

Running head: Longitudinal cannabis withdrawal
Progression of cannabis withdrawal symptoms in people using medical cannabis for chronic
pain

Lara N. Coughlin, PhD ¹

Mark A. Ilgen, PhD ^{1,2}

Mary Jannausch, MS ^{1,2}

Maureen A. Walton, PhD, MPH ^{1,3}

Kipling M. Bohnert, PhD ^{1,2,4}

¹ Addiction Center, Department of Psychiatry, University of Michigan

² VA Center for Clinical Management Research, VA Ann Arbor Healthcare System

³ Injury Prevention Center, University of Michigan

⁴ Department of Epidemiology and Biostatistics, Michigan State University

Corresponding Author: Lara Coughlin, Ph.D., 2800 Plymouth Rd, Ann Arbor MI 48109

Email: laraco@med.umich.edu

Funding: This research was supported by grant R01 DA033397 from the National Institute on Drug Abuse. LNC's time was funded through NIAAA T32 AA007477. MAI's time was supported by Grant RCS 19-333 from the VA Health Services Research & Development.

Disclosures: MAI has partial ownership in a small company, Arborsense, that is developing a wearable alcohol sensor. The authors have no other conflicts of interest to disclose.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/add.15370](https://doi.org/10.1111/add.15370)

Keywords: cannabis, medical cannabis; withdrawal; marijuana; cohort; cannabis use disorder

Word Count: 3298

Abstract:

Background and aims: Research from cohorts of individuals with recreational cannabis use indicates that cannabis withdrawal symptoms are reported by more than 40% of those using regularly. Withdrawal symptoms are not well understood in those who use cannabis for medical purposes. Therefore, we prospectively examined the stability of withdrawal symptoms in individuals using cannabis to manage chronic pain.

Design: Using latent class analysis (LCA) we examined baseline cannabis withdrawal to derive symptom profiles. Then, using latent transition analysis (LTA) we examined the longitudinal course of withdrawal symptoms across the time points. Exploratory analyses examined demographic and clinical characteristics predictors of withdrawal class and transitioning to more or fewer withdrawal symptoms over time.

Setting: Medical cannabis clinic waiting rooms in Michigan, USA.

Participants: A cohort of 527 adults with chronic pain seeking medical cannabis certification or recertification was recruited between February 2014 and June 2015. Participants were predominantly white (82%), 49% identified as male, with an average age of 45.6 years (SD=12.8).

Measurements: Baseline, 12-month, and 24-month assessments of withdrawal symptoms using the Marijuana Withdrawal Checklist-Revised.

Findings: A three-class LCA model including a mild (41%), moderate (34%), and severe (25%) symptom class parsimoniously represented withdrawal symptoms experienced by people using medical cannabis. Stability of withdrawal symptoms using a 3-class LTA at 12 and 24 months ranged from 0.58 to 0.87 with the most stability in the mild withdrawal class. Younger age predicted greater severity and worsening of withdrawal over time.

Conclusions: Adults with chronic pain seeking medical cannabis certification or recertification appear to experience moderate to severe withdrawal symptoms. Withdrawal symptoms tend to be stable over a two-year period but younger age is predictive of worse symptoms and of an escalating withdrawal trajectory.

Introduction:

Cannabis is one of the most widely consumed drugs in the world. In the United States (US), alone, an estimated 43.5 million people (15.9% of the population) report past-year use (1). The prevalence of cannabis use has also risen steadily over the past decade, coinciding with an increase in the number of states legalizing medical and recreational cannabis use, as well as increases in the perception that cannabis use is harmless (2,3). Further, cannabis use disorder is one of the most prevalent substance use disorders, affecting approximately 1.6% of adults in the US, with 9.3% of those who use cannabis meeting diagnostic criteria (1,4).

As of October 2020, 33 states and the District of Columbia have medical cannabis laws. (5). Approximately 10-17% of those who use cannabis do so for medical reasons in the US (6–9). Although cannabis is used to manage a wide variety of medical conditions, including cancer, glaucoma, severe nausea, and seizures, severe and chronic pain is the most commonly ascribed qualifying medical condition (10–12). Individuals who use cannabis for medical purposes tend to be older, have poorer overall physical and mental health (6,13), use cannabis more frequently, and are at increased risk of developing a cannabis use disorder compared to those who use cannabis for recreational reasons (7,8,14–17).

Prior findings also indicate that symptoms of withdrawal are a common feature of sustained, frequent psychoactive substance use and are a diagnostic indicator of a substance use disorder. Indeed, consistent preclinical (18–21), clinical (22,23), and epidemiological (24,25) research document a withdrawal syndrome during periods of cessation from sustained cannabis use, and led to the addition of Cannabis Withdrawal Syndrome in the most recent version of the *Diagnostic and Statistical Manual of Mental Disorders* (26). Common features of cannabis

withdrawal include anxiety, sleep difficulties, decreased appetite, restlessness, depressed mood, and irritability, among others (27–31). Previous studies of people who use cannabis document the clinical significance of cannabis withdrawal symptoms, which are associated with impaired functioning, more difficulty reducing or quitting use, worse treatment outcomes, and increased likelihood of relapse (29,32–35).

Approximately 17% of individuals who use cannabis experience cannabis withdrawal syndrome, with 40% of those using cannabis three or more times a week experiencing multiple withdrawal symptoms (24,36). Strikingly, in a prior cross-sectional baseline paper from this study, approximately two-thirds of medical cannabis patients reported cannabis withdrawal symptoms during periods of abstinence (13). Although cannabis withdrawal is an important outcome related to health and functioning, the vast majority of studies on cannabis use are cross-sectional. Longitudinal patterns of withdrawal are poorly understood. Therefore, in the current study, we assessed cannabis withdrawal symptoms over two years in people using medical cannabis to ascertain withdrawal symptom classes, examine the degree of stability of withdrawal symptom groups over time, and identify predictors of the withdrawal symptom trajectories over time.

Methods:

Adults were recruited from three medical cannabis clinic waiting rooms in Michigan between February 2014 and June 2015. Eligible participants were 21 years or older, with subjective “usual pain” levels over the past month of 5 or more on a 0 to 10 numeric rating scale (NRS), and self-reported severe/chronic pain as a qualifying condition for medical cannabis certification or recertification. Exclusion criteria included women who reported being pregnant

(n=6) and those seeking medical cannabis certification/recertification for Alzheimer's disease (n=2) or cancer (n=71). Of the 801 participants that met study criteria, consented, and completed the baseline assessment, 527 participants were included in the current analytic sample. The analytic sample included all participants that completed the Marijuana Withdrawal Checklist-Revised (MWC-R) (22) at baseline, 12-months, and 24-months, including four participants who indicated no prior cannabis use at the start of the study so were coded as having no cannabis withdrawal symptoms at baseline. Participants were given the option of completing all assessments with paper-and-pencil or on a computer and compensated \$30, \$40, and \$50 for completion of the baseline, 12-month, and 24-month assessments, respectively.

Measures

Cannabis withdrawal symptoms. Withdrawal symptoms were assessed at each time point using the Marijuana Withdrawal Checklist-Revised (22), which is a validated 15-item measure of withdrawal symptoms (e.g., nausea, irritability, sleep difficulty) that were assessed based on the last time the participant went a significant time without using cannabis. Symptoms were rated from none (0) to severe (3) and were coded as present or not for the purposes of this analysis.

Sociodemographics. Participants provided sociodemographic information including age, gender, and pain level. Pain level was assessed as the participant's usual pain level over the past month from 0 to 10, where 10 represented the worst pain possible.

Physical and mental health. The Short Form-12 Health Survey (SF-12) provides a measure of general physical and mental health and functioning over the past 4 weeks (37). The physical and mental health summary scales were used (38) to obtain a Physical Component Summary

(PCS) and Mental Component Summary (MCS) where higher scores are indicative of better physical and mental health functioning, respectively.

Cannabis use characteristics. Participants provided details about cannabis use including the duration, frequency, amount, method of administration (vape, smoke, eat/drink, topical), number of routes of administration (oral, inhaled, transdermal), and cannabis-related problems.

Participants were able to indicate all methods of administration used in the past month including eating, drinking or ingesting cannabis; inhaling cannabis by smoking or vaping, and transdermal use including oils or lotions on the skin. Cannabis-related problems were based on responses to the Alcohol, Smoking, and Substance Use Involvement Test (ASSIST) assessed over the prior three months (39).

Statistical analysis

The research and analysis plan were not pre-registered and should be considered exploratory. Analyses followed a similar approach to those described in Bohnert et al. (40) and included four analytic steps. In *step 1*, distinct classes of baseline cannabis withdrawal symptoms were assessed using latent class analysis (LCA; 41) via software developed by Lanza, et al (42). LCA categorizes individuals across multiple observed manifest variables (e.g., in this case, withdrawal symptoms) to achieve statistically independent within-cluster response profiles. A series of LCA models with two to five latent classes were considered. Model selection was based on consideration of interpretability, parsimony, and goodness of model fit. In *step 2*, we examined potential differences between participant characteristics and the latent classes identified during step 1. Using multinomial logistic regression, each of the sociodemographic, health status, and cannabis use characteristics described above were evaluated across the

baseline latent classes. Frequencies, means, and standard deviations were used, as appropriate, to populate within-class cells for the summary in Table 1. In *step 3*, we examined how participants transitioned from the baseline latent classes identified in step 1 to other latent classes at the 12- and 24-month time points. The latent transition analysis (LTA) was conducted using measurement invariance to maintain interpretability across the latent classes at each time point. Transition probabilities were estimated for baseline to 12-months and 12-months to 24-months. Latent class membership was assigned based on the highest posterior probability at each time point. In *step 4*, the baseline characteristics (i.e., sociodemographic, health, cannabis use) were considered, using multinomial logistic regression, as potential predictors of transitioning between classes from baseline to 12-months. Odds ratios of transitioning to more or less severe classes were computed for baseline characteristics that were significant in the previous regression models. All steps were conducted in SAS version 9.4 (SAS Institute, Cary, NC USA)

Results:

The sample was predominantly white (82%), with 11% identifying as African-American, and 7% identifying as multiracial or another race. The average age was 45.6 years old (SD=12.8), and a majority of the cohort were married/partnered (54%), 49% of the sample identified as male, 30% had a high school degree or less, and 37% were employed full or part-time including those who were disabled but still employed.

Step 1: LCA at baseline

Model selection was based on goodness-of-fit indices, parsimony, and interpretability of the classes (42). The three-class model was selected among the two- through five-class models

considered (see Supplementary Table 1 for fit indices). The Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Entropy model fit indices all indicate the three class model provides better fit than the four class model. With AIC, BIC, and adjusted BIC indicating the three class model provides better fit than the two class model. The three-class model also had the advantage of being consistent with prior LCA models of the Marijuana Withdrawal Checklist (34). Figure 1 shows the three-class LCA model with the conditional probability of each of the withdrawal symptoms that were endorsed at baseline. The groupings constitute mild, moderate, and severe withdrawal classes. The mild class had very low probabilities of symptom endorsement (mean symptoms (M)=1.1, standard deviation (SD)=1.5, range:0-7), with a slight elevation around sleep and cannabis craving. The moderate class showed increasing symptom endorsement across symptoms (M=7.8, SD=3.6, range:2-22) with the exception of minimal probabilities of sweatiness or shakiness. The severe withdrawal class had high probabilities of withdrawal symptom endorsement across all symptoms (M=19.9, SD=7.1, range:8-40), with the exception of low probabilities of endorsing sweatiness.

Step 2: Associations between baseline measures and LCA classes

Multinomial logistic associations between the three LCA classes and covariates are shown in Table 1. In general, the more severe classes were younger, in better physical health but worse mental health, had used cannabis for more years, were at greater risk for cannabis-related problems (as measured by the ASSIST), used cannabis more frequently, used a larger quantity of cannabis, and smoked cannabis, as opposed to other methods of use, more frequently compared to the mild withdrawal class.

Step 3: LTA at 12 and 24 months following baseline

Using LTA, we estimated the transition probabilities for people in each of the three withdrawal classes from baseline to 12 months and from 12 months to 24 months (see Table 2). The probabilities along the diagonal in Table 2 represented the probability of staying in the current class. The off-diagonal values represent the probabilities of transitioning either to a lower or higher severity withdrawal class over time. At both transition time points, that is to 12 and to 24 months follow-up, people in the mild withdrawal class showed the most stability (i.e., highest probability of remaining in the same class). For those that did transition out of the mild symptom class, there was a higher probability of transitioning to the moderate than the severe withdrawal class. People in the severe withdrawal class had a higher probability of transitioning to the moderate severity class than the mild withdrawal class. The moderate withdrawal class had a higher probability of transitioning to the milder withdrawal class than to the more severe symptom class.

Figure 2 shows the number of individuals that transitioned to a less and more severe symptom class at 12- and 24-month time points. The majority of the sample were in the same withdrawal class at baseline and at 12 months ($n=349$, 66%) and at 12 months and 24 months ($n=410$, 78%). Transitions to less severe classes were slightly more common than transitions to more severe classes with 108 (20%) at 12 months and 75 (14%) at 24 months of the sample transitioning to a class with less severe withdrawal symptoms. In comparison, 70 (13%) at 12 months and 42 (8%) at 24 months of the sample transitioning to a class with more severe withdrawal symptoms.

Step 4: Associations between baseline measures and LTA transitions

The same baseline characteristics that were assessed in Step 2 were used in this step to explore candidate predictors of class transitions from baseline to 12 months (see Table 3). Older age was associated with lower odds of transitioning to a more severe withdrawal class and vaping cannabis was associated with lower odds of transitioning to a less severe withdrawal class compared to staying in the current class.

Discussion:

To our knowledge, this is the first study to examine longitudinal patterns of cannabis withdrawal symptoms in a cohort of people using medical cannabis over the course of two years. Cross-sectional analysis of baseline reports of cannabis withdrawal symptoms identified three latent classes, consisting of mild, moderate, and severe withdrawal symptom classes. The majority of participants remained in their initial withdrawal class throughout the two-year study period, with the highest stability among those with mild withdrawal symptoms at baseline. Of those who transitioned to another symptom class, transitioning to milder symptoms was slightly more common than transitioning to more severe symptoms. See Figure 2 for a diagram of transitions between latent classes.

People using medical cannabis were spread across the symptom classes with the largest percentage of people in the mild class (41%), followed by the moderate severity class (34%), and then the severe symptom class (25%). This finding that withdrawal symptoms manifest across a severity spectrum contrasts with a report of cannabis withdrawal symptoms in those using cannabis at least three times a week that found two withdrawal symptom presentations, one characterized by weakness and fatigue and another by anxiety and depression symptoms (24). However, the current findings are consistent with prior LCAs of

cannabis use disorder symptoms, more broadly, finding that symptoms of cannabis use disorder span across dimensions of severity as opposed to distinguishing distinct subtypes of the disorder, and are consistent with evidence that as withdrawal symptom severity increases, so too does the severity of cannabis use disorder (34,43–45). Nonetheless, the latent classes reported here are the first examination of the dimensionality of withdrawal symptoms among those that use cannabis for medical purposes.

Individuals in the mild withdrawal class had relatively low probabilities of endorsing withdrawal symptoms, with the exception of a slightly elevated probability of endorsing sleep difficulties and craving cannabis. The moderate withdrawal class was characterized by relatively elevated probabilities of endorsing sleep difficulties, depressed mood, decreased appetite, cannabis craving, restlessness, anxiety and irritability when they went without cannabis. Those in the severe symptom class had elevated probabilities of symptom endorsement across all withdrawal symptoms, except sweating. Consistent with these findings, prior work has noted that sweating is a relatively uncommon symptom of cannabis withdrawal (23,46). Aligned with prior work finding sleep problems to be one of the most frequently endorsed cannabis withdrawal symptoms (20,27,46), this symptom had a relatively high probability of endorsement across the latent classes.

Several sociodemographic, health status, and cannabis use characteristics were associated with the patient's baseline withdrawal severity class. Those with more severe withdrawal symptoms tended to be younger and have poorer mental health. This finding fits within the context of prior work documenting that young adults with mental health conditions experienced greater severity and duration of withdrawal symptoms (47). Taken together, these

findings suggest that younger individuals with greater mental health problems might be at risk of greater consequences from use, have more difficulty abstaining from use, and be more susceptible to relapse due to more acute and protracted withdrawal symptoms. Adding to prior findings that severity of cannabis use predicts cannabis withdrawal (48), we found that several cannabis use characteristics were associated with severity of withdrawal. Specifically, more severe cannabis withdrawal profiles were associated with individuals that reported smoking cannabis, longer history of use, greater frequency of use, and experiencing more cannabis-related problems.

To the best of our knowledge, this is the first study to use LTA models to examine the longitudinal course of cannabis withdrawal symptom profiles. Most participants remained in their initial withdrawal class throughout the two-year study. The mild symptom class was the most stable; though, at 12- and 24-months post-baseline, individuals in all of the baseline classes had higher than 0.5 probability of remaining in their initial class. These findings may inform physician recommendations to medical cannabis clients, especially for those experiencing more severe withdrawal symptoms. For the majority of patients, the current findings indicate that the severity of withdrawal symptoms are likely to remain stable over time. Consequently, for those experiencing moderate to severe symptoms, interventions to reduce the quantity and frequency of cannabis use to alleviate withdrawal symptoms along with consideration of alternative interventions for the management of the pain condition (e.g., behavioral interventions) may be warranted.

Although people who use cannabis for medical, as opposed to recreational, reasons tend to be older (6,13), we found that older age was inversely associated with transitions to

more severe withdrawal classes. These findings fit within the context of prior work in this area, which was mostly based in cohorts of those using for non-medical reasons. Younger age is associated with an increased risk of developing cannabis use disorder (2,3,49). Therefore, severe withdrawal symptoms in those who are younger likely contributes to increased risk for cannabis use disorders. This pattern appears to be relatively consistent irrespective of whether or not the purported use for cannabis is medical or recreational. In light of recent evidence that those using cannabis medicinally are more likely to vape than those using recreationally (50), along with coinciding efforts to develop vaporizers for use among medicinal users (51), an interesting finding from the present study is that those who vaped cannabis had lower odds of withdrawal symptom improvement, potentially signaling that vaping cannabis is a barrier to symptom reduction.

The current findings should be considered within the context of several limitations. First, the study sample consists of those who use medical cannabis for chronic pain; thus, the findings may not generalize to those using cannabis for other medical conditions or to those using cannabis recreationally. Second, nicotine use, which can have overlapping withdrawal symptom presentations, was not assessed in this study, and should be examined in future studies. Third, measurement of withdrawal symptoms, including the reliance on retrospective self-reports, is a potential limitation of this study. More detailed and/or granular information about withdrawal symptoms may be necessary in subsequent research to better understand use characteristics and temporal stability of cannabis withdrawal symptoms. For instance, withdrawal symptom profiles may differ based on varying compositions of cannabidiol (CBD) and tetrahydrocannabinol (THC) in products used. Additionally, the complex nature of chronic pain

and overlap with mental health symptoms raises the possibility that retrospective reports of cannabis withdrawal symptoms may be confounded with breakthrough pain and/or mental health symptoms during periods of abstinence. Along these lines, variability in length of time since last use in relation to the potential experience of withdrawal symptoms may create additional imprecision in measurement. Consequently, future work, including the collection of event-level data to evaluate finer-grained details of the experience and timing of withdrawal symptoms, daily product use, as well as pain and mental health characteristics, could provide critical insight regarding the causes, presentation, and stability (or instability) of withdrawal symptoms. Fourth, these analyses are based on the sample of participants who completed the withdrawal scale at the three assessment timepoints, raising the possibility that participants that were lost to follow-up may differ from those included in the present analytic sample. In post-hoc analyses, participants who did not complete all assessments had modestly higher cannabis symptom severity (ASSIST: $M=11.4$, $SD=6.4$ compared to $M=10.4$, $SD=5.4$) but comparable pain severity (NRS: $M=7.2$, $SD=1.4$ compared to $M=7.1$, $SD=1.4$) at baseline, raising the possibility that severity of cannabis use may contribute to lack of continued engagement.

Despite these potential limitations, this report of individuals using cannabis to manage pain has several key findings regarding cannabis withdrawal. First, LCA findings indicate that cannabis withdrawal symptoms are dimensional across a spectrum of severity, as opposed to distinct subtypes of withdrawal syndromes. Second, withdrawal symptoms are generally stable over time, especially among those with mild or no withdrawal symptoms. Third, younger age predicts greater odds of worsening withdrawal severity, and vaping predicts lower odds of withdrawal symptoms improving over time. Future work to prevent escalation in cannabis use,

help individuals cope with withdrawal symptoms and/or reduce use, especially among those who are younger and those who vape, may help to reduce withdrawal symptom severity and mitigate risks for developing a cannabis use disorder.

References

1. SAMHSA. Key substance use and mental health indicators in the United States: Results from the 2018 National Survey on Drug Use and Health (NSDUH). Center for Behavioral Health Statistics and Quality; 2019. Report No.: HHS Publication No. PEP19-5068, NSDUH Series H-54.
2. Hasin DS, Sarvet AL, Cerdá M, Keyes KM, Stohl M, Galea S, et al. US Adult Illicit Cannabis Use, Cannabis Use Disorder, and Medical Marijuana Laws [Internet]. Vol. 74, JAMA Psychiatry. 2017. p. 579. Available from: <http://dx.doi.org/10.1001/jamapsychiatry.2017.0724>
3. Compton WM, Han B, Jones CM, Blanco C, Hughes A. Marijuana use and use disorders in adults in the USA, 2002–14: analysis of annual cross-sectional surveys. *The Lancet Psychiatry*. 2016 Oct 1;3(10):954–64.
4. Compton WM, Han B, Jones CM, Blanco C. Cannabis use disorders among adults in the United States during a time of increasing use of cannabis. *Drug Alcohol Depend*. 2019 Nov 1;204:107468.
5. Map of marijuana legality by state [Internet]. DISA Global Solutions. 2020 [cited 2020 Apr 20]. Available from: <https://disa.com/map-of-marijuana-legality-by-state>
6. Compton WM, Han B, Hughes A, Jones CM, Blanco C. Use of Marijuana for Medical Purposes Among Adults in the United States. *JAMA*. 2017 Jan 10;317(2):209–11.
7. Lin LA, Ilgen MA, Jannausch M, Bohnert KM. Comparing adults who use cannabis medically with those who use recreationally: Results from a national sample. *Addict Behav*. 2016 Oct;61:99–103.
8. Richmond MK, Pampel FC, Rivera LS, Broderick KB, Reimann B, Fischer L. Frequency and Risk of Marijuana Use among Substance-Using Health Care Patients in Colorado with and without Access to State Legalized Medical Marijuana. *J Psychoactive Drugs*. 2015 Jan;47(1):1–9.
9. Han B, Compton WM, Blanco C, Jones CM. Trends in and correlates of medical marijuana use among adults in the United States. *Drug Alcohol Depend*. 2018 May 1;186:120–9.
10. Hoffmann DE, Weber E. Medical marijuana and the law. *N Engl J Med*. 2010 Apr 22;362(16):1453–7.
11. Park J-Y, Wu L-T. Prevalence, reasons, perceived effects, and correlates of medical marijuana use: A review. *Drug Alcohol Depend*. 2017 Aug 1;177:1–13.
12. Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert ASB, Walton M, et al. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend*.

2013 Oct 1;132(3):654–9.

13. Perron BE, Holt KR, Yeagley E, Ilgen M. Mental health functioning and severity of cannabis withdrawal among medical cannabis users with chronic pain. *Drug Alcohol Depend.* 2019 Jan 1;194:401–9.
14. Woodruff S, Shillington A, Reed M. Sociodemographic and Problem Area Differences between Medical Marijuana Users and Non-Medical Users Visiting the Emergency Room. In: APHA 2016 Annual Meeting & Expo (Oct 29-Nov 2, 2016) [Internet]. American Public Health Association; 2016. Available from: <https://apha.confex.com/apha/144am/meetingapp.cgi/Paper/363777>
15. Wall MM, Liu J, Hasin DS, Blanco C, Olfson M. Use of marijuana exclusively for medical purposes. *Drug Alcohol Depend.* 2019 Feb 1;195:13–5.
16. Choi NG, DiNitto DM, Marti CN. Nonmedical versus medical marijuana use among three age groups of adults: Associations with mental and physical health status. *Am J Addict.* 2017 Oct;26(7):697–706.
17. Roy-Byrne P, Maynard C, Bumgardner K, Krupski A, Dunn C, West II, et al. Are medical marijuana users different from recreational users? The view from primary care. *Am J Addict.* 2015;24(7):599–606.
18. Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol.* 2003 Aug;112(3):393–402.
19. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology.* 1999 Feb;141(4):395–404.
20. Kouri EM, Pope HG Jr. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol.* 2000 Nov;8(4):483–92.
21. Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, et al. Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict.* 2006;15(1):8–14.
22. Budney AJ, Novy PL, Hughes JR. Marijuana withdrawal among adults seeking treatment for marijuana dependence. *Addiction.* 1999 Sep;94(9):1311–22.
23. Budney AJ, Hughes JR. The cannabis withdrawal syndrome. *Curr Opin Psychiatry.* 2006 May;19(3):233–8.
24. Hasin DS, Keyes KM, Alderson D, Wang S, Aharonovich E, Grant BF. Cannabis withdrawal in the United States: results from NESARC. *J Clin Psychiatry.* 2008 Sep;69(9):1354–63.
25. Agrawal A, Pergadia ML, Lynskey MT. Is there evidence for symptoms of cannabis

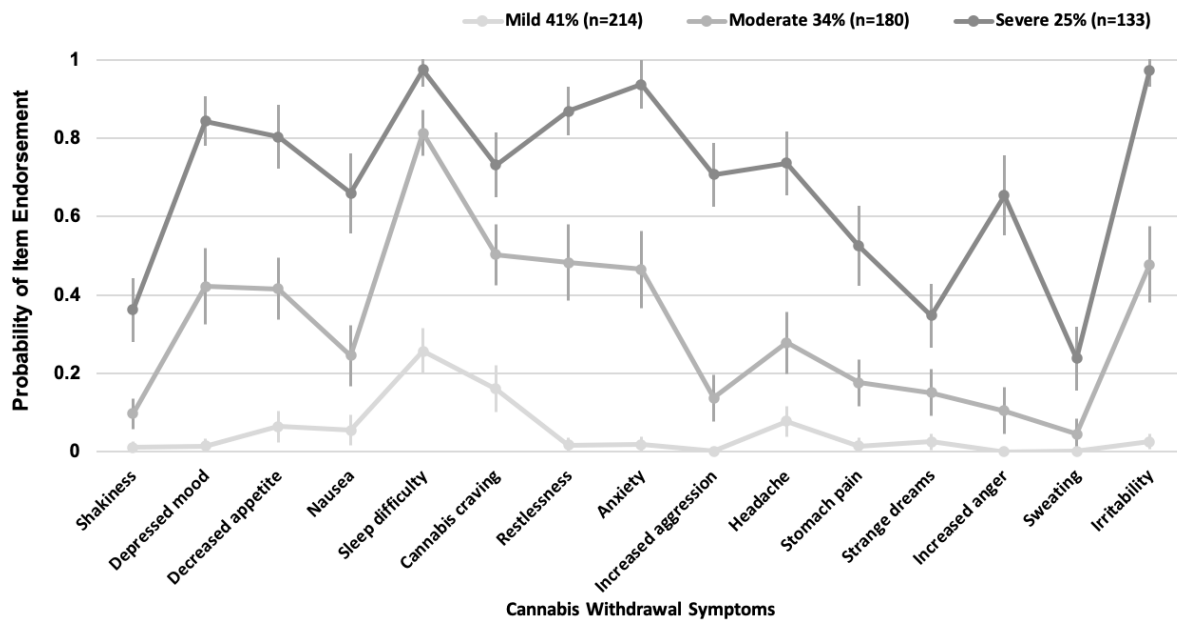
withdrawal in the national epidemiologic survey of alcohol and related conditions? *Am J Addict.* 2008 May;17(3):199–208.

26. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington: American Psychiatric Publishing [Internet]. 2013; Available from: <http://www.lsw2014.org/StamMcCrackenDSMV.pdf>
27. Bonnet U, Preuss UW. The cannabis withdrawal syndrome: current insights. *Subst Abuse Rehabil.* 2017 Apr 27;8:9–37.
28. Hesse M, Thylstrup B. Time-course of the DSM-5 cannabis withdrawal symptoms in poly-substance abusers [Internet]. Vol. 13, *BMC Psychiatry*. 2013. Available from: <http://dx.doi.org/10.1186/1471-244x-13-258>
29. Levin KH, Copersino ML, Heishman SJ, Liu F, Kelly DL, Boggs DL, et al. Cannabis withdrawal symptoms in non-treatment-seeking adult cannabis smokers. *Drug Alcohol Depend.* 2010 Sep 1;111(1-2):120–7.
30. Lee D, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, et al. Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. *Am J Addict.* 2014 May;23(3):234–42.
31. Budney AJ. Are specific dependence criteria necessary for different substances: how can research on cannabis inform this issue? *Addiction.* 2006 Sep;101 Suppl 1:125–33.
32. Allsop DJ, Copeland J, Norberg MM, Fu S, Molnar A, Lewis J, et al. Quantifying the clinical significance of cannabis withdrawal. *PLoS One.* 2012 Sep 26;7(9):e44864.
33. Greene MC, Claire Greene M, Kelly JF. The Prevalence of Cannabis Withdrawal and Its Influence on Adolescents' Treatment Response and Outcomes [Internet]. Vol. 8, *Journal of Addiction Medicine*. 2014. p. 359–67. Available from: <http://dx.doi.org/10.1097/adm.0000000000000064>
34. Chung T, Martin CS, Cornelius JR, Clark DB. Cannabis withdrawal predicts severity of cannabis involvement at 1-year follow-up among treated adolescents. *Addiction.* 2008;103(5):787–99.
35. Cornelius JR, Chung T, Martin C, Scott Wood D, Clark DB. Cannabis withdrawal is common among treatment-seeking adolescents with cannabis dependence and major depression, and is associated with rapid relapse to dependence [Internet]. Vol. 33, *Addictive Behaviors*. 2008. p. 1500–5. Available from: <http://dx.doi.org/10.1016/j.addbeh.2008.02.001>
36. Bahji A, Stephenson C, Tyo R, Hawken ER, Seitz DP. Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2020 Apr 1;3(4):e202370.

37. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996 Mar;34(3):220–33.
38. Ware JE, Kosinski M, Keller SD. SF-12: How to Score the SF-12 Physical and Mental Health Summary Scales. 1998. 97 p.
39. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction*. 2002 Sep;97(9):1183–94.
40. Bohnert KM, Sripada RK, Ganoczy D, Walters H, Valenstein M. Longitudinal patterns of PTSD symptom classes among US National Guard service members during reintegration. *Soc Psychiatry Psychiatr Epidemiol*. 2018 Sep;53(9):911–20.
41. Hagenaars JA, McCutcheon AL. *Applied Latent Class Analysis*. Cambridge University Press; 2002. 454 p.
42. Lanza ST, Collins LM, Lemmon DR, Schafer JL. PROC LCA: A SAS Procedure for Latent Class Analysis. *Struct Equ Modeling*. 2007;14(4):671–94.
43. Grant JD, Scherrer JF, Neuman RJ, Todorov AA, Price RK, Bucholz KK. A comparison of the latent class structure of cannabis problems among adult men and women who have used cannabis repeatedly. *Addiction*. 2006 Aug;101(8):1133–42.
44. Legleye S, Piontek D, Kraus L. A validation of the Cannabis Abuse Screening Test (CAST) using a latent class analysis of the DSM-IV among adolescents. *Journal of methods ... [Internet]*. 2013; Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/mpr.1378>
45. Livne O, Shmulewitz D, Lev-Ran S, Hasin DS. DSM-5 cannabis withdrawal syndrome: Demographic and clinical correlates in U.S. adults. *Drug Alcohol Depend*. 2019 Feb 1;195:170–7.
46. Smith NT. A review of the published literature into cannabis withdrawal symptoms in human users. *Addiction*. 2002 Jun;97(6):621–32.
47. Schuster RM, Fontaine M, Nip E, Zhang H, Hanly A, Evins AE. Prolonged cannabis withdrawal in young adults with lifetime psychiatric illness. *Prev Med*. 2017 Nov;104:40–5.
48. Allsop DJ, Norberg MM, Copeland J, Fu S, Budney AJ. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend*. 2011 Dec 1;119(1-2):123–9.
49. Lopez-Quintero C, de los Cobos JP, Hasin DS, Okuda M, Wang S, Grant BF, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: Results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115(1-2):120–30.

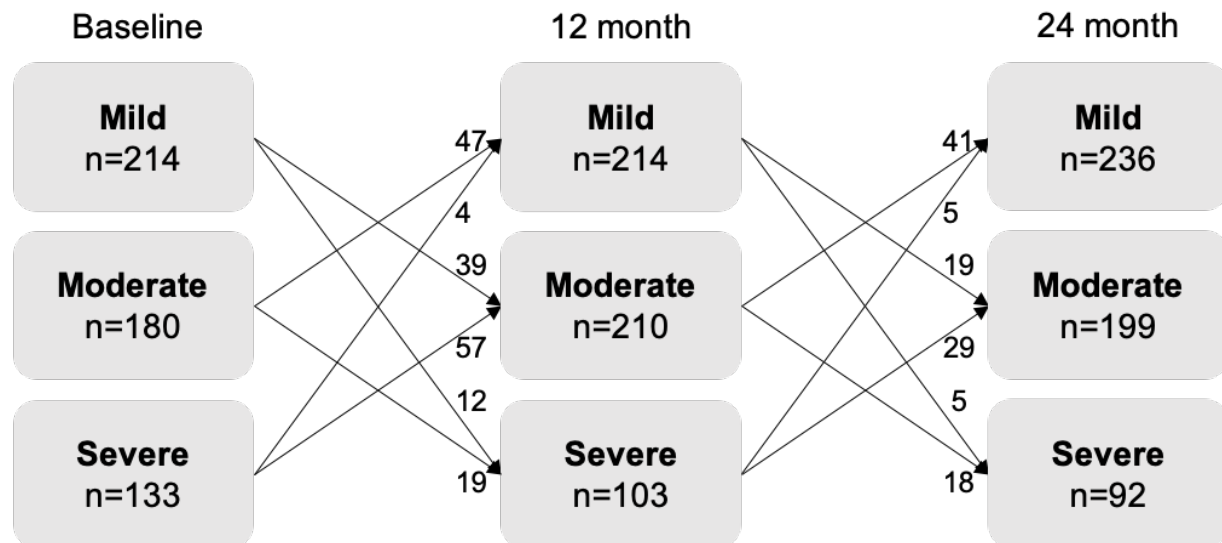
50. Salazar CA, Tomko RL, Akbar SA, Squeglia LM, McClure EA. Medical Cannabis Use among Adults in the Southeastern United States. *Cannabis*. 2019 Feb 9;2(1):53–65.
51. Lanz C, Mattsson J, Soydaner U, Brenneisen R. Medicinal Cannabis: In Vitro Validation of Vaporizers for the Smoke-Free Inhalation of Cannabis. *PLoS One*. 2016 Jan 19;11(1):e0147286.

Figure 1. Three class latent class analysis (LCA) model at baseline showing the estimated probabilities of cannabis withdrawal symptom endorsement by class



Error bars denote 95% confidence intervals calculated as $\pm 1.96 \times$ standard error of the mean.

Figure 2. Transitions to more and less severe withdrawal symptom classes from baseline to 12 months.



Number of participants per class is shown in gray boxes for each timepoint. The estimated number transitioning between classes from one time point to the next are denoted at the end of each arrow. At 12-months, 163 (76%), 114 (63%), and 72 (54%) participants remained in the mild, moderate, and severe classes, respectively. At 24 months, 190 (89%), 151 (72%), and 69 (67%) participants remained in the mild, moderate, and severe classes, respectively.

Table 1. Association between baseline LCA and included baseline characteristics.

	Mild		Moderate		Severe		<i>p</i> -value	ES	Respondents
	n/avg.	%/SD	n/avg.	%/SD	n/avg.	%/SD			
N	214	41%	180	34%	133	25%			527
Age	48.2	13.0%	45.4	12.9%	41.8	11.4%	<0.01	0.04	527
Sex (male)	107	50%	91	51%	61	46%	<i>ns</i>	<0.01	527
Pain severity (NRS)	7.1	1.4	7.0	1.3	7.0	1.3	<i>ns</i>	<0.01	527
Physical health (SF-12 PCS)	32.2	8.2	32.6	7.6	35.4	7.3	<0.01	0.03	506
Mental health (SF-12 MCS)	48.7	11.4	45.1	11.1	40.8	10.8	<0.01	0.07	506
Medical card for use (yes)	142	67%	114	65%	91	68%	<i>ns</i>	<0.01	521
Duration of cannabis use (years)	7.8	10.5	11.8	12.6	10.0	9.9	0.03	0.02	506
Cannabis-related problems (ASSIST)	8.4	5.1	11.0	5.0	12.3	5.6	<0.01	0.09	521
Frequency of use									
None to rarely	35	16%	15	8%	8	6%	<0.01	0.03	527
Monthly to weekly	42	20%	26	14%	15	11%			
Daily	137	64%	139	77%	110	83%			
Amount used per week									
None to <1/8 oz.	85	41%	44	25%	15	11%	<0.01	0.08	515
1/8 to < ½ oz.	81	39%	78	44%	75	57%			
½ oz. or more	41	20%	55	31%	41	31%			
Method of administration									
Smoke	157	75%	151	86%	113	87%	<0.01	0.01	516

Routes of administration	Vape	76	36%	66	37%	50	38%	<i>ns</i>	<0.01	516
	Eat	84	40%	79	45%	63	48%	<i>ns</i>	<0.01	516
	Skin/topical	29	14%	20	11%	14	11%	<i>ns</i>	<0.01	516
	0	27	13%	13	7%	7	5%	<i>ns</i>	0.02	516
	1	102	49%	87	49%	59	45%			
	2	62	29%	59	33	55	42%			
	3	19	9%	17	10%	9	7%			

ES=effect size, reported as R^2 , where 0.01, 0.09, and 0.25 correspond to small, medium, and large effect sizes, respectively. Respondents indicates the number of participants providing responses after accounting for those that skipped or refused each item.

Table 2. Latent transition analysis (LTA) transition probabilities for the three withdrawal symptom classes from baseline to 12 months and 12 months to 24 months (n=527).

Baseline	12 months		
	Mild	Moderate	Severe
Mild	0.81	0.14	0.05
Moderate	0.24	0.68	0.08
Severe	0.03	0.39	0.58
12 months	24 months		
	Mild	Moderate	Severe
Mild	0.87	0.11	0.02
Moderate	0.19	0.72	0.09
Severe	0.05	0.27	0.68

Table 3. Association between baseline characteristics and transitioning to a new class at 12 months

Baseline Characteristics	Omnibus Wald X^2	df	Less Severe OR (95% CI)	More Severe OR (95% CI)	Respondents
Age	6.63*	2	0.99 (0.97-1.00)	0.96 (0.96-1.00)*	527
Sex (male)	1.05	2	--	--	527
Pain severity (NRS)	0.33	2	--	--	527
Physical health (SF-12 PCS)	1.82	2	--	--	506
Mental health (SF-12 MCS)	4.68	2	--	--	506
Medical card for use (yes)	2.42	2	--	--	521
Duration of cannabis use (years)	0.34	2	--	--	506
Cannabis-related problems (ASSIST)	0.37	2	--	--	521
Frequency of use	7.56	4	--	--	526
Amount used per week	6.90	4	--	--	526
Method of administration					
Eat	0.32	2	--	--	516
Topical	2.86	2	--	--	516
Smoke	1.90	2	--	--	516
Vape	8.63*	2	0.47 (0.28, 0.78)*	0.84 (0.51, 1.38)	516
Number of routes	2.87	6	--	--	516

* indicates significance at $\alpha=0.05$. Odds of transitioning to more or less severe classes are based on a reference group of staying in the same class and are only

reported for baseline characteristics that were significant in the omnibus multinomial logistic regression. Abbreviations: OR=Odds ratio, 95% CI= 95% confidence interval.