

# UC San Diego

## UC San Diego Previously Published Works

### Title

Medical and non-medical cannabis use and risk of prescription opioid use disorder: Findings from propensity score matching

### Permalink

<https://escholarship.org/uc/item/16w9n4p8>

### Journal

Drug and Alcohol Review, 38(6)

### ISSN

0959-5236

### Authors

Liang, Di  
Wallace, Mark S  
Shi, Yuyan

### Publication Date

2019-09-01

### DOI

10.1111/dar.12964

Peer reviewed



# HHS Public Access

Author manuscript

*Drug Alcohol Rev.* Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

*Drug Alcohol Rev.* 2019 September ; 38(6): 597–605. doi:10.1111/dar.12964.

## Medical and Nonmedical Cannabis Use and Risk of Prescription Opioid Use Disorder: Findings from Propensity Score Matching

**Di Liang, PhD,**

Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA

**Mark S. Wallace, MD,**

Department of Anesthesiology, University of California San Diego, La Jolla, CA, USA

**Yuyan Shi, PhD\***

Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, USA

### Abstract

**Introduction and Aims.**—Previous research suggested that cannabis use was associated with increased risks of prescription opioid misuse and use disorder. This study examined whether these associations differed by cannabis use purpose.

**Design and Methods.**—This is a secondary analysis of cross-sectional surveys with propensity score matching. Medical cannabis users (N=1,295), cannabis dual users with both medical and nonmedical purposes (N=707), and nonmedical cannabis users (N=18,666) were compared with cannabis nonusers (N=57,196) in the pooled 2013-2016 U.S. nationally representative National Survey on Drug Use and Health. Propensity score models were applied to match cannabis nonusers to cannabis users with different purposes with respect to potential confounders in individual socioeconomic characteristics, other substance use disorders, and health conditions. In matched sample, logistic regressions were used to assess associations.

**Results.**—Propensity score matching considerably improved balance on the potential confounders between cannabis nonusers and users. In matched sample, nonmedical cannabis use was associated with increased risks of prescription opioid misuse (OR=3.15, 95%CI: 2.89-3.44) and use disorder (OR=2.52, 95%CI: 2.06-3.10). Cannabis dual use and medical cannabis use were associated with increased risks of prescription opioid misuse (OR=2.55, 95%CI: 1.78-3.65; OR=2.15, 95%CI: 1.58-2.91, respectively), but they were not associated with prescription opioid use disorder.

---

\* **Corresponding author:** Yuyan Shi, PhD, 9500 Gilman Drive, La Jolla, CA 92093-0607, USA, Phone number: 1(858)534-4273, yus001@ucsd.edu.

Contributors

Study design: Y.S.

Statistical analyses: D.L. and Y.S.

Finding interpretation, manuscript writing, and critical revision: D.L., M.W., and Y.S.

Final approval of the submitted manuscript: D.L., M.W., and Y.S.

Data Source

National Epidemiologic Survey on Alcohol and Related Conditions-III Data were obtained through a data use agreement with National Institute on Alcohol Abuse and Alcoholism (PI: Shi).

**Conclusions.**—Medical and nonmedical cannabis use were both associated with increased risks of prescription opioid misuse. Medical cannabis use, however, was not associated with prescription opioid use disorder as nonmedical cannabis was. There appeared to be differential associations between cannabis use and prescription opioid use disorder by cannabis use purpose.

### Keywords

medical cannabis; opioid misuse; opioid use disorder; propensity score matching

---

### Introduction

Prescription opioid misuse and use disorder are becoming a global problem, particularly in the U.S. The number of opioids prescribed in 2015 was approximately three times as high as in 1999 [1]. In 2016, an estimated 11.8 million or 4.4% population misused prescription opioids and an estimated 2.1 million or 0.8% population suffered from prescription opioid use disorder [2]. Prescription opioid misuse and use disorder were also strong risk factors for illicit opioid use and related consequences [3]. The prescription opioid crisis imposed \$26 billion annually to healthcare system and \$78.5 billion in total to the society [4].

Due to the concern about negative consequences of using prescription opioids in the treatment of pain, non-opioid alternatives such as medical cannabis are increasingly being considered. [5]. Systematic reviews of randomized controlled trials were still debating upon the level of confidence, but all agreed that there is at least some evidence for cannabis as an effective treatment for chronic pain in adults [6–8]. The hypothesis of patients substituting cannabis for prescription opioids has been supported, albeit indirectly, by a series of ecological studies emerged recently. They consistently reported that substantial reductions in prescription opioid overdose deaths, misuse, prescribing, traffic fatalities, and hospital stays were observed in U.S. states following their legalization of medical cannabis, compared to states not legalizing medical cannabis [9–16].

These ecological studies share the same problem of ecological fallacy [17, 18], which use findings derived from ecological population data to imply individual-level associations. To fill this knowledge gap, Olfson et al. [19] used a prospective cohort in the U.S. National Epidemiology Survey on Alcohol and Related Conditions to evaluate the associations of individuals' cannabis use status in 2001-2002 with their prescription opioid misuse and use disorder in 2004-2005. They found that cannabis use at baseline was associated with increased risks of prescription opioid misuse (OR=2.62) and use disorder (OR=2.18) at the follow-up and such associations held when analyses were restricted to individuals with pain.

The findings conveyed in Olfson et al. [19], however, did not resolve the controversy about the risks of cannabis use in the contexts of prescription opioid crisis and medical cannabis legalization. The study failed to differentiate nonmedical cannabis use from medical cannabis use, the primary outcome that medical cannabis laws were designed to promote. Approximately 90% cannabis users in 2013-2014 in the U.S. used cannabis nonmedically [20]; this prevalence should be even greater a decade ago when medical cannabis laws were not widely adopted. The findings in Olfson et al. [19] therefore primarily represented the use of nonmedical cannabis that was obtained from illicit market.

Recent individual-level studies addressed some limitations in Olfson et al. [19] by examining prescription opioid and medical cannabis use among chronic-pain patients [21–24]. Substitution patterns from prescription opioids to medical cannabis were common in this population. Using nationally representative survey data on general population, Caputi et al. 2018 [25] also found that medical cannabis users had greater odds of prescription opioid misuse. But these studies did not compare medical and recreational cannabis use or examine prescription opioid use disorder.

In this study, we aimed to examine the associations of medical and nonmedical cannabis use with prescription opioid misuse and use disorder. Two large nationally representative surveys in the U.S. were used, both conducted after 2012 when more than one third of states had legalized medical cannabis in the U.S. By differentiating nonmedical from medical cannabis use, we were able to determine whether differential associations existed by cannabis use purpose.

## Method

This is a secondary data analysis comparing cannabis nonusers to cannabis users with different purposes in U.S. nationally representative population samples. Propensity score matching (PSM) method was adopted to make a balanced comparison between cannabis nonusers and users. The main analysis was conducted on samples from the National Survey on Drug Use and Health (NSDUH). To address data limitations in NSDUH, the secondary analysis was conducted on samples from the National Epidemiology Survey on Alcohol and Related Conditions-III (NESARC-III) using the same methods.

### Main Analysis on NSDUH Sample

**Data and Sample**—NSDUH is the largest repeated cross-sectional survey on drug use and related health in the U.S. We pooled the 4 most recent surveys in 2013-2016 that queried medical cannabis use to maximize sample size.

In NSDUH, medical cannabis use was defined as cannabis use recommended by a doctor. As doctor's recommendation to use cannabis is not approved in states without medical cannabis legalization, the study sample was restricted to respondents living in states that had legalized medical cannabis before the interview. The sample was further restricted to adults aged 18 years or older, because medical cannabis use among adolescents was very rare [26]. In total, 1,295 medical cannabis users, 707 cannabis users using cannabis for both medical and nonmedical purposes (cannabis dual users), 18,666 nonmedical cannabis users, and 57,196 cannabis nonusers were identified and analyzed in the statistical analysis.

### Measurements

**Prescription opioid use outcomes.:** The primary outcomes of interest were two dichotomous indicators related to prescription opioid use: 1) *Prescription opioid misuse* was defined as prescription opioid pain relievers “use in any way that a doctor did not direct you to use” in the past 12 months. 2) *Prescription opioid use disorder* was defined as past-year prescription opioid dependence or abuse screened by the 11 diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

**Cannabis use status and purpose.** The sample was categorized into 4 mutually exclusive groups based on their past-year cannabis use status and purpose. 1) *Cannabis nonusers* were those who did not use cannabis in the past 12 months. Among those who reported cannabis use in the past 12 months, NSDUH has 2 questions regarding purpose of use. The first question is: “was ANY of your marijuana use in the past 12 months recommended by a doctor...?” If the answer is affirmative, the second question follows: “was ALL of your marijuana use in the past 12 months recommended by a doctor...?” 2) *Medical cannabis users* were past-year cannabis users who responded “yes” to both questions. 3) *Cannabis dual users* were past-year cannabis users who responded “yes” to the first question but “no” to the second question. For these users, some of their cannabis use was recommended by a doctor but some was not’ they consumed cannabis for both medical and recreational purposes. 4) *Nonmedical cannabis users* were past-year cannabis users who responded “no” to the first question (the second question was not applicable).

**Covariates.** We included individuals’ sociodemographic characteristics, any other substance use disorders, and physical and mental health conditions related to prescription opioid or cannabis as covariates. 1) *Socioeconomic characteristics*: gender, age, race/ethnicity, marital status, and educational attainment. 2) *Other substance use disorders*: past-month tobacco dependence assessed by Nicotine Dependence Syndrome Scale [27] and the Fagerstrom Test of Nicotine Dependence [28], past-year alcohol use disorder assessed by DSM-IV diagnostic criteria [29], and past-year any other substance use disorder (hallucinogens, inhalants, methamphetamine, prescription tranquilizers, prescription stimulants, prescription sedatives, or cocaine) assessed by DSM-IV diagnostic criteria [29]. 3) *Physical health conditions*: self-reported current general health status and life-time cancer diagnosis. 4) *Mental health conditions*: life-time major depressive episode assessed by DSM-IV diagnostic criteria [29] and past-year mental illness.

**Statistical Analyses**—Four models were adopted to examine the associations between prescription opioid use outcomes and cannabis use. All the models compared cannabis nonusers to cannabis users with one of the three purposes (medical, both medical and nonmedical, and nonmedical), respectively.

Model 1 computed crude relative risks of prescription opioid use outcomes among cannabis users relative to cannabis nonusers without any statistical adjustments. Model 2 used multivariable regressions to compute relative risks, controlling for individual covariates.

Models 3 and 4 applied PSM before computing relative risks. Selection bias is the major concern in observational studies. Without randomizing individuals to different exposures, those with and without exposure likely have important differences in confounding factors. Although conventional multivariable regressions like Model 2 control for observed confounding factors, they are not able to address the situation where confounding factors do not adequately overlap between groups with different exposures. The validity of comparisons between exposure and non-exposure groups are therefore threatened [30]. Such situation is exactly the case when comparisons are made between cannabis nonusers and users, who have huge differences in sociodemographic characteristics and health conditions. In that regard, many cannabis nonusers may not be comparable to cannabis users. PSM has

been widely adopted in observational studies where individuals are not randomized [31]. Although PSM cannot eliminate selection bias just like conventional multivariable regressions, it can balance observed confounding factors between exposure and non-exposure groups, to some extent mimicking randomized trials [32].

Following PSM reporting guidelines [30], we conducted PSM in Models 3 and 4 in the following steps. In the first step, we fitted logistic regressions with all the covariates to estimate the propensity score of using cannabis for each individual. In the second step, we used “nearest-neighbor” matching method [33] without replacement to match each cannabis user to 2 cannabis nonusers. This matching algorithm was recommended to minimize the bias in subsequent estimations [34]. Standardized differences [32] in covariates (Technical Note S1) between matched groups and Chi-square tests on standardized differences were used to determine the improvement of balance before and after matching. To compare outcome variables in matched sample, Model 3 estimated relative risks without further statistical adjustments. Model 4 used multivariable regressions to estimate relative risks, controlling for individual covariates. We reported results for models with and without regression adjustments as both were recommended in PSM [35, 36]. To test the robustness of results to matching algorithms, we repeated Models 3 and 4 using different matching algorithms, including “nearest-neighbor” matching (cannabis user to nonuser ratio 1:1, 1:2, 1:3), “nearest-neighbor” matching with “caliper” (caliper 0.001, 0.002, and 0.003), and “weighting” [37].

### Secondary Analysis on NESARC-III Sample

NSDUH data provide comprehensive evaluations on a large nationally representative sample. Nevertheless, there are two data limitations in NSDUH that potentially threaten the validity of association estimations. First, medical cannabis use is determined by a state’s legal definition: the presence of a doctor’s recommendation. Such definition, however, does not consider the situation where cannabis is used for medical purposes without obtaining a doctor’s recommendation. It was estimated that such situation occurred to over 50% cannabis users reporting medical purposes [38]. Second, NSDUH did not provide measurements on pain symptoms that are confounded with the relationship between prescription opioid use and cannabis use.

To examine the sensitivity of association estimations to categorization of cannabis use purpose and inclusion of pain symptoms, we utilized another U.S. nationally representative sample NESARC-III to replicate NSDUH analyses. Administered in 2012-2013, NESARC-III is a cross-sectional survey of drug abuse on adults aged 18 years or older. Medical cannabis use was determined if cannabis users reported using “medical marijuana in the last 12 months”; nonmedical cannabis use was determined if cannabis was used without a doctor’s prescription or in a way not recommended by a doctor in the past 12 months. Pain was assessed by a 5-point scale to measure the degree to which pain interferes with daily activities during the past 4 weeks. A binary indicator for severe pain was created to represent moderate to extreme pain. The remaining measurements in NESARC-III were largely comparable to those in NSDUH (Technical Note S2).

As NEARC-III sample is considerably smaller than the pooled NSDUH sample, we combined medical cannabis users and dual users to maximize statistical power. In the final analysis, NESARC-III sample included 3 mutually exclusive groups: 441 medical cannabis users (including 82 dual users), 3,294 nonmedical cannabis users, and 32,107 cannabis nonusers. We used the same methods for NSDUH data to analyze NESARC-III data.

## Results

### Results of Main Analysis on NSDUH Sample

Table 1 reports descriptive statistics of NSDUH sample. The prevalence rates of prescription opioid misuse among medical cannabis users, cannabis dual users, nonmedical cannabis users, and cannabis nonusers were 11.34%, 17.19%, 15.06%, and 2.96%, respectively; the prevalence rates of prescription opioid use disorder among these groups were 2.33%, 3.87%, 2.40%, and 0.44%, respectively.

Figure 1 presents the standardized differences in covariates between cannabis nonusers and users before and after PSM (detailed results in Table S1). Before matching, considerable and statistically significant imbalance was identified on almost all covariates. After matching, the standardized differences in all the comparisons were systematically reduced to below 5% and Chi-square tests suggested that most of these differences were no longer significant. PSM considerably improved the comparability of cannabis nonusers and cannabis users.

Figure 2a reports the association between prescription opioid misuse and cannabis use by cannabis use purpose. In logistic regressions in matched sample (Model 4), cannabis use was associated with higher risk of prescription opioid misuse regardless of use purposes. The risk was the greatest among nonmedical cannabis users (OR=3.15, 95%CI: 2.89-3.44,  $p<0.001$ ), followed by cannabis dual users (OR=2.55, 95%CI: 1.78-3.65,  $p<0.001$ ) and medical cannabis users (OR=2.15, 95%CI: 1.58-2.91,  $p<0.001$ ). Such associations were robust to model specifications, but the estimate of crude relative risk in unmatched sample (Model 1) was substantially greater than the other three models that had some form of statistical adjustments.

Figure 2b reports the association between prescription opioid use disorder and cannabis use by cannabis use purpose. In logistic regressions in matched sample (Model 4), higher risk of prescription opioid use disorder was observed among nonmedical cannabis users (OR=2.52, 95%CI: 2.06-3.10,  $p<.001$ ) compared to cannabis nonusers. The associations of prescription opioid use disorder with cannabis dual use and medical cannabis use, however, were nonsignificant. This null association was sensitive to the application of PSM: estimates in unmatched sample (Models 1 and 2) yielded significant associations yet estimates in matched sample (Models 3 and 4) revealed nonsignificant associations.

The results with PSM (Models 3 and 4) were robust to matching algorithms (Table S2).

### Results of Secondary Analysis on NESARC-III Sample

NESARC-III sample characteristics are reported in Table S3 and standardized differences in covariates before and after PSM are reported in Figure S1 and Table S4. As observed in

NSDUH sample, PSM considerably improved the comparability between cannabis nonusers and cannabis users.

Figure S2 reports the associations between prescription opioid use outcomes and cannabis use by cannabis use purpose. The results on NESARC-III sample with pain symptoms considered were consistent with the findings from NSDUH sample.

## Discussion

Using two U.S. nationally representative adult samples, this study found that cannabis use was associated with increased risk of prescription opioid misuse regardless of cannabis use purpose. The association of cannabis use with increased risk of prescription opioid use disorder was only evident among nonmedical cannabis users, but not detected among cannabis dual users or medical cannabis users. The findings were robust to definition of medical cannabis use and consideration of pain symptoms.

The positive association between cannabis use and prescription opioid misuse was in accordance with Olfson et al. [19] that analyzed cannabis user population as a whole and Caputi et al. [25] that focused on medical cannabis users. The estimated effect sizes were also comparable. Our study further suggested that such relationship did not differ by cannabis use purpose. It once again suggested that using cannabis, even for medical purposes, was not without risks. The negative consequences of cannabis use should not be overlooked by advocates and health professionals who recommended cannabis as an alternative to prescription opioids.

This study found no evidence for the association between medical cannabis use and prescription opioid use disorder. The current data sources did not allow us to explain the mechanisms for differential associations by cannabis use purpose. We provide tentative explanations for discussion. Laboratory research showed that cannabinoids act through a common  $\mu_1$  opioid receptor mechanism and increase dopamine concentrations as opioids [39, 40]. Clinical studies demonstrated that moderate cannabis use improved retention of naltrexone therapy and dependence outcomes among patients with opioid dependence [41, 42]. Further, population studies on cannabis users [20, 38] reported that behavioral patterns of medical and nonmedical cannabis use differ. Medical cannabis users on average had a much older onset age of first cannabis use in their 30s than nonmedical cannabis users whose onset age was around 18 [38]; they were less likely to smoke cannabis but more likely to use alternative methods to consume, such as vaporizing or eating [38]; and they used cannabis more frequently [20, 38]. Legal access to cannabis in states with medical cannabis legalization also provides medical cannabis users a considerably greater variety of chemotypic properties and cannabis products than those in illicit market. It is likely that these differences contribute to differences in prescription opioid use pattern and consequences.

PSM and conventional multivariable regressions generated different results. PSM was suggested to be less biased and more robust and precise than conventional multivariable regressions in the presence of rare events and multiple confounders [43, 44]. It was



especially appropriate to examine prescription opioid use disorder which had a very low prevalence rare (less than 1% in general population). The different results may be also attributable to the huge differences in confounding factors between groups. Comparing medical cannabis users with all cannabis nonusers may be invalid if individual confounding factors were incomparable in the first place. PSM has the potential to alleviate the bias due to confounding [45] by selecting cannabis nonusers who were most comparable to medical cannabis users.

Cannabis dual users had similar risks of prescription opioid use outcomes as medical cannabis users. They were more similar to medical cannabis users in terms of health conditions but more similar to nonmedical cannabis users in terms of other substance use [20]. While we are gaining a better understanding of health consequences related to medical and nonmedical cannabis use, whether dual use has unique behavioral pattern and consequences remains unexplored. Accounting for one third of cannabis user population [20], the dual user population are worth further investigations.

This study may contribute to the ongoing policy and clinical debates about combating prescription opioid crisis by approving cannabis use with medical cannabis laws. Ecological studies [9–16] have been widely cited in media [46, 47] as evidence to advocate medical cannabis as a solution to prescription opioid crisis. Our findings along with other individual-level studies [19, 25], however, suggested that medical cannabis is associated with increased risks of prescription opioid misuse. On the other hand, we did not find evidence to support the long-standing concern that medical cannabis may be associated with increased risks of opioid dependence [48]. We therefore encourage a holistic evaluation of its beneficial and harmful effects based on clinical evidence before medical cannabis is recommended as an alternative to prescription opioids.

The strength of this study is the use of two large U.S. nationally representative samples with comprehensive yet complementary measures. Conducted a decade after the data source in Olfson et al. [19], these surveys reflected existing legal and social contexts of cannabis use. They also allowed us to test sensitivity of findings to alternative definitions of medical cannabis use. Another strength is the application of PSM to balance confounding factors between groups. It may address limitations in conventional multivariable regressions by considerably improving comparability between cannabis nonusers and users.

The study has limitations. First, as previous studies [19, 25], we were unable to estimate causal associations without randomizing individuals to use or not use cannabis. PSM approach is only able to balance observed but not unobserved confounding factors. Casual mechanisms regarding the differential associations by cannabis use purpose were not explored either. Second, controversy remains regarding advantages of PSM over conventional multivariable regressions. PSM might increase data imbalance in certain situations.[49] Third, the sequential relationships between prescription opioid use outcomes and cannabis use could not be identified in cross-sectional data. Although the onset age of cannabis use in our samples was on average younger than the onset age of prescription opioid misuse, there may be individuals developing prescription opioid use outcomes before using cannabis. In that case, the effect sizes were overestimated. Prospective cohort studies

with long follow-up period are needed. Fourth, the lack of evidence may indicate either null associations or insufficient power to detect rare cases. Large cohort studies are warranted. Fifth, medical cannabis users and cannabis dual users were not differentiated in NESARC-III sample due to limited sample size. The estimated associations might therefore have upward bias. Sixth, due to data limitations, we only accounted for broad categories of health conditions but were unable to identify the exact motivations of medical cannabis users. Seventh, prescription opioid and cannabis use may be underestimated in self-reporting, a common concern in all survey-based studies. We were unable to assess to what extent the self-reporting bias might affect our findings, but the robust results from the 2 different surveys might provide some confidence in findings. Clinically validated measures such as urine tests are warranted in future research. Lastly, the findings may not be generalizable to adolescents or institutionalized population or population outside of U.S.

## Conclusion

Medical and nonmedical cannabis use were both associated with increased risks of prescription opioid misuse. There was no evidence, however, suggesting the association between medical cannabis use and prescription opioid use disorder. There appeared to be differential associations between cannabis use and prescription opioid use disorder by use purpose.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Disclosures and Acknowledgements

**Declarations of Competing Interest:** The three authors report no financial relationships with commercial interests.

Grant Support

This research was supported by grant R01DA042290 (PI: Shi) from the National Institute on Drug Abuse. This article is the sole responsibility of the authors and does not reflect the views of the National Institute on Drug Abuse.

## References

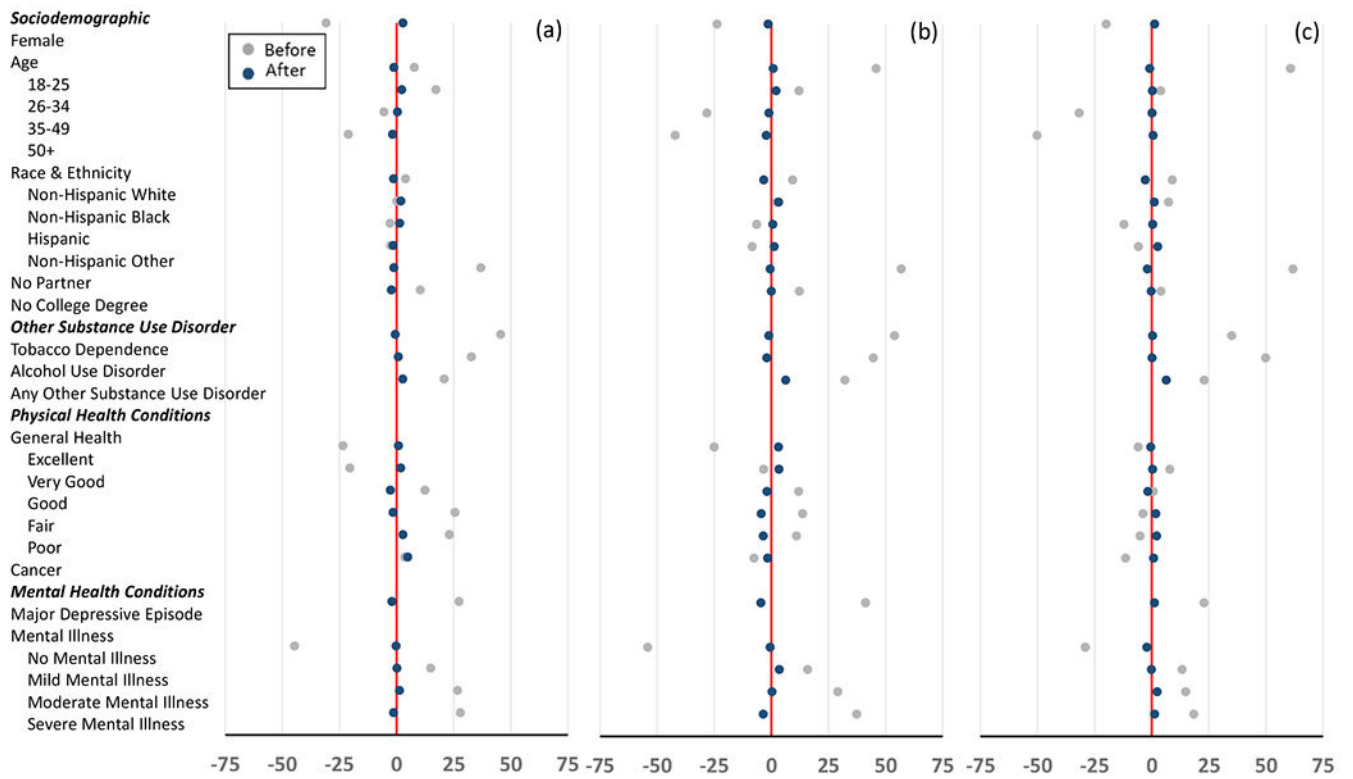
- [1]. Volkow ND. America's Addiction to Opioids: Heroin and Prescription Drug Abuse. Available at <https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse> Accessed on 2018-04-30 Archived by Webcite at <http://www.webcitation.org/6z4z3Hqvt> 2016.
- [2]. Ahrnsbrak R, Bose J, Hedden S, Lipari R, Park-Lee E. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration: Rockville, MD, USA 2017.
- [3]. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *New Engl J Med*. 2016;374:154–63. [PubMed: 26760086]
- [4]. Florence CS, Zhou C, Luo F, Xu L. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Med Care*. 2016;54:901–6. [PubMed: 27623005]

- [5]. Dr Gupta S.. Sanjay Gupta to Jeff Sessions: Medical marijuana could save many addicted to opioids. Available at <https://www.cnn.com/2018/04/24/health/medical-marijuana-opioid-epidemic-sanjay-gupta/index.html> Assessed on July 25, 2018. Archived by WebCite at <http://www.webcitation.org/71Efce3Sv> CNN 2018.
- [6]. National Academies. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies of Sciences, Engineering, Medicine: National Academies Press; 2017.
- [7]. Nugent SM, Morasco BJ, O'Neil ME, 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. [PubMed: 28806817]
- [8]. Stockings E, Campbell G, Hall WD, 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. [PubMed: 29847469]
- [9]. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174:1668–73. [PubMed: 25154332]
- [10]. Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. *Health Aff (Millwood)*. 2016;35:1230–6. [PubMed: 27385238]
- [11]. Bradford AC, Bradford WD. Medical Marijuana Laws May Be Associated With A Decline In The Number Of Prescriptions For Medicaid Enrollees. *Health Aff (Millwood)*. 2017;36:945–51. [PubMed: 28424215]
- [12]. Bradford AC, Bradford WD, Abraham A, Adams GB. Association Between US State Medical Cannabis Laws and Opioid Prescribing in the Medicare Part D Population. *JAMA Intern Med*. 2018;178:667–72. [PubMed: 29610897]
- [13]. Kim JH, Santaella-Tenorio J, Mauro C, Wrobel J, Cerda M, Keyes KM, et al. State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. *Am J Public Health*. 2016;106:2032–7. [PubMed: 27631755]
- [14]. Liang D, Bao Y, Wallace M, Grant I, Shi Y. Medical Cannabis Legalization and Opioid Prescriptions: Evidence on US Medicaid Enrollees during 1993-2014. doi:10.1111/add.14382 *Addiction* 2018.
- [15]. Powell D, Pacula RL, Jacobson M. Do medical marijuana laws reduce addictions and deaths related to pain killers? *J Health Econ*. 2018;58:29–42. [PubMed: 29408153]
- [16]. Shi Y Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend*. 2017;173:144–50. [PubMed: 28259087]
- [17]. Hall W, West R, Marsden J, Humphreys K, Neale J, Petry N. It is premature to expand access to medicinal cannabis in hopes of solving the US opioid crisis. *Addiction* 2018;
- [18]. Caputi TL, Humphreys K. Medicare Recipients' Use Of Medical Marijuana. *Health Affair*. 2016;35.
- [19]. Olfson M, Wall MM, Liu SM, Blanco C. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. *Am J Psychiat*. 2018;175:47–53. [PubMed: 28946762]
- [20]. Compton WM, Han B, Hughes A, Jones CM, Blanco C. Use of Marijuana for Medical Purposes Among Adults in the United States. *JAMA* 2017;317:209–11. [PubMed: 27992636]
- [21]. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *Plos One*. 2017;12.
- [22]. Campbell G, Hall WD, 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–E50. [PubMed: 29976328]
- [23]. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. *Eur J Intern Med*. 2018;49:44–50. [PubMed: 29398248]
- [24]. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain*. 2016;32:1036–43. [PubMed: 26889611]

- [25]. Caputi TL, Humphreys K. Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically. *J Addict Med.* 2018;12:295–9. [PubMed: 29664895]
- [26]. Boyd CJ, Veliz PT, McCabe SE. Adolescents' Use of Medical Marijuana: A Secondary Analysis of Monitoring the Future Data. *J Adolesc Health.* 2015;57:241–4. [PubMed: 26206447]
- [27]. Shiffman S, Waters A, Hickcox M. The nicotine dependence syndrome scale: a multidimensional measure of nicotine dependence. *Nicotine Tob Res.* 2004;6:327–48. [PubMed: 15203807]
- [28]. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86:1119–27. [PubMed: 1932883]
- [29]. Frances A, Pincus HA, First M. Diagnostic and statistical manual of mental disorders: DSM-IV: American Psychiatric Association Washington DC; 1994.
- [30]. Yao XI, Wang X, Speicher PJ, Hwang ES, Cheng P, Harpole DH, et al. Reporting and Guidelines in Propensity Score Analysis: A Systematic Review of Cancer and Cancer Surgical Studies. *J Natl Cancer Inst.* 2017;109.
- [31]. Thoemmes FJ, Kim ES. A Systematic Review of Propensity Score Methods in the Social Sciences. *Multivariate Behav Res.* 2011;46:90–118. [PubMed: 26771582]
- [32]. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res.* 2011;46:399–424. [PubMed: 21818162]
- [33]. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. *Stat Med.* 2007;26:734–53. [PubMed: 16708349]
- [34]. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol.* 2010;172:1092–7. [PubMed: 20802241]
- [35]. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Polit Anal.* 2007;15:199–236.
- [36]. Smith HL. Matching with multiple controls to estimate treatment effects in observational studies. *Sociol Methodol.* 1997, Vol 27 1997;27:325–53.
- [37]. Caliendo M, Kopeinig S. Some practical guidance for the implementation of propensity score matching. *J Econ Surv.* 2008;22:31–72.
- [38]. Pacula RL, Jacobson M, Maksabedian EJ. In the weeds: a baseline view of cannabis use among legalizing states and their neighbours. *Addiction.* 2016;111:973–80. [PubMed: 26687431]
- [39]. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. *Science.* 1997;276:2048–50. [PubMed: 9197269]
- [40]. Scavone JL, Sterling RC, Van Bockstaele EJ. Cannabinoid and opioid interactions: implications for opiate dependence and withdrawal. *Neuroscience.* 2013;248:637–54. [PubMed: 23624062]
- [41]. Raby WN, Carpenter KM, Rothenberg J, Brooks AC, Jiang H, Sullivan M, et al. Intermittent Marijuana Use Is Associated with Improved Retention in Naltrexone Treatment for Opiate-Dependence. *Am J Addict.* 2009;18:301–8. [PubMed: 19444734]
- [42]. Church SH, Rothenberg JL, Sullivan MA, Bornstein G, Nunes EV. Concurrent substance use and outcome in combined behavioral and naltrexone therapy for opiate dependence. *Am J Drug Alcohol Abuse.* 2001;27:441–52. [PubMed: 11506261]
- [43]. Cepeda MS, Boston R, Farrar JT, Strom BL. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol.* 2003;158:280–7. [PubMed: 12882951]
- [44]. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: Analytic strategies using propensity scores. *Ann Intern Med.* 2002;137:693–5. [PubMed: 12379071]
- [45]. Dehejia RH, Wahba S. Propensity score-matching methods for nonexperimental causal studies. *Rev Econ Stat.* 2002;84:151–61.
- [46]. Lieber M Marijuana legalization could help offset opioid epidemic, studies find. Available at <https://www.cnn.com/2018/04/02/health/medical-cannabis-law-opioid-prescription-study/>

[index.html](#) Accessed on July 26, 2018 Archived by WebCite at <http://www.webcitation.org/71Efw2WBT>. CNN 2018.

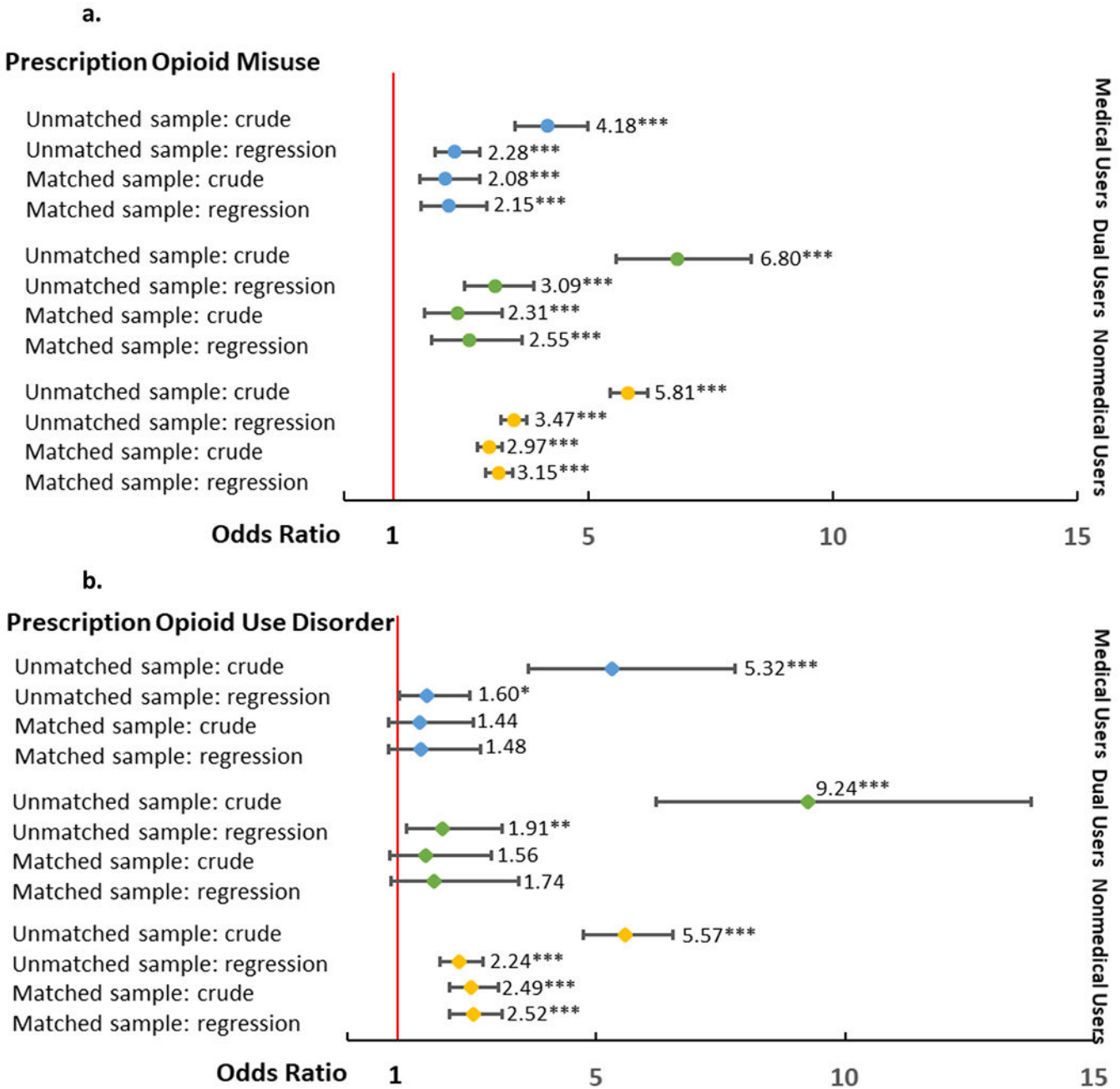
- [47]. Cohen R Would legalizing medical marijuana help curb the opioid epidemic? Available at <https://www.reuters.com/article/us-health-addiction-medical-marijuana-idUSKBN16Y2HV> Accessed on July 26, 2018 Archived by WebCite at <http://www.webcitation.org/71Eg3ewl6>. Reuters 2017.
- [48]. Ingraham C Two years after the DEA admitted marijuana is less dangerous than heroin, Jeff Sessions would like to reconsider. Available at [https://www.washingtonpost.com/news/wonk/wp/2017/03/15/two-years-after-the-dea-admitted-marijuana-is-less-dangerous-than-heroin-jeff-sessions-would-like-to-reconsider/?noredirect=on&utm\\_term=.f2e5675d15a9](https://www.washingtonpost.com/news/wonk/wp/2017/03/15/two-years-after-the-dea-admitted-marijuana-is-less-dangerous-than-heroin-jeff-sessions-would-like-to-reconsider/?noredirect=on&utm_term=.f2e5675d15a9) Accessed on July 26, 2018 Archived by WebCite at <http://www.webcitation.org/71Eg9O4LK>. Washington Post 2017.
- [49]. King G, Nielsen R. Why propensity scores should not be used for matching. Available at <https://gking.harvard.edu/files/gking/files/psnot.pdf> 2018.



**Figure 1. Standardized Differences between Cannabis Nonuser and Cannabis Users Before and After Propensity Score Matching by Cannabis Use Purpose, NSDUH 2013-2016**

The gray dots represent standardized differences before matching, and the blue dots represent standardized differences after matching.

Notes: Standardized differences (in percentage points) in individual covariates are reported for the comparisons between (a) cannabis nonusers and medical cannabis users, (b) cannabis nonusers and cannabis dual users, and (c) cannabis nonusers and nonmedical cannabis users, respectively. The exact numbers in this figure are reported in Supplemental Table S1.



**Figure 2. Relative Risks (Odds Ratios) in Prescription Opioid Outcomes among Cannabis Users Relative to Cannabis Nonusers by Cannabis Use Purpose, NSDUH 2013-2016**

\*p<.05, \*\*p<.01, \*\*\*p<.001. Dots and lines represent means and 95% confidence intervals for odds ratios.

Notes: Cannabis nonusers were the reference group in all the comparisons. Model 1 (unmatched sample: crude) estimated relative risks without any statistical adjustments. Model 2 (unmatched sample: regression) estimated relative risks adjusting for individual covariates in multivariable regressions. Model 3 (matched sample: crude) estimated relative risks in matched sample without any further statistical adjustments. Model 4 (matched

sample: regression) estimated relative risks in matched sample adjusting for individual covariates in multivariable regressions.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript



**Table 1.**

Descriptive Statistics by Cannabis Use Status and Purpose, NSDUH 2013-2016

	Medical Cannabis Users (N=1,295)		Cannabis Dual Users (N=707)		Nonmedical Cannabis Users (N=18,666)		Cannabis Nonusers (N=57,196)	
	N	%	N	%	N	%	N	%
<b>Prescription Opioid Use Outcomes</b>								
Prescription Opioid Misuse	146	11.34	120	17.19	2213	15.06	1,688	2.96
Prescription Opioid Use Disorder	30	2.33	27	3.87	352	2.40	252	0.44
<b>Covariates</b>								
<i>Sociodemographic characteristics</i>								
Female	524	40.71	308	44.13	6,764	46.04	31,850	55.95
Age								
18-25	417	32.40	354	50.72	8,467	57.64	16,405	28.81
26-34	339	26.34	168	24.07	3,037	20.67	10,881	19.11
35-49	330	25.64	115	16.48	2,232	15.19	16,001	28.10
50+	201	15.62	61	8.74	954	6.49	13,662	23.99
Race/Ethnicity								
Non-Hispanic White	748	58.12	424	60.74	8,896	60.56	31,972	56.14
Non-Hispanic Black	119	9.25	69	9.89	1,684	11.46	5,250	9.22
Hispanic	258	20.05	130	18.62	2,412	16.42	12,051	21.16
Non-Hispanic Other	162	12.59	75	10.74	1,698	11.56	7,676	13.48
No Partner	925	71.87	559	80.09	12,030	81.89	30,967	54.38
No Collage Degree	574	44.60	318	45.56	6,093	41.48	22,492	39.49
<i>Other Substance Use Disorder</i>								
Tobacco Dependence	329	25.56	204	29.23	3,099	21.10	5,013	8.80
Alcohol Use Disorder	193	15.00	137	19.63	3,200	21.78	2,986	5.24
Any Other Substance Use Disorder	39	3.03	41	5.87	509	3.46	197	0.35
<i>Physical Health Conditions</i>								
General Health								
Excellent	197	15.31	103	14.76	3,247	22.1	14,016	24.61
Very Good	363	28.21	252	36.1	6,116	41.63	21,502	37.76
Good	420	32.63	226	32.38	3,998	27.22	15,333	26.92
Fair	225	17.48	92	13.18	1,154	7.86	5,068	8.9
Poor	82	6.37	25	3.58	175	1.19	1,030	1.81
Cancer	197	15.31	103	14.76	3,247	22.1	14,016	24.61
<i>Mental Health Conditions</i>								
Major Depressive Episode	309	24.01	210	30.09	3,246	22.10	7,642	13.42
Mental Illness								
No Mental Illness	806	62.63	406	58.17	1,0253	69.80	46,753	82.10

	Medical Cannabis Users (N=1,295)		Cannabis Dual Users (N=707)		Nonmedical Cannabis Users (N=18,666)		Cannabis Nonusers (N=57,196)	
	N	%	N	%	N	%	N	%
Mild Mental Illness	182	14.14	101	14.47	1,993	13.57	5,317	9.34
Moderate Mental Illness	152	11.81	88	12.61	1,202	8.18	2,591	4.55
Severe Mental Illness	147	11.42	103	14.76	1,242	8.45	2,288	4.02

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript