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PSYCHEDELIC USE IS ASSOCIATED WITH REDUCED DAILY OPIOID USE AMONG PEOPLE WHO USE ILLICIT DRUGS IN A CANADIAN SETTING

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Abstract

Background—Research into the therapeutic and naturalistic uses of psychedelics for improving outcomes related to mental health disorders has generated increasing interest in recent years. While controlled clinical trials of psychedelics have signaled benefits for treating substance use disorders, this area has not been well studied in the context of naturalistic psychedelic use. This study sought to investigate the possible relationship between recent naturalistic psychedelic use and subsequent daily illicit opioid use among people who use drugs (PWUD).

Methods—Data (2006–2018) were drawn from three harmonized prospective cohorts of community-recruited PWUD in Vancouver, Canada. We used multivariable generalized linear mixed-effects modeling (GLMM) to estimate the independent association between psychedelic use and subsequent daily illicit opioid use.

Results—Among 3813 PWUD at baseline, 1093 (29%) reported daily use of illicit opioids and 229 (6%) reported psychedelic use in the past six months. Over study follow-up after adjusting

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Contributions

EA, MES and KD conceptualized and designed the study. EA, JC, MES and KD analyzed the data. EA wrote the first draft and integrated suggestions from all other authors. All authors made significant contributions to the interpretation of the data and drafting of the manuscript. All authors critically revised the manuscript and approved the final draft.

Declarations of Interest

Drs. Argento, Mackay and Christie are consultants to Numinus Wellness, a Canadian mental health company interested in the use of psychedelics for medical purposes. Numinus Wellness was not involved in the collection of data, the writing of this manuscript, or the decision to submit findings for publication. M-J Milloy is the Canopy Growth professor of cannabis science at the University of British Columbia, a position created by unstructured gifts to the university from Canopy Growth, a licensed producer of cannabis, and the Government of British Columbia's Ministry of Mental Health and Addictions. The University of British Columbia has also received unstructured funding from NG Biomed Ltd to support him.

Appendix. Supplementary material

for a range of potential confounders, psychedelic use remained independently associated with a significantly reduced odds of subsequent daily opioid use (Adjusted Odds Ratio: 0.45; 95% Confidence Interval: 0.29 to 0.70).

Conclusion—While confirmation in other settings is required, these findings align with growing evidence that psychedelic use may be associated with detectable reductions in subsequent substance use including illicit opioid use.

Keywords

Psychedelics; Substance use disorders; Opioid use; Mental health

INTRODUCTION

Opioid use disorder (OUD) is one of the most challenging public health issues, leading to significant morbidity and mortality in North America and other settings. For instance, more Americans died from drug overdoses in 2020 alone than in the entire Vietnam War (Ahmad, Rossen, & Sutton, 2020; National Institute on Drug Abuse, 2020). In Canada and internationally, opioid-related deaths continue to rise due to highly toxic contamination of the illicit drug supply with fentanyl and related analogues (Crabtree, Lostchuck, Chong, Shapiro, & Slaunwhite, 2020; European Monitoring Centre for Drugs & Drug Addiction, 2020). An estimated 2657 people died in Canada of an opioid-related overdose between January and June of 2020: a 54% increase from the same time frame in 2019 (Public Health Agency of Canada, 2020). In the European Union an estimated 8300 people died of drug overdoses in 2018, primarily involving opioids, with the United Kingdom accounting for one third (European Monitoring Centre for Drugs & Drug Addiction, 2020). Further dramatic spikes in overdose deaths have occurred over the course of 2020 alongside and attributable to the challenging conditions created by the COVID-19 pandemic (CBC, 2020; Norton & Kerr, 2020; Volkow, 2020). While some interventions, including opioid agonist therapy (OAT), are proven effective at improving outcomes from OUD, these interventions are not without limitations. For instance, while strategies to improve access to OAT are implemented in most settings, many people with OUD face challenges initiating and sustaining engagement in OAT (Blanco & Volkow, 2019; Socías et al., 2020; Wood, 2018). In addition, OUD is a multidimensional health problem exacerbated by often prevalent intersecting socio-structural exposures – e.g., stigma, psychological trauma, lack of economic opportunity, social disconnection, and criminalization. Thus, innovative strategies are urgently needed to augment existing public health and treatment approaches to mental health and wellbeing.

In recent years, scientific research into naturalistic psychedelic use and the therapeutic potential for addressing substance use disorders has been revivified. Accumulating evidence lends support to “classic” psychedelics in particular, which include the serotoninergic/5-HT2A agonists lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT)/ayahuasca, and mescaline (Bogenschutz et al., 2015; dos Santos & Hallak, 2020; Johnson, Garcia-Romeu, & Griffiths, 2017; Krebs & Johansen, 2012; O’Shaughnessy, Berlowitz, Rodd, Sarnyai, & Quirk, 2021). From a neurobiological perspective, activation of 5-HT2A receptors is believed to increase neural plasticity (Ly et al., 2018; Nichols, 2016), and

neuroimaging research indicates a key influence on specific areas of the brain Carhart-Harris et al. (2012), 2014 collectively thought to be responsible for modulating mood, states of consciousness and potentially anti-addictive, anti-depressive, and anxiolytic effects (dos Santos & Hallak, 2020). Classic psychedelics, when used as adjuncts to psychotherapy, have signaled benefit in early (1950s–1970s) randomized clinical trials (RCTs) for treating alcohol and opioid use disorders (Krebs & Johansen, 2012; Savage & McCabe, 1973), leading to a growing number of recent clinical trials for a range of mental health issues such as treatment-resistant depression, end-of-life anxiety (Agin-Liebes et al., 2020; Carhart-Harris et al., 2016; Davis et al., 2020; Goldberg, Pace, Nicholas, Raison, & Hutson, 2020; Griffiths et al., 2016; Palhano-Fontes et al., 2018; Romeo, Karila, Martelli, & Benyamina, 2020) and alcohol and tobacco use disorders (Bogenschutz et al., 2015; Fuentes, Fonseca, Elices, Farré, & Torrens, 2020; Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014). An ongoing pilot study of psilocybin-assisted psychotherapy has demonstrated similarly promising preliminary results for individuals with cocaine use disorder (Hendricks, 2018b). Of notable importance, psychedelics are known to elicit powerful so-called mystical experiences (characterized by a sense of unity/oneness, transcendence of space and time, sacredness, insight, deeply felt positive mood, and ineffability) and emotional responses such as awe and ego-dissolution, which appear to mediate therapeutic impacts (Bogenschutz et al., 2018; Garcia-Romeu, Griffiths & Johnson, 2014; Griffiths, Richards, McCann, & Jesse, 2006; Hartogsohn, 2018; Hendricks, 2018a; MacLean, Johnson, & Griffiths, 2011; Nour, Evans, Nutt, & Carhart-Harris, 2016).

Outside of formal clinical research settings, observational research examining possible impacts of naturalistic psychedelic use has also pointed to potential long-term beneficial impacts for individuals with substance use disorders (Fábregas et al., 2010; Garcia-Romeu et al., 2019; A. 2020; Pisano et al., 2017; Thomas, Lucas, Capler, Tupper, & Martin, 2013), and related outcomes such as reduced suicidality, psychological distress, recidivism and intimate partner violence (Argento et al., 2017; Hendricks, Clark, Johnson, Fontaine, & Cropsey, 2014, 2015; Krebs & Johansen, 2013; Thiessen, Walsh, Bird, & Lafrance, 2018; Walsh et al., 2016). Pertaining to OUD, in a large population-based study among 44,000 adults in the United States with a history of illicit opioid use, psychedelic use was associated with a 40% reduced risk of past year opioid misuse and 27% reduced risk of past year opioid dependence (Pisano et al., 2017).

Nevertheless, evidence from observational and prospective cohort-based studies that collect detailed information on substance use patterns and psychedelic use remain lacking. Therefore, the present study sought to investigate for a possible independent association between recent classic psychedelic use and subsequent opioid use among people who use drugs (PWUD) in a Canadian setting.

METHODS

This study drew on longitudinal data from three ongoing open prospective cohorts of PWUD in Vancouver, Canada: the Vancouver Injection Drug Users Study (VIDUS), the AIDS Care Cohort to Evaluate exposure to Survival Services (ACCESS), and the At-Risk Youth Study (ARYS). As previously described in detail (Urban Health Research Initiative, 2013),

study participants were recruited via community outreach using snowball sampling and self-referral beginning in 1996 and questions about psychedelic use were added in 2006. VIDUS participants include HIV-negative adults (18 years of age or older) who report any injection drug use in the past month at baseline. ACCESS participants include HIV-positive adults (18 years of age or older) who report any illicit drug use in the past month at baseline. Eligibility criteria for ARYS participants include street-involved youth (14–26 years of age at enrollment) who report any illicit drug use in the past month at baseline. All eligible participants provide written informed consent and the three cohort studies employ harmonized data collection and follow-up processes to allow for combined analyses. Participants complete interviewer-administered questionnaires and provide biosamples for serologic testing for HIV and hepatitis C virus (HCV) and HIV clinical monitoring (as appropriate) at enrollment and bi-annually. The questionnaire elicits information relating to sociodemographic characteristics, substance-use patterns including psychedelic use, engagement with healthcare services and law enforcement, and other social, behavioural and environmental factors. All participants receive an honorarium of $40 CAD at each study visit. Studies hold approval from the University of British Columbia/Providence Health Care Research Ethics Board.

The primary outcome of interest was at least daily use of any illicit opioids (including heroin, fentanyl and nonmedical use of pharmaceutical opioids) in the last six months, as used in previous research when a definitive diagnosis for OUD is unavailable (Bozinoff et al., 2018; Socías et al., 2018). The primary explanatory variable of interest was time-updated use of any classic psychedelics in the last six months. The variable for classic psychedelic use was derived from available data captured in the questionnaire under ‘other drug use’ to capture responses for classic psychedelics and the plants and fungi included in this group of psychoactive compounds: LSD/acid, magic mushrooms/psilocybin, mescaline, San Pedro, peyote, salvia, and DMT/ayahuasca.

All data were self-reported and time-updated at each follow-up using the last six months as the reference, with the exception of time-fixed demographic variables considered at baseline: age (continuous), gender (cis/trans women and ‘other’ vs. cis/trans men), ethnicity (white vs. non-white), and childhood trauma (moderate/severe vs. low/none) as measured by the Childhood Trauma Questionnaire (CTQ): a 28-item validated instrument used to retrospectively assess physical abuse, physical neglect, sexual abuse, emotional abuse, and emotional neglect (Scher, Stein, Asmundson, Mccreary, & Forde, 2001; Walton et al., 2011). Other factors included and treated as time-updated covariates and considered as potential confounders due to their known or a priori hypothesized relationship with both psychedelic use and daily opioid use included: HIV seropositivity, homelessness, incarceration, sex work, experiences of physical or sexual violence, barriers to accessing addiction treatment defined as responding affirmatively to the question “In the last six months did you try to get into any treatment for your drug or alcohol use but were unable?, being currently enrolled in drug treatment (OAT or other drug/alcohol treatment vs. none) and frequent (≥daily vs. <daily) use of non-injection or injection drugs including: cannabis, benzodiazepines, crack, cocaine, methamphetamine, and heavy alcohol use (defined as >14 drinks per week or >4 drinks on one occasion for men and >7 drinks per week or >3 drinks on one occasion for women).

Statistical analyses

The present study utilized available data for participants who were enrolled and completed at least one study visit between January 2006 and December 2018. Initially, descriptive statistics at baseline were calculated for explanatory variables stratified by psychedelic use over the study follow-up period. Differences were assessed using the Wilcoxon rank-sum test for continuous variables and Pearson's chi-square test (or Fisher's exact test for small cell counts) for categorical variables. Bivariate and multivariable relationships between explanatory variables and daily opioid use were examined using generalized linear mixed-effects models (GLMM) with a logit-link function (Fitzmaurcie, Laird, & Ware, 2004). To account for variation and repeated measurements from the same participants over time, random intercepts were applied in the model. The random intercept accounted for unmeasured individual-specific confounding that is fixed over time from individuals who contributed to multiple observations during the study period (Raudenbush & Bryk, 2002). The primary explanatory variable of interest (recent psychedelic use) was recoded so that the value at a given visit reflected the value at the preceding visit (i.e., lagged) to ensure psychedelic use always preceded the outcome of interest. As the lagged variable for psychedelic use required two or more visits, those with only one study visit were excluded from analysis with GLMM, resulting in the exclusion of 11% of data from the bivariate model. Variables significantly associated with the outcome in bivariate analysis were subsequently fitted into a multivariable GLMM confounding model, using a conservative stepwise variable selection approach (Maldonado & Greenland, 1993). The first observation of each participant was removed from the multivariable analysis, as the model included a lagged variable for psychedelic use, and observations with missing responses to the outcome or explanatory variables of interest were excluded from the analysis via listwise deletion. Starting with a full model containing our primary explanatory variable, and covariates that were associated with the outcome in bivariable analyses at p-value <0.10, we constructed reduced models in a stepwise manner, removing the covariate that resulted in the smallest relative coefficient change for the main explanatory variable. This iterative process was continued until the minimum relative change exceeded 5%. The remaining variables were considered as confounders in the multivariable analysis. Unadjusted (OR) and adjusted odds ratios (AOR) and 95% confidence intervals (CI) are reported and all p-values are two-sided. Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between January 2006 and December 2018, 3818 PWUD completed at least one study visit and were considered eligible for these analyses. Of these, 5 participants were removed due to missing data on the primary explanatory variable of interest. The remaining 3813 participants in the study contributed to a total of 34,831 observations over the study period. The median number of follow-up visits was 6 (interquartile range [IQR]: 2 to 15) and the median number of months between study visits was 6.2 (IQR: 5.6 to 7.0). Approximately 84% (n = 3192) completed at least 2 follow-up visits, 74% (n = 2827) completed at least 3 follow-up visits, and 65% (n = 2494) completed at least 4 follow-up visits. Baseline characteristics of participants stratified by psychedelic use are presented in Table 1 (see

Table S1 in the supplementary material for data stratified by ever use of illicit opioids). The median age of the sample at baseline was 32 years (interquartile range: 23–43), 65% (n = 2464) identified as white, and the study included 1307 (34%) cis/trans women and other people who identify as gender minorities. Participants who reported recent psychedelic use at baseline were significantly more likely to be younger, identify as white, have experienced recent homelessness and violence, report daily cannabis use and heavy alcohol use, and significantly less likely to be living with HIV, involved in recent sex work, and report daily opioid or crack use in the last six months (all p-values <0.001). Overall, 6% (n = 229) reported psychedelic use in the last six months at baseline and 35% (n = 1333) reported psychedelic use over the study period (2006–2018). Of those who had used psychedelics at baseline, 140 (61%) participants used LSD, 116 (51%) used psilocybin mushrooms, 7 (3%) used DMT, 3 (1%) used salvia, and 2 (<1%) used mescaline.

At baseline, 29% (n = 1093) of participants reported daily use of illicit opioids in the last six months and 22% (n = 7539) reported daily illicit opioid use at follow-up. Among those who reported daily illicit opioid use at baseline, approximately 92% (n = 1008) injected opioids, 54% (n = 587) used pharmaceutical opioids non-medically, and 54% (n = 593) ever had a prior non-fatal overdose. Table 2 displays potential confounding variables associated with daily illicit opioid use. In bivariate GLMM analysis, factors found to be positively associated with daily opioid use at p<0.001 included: younger age, identifying as a woman, recent homelessness, incarceration, sex work and violence, and experiencing barriers to accessing treatment. Participants who reported using benzodiazepines, crack, cocaine and methamphetamine daily had two and half to over three times increased odds of reporting daily opioid use (p<0.001). Living with HIV, daily cannabis use, heavy alcohol use, and being enrolled in drug treatment in the last six months were associated with significantly reduced odds of daily opioid use (p<0.001). As shown in Table 3, in bivariate analysis psychedelic use was associated with lower odds of subsequent daily illicit opioid use (OR 0.59; 95% Confidence Interval (CI): 0.40–0.87). In the final multivariable confounding model, lagged psychedelic use in the last six months remained independently associated with 55% reduced odds of subsequent daily illicit opioid use (Adjusted Odds Ratio (AOR) 0.45; 95%CI: 0.29–0.70). A sensitivity analysis restricted to participants who have ever used illicit opioids (Table S2 in the supplementary material) demonstrated a similar statistically significant association (AOR 0.58; 95%CI: 0.38–0.86). The full multivariable model with all covariates is displayed in Table S3 in the supplementary material.

DISCUSSION

This study provides data on community-recruited PWUD to elucidate the possible relationship between naturalistic psychedelic use and daily opioid use as a marker for OUD. After adjusting for potential confounders and lagging the primary exposure by six months, psychedelic use remained independently associated with significantly reduced odds of subsequent daily illicit opioid use. To the best of our knowledge, this is the first study to demonstrate that psychedelic use is linked to lower risk of subsequent daily opioid use as demonstrated by a closely followed (i.e., semi-annual follow-up) prospective cohort of PWUD with individual-level data on opioid use and a broad range of potential confounders.

These findings are consistent with previous research and growing literature lending support to the therapeutic potential of psychedelics for addressing mental health and substance use disorders in both clinical and non-clinical settings (dos Santos & Hallak, 2020; Garcia-Romeu et al., 2019; Hendricks, 2014; Kupferschmidt, 2014; Sessa, 2015; Tupper, Wood, Yensen & Johnson, 2015). Population-level studies in the US have demonstrated strong associations between naturalistic psychedelic use and lower rates of opioid, alcohol, cannabis, and stimulant use disorders (Garcia-Romeu et al., 2019; A. 2020; Pisano et al., 2017). In Canada, preliminary observational research among 12 members of a rural Indigenous community found statistically significant and sustained reductions in problematic use of cocaine, alcohol and tobacco (Thomas et al., 2013), with participants describing greatly reduced cravings and use (including complete cessation) alongside increased wellbeing and quality of life following an ayahuasca-based intervention (Argento, Capler, Thomas, Lucas, & Tupper, 2019). Furthermore, historical use of psychedelics among a community-based cohort of marginalized women in a Canadian setting was associated with a substantially reduced hazard of suicidality and had a protective moderating effect on the association between pharmaceutical opioid use and suicide (Argento et al., 2017; Argento, Braschel, Walsh, Socias, & Shannon, 2018).

As noted above, preliminary clinical trials have generated additional encouraging results, indicating potential for lasting benefits after only one or two doses of psychedelics administered in the context of psychotherapy (Bogenschutz et al., 2015; Johnson et al., 2017; Krebs & Johansen, 2012). An early RCT demonstrated efficacy following a single, high-dose of LSD for heroin dependence in the context of a residential treatment program compared to controls (37 completers in each group) at long-term follow-up (Savage & McCabe, 1973). Subsequent systematic review and meta-analysis of RCTs of LSD therapy conclude that LSD is a potentially powerful adjunct to psychotherapy, with the strongest evidence thus far being in the treatment of alcohol use disorder (Fuentes et al., 2020; Krebs & Johansen, 2012). Ketamine-assisted therapy, while not considered a classic psychedelic, has also demonstrated benefit for alcohol, opioid, and cocaine use disorders in recent RCTs (Dakwar et al., 2019; E. 2020; Krupitsky et al., 2002). A recent, albeit small (n = 10), open-label pilot study among participants with DSM-IV alcohol dependence who received one or two psilocybin-assisted sessions in addition to Motivational Enhancement Therapy, found that abstinence rates increased significantly following psilocybin-assisted therapy, and the improvements were mostly retained at 36-weeks follow-up (Bogenschutz et al., 2015). Finally, a research group at Johns Hopkins University demonstrated in an open-label study among 15 participants that two or three moderate-to-high doses of psilocybin, in conjunction with Cognitive Behavioral Therapy, had an outsize impact on tobacco smoking cessation – with abstinence rates of 80% at six-month follow-up and 67% at 12-month follow-up (Johnson et al., 2014, 2017).

In addition to proposed biological mechanisms, the spiritual or mystical components of the psychedelic experience (often referred to and quantified in structured questionnaires as mystical experiences) are thought to play a primary role in mediating therapeutic impacts (Bogenschutz & Johnson, 2016). For example, mystical experiences in psilocybin-assisted sessions were significantly correlated with positive treatment outcomes, with 87% of participants rating their psilocybin experience as among the five most personally meaningful

and spiritually significant experiences of their lives (Garcia-Romeu et al., 2014; Johnson et al., 2017). The meaning-enhancing properties of psychedelic and mystical experiences also appear to have long-lasting impacts on mood, behaviours and overall wellbeing. Study participants have endorsed sustained improvements in life satisfaction, reductions in problematic substance use, and increased belief and motivation in their ability to change (Griffiths et al., 2006, 2011; Hartogsohn, 2018; Hendricks, 2018a; Johnson, Hendricks, Barrett, & Griffiths, 2019; MacLean et al., 2011; Schmid & Liechti, 2018; Thomas et al., 2013). Importantly, classic psychedelics are not known to lead to addiction or dependence, given that almost all of them (with the exception of LSD) do not have direct effects on the dopaminergic system (Nichols, 2016; Stephen Ross, 2012). Collectively, while further research is required, a growing body of evidence suggests psychedelics have the potential to facilitate pro-social behaviors and reduced harm from addictions and other mental health disorders by enhancing one's sense of connectedness to self, others, and spirituality (Argento, Capler, Thomas, Lucas, & Tupper, 2019; Carhart-Harris, Erritzoe, Haijen, Kaelen, & Watts, 2017; Griffiths et al., 2016; S. Ross et al., 2016; Watts, Day, Krzanowski, Nutt & Carhart-Harris, 2017).

Strengths of this study include the large, community-recruited sample of PWUD and prospective design with detailed individual-level participant data. However, there are several notable limitations including the observational nature of the study which precludes inferring causation, and reliance on self-report potentially leading to recall and response biases that may have resulted in unmeasured confounding. Here, self-reported behavioural data among PWUD have generally been shown to be sufficiently reliable and valid (Darke, 1998). Psychedelic use in this study may have been underreported across the cohorts, as use in the last six months was captured in the questionnaire under 'other drug use'. Additionally, we did not have a DSM diagnosis of OUD and were required to use at least daily opioid use as a proxy, though this approach has been used previously (Bozinoff et al., 2018; Socías et al., 2018) and there is little doubt that daily opioid use is often associated with past trauma and ongoing health and social harms (Argento, Chettiar, Nguyen, Montaner & Shannon, 2015; Bozinoff et al., 2018; Cleveland, McGlothen-Bell, Scott, & Recto, 2020; Dasgupta, Beletsky & Ciccarone, 2018; Hassan, Foll, Imtiaz & Rehm, 2017; Lee et al., 2019). Due to complex data collection procedures, our measure for lifetime illicit opioid use in Table S1 may have underestimated the true prevalence of ever using opioids, which may have biased the results towards the null. To address the issue of temporality, we lagged the primary explanatory variable to ensure that psychedelic use was captured prior to the outcome. However, people who use psychedelics may have certain characteristics or personality traits (e.g., openness, spirituality) that may be associated with a reduced likelihood or interest in using opioids, which were not examined in this study. Further, people who use opioids may have certain characteristics that are associated with a reduced interest in using psychedelics. To address this potential bias, a sensitivity analysis was conducted restricting the sample to those who have ever used illicit opioids (Table S2 in the supplementary material). Results from the sensitivity analysis revealed a similar statistically significant association between psychedelic use and subsequent illicit opioid use. Given the high comorbidity with mental health challenges and socio-structural drivers of OUD (e.g., stigma, incarceration, housing instability, social marginalization), psychedelic-assisted psychotherapy should be

considered alongside interventions that address upstream and root causes of substance use disorders. Importantly, the ability to extrapolate findings to other settings and diverse populations has been limited by a largely white and male-dominant psychedelic research landscape and it is noteworthy that this study included 1307 (34%) cis/trans women and other people who identify as gender minorities (trans/two-spirit), as well as 1324 (35%) non-white participants, including 1176 (31%) who identified as Indigenous. Nevertheless, there remains a critical need to prioritize gender and ethnic diversity to address inequities in health and access to psychedelic research and future care (George, Michaels, Sevelius & Williams, 2020; Michaels, Purdon, Collins & Williams, 2018; Williams & Labate, 2020).

CONCLUSION

This study found naturalistic psychedelic use to be independently associated with a significantly reduced odds of subsequent daily illicit opioid use among a community-based sample of PWUD. More research with controlled trials and longer-term follow-up is required to elucidate the therapeutic potential of psychedelics to augment existing interventions for substance use disorders, including among more diverse populations. Additional qualitative studies would also provide opportunities to improve understanding of the possible psycho-social mechanisms underpinning psychedelic experiences. While confirmation in other settings is required, these findings align with growing evidence that classic psychedelic use may be associated with detectable reductions in subsequent substance use including illicit opioid use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

Datasets are not publicly available. Anonymized data may be made available on request subject to the UBC/Providence Health Ethical Review Board and consistent with our funding body guidelines (NIH and CIHR).

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Highlights

- Recent psychedelic use was associated with 55% reduced odds of daily opioid use.
- This is the first longitudinal study to link psychedelic use with lower daily opioid use.
- More studies are needed to elucidate the therapeutic potential of psychedelics.

Table 1.

Baseline characteristics of 3813 people who use drugs in Vancouver, Canada, stratified by classic psychedelic use in the last six months.

Characteristic	Classic psychedelic use		
	Yes N = 229(%)	No N = 3584(%)	p-value
Age (median, IQR)	21 (19 to 23)	33 (23 to 44)	<0.001
Gender (cis/trans women & 'other')	72 (31.4)	1235 (34.5)	0.373
White	175 (76.4)	2289 (63.9)	<0.001
HIV seropositive[a]	5 (2.2)	928 (25.9)	<0.001
Childhood trauma	154 (67.3)	2323 (64.8)	1
Education, high school or greater	96 (41.9)	1615 (45.1)	0.271
Homelessness[a]	146 (63.8)	1803 (50.3)	<0.001
Incarceration[a]	32 (14.0)	602 (16.8)	0.286
Sex work[a]	12 (5.2)	479 (13.4)	<0.001
Violence[a]	113 (49.3)	1078 (30.1)	<0.001
Daily opioid use[a]	27 (11.8)	1067 (29.8)	<0.001
Daily cannabis use[a]	151 (65.9)	1086 (30.3)	<0.001
Daily benzodiazepine use[a]	0 (0.0)	10 (0.3)	1[*]
Daily crack use[a]	14 (6.1)	972 (27.1)	<0.001
Daily cocaine use[a]	8 (3.5)	248 (6.9)	0.062
Daily methamphetamine use[a]	30 (13.1)	443 (12.4)	0.777
Heavy alcohol use[a]	121 (52.8)	701 (19.6)	<0.001
Barriers to accessing treatment[a]	15 (6.6)	301 (8.4)	0.379
Enrolled in drug treatment[a]			
Opioid agonist therapy	7 (3.1)	1125 (31.4)	
Other drug/alcohol treatment	42 (18.3)	566 (15.8)	
None	180 (78.6)	1861 (51.9)	<0.001

[a] In the last six months.

[*] Fisher's exact test.

Table 2.

Bivariate generalized linear mixed modeling (GLMM) analysis of factors associated with at least daily opioid use among 3813 people who use drugs in Vancouver, Canada, 2006–2018.

Characteristic	Unadjusted Odds Ratio (95% CI)	p-value
Age (per year older)	0.97 (0.96 to 0.98)	<0.001
Gender (women/other vs. men)	2.02 (1.62 to 2.51)	<0.001
White	1.02 (0.82 to 1.26)	0.893
HIV seropositive[a]	0.38 (0.30 to 0.47)	<0.001
Childhood trauma	1.28 (1.00 to 1.63)	0.049
Education, high school or greater	0.97 (0.78 to 1.19)	0.746
Homelessness[a]	2.29 (2.10 to 2.51)	<0.001
Incarceration[a]	2.05 (1.82 to 2.31)	<0.001
Sex work[a]	2.70 (2.32 to 3.14)	<0.001
Violence[a]	1.47 (1.33 to 1.62)	<0.001
Daily cannabis use[a]	0.72 (0.65 to 0.81)	<0.001
Daily benzodiazepine use[a]	3.13 (1.86 to 5.25)	<0.001
Daily crack use[a]	2.75 (2.48 to 3.04)	<0.001
Daily cocaine use[a]	2.59 (2.22 to 3.02)	<0.001
Daily methamphetamine use[a]	3.25 (2.82 to 3.74)	<0.001
Heavy alcohol use[a]	0.70 (0.61 to 0.80)	<0.001
Barriers to accessing treatment[a]	1.83 (1.57 to 2.13)	<0.001
Enrolled in drug treatment[a]		
Opioid agonist therapy (vs. none)	0.44 (0.40 to 0.49)	<0.001
Other drug/alcohol treatment (vs. none)	0.47 (0.41 to 0.54)	<0.001

[a]In the last six months.

Table 3.

Bivariate and multivariable generalized linear mixed modeling (GLMM) analyses for the association between classic psychedelic use and daily illicit opioid use among people who use drugs in Vancouver, Canada (2006–2018).

Classic psychedelic use[†]	Unadjusted Odds Ratio (95%CI)	p-value	Adjusted Odds Ratio (95%CI)	p-value
	0.59 (0.40 to 0.87)	0.007	0.45 (0.29 to 0.70) [*]	<0.001

[†]Responses lagged to prior visit.

[*]Adjusted for age, HIV, childhood trauma, homelessness, daily cannabis use, daily stimulant use, and enrolled in opioid and other drug treatment; time-updated to refer to the last six months.