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Lifetime use of MDMA/ecstasy and psilocybin is associated with reduced odds of major depressive episodes

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Abstract

Background: Depression is a major mental health issue worldwide, with high rates of chronicity and non-recovery associated with the condition. Existing treatments such as antidepressant medication and psychological treatments have modest effectiveness, suggesting the need for alternative interventions.

Aim: The aim of this study was to examine the relationships between MDMA (3,4-methylenedioxymethamphetamine)/ecstasy and psilocybin use and major depressive episodes (MDEs).

Methods: This observational study used data from a large ($N = 213{,}437$) nationally representative sample of US adults to test the association of lifetime use of MDMA/ecstasy, psilocybin and other classic psychedelics (lysergic acid diethylamide (LSD), peyote, mescaline), other illegal substances (e.g. cocaine, phencyclidine (PCP)), and legal/medicinal substances of misuse (e.g. pain relievers, tranquilizers) with lifetime, past year, and past year severe MDEs.

Results: Results revealed that lifetime MDMA/ecstasy use was associated with significantly lowered odds of a lifetime MDE (adjusted odds ratio (aOR) = 0.84; $p < 0.001$), past year MDE (aOR = 0.84; $p < 0.001$), and past year severe MDE (aOR = 0.82; $p < 0.001$). Psilocybin was associated with significantly lowered odds of a past year MDE (aOR = 0.90; $p < 0.05$) and past year severe MDE (aOR = 0.87; $p < 0.05$). All other substances either shared no relationship with a MDE or conferred increased odds of an MDE.

Conclusions: These results suggest that MDMA/ecstasy and psilocybin use is associated with lower risk of depression. Experimental studies are needed to test whether there is a causal association between use of these compounds and the alleviation of depressive symptoms.

Keywords

MDMA, psilocybin, classic psychedelics, NSDUH, depression

Depression, a mental health disorder characterized by the cardinal symptoms of low mood and anhedonia, is a major health burden that affects over 264 million people worldwide (World Health Organization, 2020). Depression can lead to major disruptions in functioning within key domains of life (work, school, social life, etc.). At its most severe, depression can lead to suicide, one of the leading causes of death worldwide (World Health Organization, 2019). Currently, depression is a disorder marked by high rates of non-recovery and chronicity (Van Randenborgh et al., 2012). Indeed, even the most effective available treatments, such as antidepressant medication and cognitive therapy, are of only modest benefit (Turner et al., 2008; Weisz et al., 2006). Thus, there is a clear need for novel approaches to the treatment of depression.

MDMA (3,4-methylenedioxymethamphetamine) and psilocybin (the active compound in "magic mushrooms") may represent two such tools. First, MDMA is a compound known to increase feelings of empathy and prosociality, heighten mood states, and facilitate the processing of difficult emotions. Historically, MDMA has been used recreationally and is the active ingredient in the recreational drug "Ecstasy" or "Molly." Although MDMA/ecstasy has been designated as a Schedule 1 substance, limiting research on this compound, there has been a recent increase in research on the potential utility of MDMA for the treatment of anxiety and related disorders. In 2011, the first randomized controlled trial of MDMA-assisted psychotherapy for treatment-resistant post-traumatic stress disorder (PTSD) found that 83% of participants achieved clinical response (defined as >30% reduction in symptom severity) compared with just 25% of those in the placebo condition (Mithoefer et al., 2011). Since then, other clinical trials have replicated these strong findings (Mithoefer et al., 2013, 2019; Oehen et al., 2013; Ot'alora et al., 2018). These results led the US Food and Drug Administration (FDA) to designate MDMA as a "Breakthrough Therapy" for treating PTSD, underscoring the promise of MDMA as a therapeutic intervention.

Although the majority of clinical research on MDMA has focused on anxiety disorders, MDMA may be useful for treating mood disorders as well. In addition to its rapid mood enhancing effects, MDMA rapidly promotes the release and selective reuptake of serotonin (Farré et al., 2007; Liechti et al., 2001) and increases the availability of serotonin receptors (5-HT) much like selective serotonin reuptake inhibitors (SSRIs), a first-line depression treatment (Patel and Titheradge, 2015). Patel and Titheradge (2015) note that that there are only two experimental studies that explore and demonstrate the antidepressant effects of MDMA: one animal study (Majumder et al., 2011) and one small volunteer study (Majumder et al., 2012). The extreme paucity of

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research on the link between MDMA and decreased depressive symptoms invites novel investigation into this important research area.

The first goal of our current study sought to fill this critical gap by testing associations between MDMA/ecstasy use and depression in a large nationally representative sample of US adults. Given the current Schedule 1 designation of MDMA, large, representative surveys offer a propitious method for robust inferences into the link between MDMA/ecstasy use and depression. This current investigation builds on a prior study using the same survey that reports that lifetime MDMA/ecstasy use is associated with significantly decreased odds of past year suicidal thinking and planning (Jones et al., in press). In light of these findings, a natural next step is to investigate whether lifetime MDMA/ecstasy use is also associated with decreased odds of a key antecedent of suicidality—depression. This study seeks to test whether lifetime use of MDMA/ecstasy is associated with decreased odds of depression across three dimensions: lifetime major depressive episode (MDE), past year MDE, and past year severe MDE.

The second goal of our study was to test whether the use of classic psychedelics, and particularly psilocybin, is also associated with reduced odds of depression. Classic psychedelics are a class of naturally occurring or naturally derived substances with powerful psychoactive properties and can elicit mystical-type experiences that have a lasting personal effect (Griffiths et al., 2006); as previously stated, psilocybin is a classic psychedelic compound that is the active compound in "magic mushrooms." Like MDMA, these substances are designated as Schedule 1 and so research on their potential therapeutic benefit has been limited. Also like MDMA, they have received renewed clinical interest due to their potential to treat a host of mental disorders; unlike MDMA, however, clinical trials have repeatedly supported the notion that psilocybin may be an effective treatment for depression (Carhart-Harris et al., 2021; Davis et al., 2021; Griffiths et al., 2016; Grob et al., 2011).

Results from recent nationally representative US survey studies also suggest that classic psychedelics, and psilocybin in particular, are associated with lowered odds of depression. For instance, Hendricks et al. (2015b) analyzed 2008–2012 survey data from the National Survey on Drug Use and Health (NSDUH) and found that the use of classic psychedelics was associated with significantly reduced odds of psychological distress as well as suicidal ideation, planning, and attempts—outcomes with possible associations to depression. Subsequently, Hendricks et al. (2015a) replicated this finding for psilocybin in particular, suggesting that this compound may be driving the overall protective effect of psychedelics. Jones and Nock (in press) examined all available NSDUH data (2008–2019) and similarly found psilocybin to be the sole classic psychedelic substance associated with lowered odds of suicidality.

Informed by these earlier findings, we sought to examine the unique associations between the use of MDMA/ecstasy and each of four individual classic psychedelics (psilocybin, lysergic acid diethylamide (LSD), mescaline, and peyote) with lifetime, past year, and past year severe MDE. In an effort to further test the specificity of the aforementioned associations, we also tested the associations between a range of other substances (e.g. cocaine, heroin, phencyclidine (PCP), inhalants, pain relievers, tranquilizers, stimulants, sedatives, and marijuana) and MDEs. Based on prior findings, we hypothesized that use of (a) MDMA/ecstasy and psilocybin would be associated with lower odds of MDEs, (b) other classic psychedelics would show weaker or no association with MDEs, and (c) other substances (both illegal and legal/medicinal) would share no association to MDEs or be associated with higher odds of MDEs.

Method

Sample

Data were from the National Survey on Drug Use and Health (NSDUH), an annual survey that assesses trends related to substance use, mental health, and overall health in the United States. NSDUH uses a stratified, multistage probability sample design and aims to assess these trends within a representative sample of the US population over the age of 12. In addition, NSDUH utilizes interviewers to administer a computer-assisted self-interviewing paradigm in participants' homes. In this current study, we utilized 5 years of the latest NSDUH data (2014–2018) (United States Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, 2014, 2015, 2016, 2017, 2018). All NSDUH data are publicly available at https://www.datafiles.samhsa.gov

Measures

The primary independent variables within this study were those from the NSDUH database assessing self-reported lifetime use (yes/no) of MDMA/ecstasy and psilocybin, other classic psychedelics (LSD, peyote, and mescaline), other illegal substances (cocaine, heroin, PCP, inhalants), and other legal/medicinal substances of misuse and abuse (pain relievers, tranquilizers, stimulants, sedatives, and marijuana (legality varies by state)).

The primary dependent variable in this study was the presence of an MDE. Respondents in the NSDUH were classified as having an MDE if they experienced five or more of the nine self-reported criteria for depression in the NSDUH instrument (depressed mood, anhedonia, weight gain/loss, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, worthlessness, concentration trouble, and suicidal ideation). We used variables assessing both lifetime and past year MDEs. Finally, respondents were classified as having a severe past year MDE if they met criteria for an MDE and also received 7 or higher of 10 on the Sheehan Disability Scale (Sheehan et al., 1996), a measure meant to assess functional impairment from a disorder within four central domains of functioning (home management, ability to work, close relationships, and social life). The NSDUH depression criteria were based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., *DSM*-IV; American Psychiatric Association, 1994) and the specific questions were adapted from the National Comorbidity Survey–Replication (Kessler and Merikangas, 2004).

Data analysis

We estimated three multiple logistic regression models using all available MDE variables in the NSDUH (lifetime, past year, and past year severe) as the dependent variables. In addition, all of the

substances mentioned above were entered simultaneously as predictors. This approach allows us to account for the unique substance use patterns within the NSDUH and account for the fact that participants may have used multiple of the aforementioned substances. Furthermore, because of the well-established sociodemographic differences between those who have and have not used illegal substances, we selected the following variables a priori and entered them as covariates in each analysis: sex (male or female), age (18–25, 26–34, 35–49, 50–64, or 65 or older), race (non-Hispanic White, non-Hispanic Black, non-Hispanic Native American/Alaska Native, non-Hispanic Native Hawaiian/Pacific Islander, non-Hispanic Asian, non-Hispanic more than one race, or Hispanic), educational attainment (fifth grade or less, sixth grade, seventh grade, eighth grade, ninth grade, 10th grade, 11th grade, 11th or 12th grade, high school diploma, some college (no degree), associate's degree, college degree, or higher), self-reported engagement in risky behavior (never, seldom, sometimes, or always), annual household income (less than $20,000, $20,000–$49,999, $50,000–$74,999, or $75,000 or more), and marital status (married, divorced/separated, widowed, or never married). Analyses were conducted in R version 3.5.3 utilizing the "Survey" package (Lumley, 2020), which enables us to account for the complex survey design of the NSDUH in our analyses.

Results

Prevalence of substance use

Among the 213,437 participants, the lifetime weighted prevalence of the use of each substance was as follows: MDMA/ecstasy (7.6%), classic psychedelics (psilocybin (9.5%), LSD (10.5%), peyote (2.3%), and mescaline (3.2%)), illegal substances (cocaine (16.1%), heroin (2.1%), and PCP (2.6%)), and commonly misused legal substances (inhalants (9.6%), pain relievers (55%), tranquilizers (22.7%), stimulants (11.8%), sedatives (12.5%), and marijuana (47.4%)). Among the total sample, 13.5% met criteria for lifetime MDE, 6.9% for past year MDE, and 4.4% for past year severe MDE.

Table 1 provides demographic information on those who have versus have not used MDMA/ecstasy (percentages for each demographic characteristic sum to ~100% column-wise). Lifetime MDMA/ecstasy users were more likely to be male, higher income (above $75k), college-educated, non-Hispanic White, and to report more engagement in risky behavior. Furthermore, MDMA/ecstasy use was most prevalent among individuals 26–39 years old and rarer in individuals 65 years and older. The demographic breakdown for psilocybin users versus non-users roughly mirrors the breakdown observed within Table 1.

Table 2 and Figures 1 to 3 provide the results of the three multiple logistic regressions predicting lifetime, past year, and past year severe MDE. Bolded p-values in Table 2 indicate a significant association between use of a given substance and a given depression outcome. This table and these figures report adjusted odds ratios (aORs), which are odds ratios yielded from models with multiple predictors. Consistent with our hypotheses, lifetime MDMA/ecstasy use was associated with significantly reduced odds of a lifetime MDE (aOR = 0.84), past year MDE (aOR = 0.84), and past year severe MDE (aOR = 0.82).

Also consistent with our hypotheses, psilocybin stood out among the classic psychedelics in being associated with significantly lowered odds of a past year MDE (aOR = 0.90) and a past year severe MDE (aOR = 0.87), although it was not significantly associated with a lifetime MDE. For both MDMA/ecstasy and psilocybin, the strength of these aORs is in line with findings from other seminal population–based psychedelics research (Hendricks et al., 2018; Sexton et al., 2020; Simonsson et al., 2021). The aORs for mescaline roughly mirrored those of psilocybin but with wider CIs, and, like all other classic psychedelics, did not demonstrate reduced odds of an MDE. In contrast, lifetime use of LSD was associated with increased odds of all MDE variables (lifetime, past year, and past year severe).

In terms of the other substances examined, the use of illegal substances was not associated with the presence of an MDE, whereas the use of each of the legal/medicinal substances was associated with increased odds of each MDE outcome tested.

Discussion

The goal of this study was to assess the associations between the use of (a) MDMA/ecstasy and psilocybin, (b) other classic psychedelics, and (c) other substances of abuse/misuse, and depression. There were three key findings in this study. First, lifetime MDMA/ecstasy use was associated with lowered odds of lifetime, past year, and past year severe MDEs. Second, psilocybin was associated with significantly lowered odds of past year and past year severe MDEs. Third, other classic psychedelics, illegal substances, and a range of legal/medicinal substances either shared no association with MDEs or increased odds of lifetime, past year, and past year severe MDEs. Each of these findings warrants further comment.

These findings support the notion that MDMA/ecstasy use is associated with lowered odds of depressive symptoms. It is notable up front that these data cannot be used to draw any causal inferences about the associations between any of these substances and MDEs. Thus, our findings provide only preliminary and suggestive evidence for the therapeutic potential of MDMA/ecstasy. Future randomized controlled trials will be critical to establish a causal link between MDMA/ecstasy and decreased depressive symptoms.

These findings also add to the growing evidence that psilocybin is associated with decreased risk of depression and may be useful for treating depressive symptoms (Carhart-Harris et al., 2021; Davis et al., 2021; Griffiths et al., 2016; Grob et al., 2011). The putative mechanisms of action of psilocybin—downregulation of the serotonin 2A receptor—may underlie the effects observed here (Mahapatra and Gupta, 2017; Van Oekelen et al., 2003; Vollenweider and Kometer, 2010), although future studies are needed to better understand whether and how psilocybin may prospectively reduce the risk of depressive symptoms. As with MDMA, more clinical trials are needed to firmly establish the antidepressant effects of psilocybin.

Interestingly, the other classic psychedelics examined in this study (LSD, mescaline, and peyote) either shared no significant relationship with depression or conferred increased odds of a depressive episode, as was the case with LSD. These findings stand in contrast to other population-based survey work (Hendricks et al., 2015a), which found that classic psychedelics conferred lowered odds of psychological distress and suicidality. Our findings suggest that classic psychedelics may not confer their effects monolithically and that individual classic psychedelics vary in the associations they share with conditions like

Table 1. Demographics of participants who have versus have not used MDMA/ecstasy.

	Have not used MDMA/ecstasy (weighted %)	Have used MDMA/ecstasy (lifetime) (weighted %)	*p* value[a]
Age, years			<0.001
18–25	13.5	21.9	
26–34	14.4	33.8	
35–49	24.2	32.7	
50–64	26.7	10.2	
65 and older	21.2	1.3	
Sex			<0.001
Male	47.4	58.0	
Female	52.6	42.0	
Race			<0.001
Non-Hispanic White	63.7	72.2	
Non-Hispanic Black	12.2	7.6	
Non-Hispanic Native American/Alaska Native	0.5	0.5	
Non-Hispanic Native Hawaiian/Pacific Islander	0.4	0.4	
Non-Hispanic Asian	5.7	3.3	
Non-Hispanic more than one race	1.6	2.8	
Hispanic	16.0	13.2	
Annual household income ($)			<0.001
Less than 20k	17.0	17.1	
20,000–49,999	30.0	30.0	
50,000–74,999	16.2	15.7	
75k or more	36.9	37.3	
Education			<0.001
Fifth grade or less	1.4	0.3	
Sixth grade	1.2	0.1	
Seventh grade	0.5	0.1	
Eighth grade	1.2	0.6	
Ninth grade	1.9	1.2	
10th grade	2.3	2.1	
11th or 12th grade	4.9	4.3	
High school diploma/general educational development	26.0	22.4	
Some college (no degree)	18.7	25.4	
Associate's degree	10.9	12.2	
College degree or higher	31.1	31.4	
Marital status			<0.001
Married	53.5	33.3	
Widowed	6.2	1.1	
Divorced or separated	14.0	13.3	
Never been married	26.3	52.3	
Self-reported engagement in risky behavior			<0.001
Never	56.8	25.4	
Seldom	31.4	43.8	
Sometimes	10.2	26.7	
Always	1.1	3.9	

[a]Chi-squared tests were utilized to examine the differences between those who have and have not used MDMA.

depression. Given the Schedule 1 designation of classic psychedelics, extant research on classic psychedelic compounds remains in its inchoate stages, with only a handful of published trials existing (Gasser et al., 2014; Osório et al., 2015; Palhano-Fontes et al., 2019; Zeifman et al., 2019, 2021). Future research that further studies the effects of individual classic psychedelic compounds would greatly enhance our understanding of these potentially therapeutic tools.

Another interesting finding within this study is that lifetime use of illegal substances (e.g. cocaine, heroin, PCP) did not confer increased odds of depression. These findings ostensibly stand in contrast to existing literature that establishes a link between illegal substance use and depression (Choi et al., 2016; Havard et al., 2006; Sordo et al., 2012). However, given that most studies have examined substance abuse/dependence, instead of lifetime use like

Table 2. Results of multiple logistic regression models predicting lifetime, past year, and past year severe MDE.

Variable	Lifetime MDE			Past year MDE			Past year severe MDE		
	aOR	95% CI	*p* value	aOR	95% CI	*p* value	aOR	95% CI	*p* value
Lifetime Ecstasy Use	0.84	0.79–0.89	**<0.001**	0.84	0.78–0.91	**<0.001**	0.82	0.74–0.91	**<0.001**
Lifetime Psilocybin Use	0.96	0.89–1.03	0.2	0.90	0.82–0.99	**0.040**	0.87	0.79–0.97	**0.015**
Lifetime LSD Use	1.16	1.08–1.24	**<0.001**	1.17	1.08–1.26	**<0.001**	1.12	1.01–1.23	**0.040**
Lifetime Peyote Use	1.08	0.95–1.24	0.2	1.12	0.95–1.30	0.2	1.14	0.96–1.35	0.15
Lifetime Mescaline Use	0.89	0.79–1.01	0.083	0.88	0.76–1.02	0.10	0.85	0.72–1.01	0.083
Lifetime Cocaine Use	1.00	0.94–1.06	>0.9	1.01	0.94–1.09	0.8	1.00	0.92–1.10	>0.9
Lifetime Heroin Use	0.95	0.84–1.07	0.4	0.93	0.81–1.07	0.3	0.92	0.80–1.05	0.2
Lifetime PCP Use	1.05	0.93–1.18	0.5	1.06	0.93–1.21	0.4	1.13	0.96–1.32	0.2
Lifetime Inhalant Use	1.48	1.39–1.57	**<0.001**	1.47	1.34–1.61	**<0.001**	1.46	1.32–1.62	**<0.001**
Lifetime Pain Reliever Use	1.27	1.22–1.32	**<0.001**	1.17	1.12–1.23	**<0.001**	1.13	1.06–1.20	**<0.001**
Lifetime Tranquilizer Use	2.10	2.01–2.20	**<0.001**	2.11	1.99–2.24	**<0.001**	2.31	2.17–2.47	**<0.001**
Lifetime Stimulant Use	1.34	1.28–1.40	**<0.001**	1.36	1.27–1.46	**<0.001**	1.46	1.35–1.57	**<0.001**
Lifetime Sedative Use	1.78	1.70–1.87	**<0.001**	1.92	1.81–2.03	**<0.001**	2.08	1.94–2.24	**<0.001**
Lifetime Marijuana Use	1.69	1.63–1.76	**<0.001**	1.66	1.59–1.74	**<0.001**	1.66	1.56–1.77	**<0.001**

MDE: major depressive episodes; aOR: adjusted odds ratio; CI: confidence interval; LSD: lysergic acid diethylamide.

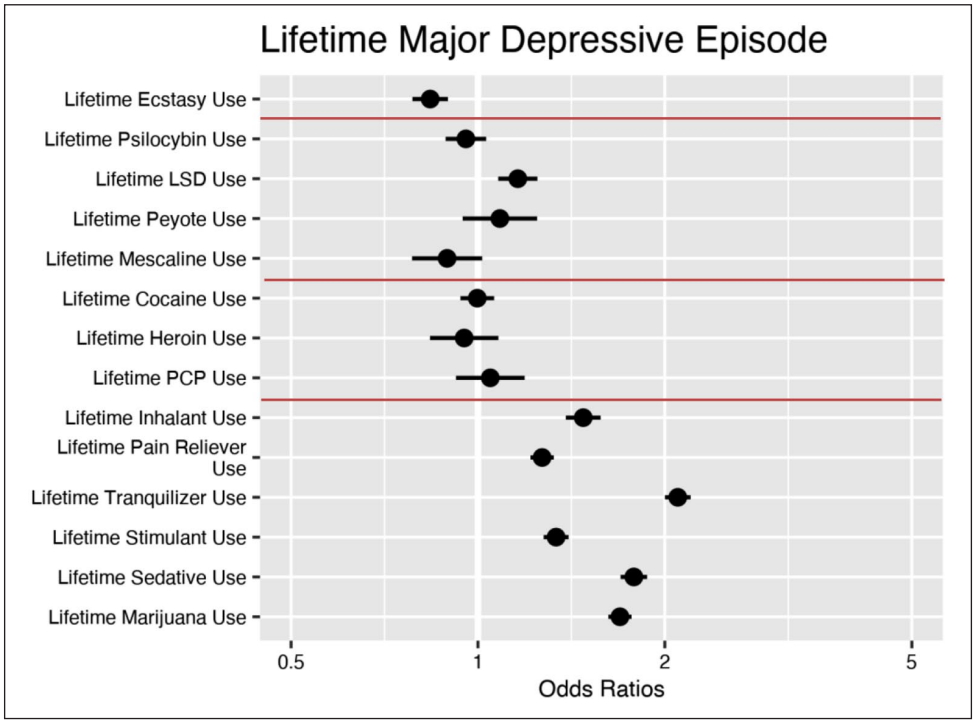

Figure 1. Result of multiple logistic regression model predicting a lifetime major depressive episode. Circles are point estimates and the bars are 95% confidence intervals.

our study, our findings may not conflict with the broader literature. Future studies with these data that examine the relationships between lifetime illegal substance use, substance dependence/abuse, and MDE can shed further light on our observed findings.

This study adds to the growing number of findings that suggest the Schedule 1 designations (indicating no medical utility and high abuse potential) for both MDMA/ecstasy and classic psychedelics should be reviewed and updated. It is of note that within our study, lifetime use of legal and medicinal substances (e.g. pain relievers, tranquilizers, stimulants, sedatives, marijuana) conferred increased odds of an MDE, whereas MDMA/ecstasy and psilocybin conferred lowered odds. Our findings are thus particularly notable and further highlight the need to review and potentially update the Schedule 1 designations of these two compounds. These designations make research on these compounds more difficult and limit further causal investigations that could expand upon correlational findings such as those from this study.

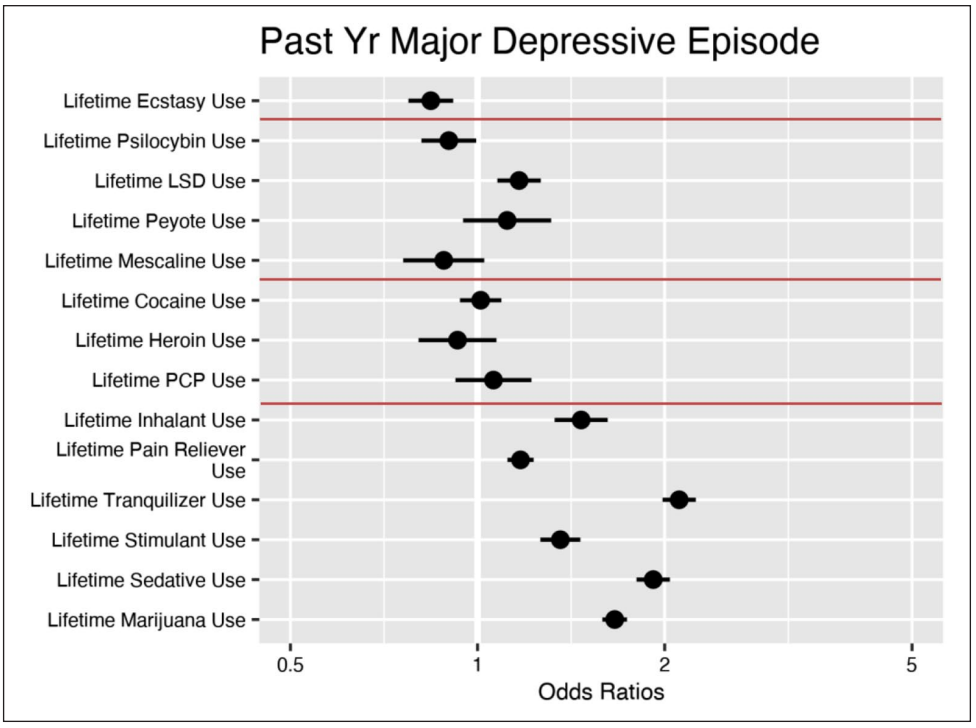

Figure 2. Result of multiple logistic regression model predicting a past year major depressive episode. Circles are point estimates and the bars are 95% confidence intervals.

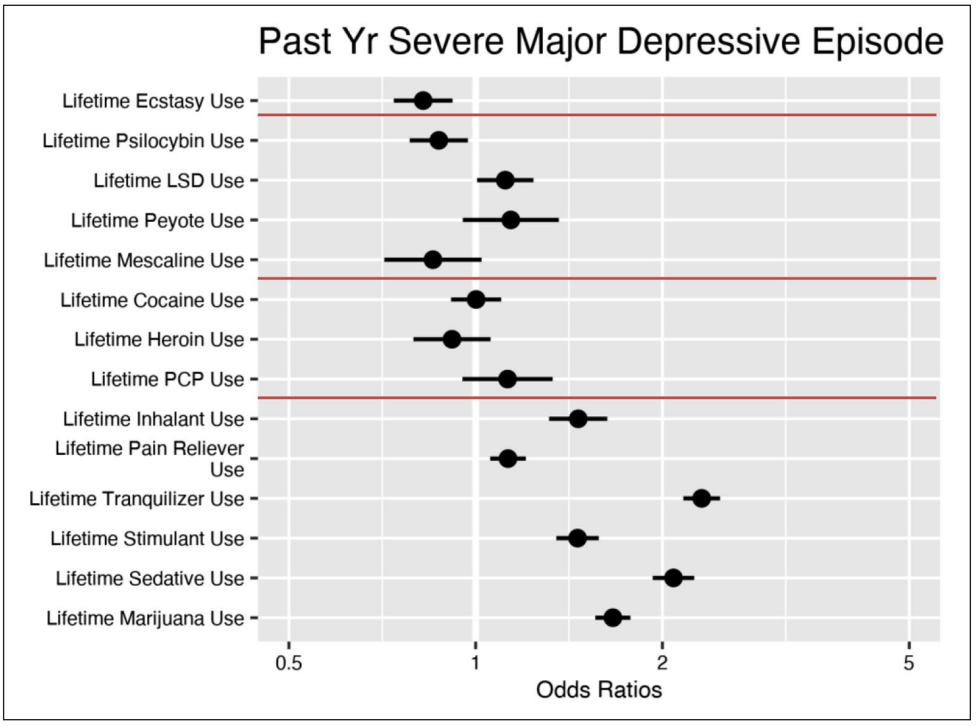

Figure 3. Result of multiple logistic regression model predicting a past year severe major depressive episode. Circles are point estimates and the bars are 95% confidence intervals.

In addition, updating Schedule 1 designations and conducting further research will also allow for more accurate assessments of any risks associated with these compounds. MDMA has demonstrated serotonin toxicity in animal studies (Green et al., 2003; Kovács et al., 2007; Meyer et al., 2004) and thus MDMA is commonly thought to increase risk for depression. Importantly,

however, most of these animal studies tested doses of MDMA that are well beyond the recommended therapeutic range; studies using doses within what is considered to be a therapeutic range show no evidence of neurotoxicity (Pantoni and Anagnostaras, 2019). Additional investigations can clarify whether MDMA carries risks when used as treatment and can shed light on potential mechanisms of MDMA as a treatment for depression (e.g. release and selective reuptake of serotonin; increasing the availability of serotonin receptors).

Limitations

There are several significant limitations of this study. First, given the cross-sectional and correlational design, we cannot make causal inferences about the observed associations. Pre-existing traits (personality differences, liberal political leanings, etc.) may simultaneously lead one to take MDMA/ecstasy and/or psilocybin and those same traits in turn may confer lowered odds of depression (Hendricks et al., 2018; Lerner and Lyvers, 2006; Lyvers and Meester, 2012; Móró et al., 2011; Nour et al., 2017; ter Bogt et al., 2006). Furthermore, our associations may have arisen by reverse causation—individuals with fewer depressive episodes may be more likely to use MDMA/ecstasy and psilocybin. Future studies that carefully attend to these confounds will be important toward establishing a causal link between these compounds and their potential anti-depressive effects.

Second, these data do not allow us to establish clear temporal precedent between substance use and depressive episodes; given that the NSDUH assesses lifetime use with a binary (yes/no) variable, we do not know whether MDMA/ecstasy and psilocybin use was recent and/or frequent. However, MDMA and psilocybin have demonstrated strong therapeutic effects that can potentially last multiple years with just a few/singular uses (Agin-Liebes et al., 2020; Grob et al., 2011; Jerome et al., 2020; Mithoefer et al., 2013), lending credibility to our findings despite this limitation. Furthermore, foundational research on psychedelics has examined NSDUH data using an identical analytical structure (Hendricks et al., 2015b; Jones and Nock, in press; Sexton et al., 2020; Simonsson et al., 2021), Thus, our observed findings are still noteworthy, regardless of these limitations related to temporal precedent.

Third, both depressive symptoms and substance use were assessed by self-report, meaning that there may be response bias and underreporting due to the sensitive nature of these topics. Future randomized controlled trials, with direct administration of these substances and clinician assessments of depressive symptoms, can help to overcome this limitation.

Fourth, this study did not assess potential mediators and moderators. Given the cross-sectional nature of the NSDUH data set, we are limited in what we can glean about mechanisms and ultimately we are limited in our understanding of the observed associations. For instance, the "setting" of administration is a moderator that is known to have a significant impact on outcomes related to psychedelic use (Carhart-Harris et al., 2018), yet we could not control for "setting" using these data. Thus, research aimed at identifying mechanisms will be an important step to better understanding MDMA/ecstasy, psilocybin, and other classic psychedelics, with the ultimate goal of maximizing their therapeutic efficacy.

Fifth, naturalistic MDMA/ecstasy samples are often adulterated (Johnson et al., 2020; Saleemi et al., 2017), weakening causal interpretations of the associations between MDMA and decreased odds of MDEs. However, this limitation may interestingly strengthen causal interpretations as well. As mentioned in Jones and Nock (in press), commonly used cutting agents for MDMA often increase the likelihood of neurotoxicity (Clemens et al., 2007; Gorska et al., 2018; Vanattou-Saïfoudine et al., 2012); hence, our findings that naturalistic MDMA/ecstasy use confers lowered odds of MDEs are particularly notable. Future studies using pure MDMA samples may demonstrate even stronger anti-depressive associations.

Conclusion

Prior research suggests that MDMA/ecstasy and psilocybin may effectively alleviate many difficult-to-treat mental health disorders. This study provides evidence that both MDMA/ecstasy and psilocybin are linked to lowered odds of depressive symptoms. In addition, this is the first such study to establish a link between MDMA/ecstasy and lowered odds of depression. In sum, the current findings indicate that MDMA/ecstasy and psilocybin use confer lowered odds of depressive symptoms and call for more controlled studies to further explore these associations.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MKN receives publication royalties from Macmillan, Pearson, and UpToDate. He has been a paid consultant in the past year for Microsoft Corporation, the Veterans Health Administration, Cerebral, and a legal case regarding a death by suicide. He is an unpaid scientific advisor for Empatica, Koko, and TalkLife.

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