Received: 21 February 2023 | Revised: 28 June 2023 | Accepted: 25 July 2023

DOI: 10.1111/ajad.13456

THE AMERICAN JOURNAL ON ADDICTIONS

RESEARCH ARTICLE

Daily cannabis use may cause cannabis-induced hyperalgesia

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Abstract

Background and Objectives: Public opinion about cannabis as a medical treatment is generally favorable. As many as 35% of primary care patients report medical use of cannabis, most commonly for pain treatment. We designed a way to test whether cannabis helps chronic pain.

Methods: A retrospective cohort study was conducted to explore whether daily long-term cannabis use was associated with increased pain sensitivity using the cold pressor test (CPT) to measure pain tolerance. Patients who used cannabis every day were compared to patients who inhaled tobacco and control patients who never used tobacco or cannabis. The effect of cannabis use on CPT was assessed using a generalized linear model.

Results: Patients using cannabis daily had a median CPT of 46 s, similar to those who did not use cannabis but who inhaled tobacco (median CPT 45 s). Patients who used both cannabis and tobacco had the lowest CPT (median 26 s). The control group had a median CPT of 105 s. Cannabis use was associated with a significantly decreased pain tolerance ($\chi^2_{(1)} = 8.0$, $p = .004$). The effect of tobacco on CPT was only marginally significant ($\chi^2_{(1)} = 3.8$, $p = .052$).

Conclusion and Scientific Significance: This suggests a phenomenon similar to opioid-induced hyperalgesia; a drug that reduces pain short term, induces pain long term—opponent process. Daily cannabis use may make chronic pain worse over time by reducing pain tolerance. In terms of risk/benefit, daily cannabis users risk addiction without any long-term benefit for chronic pain.

BACKGROUND AND OBJECTIVES

Cannabis for chronic pain

Cannabis is widely used for chronic pain treatment. Medical cannabis (MC) is currently used as an "off label" pain treatment without Food and Drug Administration approval. Public opinion about cannabis as a medical treatment is generally favorable. The main reasons Americans give for using MC is to alleviate pain (64%), for anxiety (50%), and for depression (34%).[1] As many as 35% of primary care patients report medical use of cannabis.[2] Cannabis is being advocated as a chronic pain treatment for patients on long-term opioid therapy, with a recommended gradual transition by prescribers from opioid medications to MC.[3] There is a consensus of opinion in reviews that the strongest evidence for medical benefit from marijuana is for chronic pain.[4]

The evidence that cannabis helps with chronic pain is controversial. A systematic review and meta-analysis by Wang et al. that covered 32 randomized controlled trials (RCTs) and 5174 patients, compared MC and cannabis compounds to any noncannabis control. Noninhaled MC or cannabis compounds had a small to very small analgesic effect on chronic pain.[5] Longo et al. found in their systematic review of RCTs that there was a patient-perceived benefit of MC on chronic pain while other measures of improvement of chronic pain yielded incongruent outcomes. It is possible some MC patients misattribute avoidance of discontinuation symptoms of cannabis use disorder (CUD) to a perceived benefit of continuing MC use.[6] Depressed patients' higher prevalence of CUD symptoms when using MC[7] could be concerning given the high comorbidity of depression and chronic pain.[8,9]

A relevant consideration for the efficacy of MC is the number needed to treat (NNT). According to Stockings et al.'s systematic review and meta-analysis, significantly more MC users achieved a 30% reduction in chronic noncancer pain. The difference in percentages were 29% of MC users versus 26% placebo. The change measured in pain intensity was 3 mm on a 100 mm visual analog scale. The NNT for decreased pain was 24 (95% confidence interval [CI]: 15–61). The number needed to harm was 6 (95% CI: 5–8). In spite of statistical significance of pain reduction, the intervention caused more harm than benefit.[10]

There are a few prospective, controlled trials. Campbell et al. used baseline interviews that were followed up yearly for 4 years with interviews and questionnaires for a cohort suffering from chronic noncancer pain. Cannabis use was associated with increased pain severity scores and lower pain self-efficacy scores, along with slightly worsened anxiety.[11]

Three studies have used postoperative pain ratings and need for postoperative analgesia to measure pain sensitivity in cannabis users. Liu et al. showed that patients with a history of cannabis use had higher Faces Pain Scale (FPS) postoperative pain, intensity rating, during both movement and rest, following major orthopedic surgery, relative to matched noncannabis users. The authors concluded that cannabis use may be used as indicator for a greater need of postoperative analgesics.[12] Jamal et al. reported a retrospectively chart review of 354 patients undergoing surgery for inflammatory bowel disease. It showed that daily cannabis users required higher doses of opioids postoperatively than noncannabis users. Although, when controlling for age and prior opioid use the difference was no longer significant ($p = .06$), they found a 23% increase in opioid dosing for cannabis users.[13]

At the 2022 annual meeting of the American Society of Anesthesiology, Ekrami presented the results of his 34,521-participant observational study of cannabis use and pain. Self-rated pain scores were compared between cannabis-naive patients and patients having used cannabis within 30 days of elective surgery at the Cleveland Clinic. The cannabis group reported 14% higher pain scores postoperatively within the first 24 h.[14]

Ambivalence has been reflected in varying guidelines for MC. The National Academies of Sciences, Engineering, and Medicine position is that there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults, stating that they found strong evidence in good-quality systematic reviews or meta-analyzes.[15] The International Association for the Study of Pain's official statement from 2021 deemed clinical findings lacking and therefore does not currently recommend MC for the treatment of pain.[16]

How hyperalgesia is induced by opponent process

Although acute tetrahydrocannabinol intake may provide analgesia, chronic, high doses cause a desensitization of CB1 and CB2.[17] A withdrawal state is produced by drug cessation. Over 2–4 weeks cannabinoid receptors to return to pre-drug baseline.[18]

If cannabis induces hyperalgesia, the mechanism may be similar to that of opioids.[8] The a-process is an opioid-induced positive hedonic mood state which is counterbalanced by a dysphoric b-process; increased pain, anxiety, and depression. The two processes occur sequentially to maintain homeostasis.

With repeated drug use, the negative b-process is amplified. The brain cannot return to its original homeostatic level before the next use. In an attempt to maintain balance, the chronic negative deviation becomes the new baseline. An allostatic state is created that is primarily determined by the b-process overcompensating for the drug-enhanced a-process, leading to central pain sensitization.

The brain evaluates pain signals from the periphery. Nociceptive pain drivers in the periphery are magnified by hyperalgesic patients due to central sensitization. Withdrawal results in unopposed b process, intensifying pain, anxiety, and depression.[19]

The cold pressor test (CPT) is the best way to measure pain tolerance.[20] The normal forearm is submerged in a pump-circulated, 1°C tub of icewater for as long as the patient can tolerate before needing to withdraw or 3 min has elapsed, our maximum submersion time.[21]

There are no long-term studies of the effect of cannabis on CPT. Studies of the acute effect of cannabis on experimentally induced acute pain show modest reductions of CPT,[22] and no-to-modest reductions in mechanical pressure and electrically-induced acute pain.[23,24]

In a previous communication, the senior author warned about the possibility of opponent process. “Physicians need to be careful, just as with alcohol, nicotine, and opioids, about endorsing a drug where every use gives a subjective experience that pain is improved, yet use of the drug over time has both hyperalgesic and potentially addictive properties…As cannabis use increases, additional research to support or refute the current evidence base is essential…”[8] The authors decided to take advantage of the ability to mine the electronic records of our Pain Service to investigate the possibility that cannabis-induced hyperalgesia exists by using the availability of CPT information that would measure pain tolerance for chronic pain patients who had been exposed to daily marijuana use. A retrospective cohort study was conducted to investigate whether daily cannabis use was associated with shorter cold pressor times.

METHODS

Participants—Inclusion/exclusion criteria

The EPIC computer system between the years of 2013–2021 at the Pain and Addiction Medicine Service at Upstate Medical University in Syracuse, NY was used to identify patient groups. The intake notes document lifelong drug use. Participants using opioids were eliminated because opioids induce hyperalgesia, reducing CPTs,[21,25–27] although one patient who had had a month's prescription 4 months earlier and one who had had a month-long prescription 7 months earlier were included in the nicotine-only group. Patients with current addiction to alcohol were excluded. Autistic patients were excluded because they may have high CPT/pain tolerance as an aspect of the illness.[27,28]

Intake notes were searched for patients using cannabis and/or nicotine daily, and for which a CPT had been performed. Patients who did not use either drug but had a CPT on record were identified as controls. Records did not contain information about recency of use; for example, if CPT was done after a patient using cannabis daily had used that day, or the night before. Each intake note contained data about age, gender, main clinical presentation (whether addiction or pain was the reason for visit), cannabis use, nicotine use, history of alcohol and other drug uses, diagnosis, and CPT time. CPT was administered by senior staff, psychiatry residents, medical students, or physician assistant students, who were unaware any notion of cannabis use causing hyperalgesia. We also obtained the scores for the Diagnostic Interview for ADHD in adults (DIVA) inattentive and hyperactive items, Hamilton Depression Rating Scales (Ham-D), Modified Mini-Mental State Examination of cognition (3MS), and FPS for measure of subjective pain, when available.

The SUNY Upstate Medical University institutional review board approved the use of "outcomes" of the Pain and Addiction Medicine Service to be used in retrospective chart reviews. Patients gave written informed consent for their deidentified chart data to be used. MRN numbers were used instead of patient names for data analysis. Authors Grapsas and Johnson independently reviewed EPIC medical records and conferred regarding any data entry discrepancies.

Statistical analysis

All statistical analysis was conducted using STATA 18. Gender, main clinical presentation, as well as presence or absence of alcohol use were assessed using Pearson's χ^2 test across four patient groups: those who inhaled cannabis, nicotine, or both, and those who did not use either. For rating scale measures, including the DIVA inattentive and hyperactive items, Ham-D, 3MS, and FPS, ordinal logistic regression (OLR) models were used to assess the group difference while controlling for any available demographic covariates. We use a Bonferroni corrected p-value threshold of .01 for statistical significance considering the total of five OLR tests on the rating scales.

Because CPT is a continuous measure of pain tolerance with a right-skewed distribution and censored at 180 s, we used a gamma Generalized Linear Model (GLM) with a log link function to compare the group difference. Akaike Information Criterion (AIC) was used to assess the goodness of fit of the models, which was used to compare different model specifications including alternative link functions and any inclusion of demographic and clinical characteristics as covariates. Models with the lowest AICs were used. In addition to comparing the overall group difference, we also fit a gamma GLM to assess the individual effects of cannabis or nicotine uses on CPT with cannabis or nicotine uses coded as 0 or 1. Potential interactions between the cannabis and nicotine uses, or with any other applicable covariates were evaluated and removed from the model if not significant. The final model was confirmed with a link test for correct model specification in which the squared fitted values need to demonstrate a lack of explanatory power ($p > .05$) to satisfy a good fit. We also tested residual for normality and confirmed a low deviance and a low ratio of deviance versus residual degree of freedom for measures of a good fit. Finally, we report the proportion of deviance explained for the model as "1-model deviance/null model deviance."

RESULTS

A total of 47 patients had used cannabis daily, 37 of which also inhaled tobacco daily (Cannabis+/Nicotine+). These patients were compared with 32 patients who inhaled tobacco only (Nicotine+) and 30 patients who did not use either cannabis or tobacco (Control). Demographic and clinical characteristics of the patients are shown in Table 1, contrasting the difference across the groups that used either cannabis, or nicotine, or both, and the controls. The patient groups with daily cannabis use, with or without nicotine, were younger, had more males, and were more likely to have sought for our services for addiction problems instead of chronic pain, than the Nicotine+ and Control groups. These group differences were all statistically significant (see Table 1). Similar percentages of patients in the cannabis or nicotine groups reported the use of alcohol (20%–28%, $p > .05$), in contrast to the control group in which no patients reported the use of alcohol.

For each of the five symptom scales, DIVA inattentive and hyperactive items, Ham-D, 3MS, and FPS scores, AICs of the OLR models with covariates, including age, sex, clinical presentation, and alcohol use status, were all found lower than those of the models without any or all of the above covariates, indicating a better fit when all covariates were included. Using the models adjusted with all covariates, we found no significant group differences for the DIVA inattentive and hyperactive scales, Ham-D, and 3MS scores. Note, only a small fraction of the patients had DIVA scales reported. FPS scores were different across groups with the highest scores in the Nicotine+ group (median = 8) and the lowest scores in the Cannabis+ group (median = 2, group effect $\chi^2_{(3)} = 9.2$, uncorrected $p = .03$). However, the p-value would not be significant after correcting for multiple testing. Note that the Nicotine+ group had more patients

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TABLE 1 Group demographic and clinical characteristics.

	Control	Cannabis+	Nicotine+	Nicotine+/Cannabis+	Group difference (adjusted by covariates[a])
N (total = 112)	30	10	32	37	
Age (mean/±SD)	53.0 (±17.3)	34.9 (±19.7)	48 (±11.4)	36.2 (±13.7)	$F_{(3,105)} = 9.17$, $p < .0001$
Sex	F: 16 (53.3%) M: 14 (46.7%)	F: 4 (40%) M: 6 (60%)	F: 23 (71.9%) M: 9 (28.1%)	F: 14 (37.8%) M: 23 (62.2%)	Pearson $\chi^2_{(3)} = 8.6$, $p = .04$
Alcohol+ (*n*, %)	0	2 (20%)	7 (21.9%)	10 (27.8%)	Pearson $\chi^2_{(3)} = 9.4$, $p = .02$
Main clinical presentation: addiction/pain (addiction %)	2/25 (3 unknown) (6.7%)	5/10 (50%)	8/24 (25%)	21/16 (56.8%)	Pearson $\chi^2_{(3)} = 19.4$, $p < .0001$
DIVA inattentive items (0–9): median score (IQR, range *n*)	5 (2–7, *n* = 8)	8 (7–9, *n* = 6)	8 (5.5–9, *n* = 12)	7 (5–9, *n* = 11)	OLR: $\chi^2_{(3)} = 5.3$, $p = .15$[a]
DIVA hyperactive items (0–9): median score (IQR range; *n*)	4 (1–4, *n* = 6)	5 (2–6, *n* = 6)	6 (4–8, *n* = 11)	5 (4–7, n = 11)	OLR: $\chi^2_{(3)} = 6.4$, $p = .09$[a]
Ham-D (0–52) median score (IQR range, *n*)	14.5 (7–23, *n* = 30)	16 (3–21, *n* = 10)	14 (6–25, *n* = 31)	18.5 (13.5–26.5, *n* = 36)	OLR: $\chi^2_{(3)} = 4.6$, $p = .2$[a]
3MS (0–100): median score (IQR range, *n*)	98 (95–100, *n* = 30)	98 (95–98, *n* = 9)	96 (90–99, *n* = 31)	97.5 (93–100, *n* = 36)	OLR: $\chi^2_{(3)} = 7.3$, $p = .06$[a]
Faces Pain Scale (0–10): median score (IQR range, *n*)	6.5 (6–7.5, *n* = 29)	2 (0–6, *n* = 10)	8 (6–8, *n* = 30)	6.75 (3–7, *n* = 36)	OLR: $\chi^2_{(3)} = 9.2$, $p = .03$[a]

Abbreviations: 3MS, Modified Mini-Mental State Examination; DIVA, Diagnostic Interview for ADHD in adults; Ham-D, Hamilton Depression Rating Scale.

[a]OLR: ordinal logistic regression (group difference adjusted by age, sex, alcohol status, and main clinical presentation.)

with complaints of chronic pain than the Cannabis+ group, but not the Control group. Higher FPS scores were reported in patients with complaints of pain (median FPS = 7) than the patients with addiction (median FPS = 4). We further tested the effects of cannabis and nicotine on FPS separately. In addition to the significant effect of clinical presentation ($\chi^2_{(1)} = 24.6$, $p < .0001$), we found an additional effect of nicotine, which was associated with a significant increase in FPS ($\chi^2_{(1)} = 7.1$, $p = .008$). The effect of cannabis on FPS was not significant ($\chi^2_{(1)} = 3.3$, $p = .07$).

For the gamma GLM for CPT, we compared the models with or without any of the demographic and clinical covariates, including age, gender, clinical presentation, alcohol status, Ham-D, 3MS, and FPS scores. We did not include DIVA scores due to limited numbers. The full model with all the above demographic and clinical features demonstrated the lowest AIC. Using this model, we found that the group differences in CPT were highly significant with the longest time in the Control group (median and IQR range: 105 s [31–180]), decreased drastically to 46 s (25–79) in Cannabis+ group and 45 s (10–131) in the Nicotine+ group, and the shortest 26 s (17–38) in the Cannabis+/Nicotine+ group (group effect $\chi^2_{(3)} = 15.2$, $p = .002$, Figure 1). The effect of cannabis was highly significant ($\chi^2_{(1)} = 8.0$, $p = .005$). The effect of nicotine was only marginally significant ($\chi^2_{(1)} = 3.8$, $p = .052$). The average marginal effect of cannabis on CPT was −44.3 (95% confidence interval [CI]: −76.3, −12.4; $p = .007$) and that of nicotine was −31.2 (95% CI: −65.1, 2.7; $p = .07$). There were no significant interactions between cannabis and nicotine, or with any other demographic and clinical covariates. No significant effect on CPT was found for age, gender, and any included clinical covariates. Our model explained 28.8% of the variance in CPT.

DISCUSSION

The significantly shorter cold pressor time for cannabis users relative to controls indicates increased pain sensitivity among patients using cannabis daily. Using cannabis resulted in an average of 44 s decrease in CPT. Daily use of nicotine also resulted decrease in CPT, but to a lesser degree, 31 s, and was only marginally significant in our data set.

Notably, the Cannabis+ group had more younger patients who reported fewer pain complaints on presentation, and lower scores of FPS. Our understanding of fewer pain complaints among the younger cannabis-using group is that inflammatory peripheral pain was not present in some cases. The hyperalgesia of daily cannabis use is due to less central pain damping. If there was no peripheral inflammatory pain to magnify, there would not be a pain complaint. The shorter CPT time associated with cannabis use appeared to be a central sensitization process. In contrast, the nicotine group had more older patients who had more pain complaints on presentation and had moderate to significant pain (median FPS = 8), which could be the result of peripheral pain intensified by central sensitization.

This result is in accord with the Campbell[11] prospective study over 4 years where cannabis users reported more pain when using cannabis for pain, relative to subjects who did not use cannabis, and

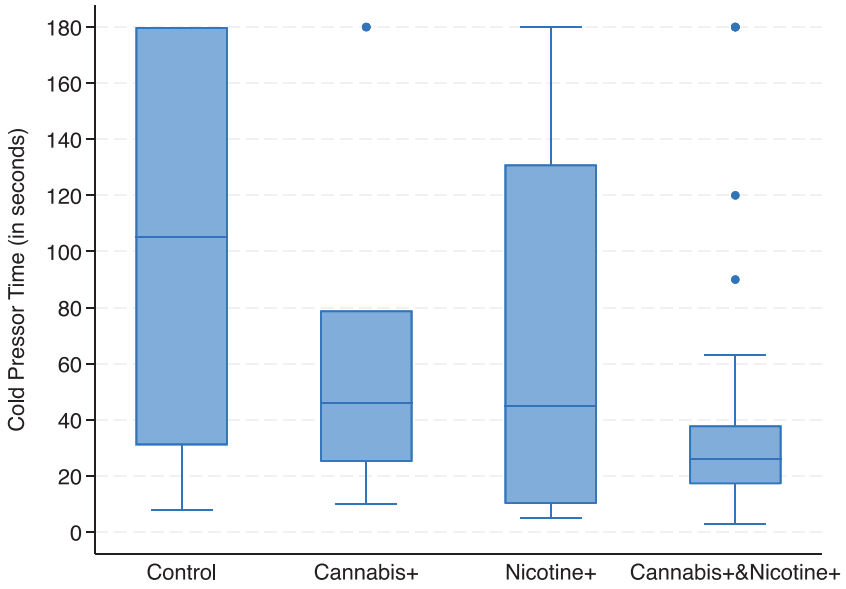

FIGURE 1 Box plot of CPT across groups. Median CPT and IQR ranges, depicted as the lines and boxes, were 105 (31–180), 46 (25–79), 45 (10–131), and 26 (17–38) for the Control, Cannabis+, Nicotine+, and Cannabis+ & Nicotine+ groups, respectively. The overall group differences were highly significant ($\chi^2_{(3)} = 15.2$, $p = .002$, adjusted by age, sex, alcohol use status, and main clinical presentation). CPT, cold pressor test; IQR, interquartile range.

the cited reports of increased need for postoperative analgesia. The mechanism of postoperative hyperalgesia would be that once a peripheral pain driver is created by surgery, the central sensitization caused by cannabis magnifies the pain.

Alcohol, nicotine opioid, and cannabis-induced hyperalgesia can be understood as examples of opponent process. Anything that has an immediate effect to diminish pain may increase pain as a long-term effect. We have repeatedly demonstrated opioid-induced hyperalgesia in pain patients treated with chronic opioid therapy.[21,25–27] CPT is substantially lowered by opioids. The current findings give evidence of the same opponent process phenomenon producing cannabis-induced hyperalgesia. Previous publications about nicotine worsening chronic pain were based on self-report using the FPS.[29,30] Stopping cigarettes significantly improved pain.[31] Our findings regarding nicotine confirm by a different methodology, the CPT, that nicotine-induced hyperalgesia exists.

Potential limitations of the study include relatively small samples and its retrospective design making it impossible to draw strong conclusions of causation, as before cannabis or nicotine pain tolerance was not measured. This study was conducted on a small number of patients in one geographic location. We balanced the narrowness of the source of information with reference to other studies and investigators. The inclusion of more patients presenting with pain complaints in the nicotine group would be expected to bias in the other direction, that is, patients with more subjective pain may have had central sensitization that magnified peripheral pain drivers. However, our adjusted regression model showed that perceived subjective pain, potentially a selection bias for the patient groups, was not significantly associated with CPT; neither was the status of the patients' main clinical presentations. The decrease in CPT was mainly driven by cannabis or nicotine uses, albeit the effect of nicotine was only marginally significant in our current study, likely due to our small sample sizes. Nevertheless, our observation of increased subjective pain and the trend of decreased pain tolerance associated with cigarette smoke is consistent with what others have reported and supports the notion of nicotine increasing central sensitization.

One of the strengths of our study lies in the inclusion of groups that used either or both cannabis and nicotine, in comparison with a control group that used neither, which allowed us to not only examine the individual effect of each drug and also their combined effect. Our results showed that the group that used both cannabis and nicotine had the lowest CPT, highlighting an additive decrease of pain tolerance.

Finally, our adjusted regression models included all demographic and clinical covariates, therefore, controlling for any group differences that may be confounding factors such as gender and age differences. Despite significant group differences in many of these covariates, we found no effect of them on CPT, consistent with our previous report in which we have found no evidence that age or gender influences CPT for normal controls.[21]

CONCLUSION

The virtue of the CPT is that it is an objective measure of pain tolerance. The FPS is a subjective opinion with an underlying assumption that all brains are the same. The brains of our control group were not the same as the other three groups because controls were not subject to the decreased pain damping of central

sensitization. The cannabis, nicotine, and cannabis/nicotine group pain reflected inflammatory pain exacerbated by central sensitization.

For example, 10/10 pain for a patient who does not use cannabis, nicotine, or opioids, reflects peripheral pain. A normal CPT is likely. The practitioner, therefore, addresses peripheral pain drivers. 10/10 pain for a patient who uses cannabis, nicotine, or opioids may indicate central sensitization. The practitioner may consider performing a CPT. With or without the CPT measure of pain tolerance, management may start with eliminating the cannabis, nicotine, and/or opioids and evaluating the pain complaint in the context of decreased central sensitization/improved pain damping.

Our results add to the evidence in the one prospective study that reported exacerbation of chronic pain induced by cannabis use, and three studies that found cannabis use increased subjective pain and caused the need for more postoperative analgesia. The reason that pain symptoms and need for analgesia were higher than for noncannabis-using controls may have been cannabis-induced hyperalgesia/central sensitization.

Opponent process is a valuable concept. It adds depth to medical practitioners' understanding that alcohol, nicotine, opioids, and cannabis may be valued by some patients for their pain-relieving effect, and yet because of the long-term exacerbation of chronic pain, be contraindicated for frequent use. Using these drugs for pain may lead to addiction with the claim that they are used to reduce chronic pain, becoming part of the denial system that propitiates continued use despite the harm of intensifying pain.

ACKNOWLEDGMENTS

The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Zhang-James Y, Wyon E, Grapsas D, Johnson B. Daily cannabis use may cause cannabis-induced hyperalgesia. *Am J Addict*. 2023;32:532-538. doi:10.1111/ajad.13456