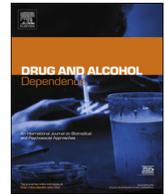




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DSM-5 cannabis withdrawal syndrome: Demographic and clinical correlates in U.S. adults

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ABSTRACT

Background: Cannabis withdrawal syndrome (CWS) was newly added to the Diagnostic and Statistical Manual of Mental Disorders in its most recent edition, DSM-5. With cannabis use increasing among U.S. adults, information is needed about the prevalence and correlates of DSM-5 CWS in the general population. This study presents nationally representative findings on the prevalence, sociodemographic and clinical correlates of DSM-5 CWS among U.S. adults.

Method: Participants ≥ 18 years were interviewed in the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) in 2012–2013. Among the sub-sample of frequent cannabis users in the prior 12 months (≥ 3 times a week; $N = 1527$), the prevalence and demographic and clinical correlates of DSM-5 CWS were examined.

Results: In frequent cannabis users, the prevalence of CWS was 12.1%. The most common withdrawal symptoms among those with CWS were nervousness/anxiety (76.3%), hostility (71.9%), sleep difficulty (68.2%) and depressed mood (58.9%). CWS was associated with significant disability ($p < 0.001$), and with mood disorders (adjusted odds ratios [aOR] = 1.9–2.6), anxiety disorders (aOR = 2.4–2.5), personality disorders (aOR = 1.7–2.2) and family history of depression (aOR = 2.5) but not personal history of other substance use disorders or family history of substance use problems.

Conclusions: CWS is highly comorbid and disabling. Its shared symptoms with depressive and anxiety disorders call for clinician awareness of CWS and the factors associated with it to promote more effective treatment among frequent cannabis users.

1. Introduction

In U.S. adults, cannabis use and cannabis use disorders (CUD) are increasing (Carliner et al., 2017; Charilaou et al., 2017; Compton et al., 2004; Gubatan et al., 2016; Hasin et al., 2015b, 2017) as is cannabis potency (ElSohly et al., 2016). Cannabis use is associated with mental and physical health problems (Hall et al., 2001; Hasin et al., 2016). Abrupt reduction or termination of long-term, frequent cannabis use is associated with a withdrawal syndrome, which includes behavioral, emotional, and physical symptoms (Budney et al., 2004). This syndrome has been shown to contribute to ongoing cannabis use and disrupted daily living (Budney et al., 2004; ElSohly et al., 2016). Neurobiological (Haney et al., 1999a, 1999b; Lichtman and Martin, 2002), clinical (Chung et al., 2008; Copersino et al., 2006; Cornelius et al.,

2008; Schuster et al., 2017), neuroimaging (Hirvonen et al., 2012), and epidemiological studies (Agrawal et al., 2008; Budney and Hughes, 2006; Hasin et al., 2008) supported adding cannabis withdrawal as a syndrome (CWS) to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) and as a criterion for CUD. CWS is diagnosed when within a week after cessation of heavy, prolonged use, ≥ 3 of 7 symptoms occur, including six behavioral or emotional symptoms and one or more of a list of physical symptoms (American Psychiatric Association, 2013). As a new diagnosis, much remains to be learned about DSM-5 CWS. A wide range of prevalences have been reported in earlier studies using varying lists of symptoms and definitions of two, three, or four symptoms (Bonnet and Preuss, 2017), but no large-scale study has reported prevalence using the DSM-5 list of 7 symptoms. Further, some studies (Copersino et al.,

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2010; Herrmann et al., 2015), but not others (Allsop et al., 2011; Budney et al., 1999), suggest that women experience higher rates of some cannabis withdrawal symptoms than men. Results on the associations of CWS with psychiatric comorbidity have been inconsistent (Allsop et al., 2012; Budney et al., 2003; Crowley et al., 1998; Hasin et al., 2008; Wiesbeck et al., 1996), as have studies of the association of CWS with family history of substance problems (American Psychiatric Association, 2013; Budney and Hughes, 2006). These inconsistencies are likely due to the wide variation in settings (inpatient, outpatient, non-patient), frequency of cannabis use, and measures used in previous studies. Additionally, to our knowledge, family history of depression has not been examined, but is warranted due to the anxious/depressed nature of many CWS symptoms.

Two earlier studies examined cannabis withdrawal in the 2001–2002 National Epidemiological Survey for Alcohol and Related Conditions (NESARC) (Agrawal et al., 2008; Hasin et al., 2008). Both studies showed that cannabis withdrawal symptoms were prevalent and associated with psychiatric disorders and intensity of cannabis use. However, NESARC did not cover the DSM-5 cannabis withdrawal symptoms. Furthermore, one of these studies (Hasin et al., 2008) examined lifetime cannabis withdrawal symptoms, potentially limiting recall among participants who used cannabis many years previously (Margetts et al., 2003). Additionally, NESARC data were collected over fifteen years ago. Therefore, a study of DSM-5 CWS in a more recent nationally representative sample using consistent measures across all sub-groups was needed.

Accordingly, we examined CWS using data from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions—III (NESARC-III), the only nationally representative survey that measured DSM-5 cannabis withdrawal symptoms. Among respondents who were frequent cannabis users in the past 12 months, we addressed two questions. First, what is the 12-month prevalence of CWS and its specific symptoms? Second, what sociodemographic and clinical characteristics are associated with CWS?

2. Materials and methods

2.1. NESARC-III sample

The NESARC-III target population was civilians ≥ 18 years in households and selected group quarters (Grant et al., 2013, 2015a). Respondents were selected through multistage probability sampling, including primary sampling units (counties/groups of contiguous counties); secondary sampling units (SSU; groups of Census-defined blocks); and tertiary sampling units (households within SSUs) from which respondents were selected, with Blacks, Asians, and Hispanics oversampled. Data were adjusted for nonresponse and weighted to represent the U.S. population based on the 2012 American Community Survey (United States Census Bureau, 2018). These weighting adjustments compensated adequately for nonresponse (Grant et al., 2015a). Face-to-face interviews in respondents' homes were conducted with 36,309 participants. The household response rate was 72%; person-level response rate, 84%, and overall response rate, 60.1%. NESARC-III methodology is described further elsewhere (Grant et al., 2013). Informed consent was electronically recorded; respondents received \$90.00 for participation. Institutional review boards at the National Institutes of Health and Westat (NESARC-III contractor) approved the study protocol. The analytic sample included 1527 participants who were 12-month frequent cannabis users, defined as using cannabis ≥ 3 times a week based on self-reports of 12-month frequency of use, as has been done previously (Hasin et al., 2008). This is consistent with most previous studies that investigated cannabis withdrawal and included frequent cannabis users in their samples (Allsop et al., 2012; Budney et al., 2003; Haney et al., 1999a, 1999b; Hasin et al., 2008; Herrmann et al., 2015; Wiesbeck et al., 1996).

Table 1

Prevalence of DSM-5 cannabis withdrawal symptoms experienced in the past 12-month among frequent cannabis users^a.

Cannabis withdrawal symptom	Frequent cannabis users (N = 1527) Prevalence % (SE)	Frequent cannabis users with DSM-5 CWS ^b (N = 184)
Nervousness or anxiety	12.9 (1.28)	76.3 (3.63)
Hostility (i.e., irritability, anger or aggression)	13.6 (1.30)	71.9 (4.60)
Sleep difficulty	14.4 (1.12)	68.2 (4.08)
Depressed mood	10.9 (1.09)	58.9 (4.92)
Restlessness	6.6 (0.89)	43.1 (4.62)
Decreased appetite/weight loss	4.5 (0.61)	26.7 (3.99)
Any physical symptom	16.2 (1.27)	70.4 (4.81)
Headache	11.7 (0.98)	47.9 (4.82)
Shakiness/tremors	3.8 (0.64)	24.7 (4.00)
Sweating	3.6 (0.67)	22.0 (4.35)
Abdominal pain	2.5 (0.49)	12.1 (2.72)
Chills	1.6 (0.42)	6.7 (2.15)
Fever	0.8 (0.24)	3.1 (1.15)

^a Cannabis use 3 or more days/week in the past year (DSM-5 criterion A for “heavy, prolonged use”).

^b CWS = cannabis withdrawal syndrome; DSM-5 criterion B for CWS: 3 or more of 7 symptoms, occurring within 1 week after cessation or reduction of cannabis use.

2.2. Diagnostic interview

The NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5) is a structured, computer-assisted diagnostic interview designed for lay interviewers (Grant et al., 2015b). The AUDADIS-5 covers frequency and amount of drug and alcohol use, DSM-5 substance use disorders, and psychiatric disorders.

2.3. Cannabis withdrawal

AUDADIS-5 assessed the DSM-5 withdrawal symptoms: nervousness or anxiety; irritability or aggression; insomnia or unpleasant dreams; depressed mood; decreased appetite or weight loss; restlessness; and physical symptoms: abdominal pain, shakiness or tremors, sweating, fever, chills and headache (Table 1). Participants were coded positive for “hostility” if they had responded positively to experiencing either irritability, anger or aggression. Participants were asked if these symptoms occurred when cannabis effects were wearing off (the morning after using or within a few days after stopping or cutting down), within the past 12 months. The occurrence of each withdrawal symptom was assessed in a dichotomous manner (yes/no). Criterion A (heavy, prolonged use) was satisfied for all participants by only including frequent users (use ≥ 3 days/week in the past year). A variable representing Criterion B was constructed from the cannabis withdrawal symptoms, coded positive if ≥ 3 of 7 symptoms were endorsed (Hasin et al., 2008).

2.4. Sociodemographic covariates

These included sex, race/ethnicity, age, marital status, education, 12-month household income, urbanicity, and region (Table 2).

2.5. Psychiatric and substance use disorders (SUD)

Psychiatric disorders included: any 12-month depressive disorder (major depressive disorder, dysthymia, bipolar 1, and bipolar 2); any 12-month anxiety disorder (general anxiety disorder, social phobia, agoraphobia, specific phobias, and panic disorder); any personality disorder (borderline, schizotypal, and antisocial); and 12-month post-

Table 2
Prevalence of DSM-5 Cannabis Withdrawal Syndrome and associations with sociodemographic characteristics in NESARC-III frequent cannabis users (N = 1527).

Sociodemographic characteristic	Prevalence % (SE)	Model 1: Unadjusted Odds Ratio (95% CI)	Model 2: Adjusted for sociodemographics Odds Ratio (95% CI)	Model 3: Adjusted for sociodemographics and tobacco withdrawal overlap ^a Odds Ratio (95% CI)
Total	12.1 (1.13)	NA	NA	NA
Gender				
Female	14.4 (2.02)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Male	11.0 (1.38)	0.7 (0.47-1.13)	0.8 (0.51-1.20)	0.8 (0.54-1.28)
Race/Ethnicity				
White	10.0 (1.49)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Black	15.3 (2.15)	1.6 (1.01-2.60)	1.6 (0.97-2.71)	1.8 (1.06-3.04)
American Indian / Alaska Native	13.7 (5.32)	1.4 (0.56-3.61)	1.2 (0.44-3.21)	1.1 (0.35-3.14)
Asian / Native Hawaiian / Pacific Islander	31.0 (11.92)	4.0 (1.29-12.64)	4.2 (1.32-13.53)	4.5 (1.50-13.80)
Hispanic	12.1 (2.36)	1.2 (0.71-2.13)	1.3 (0.76-2.20)	1.4 (0.84-2.42)
Age (years)				
18-29	15.2 (1.66)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
30-44	11.0 (1.71)	0.7 (0.46-1.03)	0.8 (0.52-1.27)	0.8 (0.54-1.33)
45-64	5.5 (1.72)	0.3 (0.16-0.64)	0.4 (0.17-0.97)	0.4 (0.18-1.08)
65 and older	16.6 (11.65)	1.1 (0.20-6.00)	1.3 (0.19-8.09)	1.8 (0.28-11.88)
Educational level				
Some high school or less	13.0 (2.67)	1.0 (0.58-1.75)	0.9 (0.49-1.56)	0.8 (0.45-1.46)
High school graduate (or GED)	10.6 (1.84)	0.8 (0.49-1.29)	0.8 (0.48-1.32)	0.8 (0.46-1.26)
Some college or higher	12.8 (1.55)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Household income				
\$0 - \$19,999	14.4 (1.76)	1.2 (0.66-2.17)	1.3 (0.72-2.41)	1.3 (0.68-2.28)
\$20,000 - \$34,999	10.7 (2.24)	0.9 (0.44-1.64)	0.9 (0.46-1.83)	0.9 (0.44-1.77)
\$35,000 - \$69,999	8.2 (1.84)	0.6 (0.32-1.22)	0.7 (0.35-1.28)	0.7 (0.35-1.25)
\$70,000 or greater	12.3 (2.80)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Marital status				
Married / Living with someone as if married	9.5 (1.82)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Widowed / Divorced / Separated	8.8 (2.19)	0.9 (0.46-1.80)	1.0 (0.48-2.16)	1.0 (0.45-2.09)
Never married	14.6 (1.49)	1.6 (1.03-2.56)	1.2 (0.74-2.03)	1.2 (0.72-2.01)
Urbanicity				
Urban	11.6 (1.11)	0.7 (0.37-1.46)	0.6 (0.27-1.18)	0.6 (0.28-1.28)
Rural	15.0 (4.08)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Region				
Northeast	14.7 (3.03)	1.5 (0.83-2.66)	1.3 (0.68-2.44)	1.2 (0.65-2.28)
Midwest	12.3 (1.89)	1.2 (0.75-1.95)	1.2 (0.69-2.07)	1.1 (0.63-1.90)
South	12.1 (2.42)	1.1 (0.68-2.09)	1.1 (0.59-1.92)	1.0 (0.54-1.78)
West	10.3 (1.54)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)

Note: Significant ORs appear in boldface.

^a 12-month frequent tobacco users experiencing withdrawal symptoms similar to DSM-5 cannabis withdrawal symptoms, which occurred after reduction or cessation of tobacco use.

traumatic stress disorder (PTSD). Test-retest reliability was fair to moderate for depressive disorders ($k = 0.39-0.40$), anxiety disorders ($k = 0.43-0.51$), and PTSD ($k = 0.41$), with generally good to excellent reliability for corresponding dimensional measures (intraclass correlation coefficients = 0.59-0.79) (Grant et al., 2015b). Test-retest reliability of the personality disorders was good ($k = 0.67-0.71$), and higher for corresponding dimensional measures (0.71-0.79) (Grant et al., 2003; Ruan et al., 2008). These were also validated by associations with psychiatric comorbidity and disability (Grant et al., 2003, 2004; Grant et al., 2008; Pulay et al., 2009; Ruan et al., 2008). Twelve-month substance use disorders (SUD) included alcohol use disorder (AUD), tobacco use disorder (TUD), and other drug use disorders (DUD), coded positive for the following substances: cocaine, hallucinogens, opioids, sedatives, inhalants/solvents, heroin, club drugs, stimulants, and “other drugs.” Reliability and procedural validity of the SUD diagnoses and associated criteria scales is good to excellent (Grant et al., 2015b; Hasin et al., 2015a).

To examine the association of DSM-5 CWS with the rest of the CUD diagnosis, we created a modified 12-month CUD variable in NESARC-III participants that did not include the withdrawal criterion, and was therefore based on the other ten criteria. Participants with 12-month modified CUD were classified by the DSM-5 SUD severity gradient: mild (2–3 criteria), moderate (4–5 criteria), severe (≥ 6 criteria).

To examine the association of CWS with quantity and frequency of

cannabis use in the past 12 months, we created variables indicating the frequency of cannabis use (daily, almost daily, 3–4 times a week) and number of joints usually smoked per day used (1, 2, 3–5, ≥ 6). AUDADIS-5 asked participants about the amount of cannabis used using the following question: “On the days that you used marijuana in the last 12 months, about how many joints did you usually smoke in a single day?” We explored an “intensity” variable that combined the four quantity levels with the three frequency levels, yielding 12 intensity levels (e.g., smoked one joint/day 3–4 times a week).

2.6. Family history of psychiatric problems

Separate AUDADIS-5 family history modules assessed problems with alcohol or drugs and depressive episodes among relatives by asking about observable manifestations of these conditions. These measures have previously been shown to be reliable and valid (Grant et al., 2003; Hasin et al., 1997; Meyers et al., 2015). For consistency with previous studies (Agrawal et al., 2008; Meyers et al., 2015), respondents were coded positive for “parental substance problems” if either biological parent had a history of alcohol or drug problems, and positive for “familial substance problems” if biological parents or siblings had substance problems. “Parental depression” and “familial depression” were coded similarly.

Table 3

Prevalence of DSM-5 Cannabis Withdrawal Syndrome and associations with 12-months psychiatric disorders and SUD in NESARC-III frequent cannabis users (N = 1527).

Comorbid psychiatric disorders	Prevalence % (SE)	Model 1: Unadjusted	Model 2: Adjusted for sociodemographics	Model 3: Adjusted for sociodemographics and tobacco withdrawal overlap ^a
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Any mood disorder	19.3 (2.20)	2.3 (1.60-3.40)	2.6 (1.65-4.13)	2.3 (1.46-3.61)
MDD	20.0 (2.21)	1.9 (1.32-2.79)	1.9 (1.17-2.98)	1.7 (1.09-2.73)
Bipolar 1	22.2 (4.42)	2.2 (1.28-3.82)	2.8 (1.66-4.68)	2.2 (1.31-3.72)
Bipolar 2	14.3 (8.56)	1.2 (0.30-4.88)	1.5 (0.35-6.33)	1.3 (0.28-5.95)
Dysthymia	22.3 (4.48)	2.3 (1.29-4.11)	2.7 (1.34-5.36)	2.5 (1.31-4.79)
Any anxiety disorder	18.2 (2.84)	1.9 (1.28-2.95)	2.0 (1.27-3.23)	1.8 (1.11-2.86)
Panic disorder	22.5 (6.45)	2.3 (1.12-4.83)	2.4 (1.06-5.53)	2.1 (0.93-4.74)
Agoraphobia	21.1 (7.17)	2.0 (0.83-4.79)	2.2 (0.90-5.33)	1.8 (0.68-4.92)
Social phobia	22.9 (6.47)	2.3 (1.08-4.93)	2.5 (0.98-6.47)	2.4 (0.92-6.06)
Specific phobia	15.8 (3.29)	1.4 (0.84-2.35)	1.5 (0.87-2.48)	1.4 (0.80-2.39)
Generalized anxiety disorder	22.8 (5.01)	2.5 (1.36-4.46)	2.5 (1.27-5.07)	2.2 (1.12-4.52)
PTSD	22.9 (3.63)	2.5 (1.63-3.93)	2.4 (1.48-3.80)	2.2 (1.39-3.47)
Any personality disorder	16.5 (2.03)	1.9 (1.26-2.92)	2.0 (1.24-3.13)	1.8 (1.12-2.84)
Schizotypal	20.1 (3.44)	2.1 (1.30-3.48)	2.1 (1.16-3.76)	1.9 (1.07-3.50)
Borderline	18.1 (2.42)	2.2 (1.41-3.35)	2.2 (1.35-3.61)	2.0 (1.22-3.26)
Antisocial	17.2 (2.53)	1.6 (1.07-2.44)	1.7 (1.07-2.70)	1.6 (1.03-2.59)
Substance use disorders				
AUD	14.2 (1.49)	1.4 (0.95-2.20)	1.5 (0.95-2.31)	1.3 (0.85-2.04)
TUD	13.7 (1.58)	1.5 (0.97-2.20)	1.5 (0.93-2.33)	0.8 (0.52-1.31)
Other DUD	9.5 (2.74)	0.7 (0.36-1.47)	0.8 (0.37-1.54)	0.6 (0.33-1.24)

Note: Significant ORs appear in boldface.

Abbreviations: MDD, major depressive disorder; PTSD, post-traumatic stress disorder; AUD, alcohol use disorder; TUD, tobacco use disorder; DUD, drug use disorder.

^a 12-month frequent tobacco users experiencing withdrawal symptoms similar to DSM-5 cannabis withdrawal symptoms, which occurred after reduction or cessation of tobacco use.

2.7. Disability

The 12-item Short-Form Health Survey (SF-12v2) assessed current physical and mental disability, using the respective summary scores. These are reliable and valid measures of current impairment used in population surveys (Gandek et al., 1998). Each SF-12v2 norm-based disability score has a mean of 50, standard deviation of 10, and range of 0–100. Lower scores indicated greater disability.

2.8. Statistical analysis

Weighted prevalences were calculated for CWS and withdrawal symptoms. Logistic regression was used to evaluate the association of CWS with predictors: sociodemographic variables, psychiatric disorders, other substance use disorders, cannabis use variables, and family history of psychiatric problems. Odds ratios (OR) and 95% confidence intervals indicated the association between CWS and predictor variables in two models: uncontrolled (“unadjusted model”) and controlled for sociodemographic characteristics (“adjusted model”). Linear regression, controlling for sociodemographic characteristics, withdrawal from other substances, and CUD (all levels), evaluated the relationship of CWS to SF-12v2 disability scales. Analyses were conducted using SUDAAN 11.0 (Research Triangle Institute, 2012), accounting for the complex sample design.

Sensitivity analyses were conducted to determine if associations of CWS with predictor variables were confounded by symptoms of withdrawal from other substances (alcohol, tobacco, non-medical opioids, heroin, sedatives/tranquilizers, stimulants, cocaine). For each substance, a withdrawal overlap variable was created representing whether any of the cannabis withdrawal symptoms that overlapped with withdrawal symptoms of other substances (Supplementary Table 1) occurred after reduction or cessation of frequent use of the other substance within the past 12 months. For example, frequent tobacco users who reduced or stopped using tobacco and subsequently experienced nervousness or anxiety; irritability, anger or aggression; insomnia;

depressed mood; or restlessness were coded as positive for “tobacco withdrawal overlap.” Logistic regression tested the association of each substance overlap variable with CWS, adjusted for sociodemographics and all other substance withdrawal overlap variables (Supplementary Table 1). Only tobacco withdrawal overlap was associated with CWS. Therefore, additional adjusted models of the association of CWS with other characteristics controlled for sociodemographic characteristics and also tobacco withdrawal overlap.

3. Results

3.1. Prevalence of CWS

Frequent cannabis users in the prior 12 months (N = 1527) represented 3.7% (SE = 0.15) of the NESARC-III sample. Among frequent cannabis users, 12.1% (SE = 1.13) experienced 12-month CWS. Among those with CWS, the most commonly endorsed symptoms were nervousness/anxiety; hostility; any physical symptom; and sleep problems; followed by depressed mood; restlessness; and decreased appetite/weight loss; the individual physical symptoms of fever, chills, and abdominal pain were the least common symptoms (Table 1).

3.2. Association with sociodemographic and clinical characteristics

Frequent cannabis users were primarily male (66%), white (59%), ages 18–29 (50%), college educated (49%), never married (54%), and had low household income (45%) (Table 2). Gender, education, income, urbanicity and region were not associated with CWS. Race/ethnicity and age were significantly associated with CWS in unadjusted and adjusted models (Table 2). Asians/Native Hawaiians/Pacific Islanders had higher odds of CWS compared to Whites, which constituted the reference group (adjusted OR [aOR] = 4.2; 95% CI = 1.32–13.53); Blacks had higher odds of CWS compared to Whites in unadjusted models only. Participants aged 45–64 had lower odds of CWS compared to those aged 18–29 (aOR = 0.4, 95% CI = 0.17–0.97).

Table 4

Prevalence of DSM-5 Cannabis Withdrawal Syndrome and associations with cannabis use variables and family history of psychiatric problems in NESARC-III frequent cannabis users (N = 1527).

	Prevalence % (SE)	Model 1: Unadjusted	Model 2: Adjusted for sociodemographics	Model 3: Adjusted for sociodemographics and tobacco withdrawal overlap ^a
		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Cannabis use				
Frequency of use				
3-4 times a week	9.7 (1.85)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Almost daily	12.3 (1.80)	1.3 (0.77-2.24)	1.4 (0.77-2.46)	1.3 (0.76-2.34)
Daily	13.3 (1.76)	1.4 (0.87-2.35)	1.6 (0.94-2.65)	1.5 (0.88-2.44)
Joints per day				
1 joint per day	8.1 (1.60)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
2 joints per day	10.8 (2.12)	1.4 (0.76-2.44)	1.3 (0.69-2.24)	1.2 (0.68-2.14)
3-5 joints per day	13.8 (1.80)	1.8 (1.05-3.10)	1.6 (0.88-2.74)	1.5 (0.85-2.65)
Over 6 joints per day	25.8 (4.38)	3.9 (2.20-7.01)	3.5 (1.75-7.09)	3.1 (1.55-6.36)
Modified DSM-5 CUD diagnosis (excluding withdrawal)				
No CUD	1.7 (0.45)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
CUD	24.6 (2.20)	19.1 (10.46-34.89)	22.4 (11.47-43.95)	21.5 (10.89-42.30)
Mild	10.7 (1.80)	7.0 (3.51-13.94)	8.5 (4.06-17.73)	8.3 (3.94-17.46)
Moderate	29.0 (5.08)	23.9 (11.24-50.79)	29.5 (12.93-67.40)	27.5 (12.00-63.20)
Severe	54.6 (5.19)	70.2 (36.00-136.78)	91.6 (43.68-192.05)	88.4 (42.79-186.86)
Family history of psychiatric problems				
Parental substance problems	12.4 (1.55)	1.1 (0.71-1.60)	1.0 (0.64-1.50)	1.0 (0.60-1.47)
Familial substance problems	12.6 (14.35)	1.2 (0.74-1.81)	1.2 (0.74-1.84)	1.2 (0.73-1.81)
Parental depressive episodes	16.3 (1.87)	2.2 (1.43-3.36)	2.5 (1.56-4.12)	2.4 (1.45-3.87)
Familial depressive episodes	15.3 (1.73)	2.1 (1.29-3.28)	2.5 (1.54-4.22)	2.4 (1.42-3.94)

Abbreviations: CUD, cannabis use disorder.

Note: Significant ORs appear in boldface.

^a 12-month frequent tobacco users experiencing withdrawal symptoms similar to DSM-5 cannabis withdrawal symptoms, which occurred after reduction or cessation of tobacco use.

With few exceptions, CWS was associated with psychiatric disorders (major depressive disorder, dysthymia, bipolar 1 disorder, generalized anxiety disorder, panic disorder, PTSD, and personality disorders) in unadjusted and adjusted models (aOR range = 1.7–2.8) (Table 3). However, CWS was not significantly associated with AUD, TUD or DUD (Table 3).

The prevalence of CUD among the analytic sample was 47.6%. The prevalence of modified CUD among the analytic sample was 45.4%. Odds of CWS were increased among individuals with modified CUD compared to those without CUD, in unadjusted and adjusted models (aOR = 22.4, 95% CI 11.47–43.95); this association was stronger as CUD severity increased (Table 4).

Frequency of use was not significantly associated with CWS (Table 4). However, amount smoked per day was associated with CWS (Table 4). Smoking six or more joints per day showed significant associations with CWS in unadjusted and adjusted models (aOR = 3.5, 95% CI = 1.75–7.09), while smoking two or 3–5 joints per day was not significantly associated with CWS. Exploration of the multi-level intensity of use variable (combined quantity and frequency) showed that regardless of frequency, only levels of intensity including ≥ 6 joints per day were associated with CWS (Supplementary Table 2).

3.3. Family history of psychiatric problems

CWS was not significantly associated with family history of drug or alcohol problems, but was significantly associated with family history of depression (aOR = 2.5, 95% CI 1.54–4.22) (Table 4).

3.4. Disability

On average, participants with CWS scored 5.67 points (about one-half of a standard deviation) lower on the SF-12v2 mental disability score than those without CWS ($p < 0.001$). Further, models adjusted

for CUDs and for mood and anxiety disorders demonstrated that on average, participants with CWS scored 4.3 points and 3.49 points lower on the SF-12v2 mental disability score, respectively, than those without CWS ($p < 0.001$). CWS was not associated with the SF-12v2 physical disability component ($\beta = 0.70$, $p = 0.47$).

3.5. Sensitivity analysis

Sensitivity analyses that also controlled for tobacco withdrawal overlap (Model 3, Tables 2,3, and 4) produced similar results to models adjusted only for sociodemographic characteristics, with a few exceptions. Black race was significantly associated with CWS, while age and panic disorder were no longer significantly associated with CWS.

4. Discussion

In a rapidly changing landscape of marijuana laws and attitudes, cannabis use continues to increase among U.S. adults (Bonn-Miller et al., 2012; Compton et al., 2004; Hasin et al., 2017). Thus, understanding the potential health consequences of cannabis use has become increasingly important. One potential consequence is cannabis withdrawal. We therefore conducted the first large-scale study of the prevalence and correlates of DSM-5 cannabis withdrawal syndrome (CWS) in the US adult general population. Findings showed that 12.1% of frequent cannabis users experienced CWS. Limiting the sample to heavier cannabis users by excluding frequent users that smoked lower amounts of joints/day could have yielded a higher prevalence of CWS; however, given that this is the first study to examine DSM-5 CWS in a representative sample of the US population, setting a relatively lower bar for “heavy use” was utilized to help capture all potential cases. Among withdrawal symptoms, nervousness and hostility were reported most frequently. CWS was associated with CUD, psychiatric disorders, family history of depression, and mental disability. CWS was generally

not associated with sociodemographic characteristics or SUD-related variables.

Previous studies examining the prevalence of cannabis withdrawal used 2-, 3-, and 4-symptom thresholds and reported a wide range of cannabis withdrawal prevalence, 35%–90% (Allsop et al., 2012; Budney and Hughes, 2006; Chung et al., 2008; Copersino et al., 2006; Cornelius et al., 2008). Only one large-scale, cross-sectional study (Hasin et al., 2008) examined the occurrence of ≥ 3 cannabis withdrawal symptoms, and reported lifetime prevalence of 34.1% among frequent cannabis users. While prevalence is usually higher for lifetime than for 12-month disorders, another possible explanation for the earlier higher prevalence may be that earlier studies included additional symptoms not included in the DSM-5. Therefore, this report of 12-month DSM-5 CWS prevalence adds new information.

The most common withdrawal symptoms were nervousness/anxiety and hostility, consistent with previous human laboratory (Haney et al., 1999a; Jones et al., 1976) prospective and retrospective studies (Budney et al., 1999; Crowley et al., 1998; Kouri and Pope, 2000; Wiesbeck et al., 1996). While physical symptoms were reported less frequently than behavioral and emotional symptoms, headaches, shakiness/tremors, and sweating were prevalent, and at least one physical symptom was reported by $\sim 70\%$ of those with CWS. Whether to include physical symptoms as diagnostic criteria for CWS in the 11th revision of the International Classification of Diseases is currently under discussion (Bonnet and Preuss, 2017). While our results indicate the clinical relevance of these symptoms, further studies (e.g., item response theory analysis) should determine their diagnostic relevance, i.e., to what extent each symptom contributes information about the underlying CWS.

No significant difference in odds of CWS by gender was found, corroborating some previous findings (Arendt et al., 2007; Crowley et al., 1998; Preuss et al., 2010). Results demonstrating higher odds of CWS among certain race groups (Asians/Native Hawaiians/Pacific Islanders, Blacks) and lower odds among 45–64-year-olds were not previously reported and warrant further examination.

This study is the first large-scale report of significant associations between CWS and DSM-5 psychiatric disorders among frequent cannabis users. Findings suggest higher odds of cannabis withdrawal among individuals with depression, anxiety, and antisocial personality disorder (Allsop et al., 2011; Cornelius et al., 2008; Crowley et al., 1998; Hasin et al., 2008). However, no significant association between CWS and 12-month SUDs was observed. These findings are inconsistent with a few reports (Allsop et al., 2011; Greene and Kelly, 2014) demonstrating higher odds of cannabis withdrawal symptoms among individuals with SUD. However, those studies were not nationally representative and did not adhere to the DSM-5 CWS diagnostic criteria. Association between CWS and family history of depression was observed, while no association with family substance problems was observed, inconsistent with results from the NESARC sample showing association of parental substance problems with certain cannabis withdrawal symptoms (Agrawal et al., 2008). Our findings showing no association on the individual or familial level with SUD, and associations on the individual and familial level with anxiety/depression, suggest a specific relationship of affective/anxiety disturbances and CWS. However, prospective studies are needed to understand the directionality of these relationships.

The association between CWS and CUD (without the withdrawal criterion) is consistent with previous reports (ElSohly et al., 2000; Herrmann et al., 2015; Margetts et al., 2003). Moreover, the increased association as CUD severity increases supports previous indications that severity of cannabis withdrawal increases with that of cannabis dependence (Budney et al., 2004; Budney and Hughes, 2006). Only participants smoking ≥ 6 joints/day had higher odds of CWS compared to those smoking one joint/day; this association may be due to severe CUD among very heavy users. Smoking 3–5 joints/day compared to one joint/day and higher frequency of cannabis use compared to lower

frequency, were not significantly associated with CWS. This lack of association may be due to lack of consideration of modes of administration other than smoking and hence, an underestimation of the amount of cannabis used. Further, the intensity variable constructed for this study (combining frequency and quantity of use) may have had low validity, since it did not consider concentrations of THC. The significant association of CWS with SF-12v2 mental disability, even when controlling for CUDs and for mood and anxiety disorders, indicates the clinical importance of CWS. Nevertheless, as mood and anxiety disorders are strongly associated with mental disability (Hasin et al., 2005), there is a need for further studies that can verify our findings, while controlling for other potential confounders.

Study limitations are noted. First, directionality of association cannot be established in cross-sectional NESARC-III data; prospective studies are necessary to establish causality. Second, while DSM-5 requires distress or impairment caused by withdrawal symptoms for a CWS diagnosis, this information was not available in NESARC-III. Third, DSM-5 states that cannabis withdrawal symptoms should not be due to withdrawal or intoxication from other substances. This could not be directly assessed due to the challenge of disaggregating the substance responsible for the withdrawal symptoms among users of multiple substances. Therefore, we addressed the possibility of confounding by withdrawal from other substances in sensitivity analyses. Of the substances assessed, only tobacco withdrawal overlap was associated with CWS. Controlling for tobacco withdrawal overlap had little effect on our findings, suggesting that withdrawal from other substances did not drive the reported results. Further investigation of non-cannabis substances and CWS is warranted in studies designed specifically for this purpose. Fourth, psychosis was assessed only with a single question in NESARC-III. Examining associations between CWS and schizophrenia, although important, would require further analyses that are beyond the scope of the present study. Further research is warranted to examine this association. Finally, inclusion in the analytic sample was based on frequency of use, which was consistent with previous studies investigating cannabis withdrawal among heavy cannabis users (Allsop et al., 2012; Budney et al., 2003; Haney et al., 1999a, 1999b; Hasin et al., 2008; Herrmann et al., 2015; Wiesbeck et al., 1996), but did not account for the amount of cannabis used. NESARC-III does not include data regarding the potency, concentrations, or mode of administration of different cannabinoids used, although most users of newer modes of administration (vaping, edibles) also smoke cannabis (Cranford et al., 2016; Schauer et al., 2016). Therefore, among participants using cannabis, frequency of consumption is unlikely to be underestimated, but for users in modes other than smoking joints, the amount of consumption could be underestimated. Given the increase in cannabis potency in recent decades (Compton et al., 2004; ElSohly et al., 2000), developing reliable measures to investigate the effect of cannabinoid concentration and mode of administration will be important in advancing our understanding of CWS.

Our study also had several important strengths. It is the first to examine the prevalence and correlates of DSM-5 CWS in the adult US general population. Focusing on diagnoses of CWS in the past 12 months reduced the possibility of recall bias, improving the quality of data compared to prior lifetime reports. A rich array of clinical covariates was available to test for their relationship to DSM-5 CWS.

4.1. Conclusions

In summary, CWS is a highly comorbid, disabling condition. Cannabis use is increasing in the US (Compton et al., 2016). With commercial interests likely to further increase the number of cannabis users (Moon and Prentice, 2017), public education about the possibility of cannabis withdrawal is important.

Further, since there is considerable overlap between symptoms of cannabis withdrawal, depression, and anxiety, clinicians should consider screening depressed, anxious patients for regular cannabis use.

Given the increase in public beliefs that cannabis is an effective treatment for depression (Keyhani et al., 2018)—although evidence currently suggests otherwise (Whiting et al., 2015; Wilkinson et al., 2015)—clinicians should ensure that these patients' efforts to self-medicate with cannabis are not unintentionally perpetuating cannabis withdrawal.

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Contributors

Dr. Hasin had full access to all data in the study and takes responsibility for the integrity of the data. All authors played a role in agreement to be accountable for all aspects of the work and have approved the final manuscript. *Study concept and design:* Livne, Hasin. *Acquisition, statistical analysis, interpretation of data:* Livne, Shmulewitz. *Drafting of manuscript:* Livne. *Critical revision of manuscript:* Shmulewitz, Lev-Ran, Hasin. *Intellectual content:* All authors. *Administrative support and study supervision:* Hasin.

Conflict of interest

No conflict declared by any author.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.drugalcdep.2018.09.005>.

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