Full length article

Mental health functioning and severity of cannabis withdrawal among medical cannabis users with chronic pain

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ARTICLE INFO

ABSTRACT

Purpose:To describe patterns of cannabis withdrawal among a large sample of those who use medical cannabis and test the association between withdrawal symptomology and functioning.

Procedures:Adults ages 21 and older (N = 801) who were seeking medical cannabis certification (either for the first time or as a renewal) for chronic pain at medical cannabis clinics in southern Michigan completed baseline measures of cannabis use, withdrawal symptomology, functioning and other related constructs. Patients were included in the current study if they endorsed using cannabis at least weekly over the past three months. Of the persons in the baseline sample (N = 801), 83% endorsed using cannabis at this level of frequency and duration (N = 665).

Findings:Approximately two-thirds of the sample (67.8%) reported at least one moderate or severe withdrawal symptom. The most commonly observed symptom was sleep difficulties (50.3%), followed by anxiety (27.8%), irritability (26.7%), and appetite disturbance (25.2%). Patients with low mental functioning had significantly higher rates of withdrawal symptom endorsement than patients with high mental functioning. However, no association was observed between physical functioning and withdrawal symptom endorsement. These patterns of association were consistent in multivariate analyses that controlled for other potentially confounding variables.

Conclusions:Cannabis withdrawal symptomology is highly prevalent among patients who use medical cannabis at least three times a week. Helping patients recognize the association between poorer functioning and withdrawal may be an effective way to highlight potentially negative consequences of regular and moderate heavy use.

1. Introduction

Cannabis withdrawal is now a codable disorder in the 5th edition of the Diagnostic and Statistical Manual (DSM-5, 2013). Considerable evidence has accumulated showing that abrupt cessation of prolonged and heavy cannabis use is associated with a variety of withdrawal symptoms, including (but not limited to) headaches, sleep disturbances, irritability, and anxiety (Bonnet and Preuss, 2017; Hesse and Thylstrup, 2013; Lee et al., 2014; Levin et al., 2010). Cannabis withdrawal symptoms can occur within 24 h of cessation and lead to clinically meaningful distress and functional impairments (Allsop et al., 2012). Symptoms of cannabis withdrawal are important because they can sustain cannabis use as a means of avoiding aversive physical and mental discomfort, reducing odds of quitting, and increasing risk of relapse (Schlienz et al., 2017).

Cannabis withdrawal is a common experience among those who frequently use cannabis. For example, data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Wave I) show that approximately one-third of frequent users (≥ 3 times per week) experienced three or more withdrawal symptoms following cessation (Hasin et al., 2008), and approximately 44% experienced two or more. As reviewed by Bonnet and Preuss (2017), cannabis withdrawal syndrome occurs in approximately 90% of patients with cannabis dependence. Other studies show that 35–75% of patients seeking cannabis detoxification also experience a post-cessation cannabis withdrawal (Bonnet and Preuss, 2017). With the rapidly changing laws for both medical and recreational cannabis (Hasin, 2018), the population of frequent cannabis users is likely to increase (Wilkinson et al., 2016), as is cannabis potency and availability (Sevigny et al., 2014), and consequently, incidence of cannabis withdrawal.

The strongest and most consistent predictors of cannabis withdrawal are frequency, duration, and amount of use. Together, these predictors make a pattern that is consistent with other substances that have a corresponding withdrawal syndrome (Hasin et al., 2013). Cannabis withdrawal symptoms are also associated with having depression, anxiety, panic, and personality disorders (Hasin et al., 2008), and Schuster et al. (2017) found that patients with a psychiatric disorder reported a longer duration and increased severity of withdrawal symptoms than those without a disorder. Although cannabis use is higher among males, females progress more quickly to cannabis dependence and show greater withdrawal severity (Schlienz et al., 2017). Almost no other socio-demographics have been found to be associated with cannabis withdrawal. For example, using the NESARC, Hasin et al. (2008) found almost no differences in cannabis withdrawal presentation across age, sex, ethnicity, and education.

While research has linked psychopathology to cannabis withdrawal, the focus has been primarily on the association with specific psychiatric disorders (e.g., Chauchard et al., 2018; Gillespie et al., 2018; Hasin et al., 2008). These linkages are important for understanding potential risk factors for cannabis withdrawal, but our knowledge is limited. More specifically, this research is unclear as to whether the risk for cannabis withdrawal is linked to specific disorders or specific symptoms of a disorder, or whether the risk is linked to broader measures of functioning that are characteristic of disorders.

Clarifying these relationships is important for developing targeted intervention and patient education materials. More broadly, much of the research on cannabis withdrawal was conducted prior to legalization of cannabis for medical uses. Twenty-nine states and the District of Columbia, Guam and Puerto Rico have legalized cannabis use for individuals with qualifying medical conditions (Marijuana Policy Project, 2018). Analyses of the 2013 National Survey on Drug Use and Health (NSDUH) indicates that the prevalence of any past year "medical" use of cannabis in adults is approximately 1%, which translates into slightly more than 2.8 million US adults (Lin et al., 2016). These numbers have likely increased over recent years.

Basic data are lacking on the prevalence and correlates of cannabis withdrawal among those who use medical cannabis, especially among those who use medical cannabis for chronic pain. In a review by Park and Wu (2017), chronic pain was found to be the most commonly reported reason for cannabis use. Chronic pain often leads to functional impairments, which may be an important factor related to the experience of cannabis withdrawal. Based on Lazarus and Folkman's (1984) cognitive-phenomenological model of stress and coping, an individual's level of stress associated with the cessation of cannabis depends on her or his appraisal of the situation vis-à-vis the availability of internal and external resources (Dysvik et al., 2005; Sinclair, 2001). Functional impairments, both psychological and physical, may result in magnification of withdrawal symptoms, or erode one's internal resources that are necessary to cope. In addition, for individuals who regularly use cannabis for medical reasons and are not seeking treatment, highlighting the presence of withdrawal symptoms and the potential link with functional impairment could potentially motivate them to look at options for modifying their use.

The current study builds on this research by describing patterns of cannabis withdrawal among a large sample of adults who use medical cannabis for chronic pain and tests the association between withdrawal symptomology and functioning. We specifically test the hypothesis that mental functioning and physical functioning are inversely related to cannabis withdrawal symptomology.

2. Methods

2.1. Participants

Data from this study are from a larger project designed to identify patterns of cannabis use in medical cannabis patients with chronic pain.

Adult patients (≥ 21 years old) attending a medical appointment for certification or recertification for a state medical cannabis card were eligible for screening. Patients were approached by trained research assistants in clinic waiting areas at two different certification centers in the state of Michigan. Consenting participants completed a 15–30-min self-administered screening survey, and their responses were used to determine study eligibility. To help minimize response bias, potential participants were informed that participation in the study was entirely separate from the cannabis card eligibility process and none of the data collected as part of the research process would be available to anybody beyond the study team.

Inclusion criteria were: self-report of pain in the past month, of at least "usual pain" 5 or greater on a 0–10 numeric rating scale (Farrar et al., 2001), and self-reported chronic pain as a medical reason for seeking medical marijuana. Patients were excluded from the study if they were seeking medical cannabis for Alzheimer's disease or cancer. Women were excluded if they reported being pregnant.

Of the 2569 patients who presented to the study sites during the recruitment period, a total of 1485 patients (58%) completed the screening survey. This response rate indicates a possible sampling bias, which is given further consideration in the discussion section. Of the 1485 patients who completed the screening survey, a total of 801 patients (54%) met eligibility and agreed to participate in the study. The current study is an analysis of a subset of patients from the baseline sample who were moderate to heavy recent users of cannabis (N = 665).

2.2. Measures

2.2.1. Past 3-month cannabis use

In the current study, we identified moderate to heavy recent users of cannabis with the following question: *In the past 3 months, how often have you used cannabis?* Response options were based on a 5-point ordinal scale: Never, once or twice, monthly, weekly, or daily (or almost daily). Patients who endorsed using cannabis weekly or daily (or almost daily) were included in the current study.

2.2.2. Cannabis-related problems

The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) was used to assess for cannabis-related problems. This included six items that specifically assess problematic cannabis use within the past three months (e.g., strong urge to use cannabis, failure to do what's normally expected). A sum score was created and re-weighted based on the scoring algorithm provided by the World Health Organization (Humeniuk et al., 2006).

2.2.3. Other substance use

We assessed for past 6-month use of other substances including methamphetamines, heroin, and cocaine, along with non-medical use of prescription stimulants, prescription opioids, and prescription sedatives. Responses were coded as never, once or twice, monthly, weekly, and daily (or almost daily). From these data, we created a comorbid substance use indicator if the respondent reported weekly or daily (or almost daily) use of any substances that were assessed.

We also included a summed score based on the Alcohol Use Disorders Test (AUDIT; Babor et al., 2001) based on past 6-month patterns of alcohol use. This includes questions of frequency of alcohol consumption, typical number of drinks, and number of occasions in which six or more drinks were consumed. Each item was scored on a 5-point response scale, which results in an overall score ranging from 0 to 12.

2.2.4. Cannabis withdrawal

Cannabis withdrawal symptoms were measured with the Marijuana Withdrawal Checklist (Budney et al., 2003, 1999). This checklist includes 15 different withdrawal symptoms (e.g., sleep difficulty,

irritability, depression). Patients were asked to rate the severity of each withdrawal symptom when they do not use cannabis for a significant amount of time. Response options were: 0 = *None*, 1 = *Mild,* 2 = *Moderate,* 3 = *Severe.* A severity rating was computed by summing all the items. A symptom count score was also computed by counting the number of withdrawal symptoms that received a rating of *Moderate* or *Severe.*

2.2.5. Mental and physical functioning

The primary measures of mental and physical functioning were based on the mental component score (MCS) and physical component score (PCS) of the Short Form-12 Health Survey (SF-12; Ware et al., 1996). The MCS and PCS measure the perception of impact of mental health symptoms and physical problems (respectively) on one's daily activities using a 6-point Likert-type response scale (1 = *all of the time*, 6 = *none of the time*). For both the MCS and PCS, standardized scores were computed and ranged from 0 to 100, with a higher score representing a higher level of functioning.

Two additional measures of functioning were also included in the current study: emotion regulation and pain severity. Emotion regulation was measured using an 8-item version of the Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004). This scale is used to assess how patients respond to emotionally challenging situations (e.g., *When I'm upset, it takes me a long time to feel better.*) All responses are based on a 5-point Likert-type scale (1 = Almost never, 5 = Almost always). Higher scores indicate more difficulties regulating emotion. It should be noted that this measure was introduced after the commencement of the parent project. Thus, about 35% of the sample in the current study does not have data on this measure.

Pain severity was assessed using three items from the West Haven-Yale Multidimensional Pain Inventory (WHY-MPI; Kerns et al., 1985). Each item was rated using a 7-point response scale. The specific items included: Level of pain at the present moment (0 = *No pain*, 6 = *Extreme pain*); average pain severity over the past week (0 = *No pain,* 6 = *Extreme pain*); and the amount of suffering experienced because of pain (0 = *No suffering*, 6 = *Extreme suffering*). These three items were summed to produce an overall pain severity score.

2.2.6. Demographics

The screening and baseline survey included a large number of demographic variables. In the current study, we include a subset of these variables, including sex, age, race/ethnicity, and education (highest grade completed in school).

2.3. Statistical analysis

With the exception of the DERS, < 7% of the study variables had missing data. As previously noted, the secondary measure of mental functioning (DERS) was introduced after the commencement of the baseline survey and, therefore, complete data are available only for 65% of the sample. Approximately 92.3% of subjects provided responses to all items on the cannabis withdrawal index, which was required to compute a withdrawal symptom count and withdrawal severity score. No differences were observed among participants with and without missing data. Because of the large sample size, case wise deletion was used for each analysis. Pairwise deletion was used for handling missing data in bivariate analysis, and listwise deletion was used in multivariate analysis. Subsequent sensitivity analyses showed the results were robust to how missing data were handled.

Descriptive statistics were performed to characterize the sample and study variables. The frequency, rate, severity, and total symptom count were also computed for the overall sample and by various levels of functioning. Each measure of functioning was used as a continuous measure (raw score) and a categorical measure based on a median split of the variable (low functioning vs. high functioning).

Multivariate linear regression models were used to test the

hypothesis that mental and physical functioning is inversely related to cannabis withdrawal symptom severity, while controlling for other study variables. Separate models were specified for different measures of functioning to address problems of variance inflation given their strong intercorrelations. All analyses were conducted using the statistical programming language R (R Core Team, 2013, v3.5.1), and data visualizations were created using Tableau (Hanrahan, 2003, v2018).

3. Results

3.1. Sample description

Patients were included in the current study if they endorsed using cannabis at least weekly over the past three months. Of the persons in the baseline sample (N = 801), 83% endorsed using cannabis at this level of frequency and duration (N = 665). The majority of patients reported daily (or almost daily) use of past 3-month cannabis use (87.2%, N = 580), which was significantly greater than patients reporting weekly use (12.8%, N = 85).

Among those who reported daily (or almost daily use) over the past three months, 97.2% (N = 564) reported the same amount of use over the past 6-month period. This shows a very stable pattern of use among the daily (or almost daily) users. The majority of patients who reported weekly cannabis use over the past three months also reported the same pattern over the past six months (85.9%, N = 73). Reduction in use was more common than an increase in cannabis use (N = 9, vs. N = 3).

3.1.1. Demographics

As summarized in Table 1, this study was comprised of slightly more males than females (53.6% vs. 46.4%). Most patients were white (86.7%) and married or in a long-term relationship (54.0%), with a mean age of 45.0 years (*SD* = 12.87). Over half the sample reported having more than a high school education (65.7%).

3.1.2. Cannabis-related problems

Cannabis-related problems were measured using the ASSIST. The ASSIST scores ranged from 4 to 34, with a mean of 11.65 (*SD* = 5.25). The suggested cutoff for high risk (dependence) cannabis use is 27 or greater (Humeniuk et al., 2006). Only 12 patients in the study sample (1.8%) reached this level of use.

3.1.3. Comorbid substance use

Over 94% of participants denied any use of cocaine, methamphetamines, and heroin, as well as non-medical use of prescription stimulants, prescription sedatives, and prescription opioids during the past six months. Among those who endorsed use, the modal response was *once or twice.* Overall, only 1.6% of the sample (N = 10) had comorbid *weekly* or *daily / almost daily* drug use. AUDIT-C scores ranged from 0 to 12 (Mode = 0, Mean = 1.89, Median = 1, SD = 2.36). The percent of hazardous drinking was significantly higher for males compared to females (30.3% vs. 21.8%), using differential scoring thresholds.

3.1.4. Mental and physical functioning

The two primary measures of mental and physical functioning are derived from the SF-12, including the SF-12 Mental Component Score (SF-12 MCS) and the SF-12 Physical Component Score (SF-12 PCS). For these measures, higher scores indicate higher levels of functioning. The SF-12 MCS ranged from 10.59 to 72.33 (*M* = 45.63, *SD* = 11.40). The SF-12 PCS ranged from 8.85 to 56.58 (*M* = 33.58, *SD* = 7.82). A median split was used to create categorical measures of functioning (low vs. high). Approximately one-fourth of the sample (23.5%) was high functioning on both measures; 18.0% was low functioning on both measures; and almost half the sample was low functioning on either the physical or mental functioning measure (53.3%).

Two secondary measures of functioning were included in this study to provide a more robust test of the relationships. These are

Table 1

Sample description of medical cannabis patients.

Variable	Value
Age, Mean (sd)	45.05 (12.87)
Gender – Male, N (%)	331 (53.6)
Race – N (%)	
Black	66 (10.7)
White	536 (86.7)
Other	16 (2.6)
Marital status – N (%)	
Divorced, separated, widowed	140 (22.7)
Married, long-term relationship	334 (54.0)
Never married	144 (23.3)
Education – N (%)	
< High school	43 (7.0)
High school or equivalent	169 (27.3)
> High school	406 (65.7)
ASSIST, Mean (sd)	11.65 (5.25)
Past 6-month weekly or daily / almost daily comorbid drug use[1] N (%)	10 (1.6)
AUDIT-C raw score, Mean (sd)	1.89 (2.36)
AUDIT-C hazardous drinking N (%)	
Men	29.9% (99)
Women	21.3% (61)
SF12 Physical, Mean (sd)	33.53 (7.88)
SF12 Mental, Mean (sd)	45.90 (11.44)
Emotion regulation, Mean (sd)	14.90 (5.56)
Pain severity, Mean (sd)	3.89 (1.04)
Withdrawal symptom severity, Mean (sd)	8.75 (8.48)
Withdrawal symptom count, Mean (sd)	2.74 (3.14)

Note: [1]Based on whether the respondent indicated weekly or daily/almost daily use of cocaine, methamphetamines, or heroin, or non-medical use of prescription stimulants, prescription opioids, or prescription sedatives.

conceptually similar but empirically distinct constructs. The supplemental mental functioning measure was the Difficulty with Emotion Regulation Scale (DERS). Scores on the DERS ranged from 8 to 40 ($M = 15.0$, $SD = 5.5$). Unlike the SF-12 MCS, higher scores on the supplemental measures indicate lower levels of functioning. Thus, a negative correlation between the SF-12 PCS and DERS was expected and observed ($r = -0.54$, $p < .0001$). A pain severity score was also computed as a secondary measure of physical functioning. Scores on pain severity ranged from 0.67 to 6.0 ($M = 3.91$, $SD = 1.03$). Higher scores on the pain severity scale indicate lower levels of functioning. Thus, a negative correlation between the SF-12 MCS and pain severity was also expected and observed ($r = -0.38$, $p < .0001$).

3.2. Cannabis withdrawal symptoms

3.2.1. Univariate summary and trend analyses

A total of 15 different withdrawal symptoms were assessed (excluding "other"). Withdrawal severity scores ranged from 0 to 40 ($M = 8.75$, $SD = 8.48$). A count of symptom scores was computed for symptoms that patients endorsed as being *moderate* or *severe*. Fig. 1 displays the percentages of each individual symptom endorsed for the entire sample and separately for those who used cannabis weekly but less than daily and those who used cannabis daily. In the overall sample, 67.8% (N = 419) reported at least one moderate or severe withdrawal symptom. The most commonly observed symptom was sleep difficulties (50.3%), followed by anxiety (27.8%), irritability (26.7%), and appetite disturbance (25.2%). Those who used cannabis daily endorsed each symptom at a higher rate than those who used weekly, except for anger (11.9% vs. 15.9%). The differences between those who used less than daily versus daily was not subjected to statistical tests due to the multiple comparisons and the risk of Type I error.

The number of withdrawal symptoms endorsed at the moderate or

severe level ranged from 0 to 15 ($M = 2.64$, *Median* = 1.0, *Mode* = 0, $SD = 3.17$). Fig. 2 shows the rate of co-occurrence for each symptom endorsed. The figure is read from left to right (by column), and then top to bottom (by row) using an *if-then* statement. More specifically, *if* a respondent endorsed a sleep problem (column variable), *then* the rate of co-occurring symptoms is found in the corresponding row. Using sleep as an example, the figure shows high rates of co-occurrence with anxiety (0.45), irritability (0.45), and restlessness (0.42). Overall, among respondents who endorsed any withdrawal symptom, 0.45 and 0.91 of these respondents also endorsed problems with sleep, anxiety, or irritability.

3.2.2. Bivariate associations among functioning and withdrawal symptoms

Low and high functioning groups were constructed using a median split based on the secondary measures of functioning. Fig. 3 shows the differences in cannabis withdrawal symptoms based on this measurement approach. More specifically, patients with low functioning on the SF-12 MCS had significantly higher rates of withdrawal symptoms on 13 of 15 withdrawal symptoms. No differences were observed for vivid dreams and sweating, which were also among the withdrawal symptoms with the lowest base rate of endorsement. The largest differences in rates of symptoms endorsement were for sleep disturbance (low functioning = 59%, high functioning = 42%) and depressed feelings (low functioning = 32% vs. high functioning = 9%).

The patterns of association for physical functioning were considerably different than the mental functioning. More specifically, significant differences between the different groups based on physical functioning exhibited significant differences on five of the items, compared to 13 on mental functioning. Moreover, whereas the low physical functioning group showed higher rates of symptom endorsement on all withdrawal items with significant differences, the direction of effects was reversed. The magnitude of the differences was smaller. For example, the largest differences observed was for headaches (low functioning = 14% vs. high functioning = 22%) and vivid dreams (low functioning = 5% vs. high functioning = 12%).

3.2.3. Secondary measures of functioning and withdrawal symptoms

Low and high functioning groups were constructed using a median split based on the secondary measures of functioning. As shown in Fig. 3, the pattern of association as very similar to the primary measures of functioning. More specifically, on difficulties with emotion regulation, low functioning patients had significantly higher rates on 12 of the 15 withdrawal symptoms. The non-significant differences were observed for vivid dreams, shakiness, and sweating, all of which were the symptoms with the overall lowest base rates. Depressive feelings exhibited the largest group differences (low-functioning = 34% vs. high-functioning = 12%), following by anxiety (low-functioning = 39% vs. high-functioning = 17%) and irritability, (low-functioning = 36% vs. high-functioning = 16%).

Low-functioning patients, defined by the pain severity score, had higher rates of endorsement on four symptoms in comparison to high functioning patients. Sleep disturbances exhibited the largest difference (58% vs. 42%), followed by restlessness (29% vs. 20%), nausea (22% vs. 15%), and stomach problems (14% vs. 9%).

3.2.4. Multivariate associations among functioning and withdrawal symptoms

A series of multivariate regression models were specified to test the association between functioning and withdrawal symptoms, while controlling for potentially confounding variables (i.e., gender, age, race, ASSIST). Two different regression models were specified. The outcome variable for the first model was the symptom severity score on the measure of withdrawal. The primary independent variables were the primary measures of functioning (SF-12 MCS and SF-12 PCS), along with the ASSIST score, and demographic variables (gender, age, race). The second model was specified in the same manner but the secondary
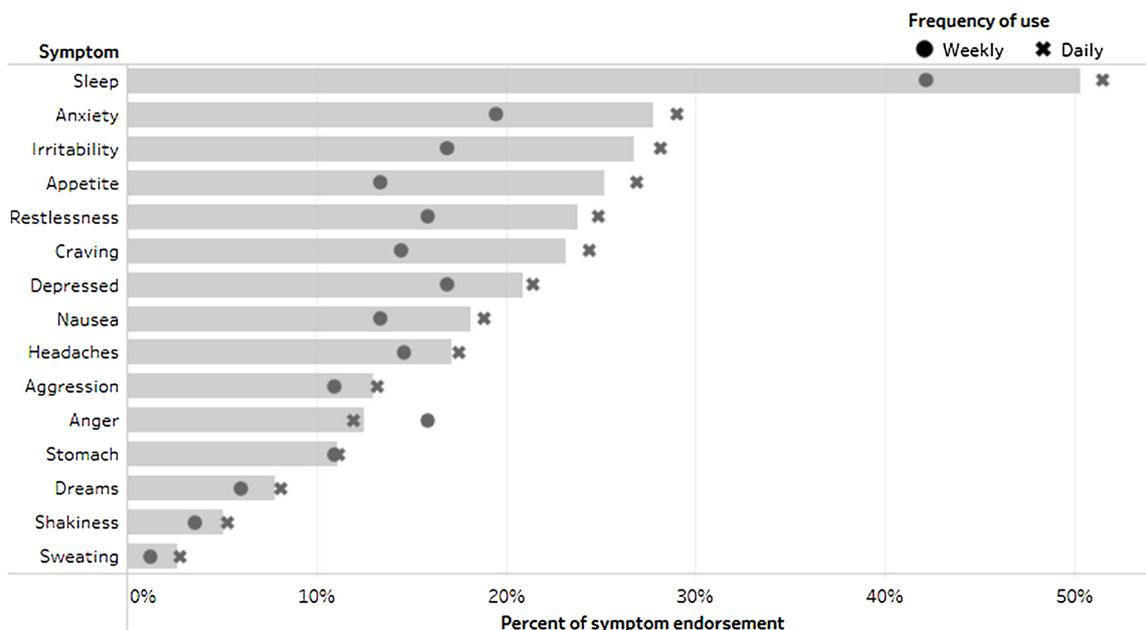
Fig. 1. Prevalence estimates of cannabis withdrawal symptoms by frequency of cannabis use.

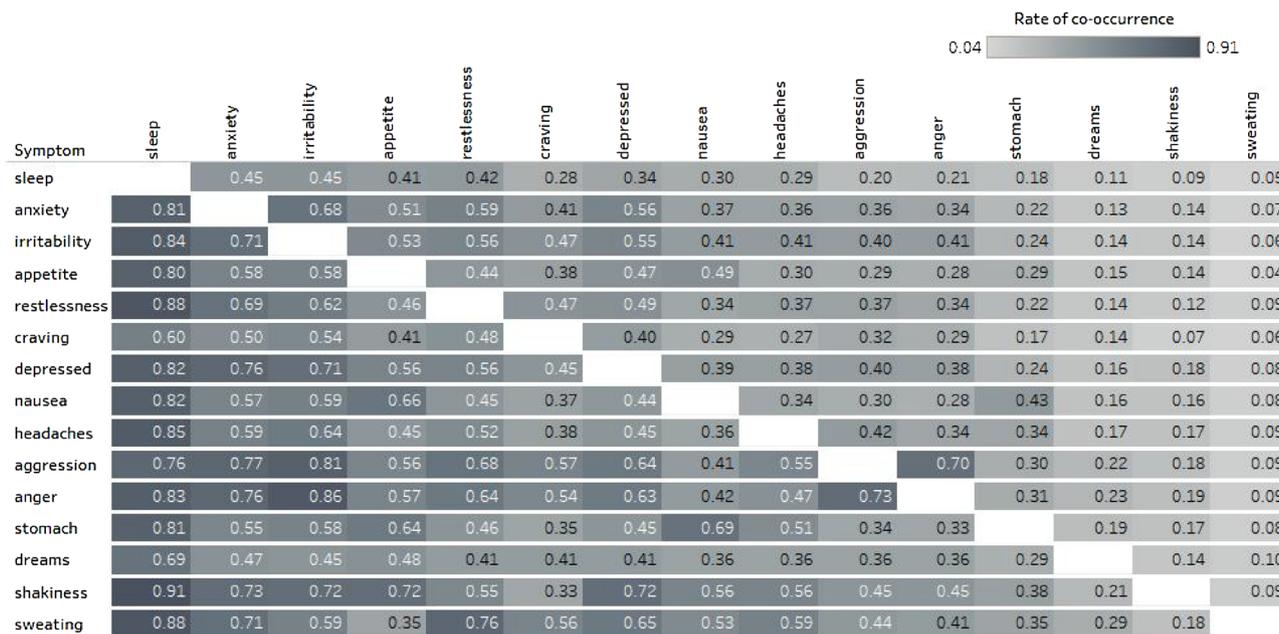| Symptom	sleep	anxiety	irritability	appetite	restlessness	craving	depressed	nausea	headaches	aggression	anger	stomach	dreams	shakiness	sweating
sleep		0.45	0.45	0.41	0.42	0.28	0.34	0.30	0.29	0.20	0.21	0.18	0.11	0.09	0.05
anxiety	0.81		0.68	0.51	0.59	0.41	0.56	0.37	0.36	0.36	0.34	0.22	0.13	0.14	0.07
irritability	0.84	0.71		0.53	0.56	0.47	0.55	0.41	0.41	0.40	0.41	0.24	0.14	0.14	0.06
appetite	0.80	0.58	0.58		0.44	0.38	0.47	0.49	0.30	0.29	0.28	0.29	0.15	0.14	0.04
restlessness	0.88	0.69	0.62	0.46		0.47	0.49	0.34	0.37	0.37	0.34	0.22	0.14	0.12	0.09
craving	0.60	0.50	0.54	0.41	0.48		0.40	0.29	0.27	0.32	0.29	0.17	0.14	0.07	0.06
depressed	0.82	0.76	0.71	0.56	0.56	0.45		0.39	0.38	0.40	0.38	0.24	0.16	0.18	0.08
nausea	0.82	0.57	0.59	0.66	0.45	0.37	0.44		0.34	0.30	0.28	0.43	0.16	0.16	0.08
headaches	0.85	0.59	0.64	0.45	0.52	0.38	0.45	0.36		0.42	0.34	0.34	0.17	0.17	0.09
aggression	0.76	0.77	0.81	0.56	0.68	0.57	0.64	0.41	0.55		0.70	0.30	0.22	0.18	0.09
anger	0.83	0.76	0.86	0.57	0.64	0.54	0.63	0.42	0.47	0.73		0.31	0.23	0.19	0.09
stomach	0.81	0.55	0.58	0.64	0.46	0.35	0.45	0.69	0.51	0.34	0.33		0.19	0.17	0.08
dreams	0.69	0.47	0.45	0.48	0.41	0.41	0.41	0.36	0.36	0.36	0.36	0.29		0.14	0.10
shakiness	0.91	0.73	0.72	0.72	0.55	0.33	0.72	0.56	0.56	0.45	0.45	0.38	0.21		0.09
sweating	0.88	0.71	0.59	0.35	0.76	0.56	0.65	0.53	0.59	0.44	0.41	0.35	0.29	0.18	

Fig. 2. Rates of co-occurring cannabis withdrawal symptoms among frequent and heavy cannabis users.
Note: Rates of co-occurrence are identified by reading the matrix by column, and then by row using an "if-then" Formulation. For example, if "sleep" is a reported withdrawal symptom, then .85 of users will also report a headache.

measures of functioning (DERS and pain severity) were used in place of primary measures of functioning. Although the primary and secondary measures of functioning were correlated at the bivariate level (SF-12 MCS and SF-12 PCS, $r = -0.30$, $p < .0001$; DERS and pain severity, $r = 0.18$, $p < .0001$), the variance inflation index observed in the regression diagnostics was not inflated.

Both multivariate models, summarized in Table 2, exhibited a good fit with the data.

For the primary measures of functioning, higher levels of mental functioning were associated with lower levels of withdrawal symptom severity, but physical functioning was not. An effects plot showing the adjusted regression line and 95% confidence interval is presented in Fig. 4 to show the relationship between these two variables. It should also be noted that this regression model showed age to be negatively

associated with symptom severity, and the ASSIST score to be positively associated with symptom severity.

The second regression model with the secondary measures of functioning showed a similar pattern of association. Higher levels of difficulties with emotion regulation was associated with higher withdrawal severity scores, but pain severity was not significant. The regression line and confidence interval are presented in Fig. 3b. Similar to the regression model with the primary measures of functioning, age was negatively associated with withdrawal severity and ASSIST scores were positively associated with withdrawal severity in the model with the secondary functioning measures.
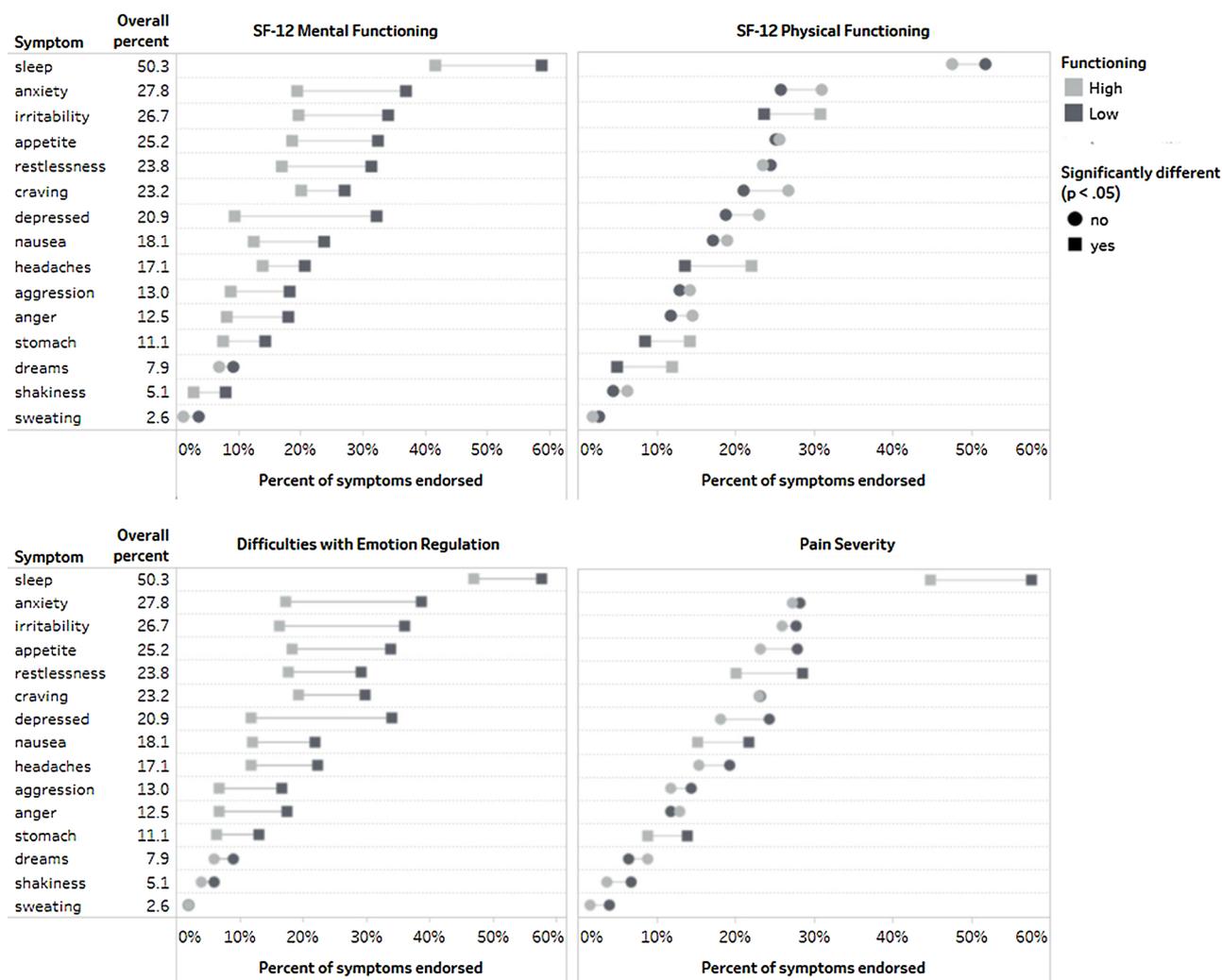
Fig. 3. Prevalence estimates of withdrawal symptoms and differences by levels of mental and physical functioning.

Table 2
Test of association between functioning and withdrawal severity using multivariate linear regression.

Variable	Primary measures of functioning			Secondary measures of functioning		
	Estimate	Standard error	p-value	Estimate	Standard error	p-value
Intercept	20.20	3.19	< .0001	.87	2.60	.739
Gender			.335			.421
Female	Ref	–		Ref	–	
Male	−.56	.67		−.62	.77	
Age	−.13	.03	< .0001	−.12	.03	< .0001
Race						
Black	Ref	–	–	–	–	–
White	1.04	1.07	.34	1.46	1.24	.17
Other	−1.27	2.22	.57	.75	2.34	.65
ASSIST	.29	.07	< .0001	.33	.08	< .0001
AUDIT-C hazardous drinking	−.82	.74	.273	−.20	.85	.819
SF-12 MCS	−.19	.03	< .0001	NA	NA	NA
SF-12 PCS	−.002	.05	.97	NA	NA	NA
DERS	NA	NA	NA	.44	.07	< .0001
Pain severity	NA	NA	NA	.53	.38	.170
Overall model fit	N = 578, F = 12.46 (DF = 9, 568), p < .0001 Adjusted R-square = .15			N = 418, F = 11.04 (DF = 9, 408), p < .0001 Adjusted R-square = .18		

Note: ASSIST = Alcohol, Smoking, and Substance Involvement Screening Test, SF-12 MCS = Short Form Health Survey – Mental Component Score, SF-12 PCS = Short Form Health Survey – Physical Component Score, DERS = Difficulties in Emotion Regulation Scale, AUDIT-C = Alcohol Use Disorder identification test (in men, 4 or greater is considered positive; in women, 3 or greater is considered positive). [1]Comorbid drug use: weekly or daily use of other substances (over the past 6 months) for non-medical reasons including prescription sedatives, prescription opioids, prescription stimulants, methamphetamines, heroin, and cocaine.
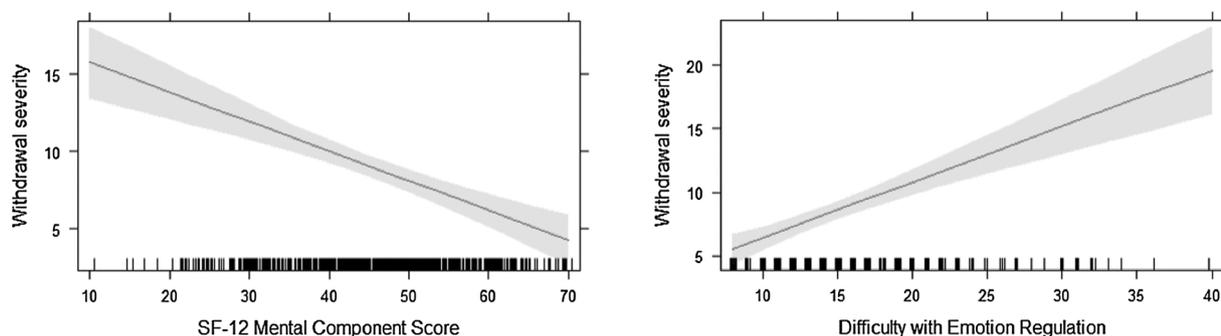
Fig. 4. Adjusted effects of mental functioning on withdrawal severity.
Note: Effects plots are based on the multivariate models presented in Table 2. Higher scores on the SF-12 indicate higher levels of mental functioning. Lower scores on Difficulty with Emotion Regulation indicate higher levels of mental functioning. The strip plot at the bottom of each figure indicates the observed values for the respective measure. The band around the regression line is the 95% confidence interval for the respective estimate.

4. Discussion

4.1. Study objectives and reprise of findings

The purpose of this study was to describe patterns of cannabis withdrawal symptoms in adults who regularly use medical cannabis and test associations between withdrawal symptoms and functioning to determine if mental and physical functioning may serve as risk markers for cannabis withdrawal among frequent medical cannabis users. Limiting the sample to those who used cannabis at least weekly (during the past three months), we found high rates of self-reported withdrawal symptoms. However, only a small percentage of the sample (1.8%) met the ASSIST threshold of having a probable cannabis use disorder. One possible explanation is that medical cannabis users may not be concerned about their patterns of use if they perceive their use as being for medical purposes. This suggests a need for further analyses of the ASSIST and other instruments that have been primarily validated among samples of recreational cannabis users.

Approximately 67% of those who regularly use cannabis experience one or more moderate or severe withdrawal symptoms and withdrawal symptoms were more common in those with more frequent cannabis use. Sleep problems were observed among half the sample, and about one in four respondents reported anxiety or irritability. These withdrawal symptoms co-occurred with other endorsed symptoms at a high rate. The severity and frequency of withdrawal showed consistent associations with mental health functioning, cannabis use problems, and age, but with none of the other study variables.

4.2. Cannabis withdrawal symptomology

Results of this study provide evidence that having at least one withdrawal symptom at a moderate or severe level is the rule rather than the exception among medical cannabis users. Sleep was the most commonly reported withdrawal symptom and exhibited high rates of co-occurrence with other cannabis withdrawal symptoms. A recent review of sleep and cannabis suggests cannabis may have therapeutic potential for treatment of insomnia but could impair sleep quality long-term (Babson et al., 2017). Prior analyses of the data from the same sample documented high rates of sleep problems in medical cannabis patients (Cranford et al., 2017) and the findings of the current study show that sleep-related difficulties are often linked to cannabis withdrawal symptomology. However, further research is needed to understand how cannabis withdrawal and sleep are causally related, or whether a third unmeasured variable may be accounting for this relationship.

Anxiety was another symptom that was endorsed at a high rate among the current sample. However, the association between anxiety

as a withdrawal symptom and cannabis withdrawal is unclear. Recently, Sarvet et al. (2018) suggested that medical cannabis laws may lead individuals to self-medicate, particularly for mood and anxiety disorders. Using data from the NESARC, Wave 2, Sarvet et al. (2018) found self-medication with drugs was over 20 percentage points higher in states with medical cannabis laws. Our current study does not have the methodological design for testing the self-medication hypothesis. Anxiety may be a consequence of cannabis use, or a problem that is effectively being masked by cannabis. As discussed in the following section, cannabis withdrawal is strongly associated with mental health functioning more broadly, so anxiety itself may not be a particularly useful risk factor indicator with more general measures being potentially useful.

4.3. Functioning and cannabis withdrawal

This study systematically tested the associations between socio-demographic variables, clinical variables, and cannabis withdrawal symptoms. Among the full set of variables, two measures of mental health functioning exhibited the strongest and most consistent relationship with cannabis withdrawal. Although our measures of mental and physical functioning were associated with a moderate relationship, cannabis withdrawal symptomology was associated with mental functioning, but not physical functioning.

This study showed that lower levels of mental functioning were associated with more cannabis withdrawal symptoms, which was consistent with our hypothesis. Evidence for this was stable with respect to direction and magnitude of effects for two different measures of mental functioning.

Psychological factors may have a significantly larger drain on the individual's internal coping resources than physical factors. Thus, persons with lower levels of psychological functioning experience greater difficulties in managing various manifestations of cannabis withdrawal and, therefore, report a broader range and increased severity of withdrawal symptoms. Alternatively, the possibility exists that many of the patients who have low mental functioning are self-medicating mental health symptoms, consistent with the recent research by Hasin (2018). The emergence of symptoms like the most common symptoms in this study following cessation of cannabis, e.g., sleep difficulties, anxiety, and irritability, may be mental health symptoms being masked by cannabis, rather than being a distinct cannabis withdrawal syndrome. The current study did not have data to definitely answer whether these explanations may account for the findings.

The study findings have potential relevance for treating persons with cannabis use disorders. More specifically, the rapid alleviation of withdrawal symptoms may be viewed by patients that cannabis is effective for managing physical and psychological distress. This may

result in lack of motivation to reduce cannabis use. Helping patients recognize the association between poorer functioning and withdrawal may be an effective way to highlight potentially negative consequences of regular and moderate to heavy use.

4.4. Strengths, limitations, and next steps

There were several limitations to this study. First, this work is based on cross-sectional survey, limiting our ability to determine the temporal direction of associations. Our survey had a modest response rate during the screening process (58%), which represents a possible response bias. No data are available to determine whether non-survey participants are different than our current sample. Second, our results are based on self-reported data from adults seeking medical cannabis certification in Michigan and, given the variability in marijuana laws across the country, results could look different in others states and include more diverse socio-demographic factors. Relatedly, the present study does not have detailed data on the components of cannabis used, which could impact patterns of use as well as the level and correlates of withdrawal symptoms. Third, we were unable to distinguish differences in withdrawal symptomology and functioning between those who use cannabis for medical and recreational purposes. Additionally, study participants were likely not in a withdrawal state at the time of the study. Therefore, their reports of withdrawal symptomology may be subject to a recall bias.

4.5. Conclusions

Despite these limitations, this is one of few studies to compare symptoms of cannabis withdrawal with broader symptoms of functioning, rather than to specific DSM disorders, which may allow for more effective strategies for intervention. For example, from this work, it may be beneficial to tailor interventions that address sleep difficulties as a high potential cannabis withdrawal symptom for those who display lower physical and emotional functioning. Future research should make systematic comparisons of withdrawal among medical and recreational cannabis users. Additionally, further knowledge is needed to better understand how differences in state laws may affect cannabis use disorders in general and withdrawal specifically.

Contributors

Dr. Perron conceptualized and designed the study with Dr. Ilgen, Ms. Holt, and Ms. Yeagley. Dr. Perron performed data analysis. All authors contributed to the development of the manuscript and approved the final version.

Conflict of interest

No conflict declared.

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