



Co-use of cannabis and prescription opioids in adults in the USA: a population-based, cross-sectional analysis of the NHANES from 2009 to 2018

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ABSTRACT

Introduction Cannabis and cannabinoids continue to gain popularity as adjuncts or alternatives to opioids in pain management, with evolving evidence of effectiveness. The relationship between cannabis and opioid use has previously been investigated in smaller cohorts or ecological samples, but not yet in a nationally representative sample.

Methods A cross-sectional analysis of adults in the USA was undertaken using National Health and Nutrition Examination Survey (NHANES) data from 2009 to 2018. The primary exposure was self-reported use of at least one opioid-containing prescription medication in the 30 days prior to survey administration. The outcome of interest was self-reported cannabis use in the same period. Multivariable logistic regression was used to adjust for sociodemographic and health-related covariates, and NHANES survey sample weights were included in modeling. Prescription opioid users were then subclassified as short-term users (<90 days) or chronic users (≥90 days) in secondary analysis.

Results A total 10,928 survey respondents were included in analyses, representing 110 million adults in the USA aged 18–59. In this weighted cohort, 5.6%±0.4% reported a recent opioid prescription. Among prescription opioid users, 18.4%±3.1% reported recent cannabis use, not significantly different from 17.7%±0.7% among non-users (OR 1.05, 95% CI 0.81 to 1.36, p=0.714). After adjustment for covariates, opioid users were significantly less likely to have recently used cannabis (adjusted OR, aOR 0.70, 95% CI 0.51 to 0.97, p=0.032). When opioid users were subclassified by duration of prescription, there was no detectable difference in recent cannabis use between chronic opioid users and short-term opioid users (aOR 1.11, 95% CI 0.70 to 1.78, p=0.649).

Conclusion Recent prescription opioid use was associated with decreased odds of cannabis use in this cross-sectional analysis of a nationally representative cohort. These findings suggest that use of cannabis or prescription opioids may not independently promote use of the other.

INTRODUCTION

Ongoing decriminalization and improved access to cannabis across the USA has been strongly associated with an increasing prevalence of use.¹ For people using cannabis for medicinal or therapeutic purposes, reports consistently cite seeking pain relief

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cohort and ecological studies have demonstrated an inverse relationship between cannabis use and opioid use.

WHAT THIS STUDY ADDS

⇒ This study is the first to investigate the relationship between cannabis use and prescription opioid use in a nationally representative sample and demonstrates findings similar to previous cohort and ecological studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ With the increasing use of cannabis and cannabinoids for their analgesic properties, clinicians must safely integrate these products into existing opioid-based pain practices.

as one of the top reasons.^{2–4} As a result, cannabis and cannabinoid products are being increasingly adopted as adjuncts or even alternatives to traditional opioid-based pain management strategies. Survey data suggest possible advantages of these combinatory approaches may include synergistic analgesia, reductions in opioid requirements, and prevention of opioid tolerance or withdrawal.⁵

At the same time, the potential harms of co-use need to be considered. In addition to the side effects and risks associated with each agent on its own, co-use has been reported to worsen symptoms related to anxiety, depression, and substance use disorders.^{6–7} Given the morbidity and mortality associated with substance dependence and use disorders, understanding the patterns of opioid and cannabis co-use is important to balancing analgesic efficacy with patient safety when prescribing these agents.

Previous literature examining the relationship between opioid use and cannabis use have mostly reported a negative (inverse) association between the two, suggesting that use of one does not necessarily promote use of the other.^{8–10} However, these studies have been conducted in relatively small cohorts or using ecological data, which may be at risk of ecological fallacy where the associations observed in aggregate cohorts may not apply at the individual level. To date, there are no studies



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investigating co-use patterns in individuals at the population level to unify these previous findings. This study was conducted to address this gap by exploring the relationship between prescription opioid use and cannabis use in a nationally representative sample. Based on previous literature, we hypothesized that opioids users were less likely to concurrently use cannabis.

METHODS

Study setting and population

Data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES), which is a cross-sectional survey designed by the National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention and administered on a 2-year cycle. The NHANES is designed to yield nationally representative data for the non-institutionalized civilian population of the continental USA every survey cycle. This is achieved using a multistage area probability sample selection: (1) selection of primary sampling units (PSUs), (2) segments within PSUs (one or more blocks containing a cluster of households), (3) households within segments, and (4) at least one participant within each household. Sample weights and adjustments are then made to account for oversampling and control for non-response. Further details and statistical validation of these sampling and weighting methods can be found in previously published NHANES official reports.¹¹ For this study, a data set was constructed using publicly available files from five 2-year cycles of NHANES responses (2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018). These cycles were selected as they were contiguous and contained survey data about prescription medication use, which is needed for our primary exposure variable. The study population consisted of all adult respondents to the NHANES cannabis questionnaire, which was administered to participants 18–59 years of age.

Exposure

The primary exposure was recent prescription opioid use. Participants were classified as recent prescription opioid users if they reported using at least one prescription opioid-containing medication within the 30 days prior to survey administration. Participants were also asked to report the duration for which they had used each listed prescription medication. Opioid agents are listed in online supplemental table S1.

Outcome

The primary outcome was recent cannabis use. Survey respondents were classified as recent cannabis users if they reported any cannabis use in the 30 days prior to survey response. This is consistent with the definition commonly used in population-based cannabis questionnaires such as the NHANES and the National Survey on Drug Use and Health.¹² Participants were also asked on how many of those 30 days they had used cannabis. For secondary analyses, we considered other commonly used definitions of cannabis use: (1) use in the past 7 days and (2) use on ≥ 20 of the past 30 days.^{13 14}

Covariates

Covariates were selected a priori based on biological plausibility for confounding the relationship between the exposure and primary outcome. Demographic variables included age (categorical; 18–25, 26–40, and 41–59 years), biological sex, and race/ethnicity (categorical: Hispanic, white, black, or other). Education beyond high school (binary), family income-to-poverty ratio (categorical: ≤ 1 , 1–3, or >3 ; ratio of reported

individual or family income to the regional poverty threshold for that year) and health insurance coverage from any source (binary) were considered as socioeconomic factors. Self-rated health status (binary: poor/fair or good/very good/excellent) was also included. Hypertension, diabetes, coronary artery disease, heart failure, stroke, body mass index (BMI; categorical: <25 kg/m², 25–30 kg/m², or ≥ 30 kg/m²), asthma, chronic obstructive pulmonary disease, prior cancer diagnosis, arthritis, and depression (defined as a Patient Health Questionnaire (PHQ-9) score ≥ 10) were included as comorbidities as binary variables (except for BMI). Behaviors such as smoking, heavy alcohol use (≥ 4 drinks per day, on average), and any reported history of prior illicit substance (cocaine, heroin, methamphetamine) use were included as binary variables. Finally, the 2-year survey cycle in which participants were interviewed and examined was included in statistical modeling. Respondents with missing values for covariates were excluded from analyses (complete-case analyses).

Data analysis

The weighted prevalence of recent prescription opioid use, recent cannabis use, and co-use of the two was calculated for the entire study cohort, and for each separate 2-year survey cycle to identify population trends in use. Weighted differences in baseline characteristics between non-users and users of prescription opioids were analyzed by using t-tests or χ^2 tests as appropriate. Multivariable logistic regression was used to determine the association between recent prescription opioid use and recent cannabis use while accounting for covariates. To test for potential differences over time related to evolving attitudes toward cannabis use and opioid use, an interaction term between the exposure variable and year of survey administration was subsequently added to the primary regression model. Secondary analyses using different definitions of the outcome, as described above, were also performed.

An additional secondary analysis was subsequently performed to test for a biological gradient between exposure and outcome. Prescription opioid users were further subclassified as short-term users or chronic users if they reported a duration of <90 or ≥ 90 days, respectively, and were compared with non-users. Chronic opioid users were then compared directly to short-term opioid users in the same model.

To assess the impact of data missing at random on the primary regression model, a multiple imputation strategy was employed. Predictive mean matching was used to impute five replications of our data set. Sample-weighted logistic regression models were constructed for each of these data sets, as with our primary analytic model, and the resultant model coefficients and ORs pooled.

Statistical significance was defined as a two-tailed $p < 0.05$ for all analyses. All analyses took into consideration NHANES sample weights which were adjusted by the number of years of survey data to represent a single cohort and population. All models that accounted for adjusted sample weights and maintained the complex survey design of the NHANES were built using the open source ‘survey’ package, with guidance from published statistical methods.¹¹ Data analyses were performed using R V.3.5.2 (R Core Team, Vienna, Austria). Regression sample size was based on the available data and no a priori power calculations were performed.

RESULTS

Between 2009 and 2018, a total of 19,863 adults were invited to complete the NHANES cannabis use questionnaire. After

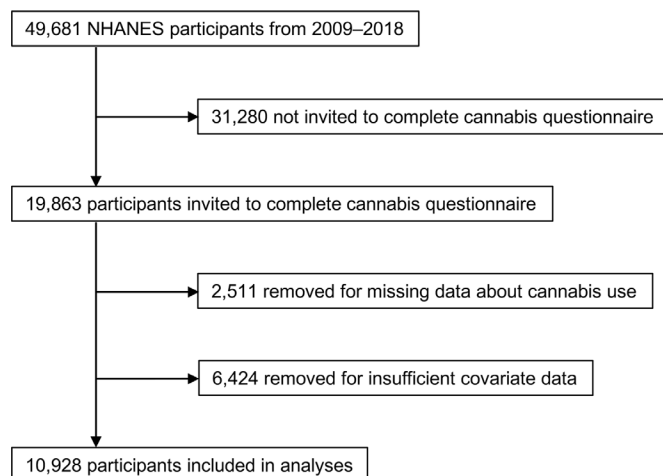


Figure 1 Participant inclusion flow chart from the National Health and Nutrition Examination Survey (NHANES), 2009–2018.

excluding participants with missing data related to cannabis use or covariates, 10,928 were included in analyses (figure 1), representing 109,582,091 adults aged 18–59 of the continental, non-institutionalized population of the USA. Across the study period, $5.6\% \pm 0.4\%$ of the weighted sample reported using prescription opioids in the past 30 days, $17.7\% \pm 0.7\%$ reported cannabis use in the past 30 days, and $1.0\% \pm 0.2\%$ reported both. The reported prevalence of recent prescription opioid use decreased from $6.3\% \pm 1.0\%$ in 2009–2010 to $5.1\% \pm 1.0\%$ in 2017–2018, while that of cannabis use increased from $15.6\% \pm 1.5\%$ to $20.4\% \pm 1.8\%$ for the same period (these data are presented in online supplemental table S2 and online supplemental figure S1). Sample characteristics within strata defined by prescription opioid exposure are presented in table 1.

In unadjusted analysis, participants reporting recent prescription opioid use were no more or less likely to report recent cannabis use compared with those not using opioids ($18.4\% \pm 3.1\%$ vs $17.7\% \pm 0.7\%$; OR 1.05, 95% CI 0.81 to 1.36, $p=0.714$). After adjusting for covariates, recent opioid users were found to be significantly less likely to have recently used cannabis (adjusted OR, aOR 0.70, 95% CI 0.51 to 0.97, $p=0.032$) (the primary model can be found in online supplemental table S3). When including an interaction term between the exposure variable and year of survey administration in the model, this was not statistically significant and thus excluded from all subsequent analyses (online supplemental table S4). The negative association between recent prescription opioids use and cannabis use persisted even when the definition of cannabis use was changed in secondary analyses to: (1) having used cannabis in the past 7 days (aOR 0.62, 95% CI 0.43 to 0.91, $p=0.013$) or (2) having used cannabis on ≥ 20 of the past 30 days (aOR 0.60, 95% CI 0.38 to 0.95, $p=0.029$) (table 2).

When opioid users were subclassified by duration of current opioid use, short-term opioid users were less likely than non-users to have recently used cannabis (aOR 0.62, 95% CI 0.40 to 0.96, $p=0.031$), while chronic opioid users were not statistically different from non-users (aOR 0.75, 95% CI 0.50 to 1.10, $p=0.143$). When compared directly to short-term opioid users, chronic opioid users were neither more nor less likely to have recently used cannabis (aOR 1.11, 95% CI 0.70 to 1.78, $p=0.649$). These findings persisted across various definitions of cannabis use (table 2).

Table 1 Characteristics of participants from the National Health and Nutrition Examination Survey 2009–2018, by prescription opioid use exposure

| | Rx opioid use in past 30 days? | | P value |
|--------------------------------------|--------------------------------|-------------|---------|
| | No (n=10,340) | Yes (n=588) | |
| Represented no. of adults in the USA | 103 455 987 | 6 126 104 | |
| Age (years) | | | |
| 18–25 | 1788 (17.0%) | 44 (7.6%) | <0.001 |
| 26–40 | 4074 (37.3%) | 185 (28.5%) | |
| 41–59 | 4478 (45.7%) | 359 (63.9%) | |
| Sex | | | |
| Female | 4962 (48.0%) | 337 (55.4%) | <0.001 |
| Male | 5378 (52.0%) | 251 (44.6%) | |
| Race/ethnicity | | | |
| Hispanic | 2510 (15.4%) | 86 (8.2%) | <0.001 |
| White | 4196 (65.9%) | 335 (75.5%) | |
| Black | 2188 (11.0%) | 121 (10.2%) | |
| Other | 1446 (7.7%) | 46 (6.1%) | |
| Education beyond high school | 6479 (68.5%) | 319 (60.0%) | <0.001 |
| Family income-to-poverty ratio | | | |
| ≤ 1 | 2116 (13.8%) | 186 (20.7%) | <0.001 |
| 1–3 | 4029 (32.9%) | 238 (37.3%) | |
| >3 | 4195 (52.3%) | 164 (42.0%) | |
| Health insurance | 7615 (80.2%) | 470 (84.1%) | 0.018 |
| Self-rated health status | | | |
| Poor or fair | 1734 (12.6%) | 255 (36.9%) | <0.001 |
| Good, very good, or excellent | 8606 (87.4%) | 333 (63.1%) | |
| Hypertension | 2260 (21.2%) | 246 (37.6%) | <0.001 |
| Diabetes | 618 (5.0%) | 74 (9.1%) | <0.001 |
| BMI (kg/m ²) | | | |
| <25 | 3230 (31.5%) | 144 (25.7%) | <0.001 |
| 25–30 | 3247 (32.0%) | 152 (29.5%) | |
| ≥ 30 | 3863 (36.5%) | 292 (44.8%) | |
| Coronary artery disease | 82 (0.8%) | 15 (1.9%) | 0.006 |
| Heart failure | 86 (0.6%) | 16 (1.5%) | 0.006 |
| Stroke | 113 (0.9%) | 28 (3.1%) | <0.001 |
| Asthma | 1623 (15.4%) | 156 (24.2%) | <0.001 |
| COPD | 508 (4.8%) | 109 (15.5%) | <0.001 |
| Cancer | 355 (4.7%) | 72 (13.2%) | <0.001 |
| Arthritis | 1324 (13.7%) | 293 (50.5%) | <0.001 |
| Depression | 820 (6.9%) | 150 (22.2%) | <0.001 |
| Smoker | 2596 (22.2%) | 263 (42.2%) | <0.001 |
| Heavy alcohol use | 2760 (25.5%) | 156 (23.8%) | 0.359 |
| Any illicit substance use | 1989 (20.9%) | 223 (37.1%) | <0.001 |
| Survey cycle | | | |
| 2009–2010 | 2235 (18.8%) | 150 (21.5%) | 0.004 |
| 2011–2012 | 1992 (19.8%) | 133 (23.5%) | |
| 2013–2014 | 2190 (20.2%) | 125 (21.4%) | |
| 2015–2016 | 2034 (20.2%) | 89 (14.8%) | |
| 2017–2018 | 1889 (21.0%) | 91 (18.8%) | |

Opioid use is defined by self-reported use of at least one prescription opioid-containing medication in the past 30 days.

All proportions displayed are weighted to represent the non-institutionalized population of the continental USA. Survey weights are adjusted by the number of years of data included in analysis.

BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Table 2 Weighted and adjusted ORs of cannabis use for prescription opioid users, including various definitions of cannabis use

| Cannabis use: | In past 30 days | | In past 7 days | | On ≥20 of past 30 days | |
|---------------------|----------------------------|--------------|----------------------------|--------------|----------------------------|--------------|
| | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | P value |
| Primary analysis | | | | | | |
| No opioid use | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| Opioid use | | | | | | |
| Unadjusted | 1.05 (0.81 to 1.36) | 0.714 | 1.02 (0.77 to 1.34) | 0.893 | 0.94 (0.64 to 1.39) | 0.761 |
| Adjusted | 0.70 (0.51 to 0.97) | 0.032 | 0.62 (0.43 to 0.91) | 0.013 | 0.60 (0.38 to 0.95) | 0.029 |
| Secondary | | | | | | |
| No opioid use | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| Opioid use <90 days | 0.62 (0.40 to 0.96) | 0.031 | 0.52 (0.29 to 0.95) | 0.032 | 0.55 (0.26 to 1.16) | 0.115 |
| Opioid use ≥90 days | 0.75 (0.50 to 1.10) | 0.143 | 0.68 (0.45 to 1.02) | 0.063 | 0.63 (0.36 to 1.10) | 0.101 |
| Secondary | | | | | | |
| Opioid use <90 days | 1 (reference) | | 1 (reference) | | 1 (reference) | |
| Opioid use ≥90 days | 1.11 (0.70 to 1.78) | 0.649 | 1.19 (0.69 to 2.02) | 0.532 | 1.34 (0.58 to 3.06) | 0.493 |

Bold values represent statistically significant estimates.

To assess the impact of missing data in this study, the primary regression model was reconstructed in five imputed data sets and demonstrated similar effect estimates to our primary analysis results (pooled aOR 0.77, 95% CI 0.59 to 1.00, $p=0.053$).

DISCUSSION

In this nationally representative cohort of adults in the USA aged 18–59, the prevalence of cannabis use steadily increased within the past decade, while prescription opioid use plateaued and had possibly begun to decline. Recent users of prescription opioids were less likely than non-users to have recently used cannabis. There was no detectable difference between short-term and chronic opioid users in terms of recent cannabis use. These findings and trends were consistent across various definitions of cannabis exposure and between survey years.

As the prevalence of cannabis use in North America began to increase rapidly in the early 2000s, concerns arose about whether individuals already using illicit or even high-risk prescription substances such as opioids would be at further risk of cannabis misuse. While such an association between opioid use and cannabis use has been historically detected in select cohorts,¹⁵ majority of contemporary studies investigating this relationship have reported the inverse in samples of chronic pain patients.^{8–10} For example, Sohler *et al* reported that recent cannabis use was associated with 0.57 lower odds of prescription opioid use, not dissimilar to our own results. As in these previous studies, our analyses are not meant to infer causality but rather to further investigate this association. The mechanism underlying this inverse relationship is thought to be related to the increased access and use of cannabis (either prescribed or non-prescribed) as an effective alternative to opioid agents for select patients.

Building on this literature, our study is the first to examine if short-term and chronic opioid users differ in their cannabis use behaviors. When directly comparing short-term users to chronic users, neither group appeared more likely than the other to have recently used cannabis. Further study is warranted to identify potential differences in concurrent cannabis use behaviors between short-term and chronic opioid users, as these may have implications for distinct pain management pathways involving both cannabinoids and opioids.

In the context of the ongoing opioid crisis, clinicians and patients have increasingly sought alternatives to opioid-based therapies for pain management in recent decades.¹⁶ Cannabis and cannabinoids have received much of this attention with their improved access

owed to ongoing decriminalization, with many jurisdictions now permitting medicinal or even recreational cannabis use.¹⁷ This improved access has led to marked decreases in prescription and non-prescription opioid use^{18–20} and ultimately reduced regional rates of opioid overdoses and related deaths.^{21–22} Furthermore, trials of adjunctive cannabinoid therapy in humans have demonstrated opioid-sparing effects^{5–10} and prevented the development of tolerance to (and withdrawal from) opioids.^{2–23} These findings are supported by ongoing physiological research elucidating interactions between cannabinoid and opioid receptor pathways in the nervous system.²⁴ However, as enthusiasm grows for the analgesic applications of cannabinoids, definitive evidence for their use as standalone therapies in acute and chronic pain populations remains elusive.^{23–25}

With co-use of opioids and cannabinoids, the potential harms must also be considered. In addition to the side effects and risk profiles of either opioid use or cannabinoid use on their own, co-use can affect cognition and worsen symptoms related to anxiety, depression, or polysubstance misuse, all of which may already be comorbid in this patient population.^{6–7,26} Further research is needed to study the short-term and long-term effects of these agents and products to identify patients in which combination therapies are not just effective, but also safe. Such trials will ultimately inform the development of clinical guidelines for the integration of cannabinoids into existing pain management practices.

Our study has several limitations inherent to NHANES data collection methods and available variables. First, data collected from survey questionnaires such as the NHANES are self-reported and subject to selection bias; only persons willing and able to participate in the extensive survey and examination process were included. Additionally, the stigma associated with either cannabis or opioid use may have impacted participants' responses, resulting in underestimations of their true prevalence. Second, these data are cross-sectional and may be subject to residual confounding not measured by NHANES. We were unable to account for confounding by factors such as the formulations and indications for cannabis use (ie, medical vs non-medical), as well as indications for prescription opioid use (ie, acute vs chronic pain syndromes). While the legalization status of cannabis in states in which participants resided could have an impact on both the prevalence of cannabis use and also participants' willingness to respond to cannabis-related questions, this could not be further explored as the NHANES does not release state of residence as a data variable. The cross-sectional nature of our analysis also inhibits exploration of the temporal association

between cannabis and prescription opioid use. Third, generalizability of our results is limited by the restricted age range (18–59 years) in our sample. Adults beyond this range are known to have a higher prevalence of prescription opioid use for pain related to greater burdens of comorbidities.^{27,28} Availability and inclusion of data from this demographic would have allowed for further analysis of the relationship between cannabis and prescription opioids.

CONCLUSION

Individuals in this nationally representative sample who reported recent prescription opioid use were less likely to report recent cannabis use. Access to cannabis and cannabinoid products continues to increase, which has implications for their use as adjunctive or alternative therapies to opioid-based pain management strategies. The analgesic effectiveness and safety of the interactions between opioids and cannabinoids require further study to inform the development of clinical guidelines for potential co-use in populations with pain syndromes.

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Contributors CD and KSL designed the study. CD and KSL obtained, coded, and analyzed the data. CD, AG, DNW, HC, and KSL prepared the manuscript. KSL accepted responsibility for the conduct, content, and publication of this study as guarantor.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Data for this study were obtained from the National Health and Nutrition Examination Survey (NHANES), which is a cross-sectional survey designed by the National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC). These data collection protocols are approved by the NCHS Ethics Review Board and all survey participants provide informed consent prior to being interviewed and examined. Therefore, no ethics approval was required from the local institutional ethics boards at which our analysis and manuscript were produced. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

All data used in this study are publicly available from the National Health and Nutrition Examination Survey (<https://www.cdc.gov/nchs/nhanes/>).

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