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The association of psychedelic use and opioid use disorders among illicit users in the United States

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Vincent D Pisano[1,2], Nathaniel P Putnam[3], Hannah M Kramer[4], Kevin J Franciotti[5], John H Halpern[6,7] and Selma C Holden[8,9]

Abstract

Background: Preliminary studies show psychedelic compounds administered with psychotherapy are potentially effective and durable substance misuse interventions. However, little is known about the association between psychedelic use and substance misuse in the general population. This study investigated the association between psychedelic use and past year opioid use disorders within illicit opioid users.

Methods: While controlling for socio-demographic covariates and the use of other substances, the relationship between classic psychedelic use and past year opioid use disorders was analyzed within 44,000 illicit opioid users who completed the National Survey on Drug Use and Health from 2008 to 2013.

Results: Among respondents with a history of illicit opioid use, psychedelic drug use is associated with 27% reduced risk of past year opioid dependence (weighted risk ratio = 0.73 (0.60–0.89) $p = 0.002$) and 40% reduced risk of past year opioid abuse (weighted risk ratio = 0.60 (0.41–0.86) $p = 0.006$). Other than marijuana use, which was associated with 55% reduced risk of past year opioid abuse (weighted risk ratio = 0.45 (0.30–0.66) $p < 0.001$), no other illicit drug was associated with reduced risk of past year opioid dependence or abuse.

Conclusion: Experience with psychedelic drugs is associated with decreased risk of opioid abuse and dependence. Conversely, other illicit drug use history is largely associated with increased risk of opioid abuse and dependence. These findings suggest that psychedelics are associated with positive psychological characteristics and are consistent with prior reports suggesting efficacy in treatment of substance use disorders.

Keywords
Abuse, dependence, heroin, opioid, psychedelics

Introduction

Abuse of prescription and illicit opioids is an ongoing problem within the United States: nearly one in five adults aged 19–30 years have used opioids illicitly and rates of opioid abuse more than doubled between 1991 and 2001 (Johnston et al., 2008; McCabe et al., 2008). Opiate dependence substantially impacts quality of life and is associated with increased unemployment, crime, legal issues, comorbid health issues and mortality (Haug et al., 2005). These issues are compounded over time, as opioid dependence often has a long and chronic course (van den Brink and Haasen, 2006). Unlike other recreational substances, illicit opioid use likely stems from overprescribing of pain medications by the medical community: about 60% of illicit prescription pain killer (PPK) users reported receiving the drug from one doctor or for free from friends or family who received the drug from one doctor. Less than 6% reported a dealer or stranger and only about 4% reported their source as multiple doctors (United States Department of Health and Human Services, 2014). Recently, a number of strategies to reduce illicit prescription opioid use were implemented, including registration of controlled substance handlers, production quotas, record keeping and security requirements (Zacny et al., 2003). However, these strategies may have unintended consequences: an anonymous survey of over 15,000 opioid dependent patients showed that use of only prescription opioids fell from about 70% to 50% between 2010 and 2014, but concurrent use of prescription opioids with heroin, as well as heroin use alone, effectively doubled from 2008 to 2014 (Dart et al., 2015). Analysis of the National Survey of Drug Use and Health (NSDUH) from 2007 to 2013 also showed a similar increase in heroin users, from 373,000 to 681,000 (United States Department of Health and Human Services, 2014).

Despite advances in pharmacology and drug discovery, the maintenance model treatment approach for opioid dependence

[1]Laboratory for Integrative Psychiatry, McLean Hospital, Belmont, USA
[2]Touro College of Osteopathic Medicine, New York, USA
[3]School of Social Work, Boston University, Boston, USA
[4]Multidisciplinary Association of Psychedelic Studies, Santa Cruz, USA
[5]The New School for Social Research, New York, USA
[6]The Boston Center for Addiction Treatment, , A Recovery Center of America Company, Danvers, USA
[7]Harvard Medical School, Laboratory for Integrative Psychiatry, Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, USA
[8]University of New England, School of Osteopathic Medicine, Beth Israel Deaconess Medical Center, Boston, USA
[9]Beth Israel Deaconess Medical Center, Boston, USA

Corresponding author:
Vincent Pisano, Touro College of Osteopathic Medicine, 230 W 125th St, New York, NY 10027, USA.
Email: vpisano@student.touro.edu

has remained conceptually static for almost a half century. Meta-analysis of methadone, the gold standard for pharmacological maintenance, compared with non-pharmacological interventions for opioid dependence found methadone to significantly decrease heroin use and increase treatment retention (Mattick et al., 2009). Due to methadone's side effects and potential for abuse and overdose, patients are often required to travel to a clinic every 24 hours for single doses (Ballantyne and Mao, 2003). Naltrexone demonstrated no significant difference when compared with no pharmacological intervention on all three primary outcomes in a large Cochrane meta-analysis (Minozzi et al., 2011). Finally, buprenorphine has a better safety profile than methadone due to its decreased potential for respiratory depression (Wedham et al., 2007). A meta-analysis of over 5000 subjects in 31 trials found all buprenorphine dosages to significantly increase retention compared with placebo, but only doses of 16 mg or greater were effective in suppressing illicit opioid use (Mattick et al., 2014). The ineffectiveness of these treatment methods was validated in a large, multisite clinical trial that found that 47% of methadone or buprenorphine subjects were still using five years later (Hser et al., 2016). Psychosocial interventions alone are also ineffective; however, the addition of any psychosocial treatment compared with pharmacological maintenance alone is superior in terms of retention and reduced opiate use (Amato et al., 2011). Despite interaction with the dysregulated opioid system, treatment approaches based on the maintenance model have thus far been insufficient.

In addition to the opioid system, serotonin system dysregulation is also evident in opioid use disorders. Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, have shown some evidence in the treatment of physical pain with or without depression, diabetic neuropathy and other pain syndromes (Jann and Slade, 2007). Reports of SNRI use as opioid misuse interventions are lacking, although one study found that venlafaxine attenuated morphine dependence and withdrawal in rats (Lu et al., 2001). The use of psychedelic compounds, which interact primarily with serotonin 5-HT_{2A} receptors, in treating substance use disorders is an area of active investigation, although use in opioid treatment has been minimal. A meta-analysis of 31 studies with over 1,100 alcohol dependent subjects demonstrated improvement in 75% of the lysergic acid diethylamide (LSD) treatment group compared with 44% of the control group at 10 month follow-up (Abuzzahab and Anderson, 1971). A pilot study of dipropyltryptamine for alcohol dependence found 92% of 51 participants had significant clinical improvement at six month follow-up (Grof et al., 1973). More recently, a proof-of-concept study using psilocybin to treat 10 individuals with alcohol dependence found significantly decreased drinking was largely retained through the nine month follow-up (Bogenschutz et al., 2015). A pilot study of psilocybin for smoking cessation reported that 80% of 15 nicotine dependent subjects maintained biologically confirmed abstinence at six month follow-up (Johnson et al., 2014). In an observational study, 11 participants of an addiction and stress retreat receiving ayahuasca reported decreases in alcohol, cocaine and tobacco use and significant improvements in mindfulness, empowerment, hopefulness, quality of life-meaning and quality of life-outlook measurements over a six month period (Thomas et al., 2013). A retrospective study of American members of the Santo Daime Church who attended weekly ayahuasca ceremonies found that 22 of 24 respondents with substance abuse or dependence histories were in full remission (Halpern et al., 2008). Savage and McCabe conducted one of the few trials of LSD therapy in 74 narcotics addicts. Compared with outpatients receiving general therapy, about three times as many residential LSD treatment subjects were abstinent at six and 12 months (Savage and McCabe, 1973). The use of psychedelic-assisted therapy for opioid dependence could expand clinical treatment options beyond the simple maintenance model.

Research into psychedelics as substance misuse interventions is currently limited by the lack of multi-center clinical trials: most, if not all, reported studies have sample sizes restricted to individuals from local communities. An investigation using a broader, nationally representative sample can give initial insight into the association of psychedelics and risk of opioid use disorders. To date, there are few population studies examining psychedelic use and mental health. Hendricks et al. found hallucinogen use was associated with reduced recidivism among 25,000 subjects with substance abuse history under community corrections supervision (Hendricks et al., 2014). Also using the NSDUH, Hendricks et al. found that classic psychedelic use was associated with decreased odds of past month psychological distress, past year suicidality, suicidal planning and suicide attempt (Hendricks et al., 2015).

The purpose of the present study was to explore the relationship between psychedelic use history and opioid use disorders within the general population of illicit users in the United States. Given positive results in preliminary studies of psychedelic therapy for substance use disorders and previous population studies indicating positive psychological effects, we hypothesized that a history of classic psychedelic use would be associated with decreased risk of past year opioid abuse and dependence. A secondary analysis was performed to explore whether individual DSM-IV dependence criteria were influenced by psychedelic drug use.

Methods

The NSDUH is an annual, in person interview conducted to gain information on alcohol, tobacco, illicit and prescription drug use and mental health. Non-institutionalized civilians 12 years or older are selected from a sample of households and compensated US$30. An interviewer visits each household and administers the computer survey. The current dataset was drawn from six years of the NSDUH (2008–2013) that reported consistent variables (United States Department of Health and Human Services, 2009, 2010, 2011, 2012, 2013, 2014). Additional information on survey methodology, design and weights is available at the NSDUH homepage (https://nsduhweb.rti.org/respweb/homepage.cfm). The survey was conducted by RTI International, Research Triangle Park, North Carolina and approved by their institutional review board. The current analysis was approved by the Beth Israel Deaconess Medical Center IRB.

Data analysis

NSDUH data from 2008 to 2013 was appended into one dataset and a subpopulation of individuals 18 or older who had used illicit opioids was defined. A new variable was created to denote a history of classical psychedelic use: LIFEHAL. Respondents who indicated they had ever used LSD, mescaline, psilocybin, peyote, San Pedro cactus, N,N-dimethyltryptamine/N,N-diethyltryptamine or ayahuasca were coded as positive for classic psychedelic use history, and all other respondents as negative. Variables for use of 3,4-methylenedioxymethamphetamine (MDMA), designer psychedelic tryptamines or phenethylamines, *Salvia divinorum* or dissociative psychedelics such as ketamine or ibogaine were not included in the classic psychedelic definition. Most of these excluded substances have different psychoactive mechanisms compared with classic hallucinogens or suspect authenticity on the illicit market: a recent survey of New York young adults endorsing MDMA use found only 50% of hair samples contained MDMA (Palamar et al., 2016).

Observations were limited to adults that reported lifetime use of recreational pain killers (variable ANLFLAG != 0) or lifetime heroin use (HERFLAG != 0). Primary outcome variables included meeting criteria for past year PPK abuse (ABUSEANL = 1) or heroin abuse (ABUSEHER = 1), and meeting criteria for past year PPK dependence (DEPENDANL = 1) or heroin dependence (DEPNDHER = 1). Abuse and dependence variables were defined based on the criteria listed in the DSM-IV. Respondents were coded positive for substance abuse if they did not meet dependence criteria and endorsed at least one of the following: substance related dangerous situations, issues at work, school, home, or issues with family, friends or the law.

The NSDUH's 10 dependence criteria were also analyzed for associations with psychedelic use. Variables included 'spent time getting/using substance,' 'spent time getting over effects' and 'less activities due to substance use,' 'unable to keep limits' and 'unable to cut down/stop,' 'using same amount has less effect' and 'needing to use more for same effect,' 'continued use despite emotional issues,' 'continued use despite physical issues' and 'three or more withdrawal symptoms.' NSDUH respondents endorsing at least three criteria were coded positive for substance dependence.

Multivariate logistic regression was used to test the association between psychedelic use and outcome variables while controlling for demographic factors and use of other illicit substances. Control variables included age in years (18–25, 26–34, 35–49, 50–64, 65 or older), race (non-Hispanic White, non-Hispanic African American, non-Hispanic Native American, non-Hispanic Native Hawaiian/Pacific Islander, non-Hispanic Asian, non-Hispanic more than one race and Hispanic), education (less than high school, high school graduate, some college or college graduate), income (less than US$20,000–US$49,999, US$50,000–US$74,999, US$75,000 or more), sex (male or female), marital status (married, widowed, divorced/separated, never married) and self-reported engagement in risky behavior (like to test yourself by doing risky things: never, seldom, sometimes or always) as well as use of marijuana, stimulants, tranquilizers, inhalants, ecstasy, phencyclidine, sedatives and cocaine. All analyses were conducted in Stata 14 using the svyset command to account for the complex study design, sampling weights and pooling of data from multiple survey years as recommended by the Substance Abuse and Mental Health Services Administration: http://samhda-faqs.blogspot.com/.

Results

Of 228,556 adult respondents, 44,678 (15.0% weighted) reported illicit pain killer or heroin use, of which 18,517 (44.7% weighted) reported history of classic psychedelic use. The demographic and lifetime substance use data for the illicit opioid use population is presented in Table 1. Rao–Scott chi-square tests were used to test the association between psychedelic use, demographic, and lifetime substance use variables. Classic psychedelic use was concentrated in Whites, males and those more likely to engage in risky behaviors. Additionally, the majority of psychedelic users had also used marijuana or cocaine, both of which were control variables in the logistic regression model. Of respondents with a history of opioid use, 630 met past year abuse criteria (1.2% weighted), and 2,571 met past year dependence criteria (4.3% weighted). Table 2 presents the rates of past year opioid abuse and dependence and psychedelic use by compound.

Figure 1 shows the results of multivariate logistic regression models predicting risk of past year opioid dependence within respondents with illicit use history. Psychedelic use was associated with reduced risk of past year opioid dependence (weighted risk ratio (RR) = 0.73 (0.60–0.89) p = 0.002). No other substances were associated with decreased risk of meeting past year opioid dependence criteria. History of psychedelic use had a similar effect size on dependence as education (weighted RR = 0.71), both of which were larger than age (weighted RR = 0.85) and income (weighted RR = 0.91). Figure 2 displays the results of multivariate logistic regression models analyzing risk of past year opioid abuse within respondents with illicit use history. Psychedelic use was associated with reduced risk of past year opioid abuse (weighted RR = 0.60 (0.41–0.86) p = 0.006). Marijuana use was also associated with reduced risk of past year opioid abuse (weighted RR = 0.45 (0.30–0.66) $p < 0.001$). Other than psychedelics and marijuana, use of no other substances demonstrated reduced risk of meeting past year abuse criteria. History of psychedelic use had a slightly larger effect size on abuse than education (weighted RR = 0.66), both of which were larger than income (weighted RR = 0.81). Age was not associated with a significant change in risk of past year opioid abuse.

Table 3 shows the rate at which each dependence criterion was endorsed by the illicit opioid use population, as well as multivariate logistic regression results of psychedelic use on risk of each criterion. In both psychedelic user and nonuser populations the most endorsed criteria were 'spent time getting or using,' 'inability to keep limits,' 'inability to cut down,' 'needing to use more' and 'three or more withdrawal symptoms.' Psychedelic use was associated with significantly reduced risk of reporting seven out of the 10 dependence criteria, with risk ratios ranging from 0.65 to 0.78. There was no association with 'continued use despite physical issues,' 'spent time getting over effects' or 'usual use has less effect.'

Discussion

Among respondents with a history of illicit opioid use, psychedelic use is associated with 27% reduced risk of past year opioid dependence (weighted RR = 0.73 (0.60–0.89) p = 0.002). In the same illicit opioid population, psychedelic use is associated with 40% reduced risk of past year opioid abuse (weighted RR = 0.60 (0.41–0.86) p = 0.006). These results are largely consistent with our hypothesis that psychedelic drug use would be associated with reduced opioid misuse.

Other than psychedelics and marijuana, almost all other drug use was associated with increased risk of opioid abuse and

Table 1. Demographics and lifetime substance use data for illicit opioid users.

	NSDUH variable:	Psychedelic use history:	Yes	No	*p* value
Age	CATAG6				<0.001
18–25			19.1	26.0	
26–34			26.0	23.1	
35–49			29.3	28.8	
50–64			24.5	16.9	
65+			1.1	5.2	
Gender	IRSEX				<0.001
Male			65.6	49.3	
Female			34.4	50.7	
Race	NEWRACE2				<0.001
Non-Hispanic White			84.1	66.4	
Non-Hispanic African American			3.6	13.2	
Non-Hispanic Native American			0.8	0.6	
Non-Hispanic Native Hawaiian/Pacific Islander			0.2	0.5	
Non-Hispanic Asian			1.1	2.7	
Non-Hispanic more than one race			1.9	1.5	
Hispanic			8.4	15.3	
Education	EDUCCAT2				<0.001
Less than high school			13.2	15.9	
High school graduate			30.2	31.0	
Some college			31.3	29.6	
College graduate			25.4	23.5	
Income	INCOME				0.005
<US$20,000			20.1	21.7	
US$20,000–US$49,999			32.7	33.8	
US$50,000–US$74,999			17.1	16.5	
>US$75,000			30.1	28.0	
Marital status	IRMARIT				<0.001
Married			39.1	42.7	
Widowed			1.8	2.2	
Divorced or separated			17.8	14.5	
Never married			41.3	40.6	
Like to test yourself by doing risky things	RKFQRSKY				<0.001
Never			21.6	36.8	
Seldom			44.8	40.0	
Sometimes			29.8	20.8	
Always			3.8	2.4	
Lifetime illicit substance use					
Lifetime marijuana use	MRJFLAG		98.7	66.7	<0.001
Lifetime stimulant use	STMFLAG		50.9	14.5	<0.001
Lifetime tranquilizer use	TRQFLAG		61.9	28.1	<0.001
Lifetime inhalant use	INHFLAG		50.9	12.3	<0.001
Lifetime MDMA/ecstasy use	ESCFLAG		47.1	9.8	<0.001
Lifetime PCP use	PCPFLAG		23.0	1.2	<0.001
Lifetime sedative use	SEDFLAG		25.2	5.4	<0.001
Lifetime cocaine use	COCFLAG		81.9	22.8	<0.001

Data presented as weighted percentages rounded to 0.1%. Rao–Scott chi-square was used to determine the significance of different characteristics on psychedelic use. *N* = 44,678. NSDUH: National Survey of Drug Use and Health; MDMA: 3, 4-methylenedioxymethamphetamine; PCP: phencyclidine.

dependence. History of marijuana use was associated with 55% reduced risk of past year opioid abuse (weighted RR = 0.45 (0.30–0.66) $p < 0.001$) but did not significantly correlate with past year opioid dependence. Still, marijuana has been shown to decrease pain: vaporizing marijuana significantly decreased pain by 27% in 21 morphine or oxycodone chronic pain patients (Abrams et al., 2011). Additionally, between 1999 and 2010, states with medical marijuana laws had 24.8% lower opioid overdose mortality

Table 2. Rates of abuse and dependence and psychedelic use by compound.

History of opioid use population:	NSDUH variable	*N* = 44,678	Weighted %
Abuse	ABUSEANL/HER	630	1.2
Dependence	DEPNDANL/HER	2571	4.3
LSD	LSDFLAG	12,641	34.9
Psilocybin	PSILCY2	15,038	33.6
DMT/DET	HALNEW 616	420	0.7
Mescaline	MESC2	3338	12.9
Peyote/San Pedro	PEYOTE2 or HALNEW 6077	2488	8.8
Ayahuasca	HALNEW 6103	15	0.0
Any psychedelic use	(Any of the above)	18,517	44.7

Weighted percentages rounded to nearest 0.1%. Rao–Scott chi-square used to assess relationship between first using opioids or psychedelics. NSDUH: National Survey of Drug Use and Health; LSD: lysergic acid diethylamide; DMT: N,N-dimethyltryptamine; DET: N,N-diethyltryptamine.

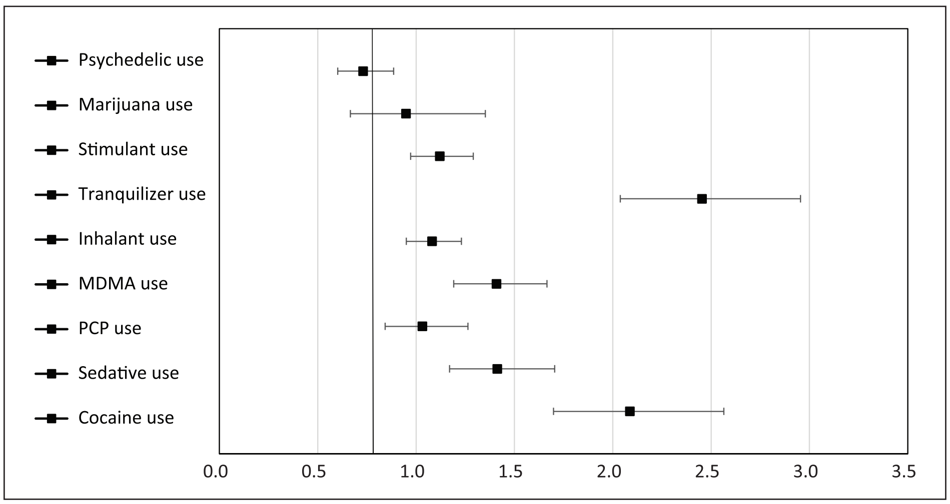

Figure 1. Logistic regression results of substance use history and meeting opioid dependence criteria in the past year. Squares are weighted risk ratio point estimates and error bars are 95% confidence intervals. N = 44,678 respondents. Control variables include age, race, education, income, sex, marital status, risky behavior and history of other illicit drug use. MDMA: 3,4-methylenedioxymethamphetamine; PCP: phencyclidine.

compared with states without medical laws (Bachhuber et al., 2014). The mechanism by which marijuana decreases opioid use likely involves its activity at kappa and delta opioid receptors, whereas psychedelic effects result from activity at 5-HT receptors, notably 5-HT_{2A} (Nichols, 2004; Pugh et al., 1996).

History of psychedelic use was associated with reduced risk of endorsing seven of NSDUH's 10 dependence criteria. The relative risk of endorsing each criterion decreased between 22% and 35% with psychedelic use (RR from 0.78 to 0.65). This secondary analysis was conducted to explore the areas psychedelic and opioid use are associated with. However, psychedelic use was associated with reduced risk of all dependence criteria that had large sample sizes. The three least endorsed criteria, 'time spent getting over effects,' 'using same amount has less effect' and 'continuing to use despite physical problems,' were all not significantly associated with psychedelic use.

Positive effects of psychedelic use outside of a structured therapy setting contrasts the conventional belief that recreational use is associated with negative outcomes. Psychotherapy and interpersonal support are considered integral to the clinical use of psychedelics (Johnson et al., 2008). However, the association with decreased abuse and dependence exists despite uncontrolled settings and psychedelics of unknown dose and purity. Psychedelics may induce psychosis in a small population of susceptible individuals (Savage et al., 1964), and, given the high comorbidity of substance use disorders and psychotic symptoms, it is likely this subgroup detracts from observed improvements. The lack of a concrete mechanism raises safety concerns, especially in regard to vulnerable populations. In recent studies using psychedelics in therapeutic settings, negative psychological effects are rare due to the tightly controlled inclusion criteria and extensive interpersonal support for subjects (Bogenschutz et al., 2015; Gasser et al., 2015; Grob et al., 2011; Johnson et al., 2014; Mithoefer et al., 2011; Oehen et al., 2013). The few cases of adverse effects were resolved with subsiding drug action, and no participants reported long-term negative psychological effects.

After psychedelic use there is evidence of an 'afterglow' period of several weeks characterized by improved mood, energy and freedom from past guilt and anxiety (Halpern, 1996). This 'afterglow' is likely the result of rapid downregulation and

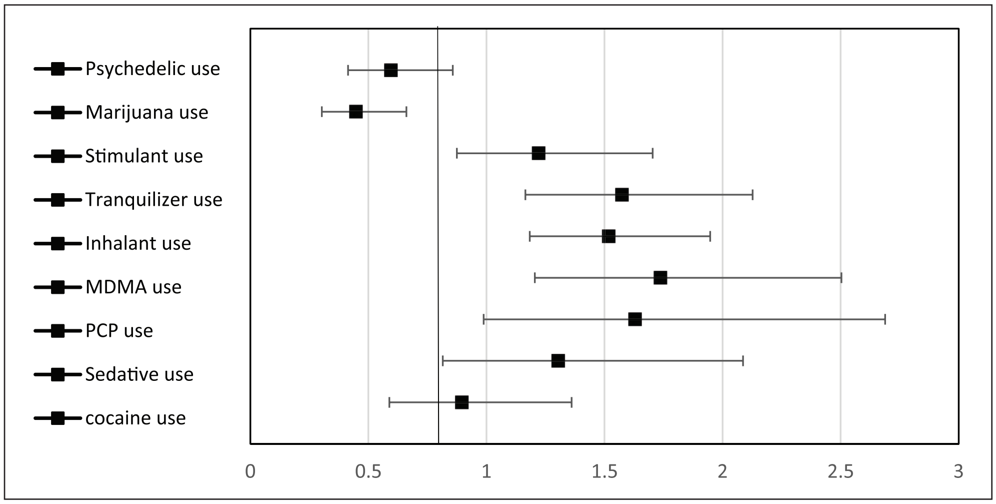

Figure 2. Logistic regression results of substance use history and meeting opioid abuse criteria in the past year. Squares are weighted risk ratio point estimates and error bars are 95% confidence intervals. N = 44,678 respondents. Control variables include age, race, education, income, sex, marital status, risky behavior and history of other illicit drug use. MDMA: 3,4-methylenedioxymethamphetamine; PCP: phencyclidine.

Table 3. Logistic regression results of classic psychedelic use and endorsement of opioid dependence criteria.

Dependence criteria	NSDUH variable	Psychedelic nonusers	%	Psychedelic users	%	Weighted RR	95% CI	*p*
Spent time getting/using	ANL/HERLOTTM	1476	2.6	1854	3.0	0.66	0.55–0.81	<0.001
Spent time getting over effects	ANL/HERGTOVR	154	0.3	129	0.3	0.65	0.38–1.09	NS
Less activities due to use	ANL/HERLSACT	688	1.2	953	1.7	0.66	0.53–0.83	<0.001
Unable to keep limits	ANL/HERKPLMT	2024	3.6	1484	2.7	0.74	0.63–0.88	0.001
Unable to cut down/stop	ANL/HERCUTEV	2724	4.3	2006	3.3	0.74	0.64–0.85	<0.001
Using same amount has less effect	ANL/HERLESFX	499	1.0	441	0.9	0.84	0.62–1.13	NS
Need to use more for same effect	ANL/HERNDMOR	1426	2.2	1977	3.2	0.78	0.65–0.94	0.010
Continued use despite emotional issues	ANL/HEREMCTD	625	1.0	966	1.8	0.71	0.58–0.85	0.001
Continued use despite physical issues	ANL/HERPHCTD	81	0.1	107	0.2	1.28	0.72–2.25	NS
3+ withdrawal symptoms	ANL/HERWDSMT	928	1.5	1263	2.2	0.74	0.60–0.92	0.007
Past year dependence	DEPNDANL/HER	1039	1.7	1532	2.6	0.73	0.60–0.89	0.002

Weighted percentages of the whole opioid use population rounded to the nearest 0.1%. *N* = 44,678 lifetime heroin or illicit prescription pain killer users. Control variables include age, race, education, income, sex, marital status, risky behavior and history of other illicit drug use. NSDUH: National Survey of Drug Use and Health; RR: risk ratio; CI: confidence interval; NS: not significant.

desensitization of 5-HT_{2A} receptors induced by psychedelics. This effect has been demonstrated in rats given repeated doses of LSD, psilocybin and 2,5-dimethoxy-4-methylamphetamine (DOM) (Buckholtz et al., 1985, 1990; Leysen et al., 1989). Opioid use causes increased 5-HT in several brain regions including the dorsal striatum, diencephalon, medial prefrontal cortex and ventral hippocampus, and polymorphisms of the HTR2A gene are associated with heroin dependence (Muller, 2015). Frontolimbic 5-HT_{2A} receptor binding positively correlates with exaggerated stress response and increased anxiety (Frokjaer, 2008). Since anxiety and stress play key roles in drug use relapse, downregulation of 5-HT_{2A} receptors may play a role in reducing stress-induced relapse to opioid use (Ross, 2012; Sinha and Li, 2007). Additionally, serotonin modulates pain perception and nociceptive processing at multiple levels in the peripheral and central nervous systems, although the role of 5-HT on nociceptive processing is not fully understood and varies based on receptor subtype (Berger et al., 2009). 5-HT_{2A} receptor agonist DOM enhanced anti-nociceptive effects of morphine and showed modest anti-nociceptive effects when administered alone in nonhuman primates (Li et al., 2011). Intrathecal administration of 2,5-dimethoxy-4-iodoamphetamine also reversed thermal hyperalgesia in a rat model of spinal nerve ligation (Obata, 2001).

When used in a clinical setting serotonergic psychedelics may enable reduced opioid use by a two phase mechanism. During the psychotherapy session, freedom from self and enhanced insight may allow for reflection and metamorphosis of personality traits, leading to initial drug abstinence (Nour et al., 2016). This process may be facilitated by the potentially anti-nociceptive activity of psychedelics at 5-HT_{2A} receptors. Following the psychedelic-assisted therapy session, downregulated 5-HT_{2A} receptors could help patients avoid stress-related relapse and maintain substance use goals set during the psychotherapy session.

There are several limitations to this analysis. All data on the NSDUH survey is self-reported and thus subject to the respondents' memory and truthfulness, resulting in potential misreporting. Additionally, the NSDUH target population consists of non-institutionalized civilians and does not include data from individuals on active military duty or residing in nursing homes, hospitals, treatment centers or prisons. The exclusion of these populations may impact reporting of less common drugs such as heroin. Other underlying factors, not captured by the NSDUH, could be responsible for decreased PPK and heroin use. Individuals who choose to use psychedelics may be more spiritual or autognostic than non-users, indicating a drive for self-growth. Psychedelic users often report greater mysticism and spirituality (Lerner and Lyvers, 2006), factors that are associated with decreased suicide attempts and suicidal ideation in large population studies (Rasic et al., 2011). A major limitation is the NSDUH's cross-sectional design, which prohibits drawing concrete causal inferences.

Despite these limitations, this study is the first to analyze the association between classic psychedelic use history and opioid abuse and dependence within a large population of illicit opioid users. Although the use of cross-sectional data restricts inferring psychedelic use directly decreases opioid misuse, the associations are pervasive and significant. This analysis contributes to the growing body of evidence suggesting psychedelic drug use is correlated with positive psychological characteristics and may be effective in treatment of substance use disorders.

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