



# The impact of naturalistic cannabis use on self-reported opioid withdrawal

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## ABSTRACT

**Objectives:** Four states have legalized medical cannabis for the purpose of treating opioid use disorder. It is unclear whether cannabinoids improve or exacerbate opioid withdrawal. A more thorough examination of cannabis and its impact on specific symptoms of opioid withdrawal is warranted.

**Method:** Two hundred individuals recruited through Amazon Mechanical Turk with past month opioid and cannabis use and experience of opioid withdrawal completed the survey. Participants indicated which opioid withdrawal symptoms improved or worsened with cannabis use and indicated the severity of their opioid withdrawal on days with and without cannabis.

**Results:** 62.5% ( $n = 125$ ) of 200 participants had used cannabis to treat withdrawal. Participants most frequently indicated that cannabis improved: anxiety, tremors, and trouble sleeping. A minority of participants (6.0%,  $n = 12$ ) indicated cannabis worsened opioid withdrawal, specifically symptoms of yawning, teary eyes, and runny nose. Across all symptoms, more participants indicated that symptoms improved with cannabis compared to those that indicated symptoms worsened with cannabis. Women reported greater relief from withdrawal with cannabis use than men.

**Discussion:** These results show that cannabis may improve opioid withdrawal symptoms and that the size of the effect is clinically meaningful. It is important to note that symptoms are exacerbated with cannabis in only a minority of individuals. Prospectively designed studies examining the impact of cannabis and cannabinoids on opioid withdrawal are warranted.

## 1. Introduction

The unmet treatment needs for persons with opioid use disorder (OUD) have led to substantial morbidity and mortality among this group, engendering an unprecedented opioid epidemic and public health crisis (Hedegaard, Minino, & Warner, 2018). Managing opioid withdrawal is integral for treatment retention and success for persons with OUD. Substantial preclinical research implicates the endocannabinoid system as having a role in the expression of opioid withdrawal. Indeed, administering exogenous cannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and increasing the endogenous cannabinoid anandamide, have all been shown to decrease opioid withdrawal severity in preclinical models (Bhargava, 1976; Cichewicz, 2004; Gamage et al., 2015; Hine, Friedman, Torrelío, & Gershon, 1975; Hine, Torrelío, & Gershon, 1975a, 1975b; Lichtman, Sheikh, Loh, & Martin, 2001; Ramesh et al., 2013; Vela, Ruiz-Gayo, & Fuentes, 1995). Very little human research on this topic exists. The only two randomized placebo-controlled studies provide evidence that dronabinol, a synthetic formulation of THC, modestly reduces opioid

withdrawal but also produces a “high” and “euphoria” as well as clinically significant levels of tachycardia (Bisaga et al., 2015; Lofwall, Babalonis, Nuzzo, Elayi, & Walsh, 2016). No other cannabinoid formulations have been empirically studied for this indication in humans and retrospective studies have not clearly delineated whether naturalistic cannabis use can improve or hinder OUD treatment retention (Epstein & Preston, 2003; Franklyn, Eibl, Gauthier, & Marsh, 2017; Noble, Best, Man, Gossop, & Stang, 2002; Socias et al., 2018). Previous reports indicate that naturalistic cannabis use may improve, (Gossop, Battersby, & Strang, 1991; Noble et al., 2002), worsen (Gossop et al., 1991), or have no effect on opioid withdrawal (Epstein & Preston, 2003, 2015).

Despite inconclusive research on whether prescribed or naturalistic cannabis use aids the treatment of OUD, at least four states have already legislatively approved OUD as an indication for medicinal cannabis and several other states have proposed similar legislation. These approvals are concerning because of the limited and conflicting evidence suggesting cannabis can both improve and worsen opioid withdrawal and treatment retention. Together, this makes it unclear whether clinicians

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should permit or discourage its use during OUD treatment (Humphreys & Saitz, 2019). To better understand the effects of naturalistic cannabis use on opioid withdrawal, this study focuses on how cannabis may differentially influence specific opioid withdrawal symptoms and opioid withdrawal severity.

## 2. Method

### 2.1. Recruitment and screening

Participants were recruited through Amazon Mechanical Turk (AMT), a crowdsourcing platform commonly used in survey-based research. Individuals register as AMT “workers” to complete human intelligence tasks (HITs) to earn money. The HIT used to recruit participants to complete the survey discussed in this report was generically advertised as a survey on “health behaviors”. To access the HIT, participants needed a  $\geq 80\%$  approval rate from completion of previous HITs and to have resided in the United States. Eligibility was assessed using a brief screening survey, which also included embedded attention checks for quality control and distractor questions to obscure the purpose of the study. To qualify for the study, participants needed to (1) respond correctly to attention checks and (2) endorse past 30-day opioid and cannabis use and (3) report having experienced opioid withdrawal in the past 30 days. Of the 3617 individuals who completed the eligibility screening, 268 (7% of screened sample) were considered eligible. Of the 268 eligible participants, 200 (75%) consented and completed the entire study survey and are included in the final analyses. All respondents received \$0.15 for completing the eligibility survey and eligible participants who completed the entire survey and successfully responded to attention checks received an additional \$3. The Johns Hopkins University IRB determined this study did not qualify as human subject research.

### 2.2. Procedures

Eligible participants completed several questionnaires about their demographics and cannabis and opioid use (including DSM-5 checklists for cannabis use disorder (CUD) and OUD).

Opioid withdrawal was assessed in several ways. First, participants indicated whether they felt that cannabis improved or worsened opioid withdrawal by answering: “What symptoms of opioid withdrawal do you believe cannabis helps? Please select all that apply.” And “What symptoms of opioid withdrawal do you believe cannabis worsens? Please select all that apply.” Opioid withdrawal symptoms were taken from the 16-item self-report Subjective Opiate Withdrawal Scale (SOWS), which asks participants to rate the severity of the following symptoms on a 0 (not at all)–4 (extremely) Likert scale: anxiety, tremors, trouble sleeping, bone/muscle aches, restlessness, nausea, cravings/feel like using, stomach cramps, vomiting, sweating, hot flashes, cold flashes, twitches, yawning, teary eyes, goosebumps, diarrhea, and runny nose (Handelsman et al., 1987). Two additional questions that were hypothesized to be sensitive to cannabis use (trouble sleeping, diarrhea) were also added and rated on the same Likert scale, resulting in a total overall score range of 0–72 (18 items).

Next, participants were instructed to think about a typical day when they *did not use* cannabis and rate the severity at which they experienced each opioid withdrawal symptom on the 16-item SOWS. Participants were then instructed to think about a typical day when they *did use* cannabis and to indicate the severity at which they experienced each symptom on the 16-item SOWS. Finally, participants also completed visual analog scale (VAS, range: 0–100) ratings of opioid withdrawal severity when using and not using cannabis. This way of measuring opioid withdrawal does not assume that symptoms of withdrawal equally contribute to total opioid withdrawal intensity and therefore may be more indicative of overall disruption.

### 2.3. Statistical analyses

Descriptive statistics were used to characterize the prevalence of cannabis use for the treatment of opioid withdrawal and whether individuals felt cannabis use improved or worsened specific opioid withdrawal symptoms. Paired-sample *t*-tests were used to compare SOWS total scores and VAS withdrawal severity scores on days that participants did and did not use cannabis.

For individual symptoms, ratios were computed to characterize the proportion of participants who experienced improvements in a withdrawal symptom relative to the number of participants who experienced a worsening of withdrawal symptoms during cannabis use. A value  $> 1$  indicates a greater number of participants experienced improvements with cannabis, and  $< 1$  indicates a greater number of participants experienced a worsening of a symptom with cannabis.

To characterize the magnitude of change in opioid withdrawal, SOWS individual symptom scores and total scores and VAS severity scores were transformed into difference scores by subtracting SOWS total scores and VAS severity scores on days with opioid withdrawal with and without cannabis use. Pearson correlation coefficients were then calculated to determine if the magnitude of total withdrawal change was related to past 30-day opioid or cannabis use, or self-reported OUD or cannabis use disorder (CUD) scores. Self-reported OUD and CUD scores were computed by summing the total number of Diagnostic and Statistical Manual (DSM)-5 criteria met for OUD or CUD (American Psychological Association, 2013). Independent *t*-tests were conducted to compare whether cannabis changed opioid withdrawal differently as a function of sex.

## 3. Results

Participant demographics and drug use characteristics are presented in Table 1. Sixty-three percent ( $n = 125$ ) of respondents reported using cannabis to treat opioid withdrawal. Of those, 72.0% reported cannabis improved opioid withdrawal, 6.4% reported cannabis worsened opioid withdrawal, and 20.0% reported cannabis improved some but worsened other opioid withdrawal symptoms. Of the 125, 2.4% ( $n = 3$ ) indicated that cannabis had no influence on opioid withdrawal.

Among the 122 respondents who indicated cannabis influenced opioid withdrawal, anxiety (76.2% of respondents), tremors (54.1%) and trouble sleeping (48.4%) were the most frequently improved, and yawning (7.4%), tearing eyes (6.6%), and running nose (6.6%) were the most frequently exacerbated SOWS symptoms (Table 2). Ratios reflecting the participants who experienced improved versus worsened symptoms indicated that more individuals found cannabis to improve rather than worsen all evaluated symptoms (Table 2).

Paired-sample *t*-tests indicated SOWS total scores were significantly lower on days with cannabis ( $M = 16.2$ ,  $SEM = 1.4$ ) compared to days without ( $M = 27.8$ ,  $SEM = 1.3$ ),  $t(121) = 9.4$ ,  $p < .05$ ,  $d = 0.84$ , and that VAS withdrawal severity scores were significantly lower during days with cannabis ( $M = 35.3$ ,  $SEM = 2.0$ ), compared to days without ( $M = 64.5$ ,  $SEM = 2.0$ ,  $t(121) = 11.2$ ,  $p < .05$ ,  $d = 0.88$ ; Fig. 1).

Changes in SOWS total scores and VAS severity scores were significantly and positively correlated with past 30-day opioid use ( $r = 0.35$ ,  $p < .001$ ,  $r = 0.36$ ,  $p < .001$ ) and past 30-day cannabis use ( $r = 0.27$ ,  $p < .01$ ,  $r = 0.30$ ,  $p < .01$ ). Change scores were not correlated with OUD nor with CUD scores.

Changes in SOWS total scores were significantly greater among women ( $M = 14.2$ ,  $SD = 14.4$ ) compared to men ( $M = 9.3$ ,  $SD = 13.0$ ),  $t(121) = -2.0$ ,  $p = .04$ . SOWS total scores without cannabis were not significantly different between men ( $M = 27.0$ ,  $SD = 14.7$ ) and women ( $M = 27.8$ ,  $SD = 16.0$ ,  $t(121) = -0.3$ ,  $p = .77$ ).

**Table 1**

Demographics and drug use characteristics of the total sample and the subset of participants who endorsed having used cannabis for opioid withdrawal.

	Total sample N = 200	Individuals who have used cannabis for opioid withdrawal n = 125
Demographics		
% male	56.0	51.6
% with ≤4-year college degree	57.0	44.0
Age (mean ± SD)	33.2 ± 9.6	31.6 ± 8.6
Drug use characteristics		
Past 30-days cannabis use (mean ± SD)	14.1 ± 9.8	15.1 ± 9.9
Past 30-day opioid use (mean ± SD)	16.1 ± 10.6	15.0 ± 9.8
DSM-5 cannabis use disorder symptoms (CUD; 0–11) (mean ± SD)	4.6 ± 3.5	5.0 ± 3.7
% no CUD (0–1 symptoms)	31.0	30.4
% mild CUD (2–3 symptoms)	16.0	16.0
% moderate CUD (4–5 symptoms)	15.5	16.0
% severe CUD (6+ symptoms)	36.4	37.6
DSM-5 opioid use disorder symptoms (OUD; 0–11) (mean ± SD)	6.5 ± 3.0	6.9 ± 2.8
% no OUD (0–1 symptoms)	7.0	3.2
% mild OUD (2–3 symptoms)	13.0	8.8
% moderate OUD (4–5 symptoms)	19.5	15.2
% severe OUD (6+ symptoms)	60.5	72.8

Note: DSM-5: Diagnostic and Statistical Manual-5, total sample and individuals who used cannabis for opioid withdrawal did not differ significantly on any demographic or drug use characteristics.

#### 4. Discussion

Recent policy changes have permitted medicinal cannabis for the treatment of OUD despite mixed evidence about whether cannabis use improves (Gossop et al., 1991; Noble et al., 2002) or worsens (Gossop et al., 1991) opioid withdrawal symptoms. The data in this manuscript indicate that individuals who experience opioid withdrawal and use cannabis may perceive cannabis to provide clinically meaningful improvements in opioid withdrawal, though a minority found cannabis did worsen some symptoms. Across all symptoms, more participants indicated that opioid withdrawal symptoms improved with cannabis relative to those who indicated that cannabis worsened a symptom. On average, withdrawal severity scores nearly doubled on days cannabis was not used. Commonly improved symptoms included anxiety, trouble sleeping, and bone/muscle aches. It is important to note that individuals without OUD report that these symptoms are some of the

most common conditions that they treat with medicinal cannabis (Kosiba, Maisto, & Ditre, 2019).

The magnitude of change in opioid withdrawal was not related to OUD nor CUD scores. This suggests that individuals with varying levels of OUD and CUD experience comparable relief from withdrawal with cannabis. Paradoxically, magnitude of changes was related to the number of days with opioid or cannabis use in the past 30 days. This suggests that individuals with greater cannabis and opioid use experience greater reductions in opioid withdrawal when using cannabis. Finally, the magnitude of change in opioid withdrawal symptoms was greatest among females. This finding identifies a new manner in which treatment of OUD may differ by sex (Huhn, Berry, & Dunn, 2019) and warrants further attention.

One limitation of this study is that it was conducted using a crowdsourcing platform and, therefore, in-person validation of substance use was not possible. Additionally, AMT workers have generally

**Table 2**

Percentage of participants (n = 122) endorsing opioid withdrawal symptom improved or made worse with cannabis use, average change in symptom severity without cannabis, and ratio of participants who experienced improvements to participants who experienced worsening symptoms.

Symptom	Improved with cannabis	Made worse with cannabis	Average change in symptom severity without cannabis (range: 0–4)	Ratio- # respondents that improved/# of respondents made worse
Anxiety	76.2	3.3	+0.7	23.3
Tremors	54.1	3.3	+0.5	16.5
Trouble sleeping	48.4	2.5	+0.6	19.7
Bone/muscle aches	45.9	2.5	+0.7	18.6
Restlessness	45.1	5.7	+0.8	7.9
Nausea	38.5	4.9	+0.6	7.8
Craving/feel like using	37.7	3.3	+0.6	11.5
Stomach cramps	30.3	3.3	+0.4	9.3
Vomiting	26.2	5.7	+0.5	4.6
Sweating	19.7	3.3	+0.3	6.0
Hot flashes	18.0	5.7	+0.3	3.1
Cold flashes	14.8	1.6	+0.3	9.0
Twitches	14.8	1.6	+0.4	9.0
Yawning	13.9	7.4	+0.3	1.9
Teary eyes	13.9	6.6	+0.2	2.1
Goosebumps	13.9	4.9	+0.4	2.8
Diarrhea	12.3	4.1	+0.2	3.0
Runny nose	9.8	6.6	+0.3	1.5

All items rated on scale of 0 (not at all)–4 (extremely). “Trouble Sleeping” and “Diarrhea” were added to the conventional 16-item Subjective Opiate Withdrawal Scale (SOWS). Values in the second and third column represent percent of all respondents who affirmatively indicated a symptom (1) improved or (2) worsened during cannabis use. Values in the fourth column represent symptom severity without cannabis – symptom severity with cannabis; values > 1 indicate improvement and values < 1 indicate exacerbation.

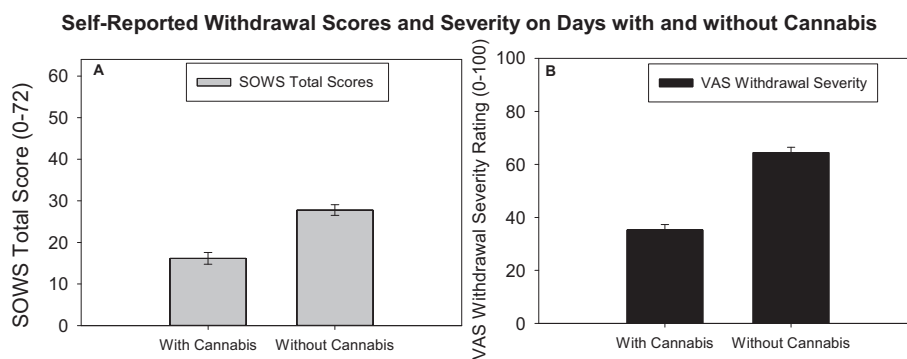


Fig. 1. Self-reported means (± SEM) SOWS total score (Panel A) and visual analog scale (VAS) withdrawal severity (Panel B) on days with and without cannabis.

been characterized as younger, more educated, and reporting poorer health quality and higher rates of depression relative to nationally representative samples (Mortensen, Alcalá, French, & Hu, 2018; Walters, Christakis, & Wright, 2018). Nevertheless, studies have validated the use of AMT for substance use-related research by comparing MTurk data with data collected in in-person laboratory settings (Chandler & Shapiro, 2016; Strickland & Stoops, 2019). We also took several steps to ensure that high quality data were collected. Another notable limitation is that the SOWS has not been specifically validated for use as a retrospective measure. However, given the paucity of data on this topic, this approach provided a feasible way to identify whether specific withdrawal symptoms may be differentially affected by cannabis use and the perceived magnitude of the effect of cannabis use on symptom severity, which can be used to support prospective evaluation of this topic.

Finally, we did not collect detailed data on the route of administration and dose amount of cannabis. Future studies should evaluate how use patterns may influence the efficacy of cannabis in treating opioid withdrawal symptoms. Previous retrospective research suggests that high frequency of cannabis use vs. occasional cannabis use can both improve (Socias et al., 2018) and harm (Franklyn et al., 2017) treatment retention among individuals with OUD, further emphasizing the need to conduct prospective research on this topic and the factors that may influence treatment response. While these data demonstrated that more frequent past 30-day cannabis use was related to greater relief from opioid withdrawal, findings are limited by not knowing the amount of cannabis consumed and the route of administration.

Cannabinoids are also being considered therapeutically within the context of opioid use because they can potentiate opioid analgesia (Cichewicz, 2004; Nielsen et al., 2017; Williams et al., 2006). In the absence of randomized clinical trials, a large number of epidemiological and convenience sample survey studies support the natural substitution of cannabis for opioids to treat pain (Boehnke et al., 2019; Corroon, Mischley, & Sexton, 2017; Corroon & Phillips, 2018; Lucas, 2017; Lucas et al., 2016; Lucas, Baron, & Jikomes, 2019; Piper et al., 2017). These data suggest that cannabis appears to be an acceptable substitute for opioids among opioid-using populations. Prospectively designed research is needed to discern the precise influence of cannabis within the context of opioid use and OUD.

Future research should also evaluate how cannabis use may impact factors other than withdrawal symptoms that also influence treatment success (e.g., psychological well-being, motivation to use opioids). Indeed, while cannabis may not largely exacerbate opioid withdrawal, there may be other mechanisms by which cannabis detrimentally disrupts the treatment of OUD.

## 5. Conclusion

In summary, these data suggest that the co-users of opioids and cannabis endorse cannabis as a method for reducing opioid withdrawal

severity. Given the shifting legal landscape, prospectively designed clinical trials that assess whether cannabis or its components can effectively treat opioid withdrawal are warranted.

## Disclosures

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## CRediT authorship contribution statement

**Cecilia L. Bergeria:** Conceptualization, Data curation, Methodology, Project administration, Formal analysis, Investigation, Writing - original draft, Visualization. **Andrew S. Huhn:** Formal analysis, Writing - review & editing, Visualization. **Kelly E. Dunn:** Conceptualization, Methodology, Formal analysis, Writing - review & editing, Visualization, Supervision, Funding acquisition, Resources.

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