



Depression and marijuana use disorder symptoms among current marijuana users



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HIGHLIGHTS

- Depression was positively associated with 8 National Household Survey of Drug Use and Health marijuana use disorder symptoms.
- Marijuana users with depression were consistently more likely to experience most marijuana use disorder symptoms.
- The relationship was consistent across all levels of marijuana use frequency from 1 day in the past month to daily use.

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ABSTRACT

Background: Depression is one of the most consistent risk factors implicated in both the course of escalating substance use behaviors and in the development of substance dependence symptoms, including those associated with marijuana use. In the present study, we evaluate if depression is associated with marijuana use disorder symptoms across the continuum of marijuana use frequency.

Methods: Data were drawn from six annual surveys of the National Survey of Drug Use and Health to include adults who reported using marijuana at least once in the past 30 days (N = 28,557).

Results: After statistical control for sociodemographic characteristics and substance use behaviors including marijuana use, alcohol use, smoking, and use of illicit substances other than marijuana, depression was positively and significantly associated with each of the marijuana use disorder symptoms as well as the symptom total score. Adult marijuana users with depression were consistently more likely to experience marijuana use disorder symptoms and a larger number of symptoms, with the magnitude and direction of the relationship generally consistent across all levels of marijuana use frequency from 1 day used in the past month to daily marijuana use.

Conclusions: Depression is a consistent risk factor for marijuana use disorder symptoms over and above exposure to marijuana suggesting that depressed individuals may represent an important subgroup in need of targeted substance use intervention.

1. Introduction

Depression is one of the most consistent risk factors implicated in both the course of escalating substance use behavior and in the development of dependence symptoms and chronic and/or heavy use. With recreational marijuana having recently been legalized in a growing number of U.S. states, an understanding of the relationship between depression, marijuana use and marijuana use disorders will assist in guiding both education and policy. Though often viewed as less addictive than other licit and illicit substances (Nutt, King, Saulsbury, & Blakemore, 2007), a diagnosis of marijuana abuse has

been estimated at approximately 4% among U.S. adults ages 24–28 years (Haberstick et al., 2014), and among those who have ever used marijuana, nearly one in ten develop dependence (Wagner & Anthony, 2002).

Evidence for the association between marijuana use and depression comes from cross-sectional and longitudinal investigations in which both depression symptoms (Crane, Langenecker, & Mermelstein, 2015; Hayatbakhsh et al., 2007; Horwood et al., 2012; Stapinski, Montgomery, & Araya, 2016; Troup, Andrzejewski, Braunwalder, & Torrence, 2016) and a diagnosis of major depression (Fairman & Anthony, 2012; Gage et al., 2015) have been shown to be

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associated with marijuana use, particularly heavy use (Rasic, Weerasinghe, Asbridge, & Langille, 2013), marijuana dependence (Mathews, Hall, & Gartner, 2011) and a decreased likelihood of successful quitting (Cornelius, Chung, Martin, Wood, & Clark, 2008; Shi, 2014). Though support for the order of onset between depression and marijuana use has been mixed with evidence for marijuana use being a risk factor for later depression (Lev-Ran et al., 2014), and depression a risk factor for later marijuana use (Stapinski et al., 2016), their co-occurrence has been consistently established. Based on a nationally representative sample of U.S. adults, individuals meeting criteria for marijuana use disorders within the past year had 6.4 times the odds of meeting criteria for major depression than those without a marijuana use disorder (Grant, 1995). Similarly, findings from the National Comorbidity Survey have shown greater frequency of marijuana use to be associated with a higher risk of having experienced a major depressive episode; with lifetime marijuana dependence associated with a 3.4 times increased risk of major depression (Chen, Wagner, & Anthony, 2002).

A discussion of the mechanism that may explain the association between depression and substance use disorder symptoms has often focused on the role of depression in elevating one's probability of use (i.e. increasing the likelihood of initiation, promoting earlier onset, and/or influencing the amount or persistence of use). Thus, the association is explained by the resulting physiological adaptations to the substance that directly lead to substance use disorder symptoms (Ouzir & Errami, 2016; Pomerleau, 1995). For example, the relationship between depression and substance use behavior has often been hypothesized to result from increased exposure to substances from the need to medicate the negative affective experiences associated with depression (Mirin & Weiss, 1991; Preisig, Fenton, Stevens, & Merikangas, 2001; Swendsen et al., 2000).

If however, depression is independently linked to substance use disorder symptoms, over and above level of exposure, this would support an alternate hypothesis that recognizes depression as a possible predisposing factor for the development of substance use disorder symptoms across a potentially wide range of substance use exposure (Dierker & Donny, 2008). First, symptoms and depression may involve overlapping neurobiological underpinnings. Evidence for this comes from research with adult animals and humans (for review see (Rao, 2006) that have implicated for example, the mesostriatal-mesocorticolimbic dopamine system, a central system in processing rewards, and one that is altered in both depression and substance use disorders. The association between depression and marijuana use disorder symptoms could also reflect latent genetic factors common to both disorders. Previous genetic studies have independently linked the DRD4 gene polymorphism to substance use and to internalizing disorders (Marques, Hutz, & Bau, 2006; Neville, Johnstone, & Walton, 2004). Further, in a study examining the associations between the DRD4 gene 48 bp VNTR polymorphism and comorbidity specifically between marijuana use frequency and depression, showed that risk for comorbidity was greater among individuals the $\geq 7R/\geq 7R$ genotype than those who carry the $< 7R/< 7R$ genotype (Bobadilla, Vaske, & Asberg, 2013).

Alternatively, the clustering of problems in individuals may not be specific to these two syndromes, but rather may be a broad vulnerability associated with risk for any form of psychopathology. That is, based on the Dunedin Multidisciplinary Health and Development Study, lifetime psychiatric disorders were best explained by a general psychopathology dimension with higher scores on this dimension associated with for example, more impairment, worse developmental histories, and more compromised early-life brain function (Caspi et al., 2014). Finally, animal studies have also shown both increases and decreases in responsiveness to substance use as a function of stress in rats possibly suggesting that internalizing symptoms such as depression may influence responses to substance use at consistent levels of exposure. For example, experimentally induced chronic stress (via twice-daily

injections or forced swim) was found to reduce the normal thermic (i.e., core temperature) response to nicotine (Flemmer & Dilsaver, 1989; Peck, Dilsaver, & McGee, 1991), whereas adolescent pre exposure to stress enhanced sensitization to the locomotor effects of nicotine in female rats (McCormick, Robarts, Gleason, & Kelsey, 2004).

To date epidemiological work evaluating the association between depression and substance use disorder symptoms above and beyond substance exposure is scarce. What evidence there is suggests that depression may be associated with substance use above and beyond exposure and across a range of substance use behaviors. Depression, for example, has been found to be associated with nicotine dependence both above and beyond cigarette smoking exposure and across a range of use from non-daily smoking to greater than a pack of cigarettes per day (Dierker & Donny, 2008). To our knowledge, no previous studies have examined these associations in the context of marijuana use. If depression predicts marijuana use disorder symptoms exclusively through increasing exposure to marijuana, intervention might best focus on minimizing use among individuals with depression. If, however, depression predicts marijuana use disorder symptoms regardless of level of exposure to marijuana, it would suggest that reducing exposure may be an insufficient approach. That is, even at low levels of use depression may increase risk for experiencing marijuana use disorder symptoms.

In the present study, we set out to evaluate whether the relationship between depression and marijuana dependence symptoms can be accounted for by marijuana exposure. Specifically, we examine the association between depression and marijuana use disorder symptoms in a nationally representative sample of marijuana users controlling for frequency of marijuana use. We ask: (1) Does depression uniquely predict marijuana use symptoms over and above frequency of use? and (2) Is the direction and strength of the relationship between depression and marijuana use symptoms consistent across levels of marijuana use frequency? We hypothesize that while frequency of marijuana use will be a significant predictor of marijuana use disorders symptoms, major depression will also be independently associated with individual marijuana use disorder symptoms and with the total number symptoms reported. With respect to the strength of the association between depression and marijuana use disorder symptoms across the continuum of marijuana use frequency from 1 day per month to daily use, we hypothesize that depression will be significantly associated with marijuana use disorder symptoms even among those reporting infrequent use. This would be evidence that the development of marijuana use dependence symptoms in the context of depression is not exclusively driven by heavy use.

2. Methods

2.1. Participants

Drawn from six annual NSDUH surveys from 2009 to 2014, the sample consisted of $N = 28,557$ individuals who (1) reported using marijuana at least once in the past month, and (2) were administered the adult depression module (i.e. participants age 18 and older). The NSDUH utilized multistage area probability methods to select a representative sample of the noninstitutionalized U.S. civilian population aged 12 or older. Persons living in households, military personnel living off bases, and residents of non-institutional group quarters including college dormitories, group homes, civilians dwellings on military installations, as well as persons with no permanent residence are included.

2.2. Measures

2.2.1. Depression

The NSDUH includes measurement of a major depressive episode (MDE) as defined by the Diagnostics Statistical Manual-5 (APA, 2013).

Lifetime MDE is defined as having at least five or more of nine symptoms of depression in the same 2-week period in a person's lifetime, in which at least one of the symptoms was a depressed mood or loss of interest or pleasure in daily activities. Respondents who had MDE in their lifetime were then classified as having past-year MDE if they had a period of depression lasting 2 weeks or longer in the past 12 months while also having some of the other symptoms of MDE. Youth ages 12 to 17 were excluded from the present analyses due to differences in the measurement of depression for this age group.

2.2.2. Marijuana use frequency

Marijuana use frequency was measured by asking participants how many days they used marijuana in the past 30 days (“Number of days used marijuana/hashish in the past 30 days?”).

2.2.3. Marijuana age of onset

Onset of marijuana use was measured with the question “How old were you the first time you used marijuana or hashish?”

2.2.4. Marijuana use disorder symptoms

The NSDUH includes items used to assess 8 of the 11 marijuana use disorder symptoms from the Diagnostic and Statistical Manual of Mental Disorders, 5 (APA, 2013): 1) used in larger amounts or over a longer period than intended (*larger/longer*), 2) repeated failed efforts to discontinue or reduce the amount that is used (*cut down*), 3) an inordinate amount of time is occupied acquiring, using, or recovering from the effects (*time*), 4) continued use despite adverse consequences from its use, such as criminal charges, ultimatums of abandonment from spouse/partner/friends, and poor productivity (*continued use*), 5) other important activities in life, such as work, school, hygiene, and responsibility to family and friends are superseded by the desire to use (*important activities*), 6) use in contexts that are potentially dangerous (*danger*), 7) use despite awareness of physical or psychological problems attributed to use (*health*) and 8) need for progressively larger amounts to obtain the psychoactive effect experienced when use first commenced, or, noticeably reduced effect of use of the same amount (*tolerance*). Table 1 presents the symptom criteria and the corresponding items. The criteria were evaluated such that a positive response to yes/no item(s) under a given criterion was coded positively as endorsing the symptom. A total score was also calculated representing the number of marijuana use disorder symptoms endorsed (range 0 to 8). The survey did not include items for marijuana withdrawal or craving.

2.2.5. Sociodemographic characteristics

Sociodemographic characteristics included age, gender, and race/ethnicity (categorized into binary variables, White vs. not White, Black vs. not Black, and Hispanic/Latino vs. not Hispanic/Latino).

2.2.6. Other substance use variables

Past month tobacco cigarette use (“During the past 30 days, on how many days did you smoke part or all of a cigarette?”), past-month alcohol use (“During the past 30 days, on how many days did you drink one or more drinks of an alcoholic beverage?”) and any past-year use of illicit substances other than marijuana (hallucinogens, heroin, cocaine, inhalants, and psychotherapeutics) was also included as covariates in the present analyses.

2.3. Analyses

First, stepwise regression analyses were conducted to answer the question does depression uniquely predict marijuana use disorder symptoms over and above frequency of use? Step 1 included only marijuana use frequency predicting number of marijuana use disorders symptoms; step 2 added major depression to the model, step 3 added all other substance use exposure variables (marijuana age of onset,

cigarettes use, alcohol use, and other illicit drug use) and step 4 added all demographic covariates as well as study year. Independent contributions to the model were evaluated by examining R-square. Next, to evaluate individual marijuana use disorders symptoms, logistic regression analyses were conducted with covariates added to the model simultaneously and each effect evaluated through Odds ratios and their corresponding 95% confidence intervals. Again, predictors in these models included current marijuana use frequency (number of days used in the past 30) and major depression. Additional covariates were marijuana age of onset, past month cigarette smoking frequency, past month alcohol use, past year other illicit substance use, demographics and survey year.

In addition, Cohen's *d* effect sizes were calculated to evaluate the magnitude of the depression effects for each marijuana use symptom. Cohen's *d* effect sizes are interpreted as differences in standard deviation units based on a standard normal distribution, for which values of 0.2, 0.5, and 0.8 are considered small, moderate, and large effect sizes, respectively (Cohen, 1988; Rosnow & Rosenthal, 1996). The Cohen's *d* effect sizes were calculated by dividing each unstandardized regression coefficient by the model residual standard deviation. The standard logit model has a residual variance equal to $\pi^2/3$, so the Cohen's *d* effect sizes for the logistic regression models were calculated by dividing the log Odds regression coefficients by the square root of the residual variance, which is equal to 1.81 (Chinn, 2000). All analyses used appropriate sample weights to correct for the differences in the probability of selection, and adjusted for survey design effects to obtain accurate standard errors via SAS (Version 9.4) survey procedures.

Varying coefficient models (VCM's) were then estimated to answer the question, is the direction and strength of the relationship between depression and marijuana use symptoms consistent across levels of marijuana use frequency? VCM's were run using a publicly available SAS macro (The Methodology Center, 2015), version 3.1.0, developed for analyzing time-varying effects of intensive longitudinal data. VCM's are regression-based models that examine moderation continuously across a variable (most often a time variable) without imposing strong parametric assumptions about the shape of the nature of the change (e.g. specifying that the coefficient varies in a linear or quadratic manner across the range of the moderating variable) (Tan, Shiyko, Li, Li, & Dierker, 2012). Instead, the curve is estimated empirically using spline methods, by fitting a lower-order polynomial curve within each interval based on the user-specified number of knots (Tan et al., 2012). This time-varying effects model (TVEM) macro produces coefficient estimates along the range of the moderating variable, along with corresponding 95% confidence bands. Here, separate VCM's were run to examine moderation along the range of marijuana use frequency (i.e. the number of days used marijuana in past month rather than time). These “marijuana frequency varying effects” were interpreted with respect to whether the 95% confidence band is different from 1 (conservatively indicating a statistically significant coefficient), and whether the confidence bands overlap (non-overlapping bands conservatively indicate a significant change in the coefficient), across different values of marijuana use frequency. Separate models were used to test each marijuana use symptom. All VCM's were run with P-spline estimation and 10 knots.

3. Results

Characteristics of the present sample (i.e. adult current marijuana users) adjusted for the complex survey design, are presented in Table 2. This sample was 35.8% female and 68.5% White. Approximately 13.3% (SE = 0.36) of the sample reported using marijuana on only 1 day in the past month, and on average, this sample had used marijuana an average of 171.7 days in the past year (SE = 1.32, range 1–365).

Table 3 presents stepwise multiple regression results for total number of marijuana use disorder symptoms. Step 1 included only marijuana use frequency and resulted in a significant *p* value and an *R*²

Table 1
Mapping marijuana symptoms with DSM-V criterion.

Criterion	Item(s)
Larger/longer: Difficulty containing use of cannabis- the drug is used in larger amounts and over a longer period than intended	During the past 12 months, ● Were you able to keep to the limits you set, or did you often use marijuana more than you intended to?
Cut down: Repeated failed efforts to discontinue or reduce the amount of cannabis that is used	During the past 12 months, ● Were you unable to stop or cut down every time you wanted to or tried to?
Time: An inordinate amount of time is occupied acquiring, using, or recovering from the effects of cannabis	During the past 12 months, ● Was there a month or more where you spent a lot of your time getting or using marijuana? ● Was there a month or more where you spent a lot of your time getting over the effects of marijuana?
Cravings or desires to use cannabis. This can include intrusive thoughts and images, and dreams about cannabis, or olfactory perceptions of the smell of cannabis, due to preoccupation with cannabis	Not included in the survey
Continued use: Continued use of cannabis despite adverse consequences from its use, such as criminal charges, ultimatums of abandonment from spouse/partner/friends, and poor productivity	During the past 12 months, ● Did you continue to use marijuana even though you thought it caused problems with your family or friends?
Important activities: Other important activities in life, such as work, school, hygiene, and responsibility to family and friends are superseded by the desire to use cannabis	During the past 12 months, ● Did using marijuana cause you to give up or spend less time with family and friends, working, going to school, or doing other important activities?
Danger: Cannabis is used in contexts that are potentially dangerous, such as operating a motor vehicle	During the past 12 months, ● Did you do things that might have put you in physical danger due to marijuana use?
Health: Use of cannabis continues despite awareness of physical or psychological problems attributed to use- e.g., anergia, amotivation, chronic cough	During the past 12 months, ● Did you continue to use marijuana even though you thought marijuana use was causing you to experience physical problems? ● Did you continue to use marijuana even though you thought marijuana use was causing you to experience emotional problems?
Tolerance to Cannabis, as defined by progressively larger amounts of cannabis are needed to obtain the psychoactive effect experienced when use first commenced, or, noticeably reduced effect of use of the same amount of cannabis	During the past 12 months, ● Did you need to use more marijuana than you used to in order to get the same desired effect? ● Did you notice that using the same amount of marijuana had less effect on you than before?
Withdrawal, defined as the typical withdrawal syndrome associate with cannabis, or cannabis or a similar substance is used to prevent withdrawal symptoms	Not included in the survey

Table 2
Sample characteristics (N = 28,557).

Variable	N (%) for categorical data; M (SE) for continuous data
Gender	
Female	11,234 (35.8%)
Male	17,323 (64.2%)
Age	33.9 years (0.17)
Race	
White	18,205 (68.5%)
Black	4194 (14.4%)
Native American	621 (0.7%)
Asian/Pacific Islander	607 (2.0%)
Multiracial	1311 (2.5%)
Hispanic/Latino	3619 (11.9%)
Past year major depressive episode (MDE)	3442 (12.1%)
Current marijuana frequency (# days in past month)	14.4 days (0.11)
Past year marijuana frequency (# days past 12 months)	171.7 days (1.32)
Age of marijuana use onset	16.0 (0.06)
Past month cigarette use	13.5 days (0.14)
Lifetime daily smoking	16,531 (64.2%)
Past month alcohol use (# of days had one or more drinks in the past 30)	8.9 days (0.10)
Any other illicit substance use in past year	13,193 (40.3%)

of 0.129. When depression was added to the model it was also found to be independently and positively associated with number of marijuana use disorder symptoms with a model R² of 0.142. In step 3, all other substance use exposure variables were added (marijuana age of onset, cigarettes use, alcohol use, and other illicit drug use) resulting in an R² of 0.17. The full model including all previously entered variables as well as demographic covariates and study year resulted in an R² 0.228.

Logistic regression analyses examining the association between a diagnosis of past-year depression and individual marijuana use disorder symptoms, are presented in Tables 4 and 5. We hypothesize that while frequency of marijuana use will be a significant predictor of marijuana use disorders symptoms, major depression will also be independently associated with individual marijuana use disorder symptoms and with the total number symptoms reported. With respect to the strength of the association between depression and marijuana use disorder symptoms across the continuum of marijuana use frequency from 1 day per month to daily use, we hypothesize that depression will be significantly associated with marijuana use disorder symptoms even among those reporting infrequent use, evidence that the development of marijuana use dependence symptoms in the context of depression is not exclusively driven by heavy use. Though as expected frequency of use is significantly associated with each marijuana use disorder symptom, depression was also independently associated, after controlling for marijuana use frequency, age of marijuana use onset, sociodemographic characteristics, past-month smoking frequency, frequency of past-

Table 3
Multiple regression for total number of marijuana use disorder symptoms.

	B	p Value	B	p Value	B	p Value	B	p Value
Number of days used marijuana in past 30	0.04	0.0001	0.04	0.0001	0.04	0.0001	0.04	0.0001
Past year depression (MDE)			0.48	0.0001	0.43	0.0001	0.50	0.0001
Marijuana age of onset					− 0.02	0.0002	− 0.0005	n.s.
Past 30 day cigarette use					− 0.002	0.0001	− 0.0002	0.0001
Past month alcohol use					0.0003	n.s.	0.0009	0.04
Past year illicit substance use (other than marijuana)					0.38	0.0001	0.30	0.0001
Age							− 0.11	0.0001
Gender								
Male vs. Female							− 0.15	0.0001
Race								
White vs. non-White							− 0.14	0.04
Black vs. non-Black							0.26	0.0004
Hispanic vs. non-Hispanic							0.11	n.s.
Survey year							− 0.02	0.02
R-Square	0.129		0.143		0.17		0.228	

month alcohol use, past-year use of illicit substances and survey year. Adult marijuana users with depression were significantly more likely than marijuana users without depression to report *larger/longer* (Cohen's *d* = 0.32), *time* (Cohen's *d* = 0.26), *continued use* (Cohen's *d* = 0.64), *cut down* (Cohen's *d* = 0.35), *important activities* (Cohen's *d* = 0.44), *danger* (Cohen's *d* = 0.32), *health* (Cohen's *d* = 0.57) and *tolerance* (Cohen's *d* = 0.35) symptoms associated with marijuana use. Effect sizes were small to moderate in size.

VCM's revealed that among adult current marijuana users, the relationship between depression and 6 of the 8 marijuana use disorder symptoms was consistent and significant across all levels of marijuana user frequency from 1 day used in the past month to use of marijuana 30 days in the past month; *time*, *larger/longer*, *continued use*, *important activities*, *danger* and *health* symptoms related to marijuana use. Fig. 1 illustrates this consistent pattern of findings across frequency of marijuana use for the *health* symptom by showing Odds ratios ranging from approximately 2.2 to 2.8 with overlapping 95% confidence intervals.

In contrast, VCM's showed that the association between depression and both *cut down* and *tolerance* symptoms varied according to how frequently an individual used marijuana in the past month (Figs. 2 and 3). Overall, depression was found to be more strongly associated with each of these symptoms at higher levels of marijuana use frequency, while depression did not significantly predict failed attempts to *cut down* among those adults using marijuana < 5 days in the past month.

Table 4
Logistic regression for marijuana use disorder symptoms. Odds ratios and 95% confidence intervals.

	Larger/longer	Cut down	Time	Continued use
Number of days used marijuana in past 30	1.05 (1.04–1.06)***	1.056 (1.05–1.06)***	1.1 (1.09–1.11)***	1.03 (1.02–1.04)***
Past year depression (MDE)	1.8 (1.56–2.19)***	1.9 (1.50–2.30)***	1.6 (1.41–1.93)***	3.2 (2.41–4.30)***
Marijuana age of onset	1.0 (0.99–1.03)	1.0 (0.97–1.03)	0.98 (0.96–0.99)*	0.96 (0.94–0.98)*
Past 30 day cigarette use	1.0 (0.99–1.002)	1.0 (0.99–1.002)	0.997 (0.994–0.997)**	0.9 (0.99–1.00)
Past month alcohol use	1.0 (0.99–1.002)	1.0 (0.99–1.003)	1.002 (1.001–1.004)*	1.0 (0.99–1.01)
Past year illicit substance use (other than marijuana)	1.3 (1.10–1.52)*	1.4 (1.15–1.64)**	1.6 (1.43–1.72)***	1.7 (1.36–2.00)***
Age	0.9 (0.89–0.93)***	0.9 (0.92–0.97)***	0.79 (0.77–0.80)***	0.89 (0.86–0.91)***
Gender				
Male vs. Female	0.9 (0.80–1.08)	1.05 (0.91–1.20)	0.7 (0.65–0.80)***	0.8 (0.63–0.98)*
Race				
White vs. non-White	0.8 (0.56–1.14)	0.9 (0.59–1.31)	0.9 (0.70–1.10)	0.70 (0.42–1.20)
Black vs. non-Black	1.8 (1.33–2.57)**	2.0 (1.35–2.96)**	1.4 (1.11–1.85)	1.5 (0.89–2.65)
Hispanic vs. non-Hispanic	0.9 (0.67–1.44)	1.3 (0.85–2.04)	1.2 (0.89–1.60)	1.5 (0.88–2.50)
Survey year	0.9 (0.94–1.02)	0.9 (0.94–1.03)	0.97 (0.94–0.99)*	0.9 (0.88–0.98)*

* *p* < 0.05.
** *p* < 0.001.
*** *p* < 0.0001.

4. Discussion

The present study examined the association between depression and marijuana use disorder symptoms among a nationally representative sample of adults who reported using marijuana at least once in the past month. After statistical control for marijuana use frequency age of marijuana use onset, as well as sociodemographic characteristics and other substance use, depression was positively and significantly associated with each of the marijuana use disorder symptoms and with a greater number of symptoms. Also, the magnitude and direction of the relationship between depression and the majority of marijuana use disorder symptoms was consistent across all levels of marijuana use frequency from 1 day used in the past month to use of marijuana 30 days in the past month, though for failed efforts to *cut down* and *tolerance* the relationship was weaker or non-significant among those using marijuana fewer than 5 days in the past month.

Notably, the relationship between depression and marijuana as well as other substance use behaviors has been hypothesized to result from increased exposure to a substance stemming from the need to medicate negative affective experiences common to depression (Mirin & Weiss, 1991). The present findings, however, show depression to be directly linked to marijuana use disorder symptoms above and beyond frequency of use. Thus, depression seems to be a risk factor for marijuana use disorder symptoms that might be interpreted in several ways. As previously reviewed, marijuana use disorder symptoms and depression may involve overlapping neurobiological underpinnings. The signal

Table 5
Logistic regression for marijuana use disorder symptoms. Odds ratios and 95% confidence intervals.

	Important Activities	Danger	Health	Tolerance
Number days used marijuana in past 30	1.01 (1.003–1.017)*	1.02 (1.01–1.03)***	1.03 (1.02–1.04)***	1.1 (1.05–1.06)***
Past year depression (MDE)	2.2 (1.7–2.75)***	1.8 (1.42–2.18)***	2.81 (2.36–3.36)***	1.9 (1.66–2.17)***
Marijuana age of onset	0.94 (0.91–0.98)**	0.97 (0.94–1.00)	0.96 (0.939–0.987)*	1.0 (0.97–1.02)
Past 30 day cigarette use	0.993 (0.990–0.996)**	0.99 (0.98–1.00)	1.0 (0.997–1.002)	0.996 (0.995–0.998)***
Past month alcohol use	1.002 (1.00–1.005)	1.0 (0.99–1.003)	1.0 (0.99–1.002)	1.0 (1.001–1.004)**
Past year illicit substance use (other than marijuana)	2.12 (1.78–2.54)***	1.6 (1.30–1.99)***	1.5 (1.31–1.76)***	1.5 (1.34–1.65)***
Age	0.88 (0.85–0.91)***	0.93 (0.90–0.96)***	0.96 (0.93–0.99)*	0.8 (0.80–0.83)***
Gender				
Male vs. Female	0.7 (0.57–0.79)***	0.6 (0.51–0.72)***	0.9 (0.83–1.09)	0.8 (0.73–0.90)***
Race				
White vs. non-White	0.7 (0.45–0.95)*	1.02 (0.61–1.70)	0.8 (0.54–1.18)	0.7 (0.61–0.91)*
Black vs. non-Black	2.0 (1.38–2.88)**	1.4 (0.80–2.40)	1.3 (0.84–1.90)	1.2 (0.93–1.47)
Hispanic vs. non-Hispanic	1.2 (0.81–1.75)	1.3 (0.75–2.28)	1.3 (0.89–2.06)	1.1 (0.84–1.32)
Survey year	0.9 (0.88–0.98)*	0.93 (0.89–0.98)*	0.95 (0.91–0.99)*	1.0 (0.98–1.03)

* p < 0.05.
** p < 0.001.
*** p < 0.0001.

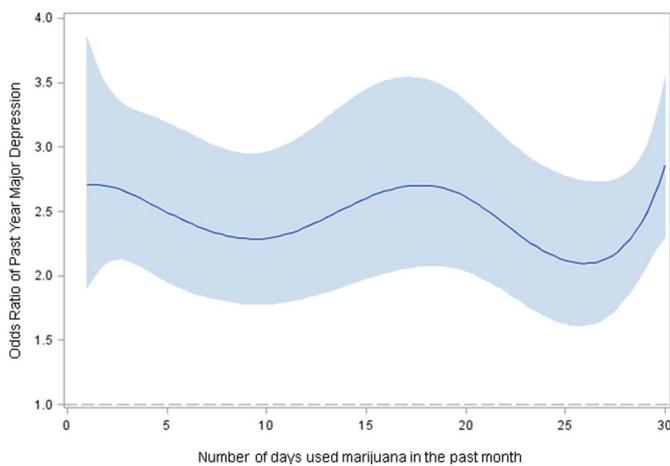


Fig. 1. No change in size of association between past year major depression and endorsement of health symptom across marijuana use frequency in the past month (Odds ratio and 95% confidence band).

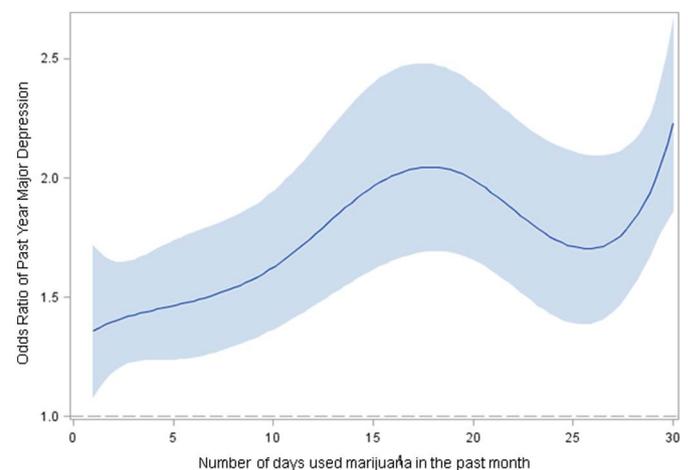


Fig. 3. Increasing size of association between past year major depression tolerance by marijuana use frequency in the past month (Odds ratio and 95% confidence band).

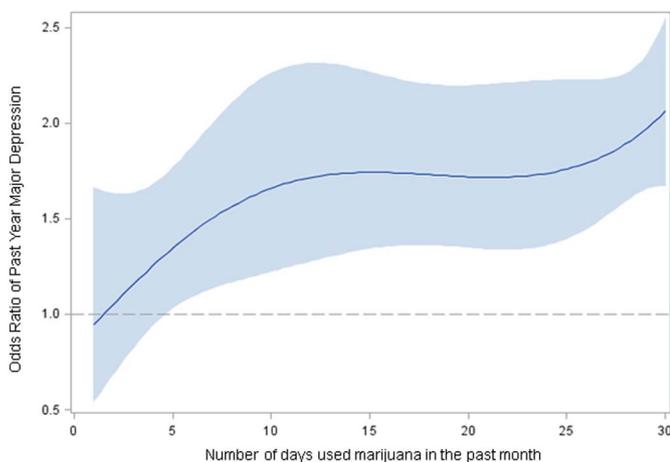


Fig. 2. Increasing size of association between past year major depression and endorsement of failed attempts to cut down by marijuana use frequency in the past month (Odds ratio and 95% confidence band).

could also reflect latent genetic and environmental factors common to both disorders (Bobadilla et al., 2013). Alternatively, the clustering of problems in particular individuals may not be specific to these two

syndromes, but rather may be a broad vulnerability associated with risk for any form of psychopathology (Caspi et al., 2014). Future research will be needed to rule out one or more of these non-exposure related theories.

Varying effects models (VCM's) showed that depression is significantly associated with elevated risk for most marijuana use disorder symptoms similarly across the continuum of past month marijuana use frequency suggesting that depression is an important risk factor for marijuana use disorder symptoms even among those using marijuana infrequently. Specifically, VCM's showed significant and consistently strong associations between depression and most of the marijuana use symptoms from those using only one day in the past month to those using all 30 days in the past month, symptoms of *cut down* and *tolerance* showing that this relationship became stronger at higher levels of use.

Taken together, these findings generally confirm previous work suggesting that depression may be uniquely associated with substance use disorders rather than with one's level of use per se. For example, evidence from a family study following adolescent tobacco smokers through the age of risk for smoking initiation and escalation showed that depression, as well as several other psychiatric disorders, was associated with the progression to nicotine dependence, but not with experimental or regular smoking in the absence of dependence (Dierker, Avenevoli, Merikangas, Flaherty, & Stolar, 2001). More recently, an investigation of young adult tobacco smokers from the

National Epidemiologic Study of Alcohol and Related Conditions (NESARC) demonstrated that daily smokers with depression were at increased risk for nicotine dependence across the continuum of daily smoking behaviors, and after controlling for smoking quantity (Dierker et al., 2001). The present findings are the first to our knowledge to confirm these patterns of risk in the context of marijuana use.

Though other past month and past year licit and illicit substance use were included in the logistic regression models as covariates, the fact that other illicit substance use in the past year was found to significantly predict endorsement of every marijuana use disorder symptom over and above both depression and marijuana use behavior suggests that marijuana use disorder symptoms are likely influenced by the use of other illicit substances and may play an important and independent role in the experience of those symptoms. Future research should also consider substance use disorder symptoms associated with illicit substance use other than marijuana to determine whether the relationship is driven largely by use or by cross over effects of symptoms from multiple illicit substances. For example, data from preclinical research has supported this possibly by showing that animals that develop tolerance to the effects of one substance may also become tolerant to the effects of the other (Funk, Marinelli, & Lê, 2006).

The current findings should be interpreted within the context of study limitations. First, though we chose marijuana use frequency in the past 30 days as the primary measure of marijuana exposure and controlled for past year marijuana use frequency, an important limitation of the present study is our inability to also consider the quantity of marijuana use. Further, differences in rates of rates of marijuana use disorder symptoms may be driven by systematic differences in subjective evaluations of those symptoms rather than physiological differences in response to marijuana. For example, those with major depression may be more likely to answer questions more negatively and to see themselves as more addicted. Future research using both experimental and epidemiological methods is needed to support or reject this explanation.

Given the cross-sectional nature of the data, it is also important to note that the present findings also have limited implications for understanding the relationship between depression and the emergence of marijuana use disorder symptoms. Longitudinal work will be needed to begin to establish the role of depression and other psychiatric disorders in the emergence of marijuana use disorder symptoms. Given the relatively low base rates of both marijuana use disorders and specific psychiatric disorders, this work may need to be further targeted at high risk samples that maximize the number of informative cases. The relative dearth of nationally representative and up-to-date data on a range of psychiatric disorders and marijuana use behaviors, however, provide limited opportunities to pursue this question from an epidemiologic perspective. Finally, it is important to note that the NSDUH does not measure all marijuana use symptoms as defined by the current Diagnostic and Statistical Manual-V (APA, 2013).

Despite these limitations, the current study has a number of strengths. First, the present study involved a large, nationally representative sample that allowed an examination of marijuana use disorder symptoms over a continuum of number of days used in the past month, and thus can generalize to a broad population of marijuana users age 18 and older. Further, this study examined endorsement of marijuana use symptoms controlling for important covariates such as age, gender, race/ethnicity, marijuana onset age, cigarettes, alcohol and illicit substances other than marijuana. This is also the first study to demonstrate the association between depression and marijuana use disorder symptoms over and above marijuana exposure and across diverse levels of marijuana use frequency.

While marijuana use is a necessary contributor to the development of marijuana use disorder symptoms, the present study provides evidence for individual variability in experiences of those symptoms based on the presence or absence of depression, an association that is not better accounted for by variability in marijuana use. If causally

associated, these findings would suggest that treatment of depression symptoms may prevent or reduce marijuana use disorders. If instead, depression is a risk factor for the development of a marijuana use disorder, best accounted for by a third variable, then individuals with depression represent an important subgroup that may benefit from intervention that directly targets this association (Barrett & Chang, 2016). Understanding the different roles that depression and other psychiatric disorders may play during periods of risk for the establishment of marijuana use behaviors will require sustained and integrated effort across epidemiology and experimental work, both animal and human. Reliance on rich and diverse measurement of marijuana exposure will further allow an identification of population subgroups more or less sensitive to marijuana use disorders across the continuum of exposure.

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Contributors

Lisa Dierker designed the analytic plan, contributed to drafting the initial manuscript, conducted the final analyses, and approved the final manuscript as submitted. Arielle Selya assisted with the analyses, contributed to drafting the initial manuscript, and approved the final manuscript as submitted. Stephanie Lanza, Runze Li and Jennifer Rose contributed to the analysis plan, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Conflict of interest

The authors have no conflicts of interest relevant to this article to disclose.

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