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Is Cannabis being used as a substitute for non-medical opioids by adults with problem substance use in the United States? A within-person analysis

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ABSTRACT

Background and Aims Ecological studies have suggested that Cannabis legalization might have led to a decrease in opioid overdose deaths. Such studies do not provide information about whether individuals are substituting Cannabis for opioids at different points in time. The current study assessed the magnitude of the daily association between Cannabis and opioid use in individual adults with and without pain who use non-medical opioids. **Design** Prospective cohort study. **Setting** The greater New York area and a suburban inpatient addiction program. **Participants** Adults with problem substance use who use non-medical opioids, recruited from May 2016–June 2019. The analytical sample included 13 271 days of observation among 211 participants (64% male, 41% white, 78% unmarried, 80% unemployed, mean age 43 years). **Measurements** Participants completed interviewer- and self-administered computerized surveys, and then responded to an interactive voice response (IVR) system daily for the following 90 days. The main exposures, Cannabis use and pain, were defined as responding affirmatively to the IVR question: 'Did you use Cannabis yesterday?' and endorsing moderate or severe pain at baseline, respectively. The main outcome, non-medical or illicit opioid use during 90-day follow-up, was defined as responding affirmatively to IVR question: 'Did you use heroin yesterday?' or 'Did you use prescription opioids more than prescribed or without a prescription yesterday?'. **Findings** The mean IVR completion rate was 70%. The unadjusted odds ratio (aOR) indicating same-day use of Cannabis and opioids was 2.00 [95% confidence interval (CI) = 1.54–2.59]. Controlling for demographic characteristics, recruitment method, opioid types at baseline and pain, the aOR was 1.86 (95% CI = 1.44–2.41). A test of interaction between pain and Cannabis use to determine if the association of Cannabis with opioid use differed between people with moderate-to-severe pain and less-than-moderate pain was inconclusive. **Conclusions** Among US adults with problem substance use who use non-medical opioids, the odds of opioid use appear to be approximately doubled on days when Cannabis is used. This relationship does not appear to differ between people with moderate or more severe pain versus less than moderate pain, suggesting that Cannabis is not being used as a substitute for illegal opioids.

Keywords Cannabis, opioids, opioid epidemic, opioid-related disorders, pain, marijuana.

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INTRODUCTION

The United States is currently in the midst of an opioid crisis. In 2017, there were more than 2 million people with opioid use disorder and more than 70000 opioid-related deaths [1,2]. As a result, the opioid crisis has been declared a national public health emergency [3] and several state-level interventions have been implemented to prevent overdose deaths, including increased treatment services [4,5], naloxone distribution programs [5,6], prescription drug monitoring programs [7,8] and other novel policy interventions [9,10].

One policy considered to impact opioid overdose deaths is increasingly permissive Cannabis legislation [11].

Currently, more than 33 states permit Cannabis use for medical purposes, and 11 states permit recreational Cannabis use [12]. However, the role of more permissive Cannabis legislation in the opioid crisis is not yet fully understood. One individual-level analysis of national survey data found that medical Cannabis laws were not associated with changes in the prevalence of opioid use disorder, and in fact were associated with a small increase in opioid use [13]. At the same time, numerous ecological studies suggest that state medical and recreational Cannabis laws are associated with reductions in opioid prescriptions, opioid-related hospitalizations and overdose deaths [14–20]. Although ecological studies cannot establish causality [21], authors have drawn upon the substitution hypothesis to interpret these findings, positing that individuals may substitute Cannabis for prescription and illicit opioids, particularly to manage pain [13,15,16,18,20].

There is some evidence to support the hypothesis that Cannabis can be substituted for opioids. Cannabis activates some similar neurological pathways as opioids, potentially providing pain relief or limiting cravings [22,23]. Moreover, pain is one of the most common reasons for which Americans use medical Cannabis [24–26], and some recent surveys of Cannabis users indicate that substitution for opioids is relatively common [27–29]. In contrast, some studies find Cannabis to have limited utility for pain management [30–32]. Two longitudinal studies further contradict the substitution hypothesis, finding that Cannabis use is a risk factor for increased opioid use [33,34]. However, these studies only measured Cannabis and opioid use at two distant time-points, and were therefore unable to explore whether Cannabis is ever used as a replacement for opioids. Therefore, whether Cannabis and opioid use are positively or negatively related remains uncertain. In order to more clearly understand whether individuals substitute Cannabis for opioids, prospective studies assessing the use of these two substances with frequent or daily measures are needed [20,35–37].

To fill this gap in knowledge, we used repeated measures to examine the direction and strength of association between Cannabis and opioid use over 90 consecutive days. Specifically, among adults who use non-medical opioids, we used daily measures to compare the probability of non-medical opioid use on days when Cannabis was used to days when Cannabis was not used. Further, to examine whether results applied only to specific subgroups, we assessed whether this relationship differed by gender, severity of opioid use disorder and self-reported pain.

METHODS

Design, setting and participants

Data for the current study came from a larger study on the reliability and validity of DSM-5 measures of substance use disorders ($n = 565$) [Hasin et al. (unpublished)]. The present research question and analysis plan were not pre-registered on a public platform, so results should be considered exploratory. Inclusion criteria included being aged ≥ 18 years, substance use [binge drinking (men, ≥ 5 drinks; women, ≥ 4 drinks), Cannabis, cocaine or opioid use] in the prior 30 days or the 30 days prior to inpatient admission, and at least one criterion endorsed for a DSM-5 substance use disorder in pre-study screening. Exclusion criteria included being non-English-speaking; actively psychotic, suicidal or homicidal, vision/hearing impairment that would preclude participation; or definite plans to leave the greater New York area within 6 months.

Participants were recruited from the community and from a suburban inpatient addiction program. Potentially eligible participants from the inpatient addiction program were informed about the study by hospital staff or posted flyers; those interested met with an on-site research coordinator who described the study, screened for eligibility, obtained informed consent and arranged the baseline assessment. Newspaper or social media advertisements also invited potentially eligible community participants to click a link or call a research coordinator for a brief explanation of the study and eligibility prescreening. Potentially eligible community participants then came to the research offices to meet with a research coordinator for further screening and informed consent. Those qualified to participate were invited to attend the study office for baseline assessment, including a battery of interviewer- and self-administered computerized surveys.

Following the baseline assessment, participants were asked to call or text an interactive voice response (IVR) system every day for the following 90 days to answer questions about their substance use the previous day. If participants did not contact the IVR on a given day, they received an automated reminder. A similar measure of daily substance use has been validated and used extensively in prior research [38–42]. If participants missed more than 2 days of IVR, they were contacted by a study staff member with a reminder.

The analytical sample included all participants who endorsed past-month non-medical opioid use in the self-administered computerized portion of the baseline assessment and used the IVR for ≥ 1 day. Opioid use was defined as any use of heroin or non-medical use of prescription painkillers (i.e. without a prescription or more than prescribed). Participants received $50 for completing the initial baseline assessment and $1 for every day of completed IVR, with bonuses of up to $50 for completing IVR milestones without gaps. All procedures were approved by the Institutional Review Boards of New York State Psychiatric Institute and South Oaks

Hospital, and were conducted between 11 May 2016 and 30 June 2019.

Measures

The main outcome, non-medical or illicit opioid use, was defined as responding affirmatively to the IVR questions: 'Did you use heroin yesterday?' or 'Did you use prescription opioids more than prescribed or without a prescription yesterday?'. The main exposure, Cannabis use, was defined as responding affirmatively to the IVR question: 'Did you use Cannabis yesterday?'. Both variables were measured daily for 90 consecutive days. Pain and all control covariates were assessed in the interviewer- or self-administered computerized baseline assessments. Pain was evaluated using an item from the 12-Item Short Form (SF-12) Survey, an extensively studied and valid measure of general health and health-related quality of life [43,44]. This item asked: 'During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?', with potential responses 'not at all', 'a little bit', 'moderately', 'quite a bit' and 'severely'. Consistent with prior research, a response of at least 'moderately' was used to indicate the presence of moderate-to-severe pain [33,45–48]. This measure has been demonstrated to produce similar pain prevalence estimates as a well-validated pain scale in national survey data [48]. Severity of opioid use disorder was assessed using DSM-5 criteria presented in an interviewer-administered survey at baseline, and categorized as 'severe' (six or more symptoms endorsed) and 'non-severe' (fewer than six symptoms endorsed). Control covariates included gender (male, female), age, race/ethnicity (white, non-white), marital status (married, living together, unmarried), employment status (employed, unemployed), recruitment method (newspaper, social media, inpatient addiction program), opioid type used at baseline (heroin, prescription opioid, both) and pain (moderate or more severe, less than moderate).

Statistical analyses

Data were analyzed using a logistic mixed model, with a random intercept for participant and a random slope for time. Cannabis use and non-medical opioid use were included as time-varying in all models. All other variables were time-invariant. The main measures of association were crude and adjusted odds ratios (aORs), which represented the change in the odds of opioid use on days when Cannabis was used compared to days when Cannabis was not used. The use of a mixed model with a logit link function allowed for interpretation of odds ratios (ORs) as within-person effects (i.e. how opioid use differed when an individual consumed Cannabis compared to when he/she did not consume Cannabis).

First, we tested the crude and adjusted association between Cannabis and opioid use. Secondly, we tested whether this association differed by participant characteristics, including pain level (moderate or more severe versus less than moderate), opioid use disorder severity (severe versus less than severe) and gender (male versus female). All stratified ORs were calculated by adding an interaction with Cannabis use to the adjusted model.

Sensitivity analyses

Some participants were in inpatient care at the start of follow-up. While these participants could have attempted to obtain and use substances while in the inpatient unit, such use was unlikely, and therefore the first sensitivity analysis dropped observations from inpatient days from the data set. Secondly, because participants from the inpatient program may have been more likely to abstain from all substance use during follow-up, a second sensitivity analysis excluded all participants who were recruited from the inpatient addiction program. Thirdly, the threshold for pain was increased from at least 'moderately' to at least 'quite a bit'. Fourthly, race/ethnicity was redefined to include five categories (non-Hispanic white, non-Hispanic black, Hispanic white, Hispanic black, other). Fifthly, marital status was redefined to include a third, 'previously married' category. Sixthly, severity of opioid use disorder OUD) at baseline (no OUD, mild, moderate, severe OUD) was added as a control variable. Finally, severity of Cannabis use disorder CUD) at baseline (no CUD, mild, moderate, severe CUD) was added as a control variable.

RESULTS

The analytical sample included 13271 days of observation and 211 participants, of whom 64% were male, 41% white, 78% unmarried and 80% unemployed (Table 1). Their mean age was 43 years [standard deviation (SD) = 12.5]. At baseline, approximately 50% of the sample reported at least moderate pain over the past 30 days, and past-month opioid use was reported on a mean of 16.0 days. Of a total possible 90 days of reporting substance use in the IVR, the mean completion rate of all possible days was 70%, or a mean of 63 days (SD = 28.7). The median completion rate was 85.6%, or a median of 77 days [interquartile range (IQR) = 39–87]. On average, participants reported using opioids without Cannabis on 14.6% of days][95% confidence interval (CI) = 11.0–18.3%], Cannabis without opioids on 15.0% of days (95% CI = 11.3–18.7%), both Cannabis and opioids on 7.1% of

Table 1 Baseline characteristics of study participants with past-month non-medical opioid use ($n = 211$).

Variable	*Frequency (%)*
Recruitment method/site	
Inpatient addiction program	76 (36.0)
Community	121 (57.3)
Social media	14 (6.6)
Gender	
Male	135 (64.0)
Female	76 (36.0)
Age (mean, SD)	43.12, 12.49
Race	
White	87 (41.2)
Non-white	124 (58.8)
Marital status	
Married or living together	47 (22.3)
Not married or living together	164 (77.7)
Employed	43 (20.4)
Have health insurance	206 (97.6)
History of treatment for substance use	130 (61.6)
Interference of pain with normal work	
Extreme	20 (9.5)
Quite a bit	50 (23.7)
Moderate	36 (17.0)
A little bit	53 (25.1)
Not at all	52 (24.6)
Opioid type misused in past month	
Heroin, but not prescription opioids	88 (41.7)
Prescription opioids, but not heroin	75 (35.5)
Both heroin and prescription opioids	48 (22.7)
Received an opioid prescription in the past 12 months	79 (37.4)
Past-month heroin use (days)	
0	74 (35.1)
1–19	76 (36.0)
≥ 20	61 (28.9)
Past-month non-medical prescription opioid use (days)	
0	89 (42.2)
1–19	104 (49.3)
≥ 20	18 (8.5)
Past-month Cannabis use (days)	
0	90 (42.7)
1–19	65 (30.8)
≥ 20	56 (26.5)
Other past-month other substance use (used ≥ 1 day)	
Alcohol	160 (75.8)
Cigarettes	165 (78.2)
Cocaine	115 (54.5)
Hallucinogens	13 (6.2)
Used Cannabis for medical reasons in the past 12 months	39 (18.9)
Main mode of Cannabis administration[a]	
Smoking	183 (97.3)
Other	5 (2.7)
OUD severity	
No OUD (0–1 symptoms)	61 (28.9)
Mild (2–3 symptoms)	8 (3.8)
Moderate (4–5 symptoms)	12 (5.7)
Severe (6+ symptoms)	130 (61.6)
CUD severity	
No CUD (0–1 symptoms)	126 (59.7)

(***Continues***)

Table 1. (Continued)

Variable	*Frequency (%)*
Mild (2–3 symptoms)	27 (12.8)
Moderate (4–5 symptoms)	18 (8.5)
Severe (6+ symptoms)	40 (19.0)

SD = standard deviation; OUD = opioid use disorder; CUD = Cannabis use disorder. [a]Among participants who reported any Cannabis use.

days (95% CI = 4.6–9.7%) and neither Cannabis nor opioids on 63.2% of days (95% CI = 58.0–68.5%).

Relative to opioid use on days without Cannabis use, the crude OR for opioid use on days with Cannabis use was 2.00 (95% CI = 1.54–2.59, $P < 0.0001$). In adjusted analyses, the OR was 1.86 (95% CI = 1.44–2.41, $P < 0.0001$). The interaction term, pain by Cannabis use, was not statistically significant [$F = 2.86$, degrees of freedom (d.f.) = 1, $P = 0.09$], suggesting no difference in the relationship between Cannabis and opioid use for people with more versus less than moderate pain. Results similarly did not differ by gender or OUD severity (Table 2). Because pain is a potential confounding factor of the relationship between Cannabis and opioid use, it was included as a control variable in the final adjusted model.

None of the sensitivity analyses meaningfully changed results. When inpatient days were excluded the adjusted OR was 1.84 (95% CI = 1.42–2.38), and the interaction with pain, OUD severity and gender remained insignificant. When all participants recruited from the inpatient addiction program were excluded from the analysis, the OR was 1.72 (95% CI = 1.32–2.25), and the interaction with OUD severity and gender were not significant. However, the interaction with pain was significant (estimate = 0.550, $P = 0.047$), indicating that the association between daily Cannabis and opioid use was more positive for individuals with moderate or more pain compared to individuals with less pain. Results were unchanged when the threshold for pain was increased to quite a bit or severe (aOR = 1.86, 95% CI = 1.44–2.40, interactions $P > 0.05$), race/ethnicity was redefined to include five categories (aOR = 1.85, 95% CI = 1.43–2.40, interactions $P > 0.05$), marital status was redefined to include a 'previously married' category (aOR = 1.86, 95% CI = 1.44–

Table 2 Daily association between daily Cannabis and opioid use among adults with non-medical opioid use ($n = 211$).

	Crude OR (95% CI) of opioid use	*Adjusted OR (95% CI)[a] of opioid use*	*Interaction P-value[b]*
Overall			
Days without Cannabis use[c]	1.00 (Reference)	1.00 (Reference)	n/a
Days with Cannabis use[d]	2.00 (1.54–2.59)[e]	1.86 (1.44–2.41)[e]	
By gender			
Days without Cannabis use	NA	1.00 (Reference)	
Days with Cannabis use among:			
Males	NA	2.10 (1.49–2.97)[e]	0.29
Females	NA	1.59 (1.08–2.35)[e]	
By severity of OUD			
Days without Cannabis use	NA	1.00 (Reference)	
Days with Cannabis use among:			
Individuals with severe symptoms (6+)	NA	1.62 (1.19–2.19)[e]	0.08
Individuals with non-severe symptoms (< 6)	NA	2.69 (1.67–4.34)[e]	
By pain status			
Days without Cannabis use	NA	1.00 (Reference)	
Days with Cannabis use among			
Individuals with pain	NA	2.27 (1.60–3.21)[e]	0.09
Individuals without pain	NA	1.46 (0.99–2.13)	

OR = odds ratio; CI = confidence interval; OUD = opioid use disorder; NA = not available. [a]Control covariates: gender, age, ethnicity, marital status, employment status, recruitment method, opioid type used at baseline and pain; [b]*P*-value < 0.05 would indicate that the association between Cannabis use and opioid use differed between individuals with and without pain, males and females or individuals with severe and non-severe OUD symptoms; [c]9975 completed days without Cannabis use; [d]3296 completed days with Cannabis use; [e]*P*-value < 0.05.

2.41, interactions $P > 0.05$), severity of opioid use disorder was controlled (aOR = 1.88, 95% CI = 1.45–2.44, interactions $P > 0.05$), and severity of Cannabis use disorder was controlled (aOR = 1.93, 95% CI = 1.49–2.51, interactions $P > 0.05$). Full sensitivity analysis results are presented in Supporting information, Table S1.

DISCUSSION

Among opioid-using adults, we examined how the odds of non-medical or illicit opioid use changed on days when Cannabis was used. On average, participants reported using opioids without Cannabis on 15% of days, Cannabis without opioids on 15% of days and both Cannabis and opioids on 7% of days. On days that participants used Cannabis, the odds of non-medical opioid use nearly doubled. The strength of this relationship did not significantly differ by gender, OUD severity or between individuals with and without moderate or more severe pain. Thus, substitution of non-medical opioids with Cannabis was unlikely, regardless of the presence of significant pain, results that applied equally to men and women and across OUD severity levels.

Our findings are consistent with those of other prospective studies of Cannabis and opioid use. For example, a cohort tudy reported that among individuals with chronic pain, Cannabis use was not associated with reduced prescription opioid use at 4-year follow up [49]. Another study of national survey data found that Cannabis use in 2001 was a risk factor for incident prescription opioid use and opioid use disorder in 2004 [33]. This is also consistent with findings that people who use Cannabis are generally more likely to use medical and non-medical opioids [34,50,51]. However, our findings are not consistent with one previous study which found a negative association between daily Cannabis use and daily illicit opioid use. Although this study followed a cohort of adults who reported chronic pain, it measured Cannabis and opioid use cross-sectionally in 6-month periods, did not assess the association between less-than-daily Cannabis and opioid use and included participants who did not use opioids at baseline [52]. Therefore, unlike previous studies, we included daily measurements of individuals, calculated within-subject changes and focused on adults who were non-medically using opioids at baseline. This finely grained time window permits a unique opportunity to examine the potential substitution of Cannabis for non-medical opioids.

Our findings also add to discussion concerning the effects of medical marijuana laws (MML) on opioid use. Numerous ecological studies have reported a negative association between MML and opioid outcomes [14–19], while one study of individual-level data found a small positive association between MML and opioid use [13]. An additional ecological study re-examined the change in opioid overdose mortality following MML using a longer timeframe, reporting an associated increase, rather than decrease, in overdose deaths [53]. All these studies conclude with a discussion of whether or not Cannabis is substituted for opioids, although ecological and cross-sectional data cannot test this hypothesis. Consistent with the demographic characteristics of medical Cannabis users [54,55] and opioid overdose fatalities [56], our sample was predominantly male, urban, unemployed, unmarried and had a high prevalence of substance misuse and pain. The current study is therefore among the first to directly test opioid substitution, suggesting that Cannabis seldom serves as a substitute for non-medical opioids among opioid-using adults, even among those who report experiencing moderate or more severe pain.

Study limitations are noted. First, the measures of substance use used self-report, making under-reporting a possibility. However, the initial computerized assessment and the IVR were self-administered, reducing potential bias. Additionally, by providing within-subject comparisons, participants who repeatedly under-reported their Cannabis use were compared only to themselves, rather than to other participants. Secondly, pain was only assessed at baseline and the quantity of Cannabis or opioids used was not measured. We were therefore unable to measure whether heavier Cannabis use acts as a substitute for opioids or whether Cannabis is associated with a reduction (rather than replacement) of opioid use. We were also unable to measure whether pain in a given day moderates the relationship between Cannabis and opioid use. To test these hypotheses, future studies with more detailed measures of Cannabis and opioid consumption, as well as daily measures of pain, are needed. Thirdly, the sample was limited to those who had problem substance use at baseline. While this allowed for the establishment of a cohort of adults who use non-medical opioids, it also precluded the ability to generalize study findings to those who use opioids and/or Cannabis in the absence of substance use problems. To examine this population, future studies are needed.

Fourthly, our sample included some individuals who were initially in treatment for a substance use disorder. These individuals may have been more likely to abstain from any substance use during the follow-up than other participants, thereby potentially causing selection bias. To address this, we conducted two sensitivity analyses, where inpatient days and all clinic-recruited participants were dropped from the analysis. Neither of these robustness checks meaningfully changed our observed results, suggesting that this portion of the sample did not cause serious bias. Fifthly, our study measured only illegal opioid and Cannabis use, and lacked information on the presence of painful medical conditions. During the study period, smoked medical Cannabis was not permitted in New York State. Different results may have been observed among opioid-using participants seeking medical marijuana or

taking medically prescribed opioids for pain conditions. The observed relationship between Cannabis and non-medical opioid use may have also differed from the relationship between Cannabis and medical opioid use. However, as described above, our sample characteristics closely match those of medical Cannabis users and those with opioid overdose deaths, suggesting potential generalizability to individuals whose overdose risks are susceptible to changes in marijuana laws. Future research should seek to measure the impact of using both medical and illegal Cannabis on using medical opioids, non-medical opioids and other substances, such as alcohol, cocaine and stimulants. Sixthly, the sensitive subject matter and financial incentives in the current study may have dissuaded adults who were more affluent or unwilling disclose information about substance use from participating. Whether these factors led to selection bias cannot be known, although we note that the current sample characteristics closely match those of the general population of adults who use non-medical opioids, those at risk of opioid overdose and those who use medical marijuana.

Finally, because Cannabis and opioid use were measured during the same 24-hour period, we were unable to examine which substance was used first on any given day. Cannabis could have led to an increase in opioid use, opioid use to an increase in Cannabis use or some third unmeasured variable could have led to an increase in both (although pain is unlikely to be such a variable, as results did not differ by level of pain). The short time measurement window allows for the examination of time-periods within which substitution may have occurred. Some prior studies have separated measurement of Cannabis and opioid use by months or years [33,49], or measured use only during large time intervals [52], complicating assessment of potential substitution effects. Moreover, unlike prior research, this study used multiple repeated measurements per individual, allowing for the calculation of an average within-person association based on up to 90 days of data. For each subject, multiple days on which Cannabis was used were compared to multiple days on which Cannabis was not used. This design feature provides a clear picture of the average daily relationship between Cannabis and non-medical opioid use for a given individual.

CONCLUSIONS

As illegal opioids, including non-medical prescription opioids, synthetic opioids and heroin, are the primary cause of overdose deaths in US adults [57], understanding how Cannabis may change non-medical opioid use is critical to informing discussions concerning Cannabis-based interventions for addressing the opioid crisis. On days when Cannabis was used, the odds of non-medical opioid use were approximately doubled. This relationship did not change when comparing people with moderate-to-severe and less-than-moderate pain, suggesting that Cannabis is not used as a substitute for non-medical opioids. While this study bears replication with other populations, the results suggest that Cannabis is not an effective means of limiting non-medical opioid use and casts doubt on this potential therapeutic indication. Future research should explore the effects of Cannabis availability, reasons for use and quantity consumed on a range of opioid-related outcomes using repeated measures and variable time-frames for substitution to occur.

Declaration of interests

None.

Author Contributions

Lauren Gorfinkel: Conceptualization; data curation; formal analysis; investigation. **Malki Stohl:** Formal analysis. **Eliana Greenstein:** Data curation. **Deborah Hasin:** Investigation; methodology; project administration; resources; supervision.

References

1. Substance Abuse and Mental Health Services Administration. Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2018.
2. Hedegaard H., Minino A.M., Warner M. Drug Overdose Deaths in the United States, 1999–2017. NCHS Data Brief 2018: pp. 1–8.
3. US Department of Health and Human Services (USDHHS). HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis. Washington, DC: USDHHS; 2017.
4. Mojtabai R., Mauro C., Wall M. M., Barry C. L., Olfson M. Medication treatment for opioid use disorders in substance use treatment facilities. *Health Aff* 2019; **38**: 14–23.
5. Lambdin B. H., Davis C. S., Wheeler E., Tueller S., Kral A. H. Naloxone laws facilitate the establishment of overdose education and naloxone distribution programs in the United States. *Drug Alcohol Depend* 2018; **188**: 370–6.
6. Abouk R., Pacula R. L., Powell D. Association between state laws facilitating pharmacy distribution of naloxone and risk of fatal overdose. *JAMA Intern Med* 2019; **179**: 805–11.
7. Haffajee R. L., Mello M. M., Zhang F., Zaslavsky A. M., Larochelle M. R., Wharam J. F. Four states with robust prescription drug monitoring programs reduced opioid dosages. *Health Aff* 2018; **37**: 964–74.
8. Wen H., Hockenberry J. M., Jeng P. J., Bao Y. Prescription drug monitoring program mandates: impact on opioid prescribing and related hospital use. *Health Aff* 2019; **38**: 1550–6.
9. Brighthaupt S. C., Stone E. M., Rutkow L., McGinty E. E. Effect of pill mill laws on opioid overdose deaths in Ohio & Tennessee: a mixed-methods case study. *Prev Med* 2019; **126**: 105736.
10. Sharp A., Jones A., Sherwood J., Kutsa O., Honermann B., Millett G. Impact of Medicaid expansion on access to opioid

analgesic medications and medication-assisted treatment. *Am J Public Health* 2018; **108**: 642–8.
11. Hill K. P., Saxon A. J. The role of Cannabis legalization in the opioid crisis. *JAMA Intern Med* 2018; **178**: 679–80.
12. The National Conference on State Legislators. State Medical Marijuana Laws. 2019 [cited 2019 April 5]. Available at: http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx (accessed 2 April 2020).
13. Segura L. E., Mauro C. M., Levy N. S., Khauli N., Philbin M. M., Mauro P. M., *et al.* Association of US medical marijuana Laws with nonmedical prescription opioid use and prescription opioid use disorder. *JAMA Netw Open* 2019; **2**: e197216.
14. Livingston M. D., Barnett T. E., Delcher C., Wagenaar A. C. Recreational Cannabis legalization and opioid-related deaths in Colorado, 2000–2015. *Am J Public Health* 2017; **107**: 1827–9.
15. Bradford A. C., Bradford W. D. Medical marijuana Laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. *Health Aff* 2017; **36**: 945–51.
16. Bradford A. C., Bradford W. D. Medical marijuana laws reduce prescription medication use in Medicare part D. *Health Aff* 2016; **35**: 1230–6.
17. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend* 2017; **173**: 144–50.
18. Wen H., Hockenberry J. M. Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med* 2018; **178**: 673–9.
19. Liang D., Bao Y., Wallace M., Grant I., Shi Y. Medical Cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014. *Addiction* 2018; **113**: 2060–70.
20. Bachhuber M. A., Saloner B., Cunningham C. O., Barry C. L. Medical Cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Intern Med* 2014; **174**: 1668–73.
21. Greenland S. Ecologic versus individual-level sources of bias in ecologic estimates of contextual health effects. *Int J Epidemiol* 2001; **30**: 1343–50.
22. Whiting P. F., Wolff R. F., Deshpande S., di Nisio M., Duffy S., Hernandez A. V., *et al.* Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; **313**: 2456–73.
23. Lucas P. Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. *J Psychoact Drugs* 2012; **44**: 125–33.
24. Kosiba J. D., Maisto S. A., Ditre J. W. Patient-reported use of medical Cannabis for pain, anxiety, and depression symptoms: systematic review and meta-analysis. *Soc Sci Med* 2019; **233**: 181–92.
25. Reiman A., Welty M., Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res* 2017; **2**: 160–6.
26. Boehnke K. F., Gangopadhyay S., Clauw D. J., Haffajee R. L. Qualifying conditions of medical Cannabis license holders in the United States. *Health Aff* 2019; **38**: 295–302.
27. Degenhardt L., Lintzeris N., Campbell G., Bruno R., Cohen M., Farrell M., *et al.* Experience of adjunctive Cannabis use for chronic non-cancer pain: findings from the pain and opioids IN treatment (POINT) study. *Drug Alcohol Depend* 2015; **147**: 144–50.
28. Lucas P., Walsh Z. Medical Cannabis access, use, and substitution for prescription opioids and other substances: a survey of authorized medical Cannabis patients. *Int J Drug Policy* 2017; **42**: 30–5.
29. Ishida J. H., Wong P. O., Cohen B. E., Vali M., Steigerwald S., Keyhani S. Substitution of marijuana for opioids in a national survey of US adults. *PLOS ONE* 2019; **14**: e0222577.
30. Nugent S. M., Morasco B. J., O'Neil M. E., Freeman M., Low A., Kondo K., *et al.* The effects of Cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med* 2017; **167**: 319–31.
31. Stockings E., Campbell G., Hall W. D., Nielsen S., Zagic D., Rahman R., *et al.* Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain* 2018; **159**: 1932–54.
32. Sturgeon J. A., Khan J., Hah J. M., Hilmoe H., Hong J., Ware M. A., *et al.* Clinical profiles of concurrent Cannabis use in chronic pain: a CHOIR study. *Pain Med* 2020; https://doi.org/10.1093/pm/pnaa060
33. Olfson M., Wall M. M., Liu S. M., Blanco C. Cannabis use and risk of prescription opioid use disorder in the United States. *Am J Psychiatry* 2018; **175**: 47–53.
34. Caputi T. L., Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and nonmedically. *J Addict Med* 2018; **12**: 295–9.
35. Finney J. W., Humphreys K., Harris A. H. What ecologic analyses cannot tell us about medical marijuana legalization and opioid pain medication mortality. *JAMA Intern Med* 2015; **175**: 655–6.
36. Powell D., Pacula R. L., Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ* 2018; **58**: 29–42.
37. Bachhuber M. A., Arnsten J. H., Cunningham C. O., Sohler N. Does medical Cannabis use increase or decrease the use of opioid analgesics and other prescription drugs? *J Addict Med* 2018; **12**: 259–61.
38. Corkrey R., Parkinson L. Interactive voice response: review of studies 1989–2000. *Behav Res Methods Instrum Comput* 2002; **34**: 342–53.
39. Perrine M. W., Mundt J. C., Searles J. S., Lester L. S. Validation of daily self-reported alcohol consumption using interactive voice response (IVR) technology. *J Stud Alcohol* 1995; **56**: 487–90.
40. Parker M. A., Ochalek T. A., Rose G. L., Badger G. J., Sigmon S. C. Feasibility of an interactive voice response system for daily monitoring of illicit opioid use during buprenorphine treatment. *Psychol Addict Behav* 2018; **32**: 956–60.
41. Aharonovich E., Stohl M., Cannizzaro D., Hasin D. HealthCall delivered via smartphone to reduce co-occurring drug and alcohol use in HIV-infected adults: a randomized pilot trial. *J Subst Abuse Treat* 2017; **83**: 15–26.
42. Hasin D. S., Aharonovich E., Greenstein E. HealthCall for the smartphone: technology enhancement of brief intervention in HIV alcohol dependent patients. *Addict Sci Clin Pract* 2014; **9**: 5.
43. Salyers M. P., Bosworth H. B., Swanson J. W., Lamb-Pagone J., Osher F. C. Reliability and validity of the SF-12 health survey among people with severe mental illness. *Med Care* 2000; **38**: 1141–50.
44. Ware J. Jr., Kosinski M., Keller S. D. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996; **34**: 220–33.
45. Gaskin D. J., Richard P. The economic costs of pain in the United States. *J Pain* 2012; **13**: 715–24.
46. Putzke J. D., Richards S. J., Hicken B. L., DeVivo M. J. Interference due to pain following spinal cord injury: important

predictors and impact on quality of life. *Pain* 2002; **100**: 231–42.
47. Wilson M. W., Richards J. S., Klapow J. C., DeVivo M. J., Greene P. Cluster analysis and chronic pain: an empirical classification of pain subgroups in a spinal cord injury sample. *Rehabil Psychol* 2005; **50**: 381–8.
48. Hasin D. S., Shmulewitz D., Cerdá M., Keyes K. M., Olfson M., Sarvet A. L., *et al*. U.S. adults with pain, a group increasingly vulnerable to nonmedical Cannabis use and Cannabis use disorder: 2001–2002 and 2012–2013. *Am J Psychiatry* 2020; **177**: 611–8.
49. Campbell G., Hall W. D., Peacock A., Lintzeris N., Bruno R., Larance B., *et al*. Effect of Cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. *Lancet Public Health* 2018; **3**: e341–e350.
50. Fiellin L. E., Tetrault J. M., Becker W. C., Fiellin D. A., Hoff R. A. Previous use of alcohol, cigarettes, and marijuana and subsequent abuse of prescription opioids in young adults. *J Adolesc Health* 2013; **52**: 158–63.
51. National Academies of Sciences, Engineering and Medicine *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: The National Academies Press; 2017.
52. Lake S., Walsh Z., Kerr T., Cooper Z. D., Buxton J., Wood E., *et al*. Frequency of Cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. *PLOS Med* 2019; **16**: e1002967.
53. Shover C. L., Davis C. S., Gordon S. C., Humphreys K. Association between medical Cannabis laws and opioid overdose mortality has reversed over time. *Proc Natl Acad Sci USA* 2019; **116**: 12624–6.
54. Ilgen M. A., Bohnert K., Kleinberg F., Jannausch M., Bohnert A. S. B., Walton M., *et al*. Characteristics of adults seeking medical marijuana certification. *Drug Alcohol Depend* 2013; **132**: 654–9.
55. Roy-Byrne P., Maynard C., Bumgardner K., Krupski A., Dunn C., West I. I., *et al*. Are medical marijuana users different from recreational users? The view from primary care. *Am J Addict* 2015; **24**: 599–606.
56. Altekruse S. F., Cosgrove C. M., Altekruse W. C., Jenkins R. A., Blanco C. Socioeconomic risk factors for fatal opioid overdoses in the United States: findings from the mortality disparities in American communities study (MDAC). *PLOS ONE* 2020; **15**: e0227966.
57. Scholl L., Seth P., Kariisa M., Wilson N., Baldwin G. Drug and opioid-involved overdose deaths—United States, 2013–2017. *Morb Mortal Wkly Rep* 2018; **67**: 1419–27.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Daily association between Cannabis and opioid use ($N = 211$): Sensitivity Analysis Results.

