the Brexit debate	34.6%	21.0%	
Leave side of the Brexit debate	15.7%	3.0%	
Lifetime substance use			
Psychedelics	17.1%	81.0%	<.001
Alcohol	82.4%	91.0%	.031
Nicotine products	51.3%	81.0%	<.001
Cannabis products	53.1%	87.0%	<.001
Major stimulants	16.7%	59.0%	<.001
Illicit narcotic analgesics or opioids	7.5%	35.0%	<.001
Illicit benzodiazepines and barbiturates	10.0%	52.0%	<.001
Inhalants	9.7%	43.0%	<.001
MDMA	12.4%	63.0%	<.001
Other substances	3.7%	26.0%	<.001
Self-reported psychiatric history			
Personal history of bipolar disorders	2.9%	10.0%	<.001

Family history of bipolar disorders	11.6%	22.0%	<.001
Personal history of psychotic disorders	1.1%	3.0%	0.086
Family history of psychotic disorders	6.8%	14.0%	<.001
Past week specific psychotic symptoms			
During the past week, …			
…did things happen that you knew were true, but that other people told you were your imagination?	4.8%	12.0%	0.002
…were you convinced that other people were watching you, talking about you, or spying on you?	6.5%	10.0%	0.134
…did you think that you were in danger because someone was plotting to hurt you?	2.1%	7.0%	0.003
…did you think that you had special powers other people didn't have?	1.7%	6.0%	0.006
…did you think that some outside force or power was controlling you body or mind?	1.3%	2.0%	0.362
…did you hear voices that other people didn't hear, or see things that other people didn't see?	1.9%	4.0%	0.095
Note: This table shows sample characteristics at T_1 of respondents who did not report psychedelic use during the study period (i.e., non-psychedelic users) and respondents who did (i.e., psychedelic users). Pearson's chi-squared tests were used to examine the characteristics of users versus non-users at T_2. All percentages were rounded to the nearest 0.1%; cumulative percentages may not add to 100.0.			

Covariate-Adjusted Models

Table 2 presents results from the five regression analyses on the association between psychedelic use in the two months prior to T_2 and the number of psychotic symptoms, including the four regression analyses with the interaction terms personal history of bipolar disorders, family history of bipolar disorders, personal history of psychotic disorders, and family history of psychotic disorders (see Supplemental Tables 4-8 for full results).

Table 2
Results from covariate-adjusted regression analyses on the number of psychotic symptoms

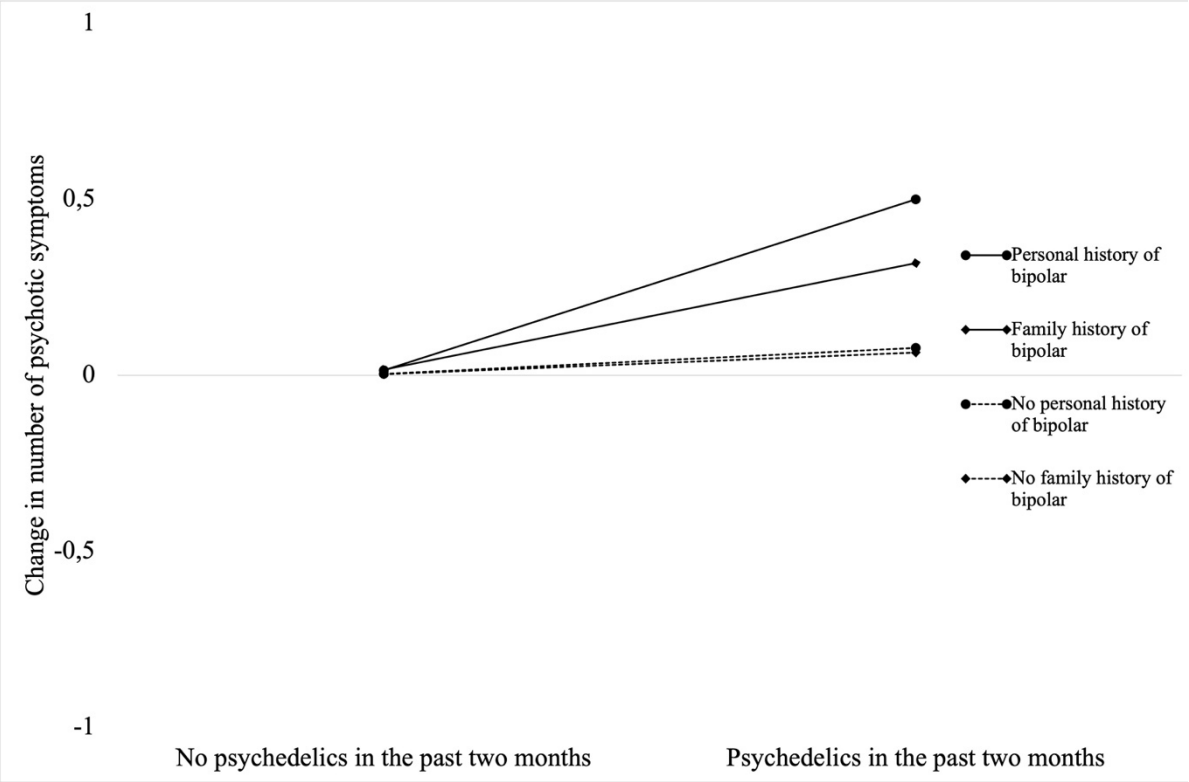
Effect	**Interaction term**	***B***	***95% CI***	***P***
Psychedelic use		0.12	-0.01, 0.24	0.076
Psychedelic use	Personal history of bipolar disorders	0.48	0.09, 0.86	0.016*
Psychedelic use	Family history of bipolar disorder	0.30	0.01, 0.59	0.046*
Psychedelic use	Personal history of psychotic disorders	-0.81	-1.5, -0.13	0.019*

Psychedelic use	Family history of psychotic disorders	-0.23	-0.56, 0.09	0.162

Note. B = the non-standardized regression coefficient that can vary between 0 and 6 where the values represent change in number of psychotic symptoms between T_1 and T_2. Positive values represent an increase in number of psychotic symptoms and negative values represent a decrease in number of psychotic symptoms. The linear regression models controlled for age, gender, educational attainment, degree of religiosity, political affiliation, past two month use of alcohol, nicotine products, cannabis products, MDMA, major stimulants, illicit narcotic analgesics/opioids, illicit benzodiazepines and barbiturates, inhalants, and other substances at T2, and psychedelic use in the past two months at T1. An asterix (*) indicates a statistically significant interaction between psychedelic use and reported history of the disorder at *P*-values < 0.05.

As shown in the table, in covariate-adjusted regression analyses, psychedelic use during the study period was not associated with a significant change in the number of psychotic symptoms. However, there was an interaction between psychedelic use during the study period and personal history of bipolar disorder such that psychedelic users with a personal history of bipolar disorder showed an increase in the number of psychotic symptoms. A similar, yet weaker, interaction effect was observed between psychedelic use during the study period and having a family history of bipolar disorder (see Figure 1).

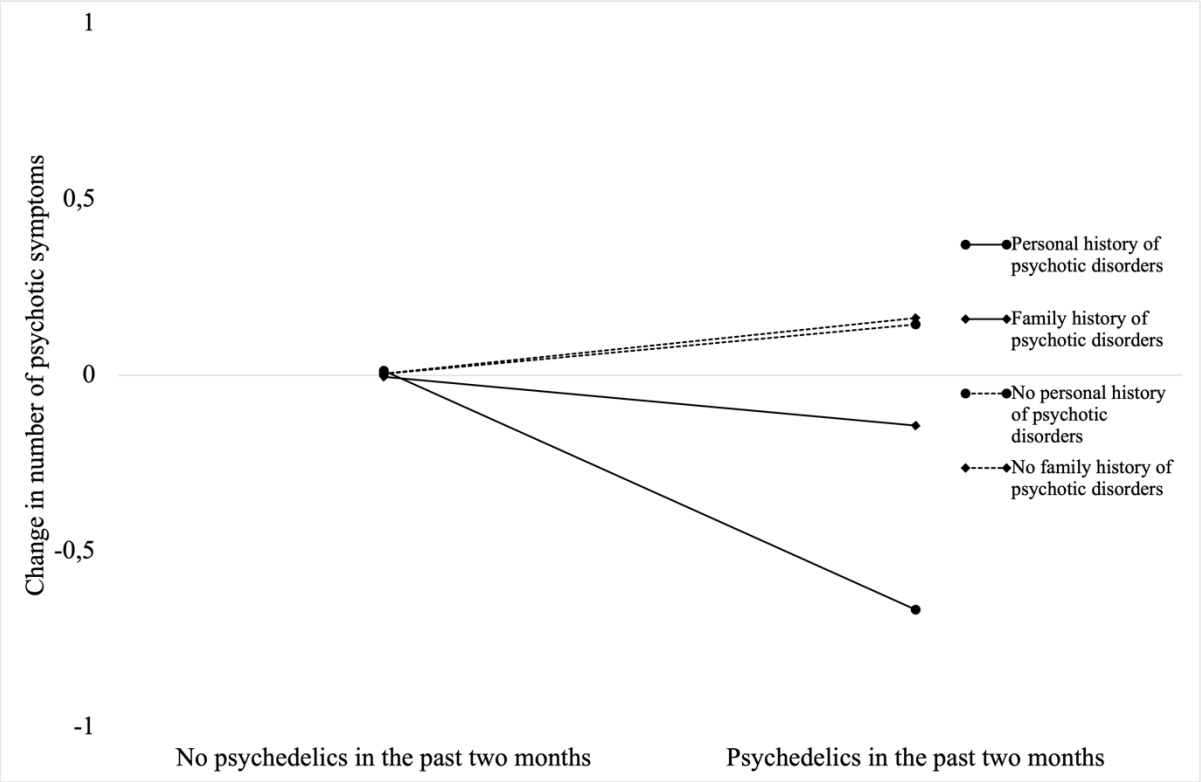
Figure 1
Interaction between psychedelic use during the study period and history of bipolar disorders on change in the number of psychotic symptoms



Note. The vertical axis represents change in number of psychotic symptoms between T_1 and T_2. The horizontal axis represents having reported used a psychedelic (or not) in the past two months at T_2. Groups represent reported history (or not) of bipolar disorders.

There was also an interaction effect between psychedelic use during the study period and personal history of psychotic disorders such that psychedelic users with a personal history of psychotic disorders showed a decrease in the number of psychotic symptoms. No such interaction was found between psychedelic use during the study period and a family history of psychotic disorders (see Figure 2). None of the significant results in this study survived false discovery rate (FDR) correction for multiple comparisons.

Figure 2
Interaction between psychedelic use during the study period and history of psychotic disorders on change in the number of psychotic symptoms



Note. The vertical axis represents change in number of psychotic symptoms between T_1 and T_2. The horizontal axis represents having reported used a psychedelic (or not) in the past two months at T_2. Groups represent reported history (or not) of psychotic disorders.

Discussion

The present longitudinal study investigated the associations between psychedelic use during the two-month study period and changes in the number of psychotic symptoms in representative samples of the US and UK adult populations regarding sex, age, and ethnicity. In a covariate-adjusted regression model, we found no association between the use of psychedelics during the two-month study period and changes in number of psychotic symptoms, which broadly corresponds to previous epidemiological findings (Krebs & Johansen, 2013; Lebedev et al., 2021; Simonsson, Goldberg, et al., 2023).

We did, however, find an interaction between personal history of bipolar disorder and psychedelic use during the study period such that psychedelic use was associated with an increase in the number of psychotic symptoms among individuals with a personal history of bipolar disorder. Research on the relationship between psychedelic use and psychotic

symptoms in individuals with bipolar disorder is still in its infancy, but there are several case reports of suspected psychedelic-induced mania with psychotic features (Barber et al., 2022; Bosch et al., 2022; Gard et al., 2021; Halim et al., 2023) and two recent cross-sectional and qualitative studies on individuals with bipolar disorder found that some of the participants retrospectively reported increases in mania and psychotic symptoms following psychedelic use (DellaCrosse et al., 2022; Morton et al., 2023). In these studies, where more than half stated mental health treatment as a motivation for using a psychedelic, experiences of attenuated depressive symptoms were often accompanied by increases in unwanted symptoms, such as increased mania severity and psychotic symptoms. Conversely, in recent clinical research involving psychedelic-assisted therapy for treatment-resistant bipolar II depression, decreases in depressive symptoms did not coincide with increases in mania, hypomania, or psychotic symptoms (S. Aaronson et al., 2023; S. T. Aaronson et al., 2023). One possible explanation could be that the risk of provoking, or exacerbating, psychotic symptoms through psychedelic use may be more elevated in naturalistic settings, especially for individuals with bipolar I disorder, a type that is marked by an elevated prevalence and severity of psychotic symptoms (Bräunig et al., 2009). An alternative explanation could be that psychedelics may increase the risk for mania with psychotic features, possibly by provoking a manic switch (i.e., a report of mania, hypomania, or mixed episodes following treatment with an antidepressant; Truman et al., 2007). Psychedelic use has been associated with reduced depressive symptoms both in clinical (Nutt & Carhart-Harris, 2021) and naturalistic settings (DellaCrosse et al., 2022; Nygart et al., 2022; Raison et al., 2022) and other drugs with antidepressant properties, such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), have been associated with an increased risk of subsequent mania (Chen et al., 2022; Patel et al., 2015). Although antidepressant-associated manic states have been found to be marked by less severe levels of psychotic

symptoms than spontaneous manic states (Stoll et al., 1994), it remains unclear whether this extends to psychedelics.

A similar, but weaker, interaction was found between psychedelic use during the study period and having a family history of bipolar disorder. Although less is known about the risks involved in psychedelic use for individuals with a genetic predisposition toward bipolar disorder, several reviews of available case reports on psychedelic-related manic and psychotic episodes suggest that individuals with a genetic predisposition toward developing bipolar disorder might be especially vulnerable (Bosch et al., 2022; Gard et al., 2021). Bipolar disorders have one of the highest estimates of hereditability for psychiatric disorders and having a family history of bipolar disorder is an important clinical predictor for the onset of bipolar disorder in patients (Vieta et al., 2018). Importantly, recent large-scale genetic studies have reported a higher heritability of bipolar I disorder than of bipolar II disorder (see, for example, Coleman et al., 2020) and it is possible that the risk of subsequent increases in psychotic symptoms following psychedelic use may be more elevated in individuals with a family history of bipolar I disorder.

Notably, we also found that a personal (but not family) history of psychotic disorders interacted with psychedelic use in such a way that their use during the study period was associated with a decrease in psychotic symptoms., which contrasts with the widespread belief that psychedelic use could put individuals with a personal history of psychotic disorders at risk of transitioning to psychosis. This result should be interpreted with caution, especially due to the low number of psychedelic users who reported a personal history of psychotic disorders (n = 3). Due to ethical considerations, no modern trials involving psychedelics have included patients with psychotic disorders, but early research on psychedelics, primarily LSD, investigated the effects of these compounds in patients

diagnosed with psychotic disorders. For example, in one of the first experiments involving a psychedelic, Werner Stoll noted that six treatment-resistant patients with schizophrenia required higher doses of LSD to experience the desired subjective effects and that their schizophrenia symptoms did not worsen (Nichols & Walter, 2021). If the results of the present study were to be replicated, it could potentially have implications for the feasibility and safety of, for instance, treatment with low-dose psychedelic-assisted therapy for the negative symptoms of schizophrenia, as proposed by Wolf et al. (2022).

Limitations

This study has several important limitations. The relatively small sample of psychedelic users (n = 100) and the limited subsample of psychedelic users who reported a personal and/or family history of bipolar and/or psychotic disorders (n = 33) may have limited statistical power and the generalizability of the results.

Second, while self-reports are frequently used in both clinical and experimental practice, clinical evaluation is considered the gold standard for the assessment of psychiatric symptoms, particularly psychotic symptoms, as their presence is considered to impair the capacity of judgment. Self-report reliability might also have influenced the variables related to psychiatric history. Some respondents may, for example, have inaccurately reported bipolar disorder as a psychotic disorder, while others may have omitted disorders they did not recognize as psychotic. It is also possible that unfamiliarity with the concepts of first and second-degree relatives may have influenced self-reports of psychiatric history.

Third, all respondents who reported having a first or second-degree relative with psychotic or bipolar disorder were categorized as having a family history, which corresponds to the degree of relatedness that would disqualify an individual from participating in clinical trials with psychedelics. However, the risk of spontaneously developing psychotic symptoms is not identical in individuals with a first-degree relative compared to those with a second-

degree relative with bipolar or psychotic disorders. The categorization used in this study precluded any investigation into possible differences between first and second-degree relatives. The respondents were also not asked to specify the type of bipolar or psychotic disorder for which they had a personal or family history, which precluded exploration of specific disorder interactions with psychedelics.

Fourth, another limitation relates to potentially important factors not controlled for in present study, such as the size of the psychedelic dose, the frequency of use, and the 'set and setting' (i.e., the internal and contextual factors that have been shown to influence responses to a psychedelic) (Gukasyan & Nayak, 2022; Haijen et al., 2018).

There may also be cumulative, or long-term, effects of psychedelic use on the prevalence of psychotic symptoms that were masked by controlling for psychedelic use during the month leading up to T_1.

Fifth, it is possible that some reactions to psychedelics that would not be clinically considered psychotic were registered as such in the present study.

Future directions

Future studies on the relationship between psychedelic use and psychotic symptoms should aim to include larger samples, or oversampling of individuals predisposed to psychotic symptoms, to ensure greater generalizability and enable investigation into any potential specific effects of the psychedelics, while taking the conditions (including the dose size and set and setting) in which they were consumed into consideration. Future research should also aim to investigate any potential differences in interaction between psychedelic use and specific disorders, especially by demarcating between different types of bipolar disorder (e.g., type I, type II) and psychotic disorders (e.g., schizophrenia), while taking the degree genetic predisposition into account (i.e., separating between first-degree and second-degree

relatives). If possible, such studies should strive to include clinical evaluation (or third-party reports) of psychotic symptoms and diagnoses set by medical professionals. It would be particularly important to include measures of mania and typical mania-related psychotic symptoms to test the hypothesis that psychedelic use increases the risk of developing mania in certain populations such as individuals with a personal or family history of bipolar I disorder.

Conclusions

The findings of the present study suggest that the relationship between psychedelic use and psychotic symptoms may be influenced by having a personal or family history of certain disorders marked by psychotic symptomatology. Specifically, the findings suggest that individuals with a personal or family history of bipolar disorder could potentially be at an elevated risk of experiencing increases in psychotic symptoms following psychedelic use. At the same time, the results indicate that psychedelic use could potentially attenuate (or not exert an influence) on psychotic symptoms in individuals with a personal (or family) history of psychotic disorders.

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