AIMS Medical Science

AIMS Medical Science, 11(1): 1–24.
DOI: 10.3934/medsci.2024001
Received: 12 October 2023
Revised: 20 December 2023
Accepted: 15 January 2024
Published: 25 January 2024

http://www.aimspress.com/journal/medicalScience

Research article

The impact of cannabis legislation on benzodiazepine and opioid use and misuse

Running title: Cannabis laws impact on benzodiazepine and opioid use and misuse

Jamie L. Flexon[1,2,*], Lisa Stolzenberg[1] and Stewart J. D'Alessio[1]

[1] Department of Criminology and Criminal Justice, Green School of International and Public Affairs, Florida International University, Miami, FL, USA
[2] Modesto A. Maidique Campus, 11200 SW 8th Street, PCA-366A, Miami, FL 33199, USA

* **Correspondence:** Email: flexonj@fiu.edu; Tel: 3053480423.

Abstract: Background: Several have claimed that the overreliance on benzodiazepines for many approved and off-label uses poses substantial human and social consequences comparable to those observed with the opioid epidemic. In light of these problems, alternatives are required to properly manage patients. Numerous states now permit the use of medical cannabis to treat conditions, such as chronic pain, that were traditionally treated with benzodiazepines, opioids, or both. As patients and physicians seek alternative treatments, little is known about whether the presence of cannabis laws helps to alleviate the burdens caused by these more traditional medications owing to the displacement of benzodiazepines and/or opioids toward cannabis. **Methods:** Using data from multiple years of the National Survey on Drug Use and Health (2017, 2018, 2019), the effect of Medical Marijuana Laws (MMLs) on benzodiazepine and/or opioid use and misuse is examined while controlling for a variety of demographic characteristics. Supplemental analysis also is performed including the 2020 and 2021 survey years. **Results:** MMLs did not affect lone, legitimate benzodiazepine usage, but lower use of opioids and combinations of benzodiazepines and opioids was observed. MMLs appear to help attenuate benzodiazepine and/or opioid misuse to a substantial degree. Additional results suggest that the presence of an MML was related to annual, varying decreases in the use and misuse of benzodiazepines, opioids, and their combination across the years of data evaluated. **Conclusions:** MMLs may serve to attenuate the consequences of benzodiazepine, opioid, and their combined use and/or misuse to varying degrees.

Keywords: medical marijuana laws; cannabis; benzodiazepines; opioids

1. Introduction

Benzodiazepines and/or opioids are relied upon by many patients despite accumulating empirical evidence indicating that these drugs are often overprescribed [1–5]. In addition to their use in treating anxiety, benzodiazepines are not infrequently relied upon to manage complex pain as a primary analgesic (e.g., antispasmodic, neuropathic pain) or an adjunct to overall pain management (e.g., induce relaxation and/or sedation for insomnia) in patient care [1,6]. This situation is not dissimilar to the reliance on opioids despite findings that they are ineffective at controlling non-cancer related chronic pain [7]. Problems with using benzodiazepines are numerous and parallel those of opioids [1,8], are amplified when opioids and benzodiazepines are co-prescribed, and concentrate among the older populations [5,9].

In tandem with the above, the legalization of medicinal cannabis is increasing as a treatment for chronic pain, pain secondary to other ailments, as well as other conditions such as anxiety (https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/). With the growing availability of medical cannabis to patients, coupled with research showing cannabis is effective at controlling pain [10–12], it is plausible that patients may be opting to use medical cannabis instead of benzodiazepines and/or opioids for relief and to manage related and distinct conditions. If this scenario is valid, replacing benzodiazepines and/or opioids for cannabis may mitigate the risks associated with these more conventional drugs, such as drug interactions, overdoses, and death because it either does or is perceived as a better way to treat chronic, complex pain, anxiety, and other disorders.

Presently, more evidence supports the use of cannabis for pain management than for other conditions [11,12]. However, cannabis may also attenuate the use of other medications beyond opioids [13,14], such as benzodiazepines, when used for pain-related conditions. Some evidence also demonstrates that people suffering from other ailments for which benzodiazepines are prescribed may seek cannabis-based treatments. For example, subjects with anxiety have reported self-medicating with cannabis, a phenomenon that occurs more often in states with medical marijuana laws (MMLs) [15]. This circumstance is occurring despite cautions against allowing for it when clinical anxiety is present [12]. In fact, contrary to those cautions, the presence of anxiety is being used as a qualifying condition for medicinal cannabis in some states, e.g., New Jersey, Pennsylvania, West Virginia, despite the current lack of evidence concerning efficacy [16]. Given such inconsistencies, the absence of knowledge surrounding the influence of medicinal cannabis for individuals and society, and the impact of medicinal cannabis in chronic pain management and other conditions, it seems prudent to assess the role of cannabis legislation in possibly mitigating or exacerbating the use and misuse of benzodiazepines and opioids.

With a focus on the aforementioned concerns, the present research aims to accelerate our understanding of cannabis as an alternative to benzodiazepine and/or opioid use and misuse among the adult population. To actualize this objective, analyses of data from the National Survey on Drug Use and Health (NSDUH) [17] and state level data are undertaken utilizing a variety of analytic methodologies and a diverse set of variables and controls. Findings indicate that MMLs reduce opioid and benzodiazepine-opioid use but not lone, legitimate use of benzodiazepines. MMLs also appear to significantly reduce benzodiazepine and opioid misuse. Additional results suggest that MMLs are

associated with annual, variable declines in benzodiazepine, opioid, and their combined misuse and use across three years of data evaluated. This information is critical for parties involved in policy decisions about cannabis legalization, especially medical cannabis, as well as those concerned about benzodiazepine and opioid use and misuse. To better anchor these findings, however, a review of the extant literature is provided before presenting and discussing the results.

1.1. Patient management, benzodiazepines, and opioids

While benzodiazepines are used to treat issues such as anxiety, they are frequently prescribed for off-label or unapproved use, having limited evidence of efficacy, such as for issues tied to the management of chronic pain, including insomnia or as a muscle relaxant. Problematically, benzodiazepine use is not without detriment. Benzodiazepines are addictive, with associated effects of depression, ataxia, irritability, cognitive impairment, among others, and carry an increased risk of falling, suicide, and automobile accidents [5]. Benzodiazepines' adverse effects, such as dizziness, disorientation, and unsteadiness, are more prevalent among the elderly due to slower drug metabolism, which can exacerbate associated risks surrounding fall-related broken bones, motor vehicle accidents, potential overdose, and hospitalizations [18]. Benzodiazepines are also prescribed for years at a time for many approved and off-label uses, though they are intended to be used for no more than two to four weeks [5]. Between 1996 and 2013, the number of individuals filling prescriptions for benzodiazepines increased by 67%, from 8.1 million to 13.5 million, while the quantity they obtained more than tripled [3,4]. As prescriptions for benzodiazepines climbed, so did the overdose death rates. Benzodiazepine related U.S. overdose fatalities from 1999 to 2021 surged from 1135 in 1999 to 11537 in 2017; though numbers dropped to 9711 in 2019, they rose again between 2019–2021 to 12499 [19]. Owing to these concerns, warnings over the threats posed by the growing overdependence on this class of drugs have grown [2,5].

Such pharmaceutical reliance does not occur in a vacuum. Inadequate treatments for individuals suffering from pain-related conditions and/or anxiety for whom benzodiazepines and often opioids are routinely given represent concurrent and frequently overlapping public health concerns. Over a hundred million Americans annually suffer from chronic pain [20,21]. Of these individuals, millions require long-term pain management [21], with a significant proportion of patients concentrating in the older adult population, roughly 40% [22,23]. In the same way that the number of people suffering from pain-related symptoms is startling, anxiety and related ailments are pervasive, and their effects differentially impact members of distinct demographic groups [24,25]. Estimates place those experiencing mild, moderate, or severe symptoms of anxiety in the recent past at around 15% [25]. Younger people are experiencing an increase in reported anxiety symptoms; however, symptoms for those aged 50 and over have remained steady [24].

The many concerns raised with benzodiazepines are similar to those with opioids. Regarding opioids, it is readily acknowledged that as attention to sufficient pain treatments rose, state medical boards relaxed regulations around opioids over the preceding two decades, and doctors, without viable alternatives, began prescribing them with alarming regularity [26]. Consequently, opioids became the most prescribed analgesic in the U.S. [23]. Similar to the upswing seen with benzodiazepines, opioid prescriptions climbed from 76 million in 1991 to 219 million by 2011 [21], and by 2014, U.S. pharmacies distributed 245 million prescriptions, not counting refills [27,28].

The documented harm caused by opioid overreliance is ubiquitous and parallels that seen with benzodiazepines as discussed previously. Opioids cost $560–635 billion in lost productivity, sick time, medication expenses, and medical treatment [20,21]. Opioid-related hospitalizations are prevalent. Opioid-related ER visits surged 117% and inpatient stays by 76% from 2005 to 2014 [29]. Prescription opioid overdose fatalities jumped from 3442 in 1999 to 17029 in 2017, while all opioid overdose deaths rose from 8048 to 47600 [30]. Opioid overdose fatalities are expected to rise to 82000 annually by 2025, totaling over 700000 between 2016 and 2025 [31]. Notably, the authors of that study contend that 80% of projected fatalities between 2016 and 2025 will be attributed to illicit use (p. 5), and problematically, the researchers only identified a modest influence on these forecasts from changes in prescription behavior, such as opiate misuse prevention methods [31]. While opioid reliance may promote opioid use disorder and abnormal medication-taking habits [32], overdose, and motor vehicle accidents, research does not support its use for improving chronic pain or function [7,32]. Similar observations have been made concerning the use of benzodiazepines in general, particularly in aging. Problematically, benzodiazepines and opioids are commonly co-prescribed, and similar prescribing behavior and challenges are observed with benzodiazepines use [1,2].

While the issues discussed above are tied to medical efforts to treat chronic pain and reduce patient suffering, the consequences of this reliance on benzodiazepines, particularly when used with other drugs such as opioids, can be grave. Significant and sometimes catastrophic respiratory depression is seen with the combination of these drugs [33], but as remarked, benzodiazepines and opioids are not uncommonly prescribed together irrespective of guidelines discouraging the practice [1,34,35]. In fact, the U.S. Food and Drug Administration issued a black box warning in 2016 against the co-prescribing of benzodiazepines with opioid medications. Older people are significantly represented among these patients while being more susceptible to compounded side effects, interaction effects, and adverse outcomes as noted above [1,34,35]. Further complicating this issue is the public's view that prescribed medications are safer to misuse than illegal drugs, and the accompanying inclination to combine opioids with other substances such as benzodiazepines is likely contributing to the aforementioned concerns [4,5,26]. These continued practices, and others, seem to be in response to inadequate pain and symptom control and ultimately contribute to increased morbidity and mortality.

1.2. Cannabis legislation and patient management

Against the backdrop of the argued benzodiazepine and opioid epidemics, many states are enacting MMLs. Boehnke and colleagues [36] report that "Chronic pain is currently and historically the most common qualifying condition reported by medical cannabis patients (64.9 percent in 2016). Of all patient-reported qualifying conditions, 85.5 percent had either substantial or conclusive evidence of therapeutic efficacy." (p. 295) Research on its pain-relieving effectiveness continues to accrue as more states allow medical cannabis [10,11,37–42]. Numerous high-quality studies support the use of cannabis as an analgesic for chronic pain, neuropathic pain, and spasticity from multiple sclerosis [11,12]. Research also demonstrates that cannabis and its derivatives may be beneficial as primary analgesics or adjuncts to traditional pharmaceuticals [10]. For example, frequent cannabis use seems to enhance the effectiveness of opioid agonist therapies (OAT) that assist in preventing or limiting withdrawal. Here, daily cannabis use is linked with a 21% increase in OAT retention compared to less frequent cannabis use [11,43] (where vaporized cannabis improved opioid efficacy to significantly lower pain). Though this area of research is hardly settled, there appears to be some

promise with using cannabis combined with lower opioid doses as it may treat pain better than opioids alone, without the dose-dependent side effects.

Others report similar findings as the above, with data indicating a preference for medical cannabis over pharmaceuticals among patients [12,36,37,39,42,44,45]. Along with cannabis' broad acceptance and usage [46], recent qualitative research on drug choice for relieving symptoms, such as chronic pain in older people, reveals that users chose cannabis intentionally since it is viewed to be a lower-risk, safer alternative to alcohol, illicit substances, and medications [45] (see also [47]). This research aligns with Reiman and colleagues [42], who interviewed patients about their cannabis and opioid usage, with subjects reporting that cannabis alleviated pain, had fewer side effects, and allowed for a lower opioid dosage. These and other studies, when considered jointly, support a legitimate role for medicinal cannabis and indicate a preference for cannabis over pharmaceuticals for pain relief.

Since a considerable number of medical cannabis users rely on the substance for pain relief, it should have a significant impact on minimizing the detrimental effects of benzodiazepines and opioids used for pain management and other conditions. In contrast to opioids, however, far less is known regarding the efficacy of cannabis as a primary alternative for benzodiazepines when used for pain and anxiety-related illnesses. Similar to opioids [10,12,42], patients may seek out this option to manage their suffering and improve their quality of life since cannabis may be more effective at pain management and related ailments with less problematic side effects. Likewise, patients may seek cannabis to alleviate anxiety-related symptoms and disorders through self-treatment or prescribed cannabis [11,15], leading to displacement. Considering this scenario, moving away from pharmaceuticals is possible, along with the risks of overdose, drug interactions, and death [36]. The legalization of cannabis may therefore aid in mitigating the above-mentioned consequences by providing a better option for patient care.

In concert with the above, newer research examines opioid overdose and other maladaptive behaviors in relation to the availability of legal cannabis [13,48,49]. These studies are insightful but limited in scope and application [50–52]. To illustrate, Bachhuber et al. [13] found fewer opioid overdoses in medical cannabis jurisdictions suggesting a shift toward cannabis, while Wen et al. [49] evinced no effect on opioid overuse or abuse. Such studies rely on a limited number of individuals who may be replacing, at a minimum, opioid medications with cannabis, though benzodiazepines were not expressly examined. Notably, since most long-term opioid users do not misuse or overdose, such a narrow focus is limiting [53].

While not an exhaustive review, the above readily demonstrates the further need to study how medical cannabis laws affect substance use among patients, with an emphasis on populations beyond misusers and overdose victims. Although evidence suggests that people are substituting cannabis for analgesics [37,38,40–42], questions remain as to whether a shift from benzodiazepine and/or opioid analgesics used for the medical treatment of pain and associated disorders toward cannabis is occurring, and if certain groups are more likely to be affected than others. There is a possibility that cannabis is supplanting more conventional medications than opioids [13,48,49] in a variable manner throughout the population.

2. Materials and methods

In a departure from much of the research in this area, the present study seeks to examine the impact of MMLs on the use and misuse of benzodiazepines and/or opioids while controlling for varying

age populations and other demographic classifications. This strategy will help illuminate any role MMLs may have in contributing to or detracting from (displacement) use or misuse of benzodiazepines and/or opioids and whether differences can be observed based on population characteristics. While there has been much discussion about the possible benefits of MMLs in reducing the iatrogenic and social costs of benzodiazepines and opioids, a concern exists that MMLs may be adding to the misuse of these drugs or engendering other unintended consequences. Such reasoning is rooted in concerns that cannabis-friendly environments may amplify the use or abuse of other substances, resulting in undesirable outcomes such as use disorder. Somewhat surprisingly, little research has investigated these concerns, and the consequences of cannabis-related regulations have not been adequately evaluated or documented. Finally, it is feasible that the legislation is not impacting benzodiazepine and/or opioid use or misuse. If displacement is occurring, however, such laws could ultimately alleviate the negative, downstream consequences associated with an overreliance on benzodiazepines and/or opioids. If they are not or exacerbating problem use, the need for information uncovering that possibility is urgent. Consequently, empirical evidence linking cannabis to benzodiazepine or opioid use in more permissive cannabis environments is needed.

2.1. Data

We analyze secondary data drawn from the National Survey on Drug Use and Health (NSDUH) for 2017, 2018, and 2019 [17]. The Substance Abuse and Mental Health Services Administration conducts a nationally representative sample of the U.S. population through the NSDUH. There are 128319 respondents included in the survey analysis for 2017 through 2019. Online access to the NSDUH is available at https://www.datafiles.samhsa.gov. No institutional review board approval is required for the use of public, deidentified secondary data. The 2020 NSDUH dataset [17] was excluded from this study because it was not directly comparable to recent past-year surveys. In addition to modifying some questions, importantly, the 2020 NSDUH shifted to a multimodal data collection design during the collection year owning to the 2019 pandemic. Similar methodological concerns are associated with the 2021 NSDUH [17]. However, the 2020 and 2021 NSDUH are included in a supplementary analysis discussed later.

The public use survey is ideally equipped to address the issues broached in this study because it contains data on prescription drug use and misuse among the public and the respondent's specific demographic characteristics. Only adults aged 18 and older are analyzed here. Notably, most states do not impose a strict or any age limit for medicinal cannabis because patients of any age may benefit from the therapy, whereas recreational laws tend to restrict access to those 21 years and older (see individual state statutes linked at the National Center of State Legislatures website https://www.ncsl.org/health/state-medical-cannabis-laws) [54]. The age restriction in these regulations is based on research suggesting that initiating cannabis use at a young age amplifies the likelihood of cannabis and other illegal drug usage and dependence [2] despite some evidence to the contrary [11]. Cannabis also is argued to affect cognitive function and other aspects of development, though evidence is limited with respect to the enduring nature of these effects, and future study is warranted [11].

2.2. Measures

2.2.1. Dependent variables

A series of dummy coded dependent variables are analyzed in this study. These variables measure whether the respondent used or misused benzodiazepine, opioid analgesics, or a combination of both during the past year. Prescription drug use is defined as using one's prescription medication as directed by a medical doctor. According to the codebook, prescription drug misuse is measured as any use not directed or supervised by a medical doctor, including use without a prescription, use in greater amounts than recommended, a higher frequency of use than prescribed, or for a longer duration of use than prescribed [17]. Questions from the survey about misuse are embodied in the language, "Think about your use of prescription pain relievers during the past 12 months as you answer these next questions. Remember, we are only interested in *prescription pain relievers* that you used in a way a doctor did not direct you to" (e.g., 2020 codebook, p. 68) [17]. Respondents must consider all of the elements noted above when indicating whether they are misusing the prescription drug.

Benzodiazepine tranquilizers include alprazolam products (Xanax, Xanax XR, generic alprazolam, generic extended-release alprazolam), lorazepam products (Ativan, generic lorazepam), clonazepam products (Klonopin, generic clonazepam), diazepam products (Valium, or generic diazepam), or past year misuse of other benzodiazepine tranquilizers. Questions in the survey to respondents about benzodiazepine use and misuse mirror the language of the survey questions noted above concerning prescription pain relievers.

Pain relievers encompass only prescription opioid analgesics: Hydrocodone, oxycodone, propoxyphene, tramadol, extended-release tramadol, codeine pills, morphine, extended-release morphine, fentanyl, buprenorphine, oxymorphone, extended-release oxymorphone, hydromorphone, extended-release hydromorphone, and methadone. The survey screens for brand names and generic versions of these drugs.

2.2.2. Independent variables

MML state is the theoretically relevant exogenous variable evaluated in the study. It is a dummy coded variable indicating whether a survey respondent resides in a state that legally permits the use of cannabis for medical purposes when the respondent's interview was conducted [17]. The MML variable is included in the NSDUH dataset as MEDMJPA2. According to the codebook, "MEDMJPA2 was coded as 1 if the respondent was in a State where a law or initiative allowing the use of marijuana for medical reasons had been passed on or before the interview date; MEDMJPA2 was coded as 2 if (a) the respondent was in a State in which a law or initiative allowing the use of marijuana for medical reasons had not been passed at any time during the survey year; or (b) the respondent was in a State where a law or initiative allowing the use of marijuana for medical reasons had been passed during the survey year but after the interview date" (e.g. 2020 Codebook, p. 182) [17].

Respondents were coded one if they resided in a state that permitted the medical use of cannabis on or before the interview date. Respondents living in states that did not have a law allowing the medical use of cannabis at any time during the survey year or in states where a law allowing the medical use of cannabis went into effect during the survey year, but after the interview date, were coded zero. Moreover, because specific states could not be identified in the data, we could not determine how long

MMLs were in force or whether MML states also enacted recreational cannabis laws. Thus, there is a possibility that states with medicinal and recreational cannabis legalization have an enhanced influence on benzodiazepine and/or opioid consumption. Additionally, in states with newly approved MMLs, it may take at least a year for cannabis to become accessible to the public through distribution centers.

Several control variables were incorporated into the analysis to vet any associations belonging to specified demographic groups, mitigate the possibility of false or repressed relationships, and account for survey year. The variables for survey year were introduced to control for any time-related effects that were not considered in the model and for potential issues associated with the overlap of MML and annual retrospective accounting of opioid usage by year. Researchers have employed these variables previously to facilitate replication and comparability [14,49]. Age, which is coded as a dummy set with 18–25-year-olds as the reference group, sex, race/ethnicity, self-reported health, cigarette smoking, health insurance, family income, county metro status, marital status, education, and job are among these factors. Variables measuring cannabis consumption levels over the past year were also used. Table 1 provides the means, standard deviations, and coding information for all variables.

Table 1. Description of variables included in the study (N = 128319; NSDUH Years 2017, 2018, 2019).

	MML state (N = 86332)		Non-MML state (N = 41987)	
	Mean	S.D.	Mean	S.D.
Benzodiazepine use (past year)	0.08	0.28	0.09	0.28
Benzodiazepine misuse (past year)	0.03	0.16	0.03	0.16
Opioid use (past year)	0.26	0.44	0.29	0.45
Opioid misuse (past year)	0.05	0.21	0.05	0.21
Benzodiazepine + opioid use (past year)	0.04	0.20	0.05	0.21
Benzodiazepine + opioid misuse (past year)	0.01	0.11	0.01	0.11
Age: 18–25 (ref.)				
26–34	0.20	0.40	0.20	0.40
35–49	0.27	0.44	0.26	0.44
50–64	0.11	0.32	0.12	0.32
65+	0.09	0.29	0.09	0.28
Female	0.53	0.50	0.53	0.50
Cannabis use (past year): no use (ref.)				
1–11 days	0.07	0.25	0.05	0.22
12–49 days	0.04	0.19	0.03	0.17
50–99 days	0.02	0.15	0.02	0.13
100–299 days	0.06	0.24	0.04	0.20
300–365 days	0.06	0.23	0.04	0.19

Continued on next page

	MML state (N = 86332)		Non-MML state (N = 41987)	
	Mean	S.D.	Mean	S.D.
Race/ethnicity: non-Hispanic white (ref.)				
Non-Hispanic black	0.11	0.32	0.15	0.36
Non-Hispanic Asian	0.08	0.27	0.04	0.20
Hispanic	0.19	0.39	0.14	0.35
Multi-racial	0.03	0.18	0.03	0.17
Self-reported health: scale (1 = excellent, 5 = poor)	2.29	0.98	2.32	0.99
Cigarette smoking: non-smoker (ref.)				
Non-daily smoker	0.09	0.29	0.10	0.31
Daily smoker	0.11	0.31	0.13	0.34
Health insurance	0.90	0.30	0.85	0.36
Family income: more than 2× federal policy threshold (ref.)				
Living in poverty	0.17	0.38	0.18	0.39
Up to 2× federal policy threshold	0.21	0.41	0.23	0.42
County metro status: non-metro (ref.)				
Living in large metro	0.51	0.50	0.33	0.47
Living in small metro	0.33	0.47	0.40	0.49
Marital status: married (ref.)				
Widowed	0.03	0.17	0.03	0.17
Divorced/separated	0.10	0.30	0.11	0.32
Never married	0.47	0.50	0.43	0.49
Education: college graduate (ref.)				
Less than high school	0.12	0.33	0.13	0.34
High school graduate	0.26	0.44	0.28	0.45
Some college	0.33	0.47	0.35	0.48
Employment: full-time employed (ref.)				
Part-time employed	0.16	0.37	0.14	0.35
Unemployed	0.06	0.24	0.05	0.23
Not in labor force	0.26	0.44	0.26	0.44
Study year: 2017 (ref.)				
2018	0.33	0.47	0.34	0.47
2019	0.35	0.48	0.31	0.46

Note: MML refers to medical marijuana law. For the purpose of analysis, a coding of 1 signifies the presence of a medical marijuana law in a state and 0 otherwise.

2.3. Analytic procedures

The effects of the MML state and the control variables on the dependent variables were ascertained using the multivariate logistic regression procedure in SPSS [55]. In logistic regression, the

e^{β} or exp(B) refers to the exponentiated value of the unstandardized coefficient (B) associated with a predictor variable. It is also often referred to as the *odds ratio* because it quantifies how a one-unit change in the predictor variable impacts the odds of the binary outcome variable occurring. The Nagelkerke R^2 is also calculated and is a measure of goodness of fit or model fit in logistic regression. It is a modification of the traditional R^2 statistic commonly used in linear regression. In logistic regression, R^2 is adapted to provide a sense of how well the model fits the data and explains the variation in the outcome variable. The Nagelkerke R^2 ranges from 0 to 1 and is used to evaluate the proportion of the variance in the dependent variable (the outcome) that is explained by the independent variables (predictors) included in the logistic regression model. It is a relative measure of fit, where 0 indicates that the model does not explain any of the variation in the outcome, and 1 indicates a perfect fit where the model explains all of the variation. The Nagelkerke R^2 is presented in the relevant tables for the equations generated for these analysis.

When values are mentioned in the text, they represent the rounded, percentage change in the log odds transformation according to the following formula: percent change in the Odds Ratio = $(e^{\beta}-1) \times 100$. The diagnostics generated from the analyses identified no problematic issues due to multicollinearity. The 0.001 than the 0.01 or 0.05 level of significance is the criterion employed for establishing a prominent link between an independent variable and each of the dependent variables because of the large sample size studied. When a large sample size is analyzed, relatively slight differences in the probabilities of prescription drug usage and misuse among the independent variables may become statistically significant. Thus, the direction and magnitude of a variable's impact in each equation should be emphasized when examining a variable's influence on the likelihood of prescription drug usage and misuse. However, the 95% confidence intervals are reported in the tables at the bequest of a reviewer and for other readers interested in this level of significance.

3. Results

3.1. Prescription drug use

Tables 2 thru 4 report the results of the logistic regression equations estimating the influence of the MML state and control variables on the likelihood of use and misuse of benzodiazepines, opioids, and a combination of both opioids and benzodiazepines. The findings depicted in these tables show a noteworthy relationship between the dummy coded MML state variable and the likelihood that a survey respondent properly used an opioid pain reliever or a combination of benzodiazepines and opioids. The coefficient for the MML variable is statistically significant in the negative direction, indicating that living in a state with an MML lowers the log odds of an opioid pain reliever being used by about 11% (Table 3) and a benzodiazepine opioid combination being used by 12% (Table 4), and net the effects of the other independent variables included in the equation. The MML variable has no discernable effect on the use of only benzodiazepines in the aggregate (Table 2).

Several other variables are also associated with less reliance on prescribed benzodiazepines and/or opioids (Tables 2–4). Regarding race and ethnicity, non-Hispanic Asians and Hispanics demonstrate a lower propensity to use benzodiazepines and/or opioids than non-Hispanic Whites, accounting for the other controls. Those who never married are less apt to report using opioids. Finally, survey respondents in 2018 and 2019 were less apt to use benzodiazepines and/or opioids than individuals surveyed in 2017.

A few other variables were also salient in predicting legitimate benzodiazepine and/or opioid use in the logistic regression equations. All age groups reported legitimate, increased use of benzodiazepines, opioids, and combinations of these drugs compared to the youngest age group and net controls including the presence of a MML jurisdiction. Thus, older individuals are more apt to use prescribed opioids and/or benzodiazepines than younger individuals aged 18–25. Tables 2–4 also reveal that this drug use increased in ascending amounts with age, peaking for the 50–64 age category compared to those in the lowest age category (Tables 2–4). Females are significantly more inclined than males to legally use benzodiazepines and/or opioids. Smokers, cannabis users, and those divorced or separated also have a greater proclivity to use benzodiazepines, opioids, and combinations of these drugs. Additionally, those individuals in poorer health and with health insurance are more likely to legitimately use benzodiazepines and/or opioids. Those with low or no labor force participation are more apt to use benzodiazepines or a combination of benzodiazepines and opioids, but no relationship was observed with solely opioid use.

Table 2. Logistic regression analysis predicting benzodiazepine use and misuse (N = 126977; NSDUH Years 2017, 2018, 2019).

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
MML state	0.935	0.003	0.895	0.977	0.813	<0.001	0.751	0.879
Age 26–34	1.486	<0.001	1.386	1.593	0.787	<0.001	0.714	0.868
Age 35–49	2.050	<0.001	1.911	2.200	0.674	<0.001	0.599	0.758
Age 50–64	2.094	<0.001	1.928	2.274	0.542	<0.001	0.454	0.648
Age 65+	1.867	<0.001	1.697	2.053	0.280	<0.001	0.205	0.382
Female	2.066	<0.001	1.977	2.160	1.167	<0.001	1.084	1.256
Cannabis use 1–11 days	1.735	<0.001	1.605	1.877	3.444	<0.001	3.026	3.919
Cannabis use 12–49 days	1.838	<0.001	1.666	2.028	5.160	<0.001	4.506	5.908
Cannabis use 50–99 days	1.771	<0.001	1.553	2.020	4.954	<0.001	4.179	5.874
Cannabis use 100–299 days	1.830	<0.001	1.682	1.992	8.078	0.000	7.254	8.995
Cannabis use 300–365 days	2.015	<0.001	1.848	2.198	9.480	0.000	8.511	10.560
Non-Hispanic black	0.455	<0.001	0.421	0.491	0.370	<0.001	0.321	0.427
Non-Hispanic Asian	0.341	<0.001	0.303	0.383	0.455	<0.001	0.372	0.556
Hispanic	0.539	<0.001	0.503	0.577	0.724	<0.001	0.651	0.805
Multi-racial	0.717	<0.001	0.639	0.806	0.936	0.420	0.797	1.099
Self-reported health	1.406	<0.001	1.376	1.437	1.165	<0.001	1.121	1.211
Non-daily smoker	1.324	<0.001	1.237	1.418	2.242	<0.001	2.044	2.459
Daily smoker	1.301	<0.001	1.225	1.382	2.150	<0.001	1.949	2.372

Continued on next page

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
Health insurance	1.469	<0.001	1.357	1.590	0.964	0.485	0.869	1.069
Living in poverty	0.856	<0.001	0.801	0.914	0.880	0.013	0.795	0.974
Living up to 2× federal policy threshold	0.890	<0.001	0.841	0.942	0.894	0.019	0.814	0.982
Living in large metro	1.182	<0.001	1.116	1.252	1.450	<0.001	1.304	1.611
Living in small metro	1.173	<0.001	1.109	1.242	1.208	<0.001	1.086	1.345
Widowed	1.132	0.021	1.019	1.258	1.046	0.817	0.715	1.529
Divorced/separated	1.263	<0.001	1.188	1.343	1.425	<0.001	1.236	1.643
Never married	1.010	0.748	0.953	1.070	1.605	<0.001	1.439	1.790
Less than high school	0.608	<0.001	0.559	0.662	0.712	<0.001	0.618	0.821
High school graduate	0.716	<0.001	0.672	0.761	0.706	<0.001	0.629	0.792
Some college	0.956	0.091	0.907	1.007	0.876	0.011	0.791	0.970
Part-time employed	1.151	<0.001	1.082	1.225	1.128	0.019	1.020	1.248
Unemployed	1.372	<0.001	1.245	1.511	1.395	<0.001	1.227	1.586
Not in labor force	1.420	<0.001	1.345	1.500	1.149	0.007	1.040	1.271
Study year 2018	0.907	<0.001	0.863	0.952	0.897	0.013	0.824	0.977
Study year 2019	0.887	<0.001	0.844	0.932	0.747	<0.001	0.684	0.816
Constant	0.012	0.000			0.008	0.000		
Nagelkerke R^2	0.109				0.202			

Table 3. Logistic regression analysis predicting opioid use and misuse (*N* = 126977; NSDUH Years 2017, 2018, 2019).

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
MML state	0.891	<0.001	0.867	0.916	0.900	<0.001	0.848	0.954
Age 26–34	1.213	<0.001	1.165	1.263	1.085	0.031	1.008	1.169
Age 35–49	1.336	<0.001	1.281	1.394	0.969	0.460	0.890	1.054
Age 50–64	1.464	<0.001	1.391	1.541	0.701	<0.001	0.621	0.792
Age 65+	1.406	<0.001	1.324	1.492	0.447	<0.001	0.373	0.537
Female	1.370	<0.001	1.334	1.407	1.012	0.665	0.958	1.070
Cannabis use 1–11 days	1.150	<0.001	1.089	1.214	2.543	<0.001	2.308	2.802

Continued on next page

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
Cannabis use 12–49 days	1.227	<0.001	1.147	1.313	3.447	<0.001	3.104	3.826
Cannabis use 50–99 days	1.241	<0.001	1.137	1.356	3.671	<0.001	3.230	4.172
Cannabis use 100–299 days	1.171	<0.001	1.106	1.240	4.160	<0.001	3.825	4.524
Cannabis use 300–365 days	1.045	0.155	0.983	1.111	5.059	0.000	4.656	5.497
Non-Hispanic black	1.112	<0.001	1.068	1.159	0.703	<0.001	0.642	0.771
Non-Hispanic Asian	0.705	<0.001	0.666	0.746	0.820	0.002	0.725	0.928
Hispanic	0.845	<0.001	0.813	0.878	0.940	0.115	0.869	1.015
Multi-racial	1.097	0.009	1.023	1.177	0.946	0.411	0.829	1.080
Self-reported health	1.326	0.000	1.307	1.344	1.236	<0.001	1.201	1.272
Non-daily smoker	1.192	<0.001	1.140	1.245	1.820	<0.001	1.691	1.960
Daily smoker	1.314	<0.001	1.262	1.368	2.055	<0.001	1.912	2.208
Health insurance	1.427	<0.001	1.365	1.492	0.953	0.221	0.883	1.029
Living in poverty	0.988	0.563	0.950	1.028	1.000	0.999	0.927	1.079
Living up to 2× federal policy threshold	0.962	0.026	0.929	0.995	0.941	0.091	0.877	1.010
Living in large metro	0.959	0.022	0.925	0.994	1.081	0.045	1.002	1.167
Living in small metro	1.026	0.152	0.990	1.063	1.079	0.047	1.001	1.164
Widowed	0.963	0.326	0.893	1.038	1.036	0.759	0.826	1.299
Divorced/separated	1.097	<0.001	1.051	1.144	1.184	<0.001	1.076	1.303
Never married	0.880	<0.001	0.850	0.912	1.198	<0.001	1.111	1.292
Less than high school	0.925	0.002	0.879	0.973	1.177	0.002	1.060	1.308
High school graduate	1.066	0.001	1.026	1.109	1.096	0.042	1.003	1.197
Some college	1.276	<0.001	1.232	1.321	1.232	<0.001	1.137	1.335
Part-time employed	1.003	0.898	0.964	1.042	0.957	0.287	0.883	1.037
Unemployed	1.033	0.280	0.974	1.096	1.380	<0.001	1.253	1.521
Not in labor force	1.128	<0.001	1.090	1.168	1.042	0.274	0.968	1.122
Study year 2018	0.920	<0.001	0.893	0.949	0.834	<0.001	0.782	0.890
Study year 2019	0.843	<0.001	0.817	0.870	0.792	<0.001	0.742	0.845
Constant	0.100	0.000			0.015	0.000		
Nagelkerke R^2	0.067				0.134			

Table 4. Logistic regression analysis predicting benzodiazepine + opioid use and misuse (*N* = 126977; NSDUH Years 2017, 2018, 2019).

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
MML state	0.882	<0.001	0.832	0.936	0.783	<0.001	0.698	0.877
Age 26–34	1.630	<0.001	1.472	1.804	0.813	0.004	0.706	0.937
Age 35–49	2.395	<0.001	2.166	2.648	0.657	<0.001	0.553	0.781
Age 50–64	2.467	<0.001	2.200	2.766	0.508	<0.001	0.389	0.663
Age 65+	2.049	<0.001	1.798	2.335	0.224	<0.001	0.132	0.381
Female	2.056	<0.001	1.934	2.186	0.947	0.331	0.849	1.057
Cannabis use 1–11 days	1.591	<0.001	1.425	1.777	3.603	<0.001	2.924	4.441
Cannabis use 12–49 days	1.830	<0.001	1.603	2.089	5.550	<0.001	4.510	6.830
Cannabis use 50–99 days	1.498	<0.001	1.243	1.805	5.794	<0.001	4.532	7.406
Cannabis use 100–299 days	1.543	<0.001	1.370	1.737	8.660	<0.001	7.365	10.184
Cannabis use 300–365 days	1.613	<0.001	1.426	1.824	10.659	<0.001	9.090	12.498
Non-Hispanic black	0.553	<0.001	0.500	0.612	0.426	<0.001	0.347	0.522
Non-Hispanic Asian	0.371	<0.001	0.315	0.436	0.536	<0.001	0.401	0.718
Hispanic	0.530	<0.001	0.481	0.584	0.697	<0.001	0.593	0.819
Multi-racial	0.831	0.017	0.714	0.968	0.941	0.603	0.748	1.184
Self-reported health	1.619	<0.001	1.572	1.667	1.224	<0.001	1.157	1.296
Non-daily smoker	1.367	<0.001	1.246	1.500	2.607	<0.001	2.268	2.996
Daily smoker	1.333	<0.001	1.232	1.443	3.092	<0.001	2.689	3.555
Health insurance	1.689	<0.001	1.506	1.894	0.931	0.321	0.807	1.073
Living in poverty	0.933	0.125	0.854	1.019	0.863	0.047	0.746	0.998
Living up to 2× federal policy threshold	0.898	0.006	0.832	0.969	0.940	0.363	0.822	1.074
Living in large metro	1.117	0.005	1.033	1.207	1.242	0.005	1.068	1.444
Living in small metro	1.166	<0.001	1.081	1.257	1.143	0.079	0.985	1.328
Widowed	1.071	0.317	0.936	1.226	0.870	0.663	0.466	1.626
Divorced/separated	1.236	<0.001	1.141	1.339	1.559	<0.001	1.271	1.913
Never married	0.908	0.018	0.838	0.983	1.499	<0.001	1.271	1.766
Less than high school	0.621	<0.001	0.554	0.697	1.034	0.756	0.836	1.279
High school graduate	0.783	<0.001	0.719	0.853	0.946	0.552	0.787	1.137
Some college	1.099	0.011	1.021	1.182	1.168	0.071	0.987	1.383
Part-time employed	1.128	0.007	1.033	1.233	1.113	0.174	0.954	1.298

Continued on next page

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
Unemployed	1.301	<0.001	1.133	1.493	1.569	<0.001	1.318	1.868
Not in labor force	1.539	<0.001	1.431	1.656	1.330	<0.001	1.152	1.535
Study year 2018	0.848	<0.001	0.794	0.906	0.812	0.001	0.717	0.919
Study year 2019	0.790	<0.001	0.738	0.845	0.685	<0.001	0.601	0.779
Constant	0.003	0.000			0.002	<0.001		
Nagelkerke R^2	0.117				0.209			

3.2. Prescription drug misuse

The results reported in Tables 2–4 also show a statistically discernible negative relationship between the dummy coded variable measuring the presence of an MML in a state and the likelihood of opioid and benzodiazepine misuse, as reported by the survey respondents. The coefficient for the MML state variable is statistically significant and is in the negative direction in all three misuse equations. The exponentiated values of the dummy coded MML state variables indicate that net of the other independent variables included in each equation, residing in a state that legally permits cannabis use for medical purposes lowers the log odds of benzodiazepine misuse by about 19%, opioid misuse by approximately 10%, and both benzodiazepine and opioid misuse by roughly 22%. The effects of the control variables are mostly compatible with those reported in the prescribed benzodiazepine and opioid use equations. These pronounced effects across all three misuse equations include the respondent's age, frequency of cannabis use, race, ethnicity, self-reported health, smoking behavior, marital status, employment status, and study year.

In summary, the results generated in the multivariate logistic regression equations show that MMLs are associated with a lower likelihood of using and misusing benzodiazepines, opioids, and both benzodiazepine and opioids. However, it is important to note that because of methodological changes and various coding schemes across the surveys in different years, the prescribed use of benzodiazepines, opioids, and both benzodiazepine and opioids could not be employed as individual control variables in the equations examining misuse. As necessarily coded, the categories for later years are rendered entirely and mutually exclusive. Introducing each of them as a control variable in their respective misuse equation would therefore serve as a constant in the models.

3.3. Prescription drug use and misuse by year

The initial analysis showed differences in the use and misuse of benzodiazepines, opioids, or both benzodiazepines and opioids associated with the survey year variable, whereas survey respondents in 2018 and 2019 were less apt to use benzodiazepines and/or opioids than individuals surveyed in 2017. To further probe these findings, supplemental analyses were performed regressing use and misuse for each drug type or combination for each year to determine if any trends were indicated by the data. In a departure from the previous analysis, the 2020 and 2021 NSDUH are included in the analysis for reader interest and at the request of a reviewer. These years are necessarily omitted from the

main analysis as there are significant methodological modifications with the surveys compared to previous years owning to the 2019 pandemic. Caution is urged when considering the results for 2020 and 2021, and they should not be used to establish or substantiate a trend. Interested readers are directed to consult the appropriate methodological codebooks for the surveys for detailed information.

Table 5 presents the results of the five logistic regression equations predicting prescription drug use and misuse on MML state by years 2017 (equation 1), 2018 (equation 2), 2019 (equation 3), 2020 (equation 4), and 2021 (equation 5). Control variables are the same as those used in the earlier analyses but are excluded from the table for space considerations. All results are available upon request. The 0.001 level of significance is again used to determine statistical significance. However, the 95% confidence levels are provided in the tables for the reasons noted above. Similar to the previous analyses, multicollinearity diagnostics indicated no complications with the data.

A visual inspection of the findings reported in Table 5 largely demonstrates an inverse effect of the MML state variable, notwithstanding whether statistically substantive, on the use and misuse of benzodiazepines, opioids, and benzodiazepines and opioids combined for the years of data analyzed. With respect to use, respondents in MML states showed a statistically noteworthy decline for opioids in all three study years used in the previous analysis, with about a 12% decline in 2017, a 12% decline in 2018, and a 9% decline in 2019. For the years of 2020 and 2021, declines of approximately 10% and 11% were observed, respectively. A decline in both benzodiazepine and opioid use was demonstrated in 2017, about 21%. The effect of the MML state variable was statistically substantive in the negative direction in the misuse of benzodiazepines and benzodiazepine and opioid equations for two of the three years analyzed (2017 and 2018) in the previous analysis. For benzodiazepines, declines in misuse of 21% (2017) and 23% (2018) are evident in Table 5. Similar reductions in misuse are revealed with the combination of benzodiazepines and opioids, having 21% and 23% negative associations with the MML variable for 2017 and 2018, respectively. A statistically significant decline of approximately 18% was observed for opioid misuse in 2018. No statistically significant associations were observed for years 2020 and 2021 with respect to MMLs and misuse of benzodiazepines, opioids, or a combination of these drugs.

Table 5. Supplemental logistic regression analysis predicting prescription drug use and misuse on MML state by year; NSDUH 2017–2021.

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
Benzodiazepines								
Study year 2017 (*N* = 42156)	0.909	0.011	0.844	0.978	0.787	<0.001	0.692	0.895
Study year 2018 (*N* = 42615)	0.953	0.220	0.883	1.029	0.775	<0.001	0.678	0.887
Study year 2019 (*N* = 42206)	0.949	0.197	0.876	1.028	0.892	0.134	0.769	1.036
Study year 2020 (*N* = 27037)	0.917	0.101	0.826	1.017	0.820	0.053	0.671	1.003
Study year 2021 (*N* = 47190)	0.977	0.581	0.899	1.062	0.814	0.011	0.694	0.954

Continued on next page

	Use				Misuse			
			95% CI				95% CI	
	Exp(B)	P-value	Lower	Upper	Exp(B)	P-value	Lower	Upper
Opioids								
Study year 2017 (*N* = 42156)	0.884	<0.001	0.844	0.926	0.895	0.023	0.813	0.985
Study year 2018 (*N* = 42615)	0.883	<0.001	0.842	0.926	0.818	<0.001	0.739	0.906
Study year 2019 (*N* = 42206)	0.910	<0.001	0.865	0.956	1.002	0.969	0.899	1.118
Study year 2020 (*N* = 27037)	0.896	0.001	0.838	0.959	1.001	0.993	0.856	1.169
Study year 2021 (*N* = 47190)	0.892	<0.001	0.847	0.941	0.920	0.171	0.816	1.037
Benzodiazepines + opioids								
Study year 2017 (*N* = 42156)	0.788	<0.001	0.716	0.867	0.728	<0.001	0.607	0.873
Study year 2018 (*N* = 42615)	0.953	0.366	0.859	1.058	0.692	<0.001	0.568	0.843
Study year 2019 (*N* = 42206)	0.945	0.316	0.846	1.055	1.016	0.891	0.809	1.275
Study year 2020 (*N* = 27037)	0.858	0.049	0.736	0.999	0.799	0.166	0.582	1.097
Study year 2021 (*N* = 47190)	0.944	0.350	0.835	1.066	0.803	0.096	0.620	1.040

Note: Control variables not shown but are available upon request.

4. Discussion and conclusions

4.1. Discussion

We aimed to elucidate whether MMLs matter to patients' reliance on benzodiazepines and/or opioids for managing their conditions. The findings reported here indicate that MMLs are linked to the use and misuse of these drugs in particular ways. While MMLs failed to influence legitimate benzodiazepine use when taken alone, a negative association with the laws was observed for the use of opioids alone or for combinations of benzodiazepines and opioids. With respect to misuse, one can interpret the consistent findings across drug type and their combination as evidence supporting the assertion that laws promoting medical cannabis may help to attenuate benzodiazepine and/or opioid misuse to a substantial degree because individuals appear to be supplanting these medications with cannabis to lessen their pain and treat associated conditions. The supplemental analysis also indicated that throughout the years for which data were analyzed, the existence of an MML was associated with yearly, variable declines in the use and misuse of benzodiazepines, opioids, and benzodiazepines and opioids combined.

Cannabis is the third most prevalent drug after alcohol and cigarettes [56]. Because of the widespread acceptance and use of cannabis, there is a fair quantity of societal information about its harmful effects and risks. In light of the results of the present research, and if other states implement legislation, there may be a further shift of patients away from benzodiazepines and/or opioids, as legislation decriminalizing the use of medicinal cannabis decreases the perception of its danger [57–59]. These patients may be more apt to try medicinal cannabis instead of conventional pharmaceuticals. For novice cannabis individuals who may be unsatisfied with benzodiazepines and opioids, legislative initiatives may be sufficient to alleviate fears and convince patients to try it who might otherwise eschew its use. Consequently, MMLs might contribute to displacement among the uninitiated, while others

may prefer cannabis over opioids for pain relief based on past knowledge. Such pathways toward cannabis use, therefore, have the potential to increase the number of medical cannabis users resulting in an unknown quantity of individual benefits and harms.

A shift toward cannabis may also carry unanticipated social repercussions, such as increased juvenile recreational cannabis use [60]. Policymakers must know the risk profile of cannabis alone and with benzodiazepines and opioids to determine if cannabis therapy is a safer and more effective alternative than these other medicines that foster a more substantial burden to society. While cannabis appears safer than benzodiazepines and opioids, more studies are needed to prevent damage from failed policy initiatives [53,61]. For an adequate assessment, the consequences of cannabis reliance must be compared to those of benzodiazepines and opioid analgesics to develop a comprehensive and effective policy that transcends anecdotes, politics, and emotions. As astutely recognized by Rehm and Fischer [62], "Cannabis policy is not formulated in a vacuum: it needs to fit into an overall coherent policy framework for psychoactive substance use, where the policy approaches should somehow—also in relative comparison—be proportional to potential harms caused." (p. 543) It is recognized that cannabis may lead to altered brain development (particularly if use began in adolescence), dependency, lung damage, auto accidents, and mental illness [11,28,62]. Compounding these issues is a general lack of empirically based treatment guidelines [63]—but see [64] for dosage research and recommendations. There also remains a concern that transferring from other pharmaceuticals to cannabis may contribute to a cannabis epidemic (also called a marijuana epidemic [53,65]), which would entail the widespread and hazardous usage of cannabis with all the attendant social costs.

Comparative risk assessments among these drugs are emerging and traditionally involve expert panel evaluations of acute and chronic toxicity, problematic use, and societal effects [66]. While these methodologies have been criticized for their subjectivity, they consistently show that cannabis has a low to moderate relative risk compared to other substances cross a wide range of personal and social aspects [66–69]. Lower toxicity and a greater safety margin are realized with cannabis than other psychotropic medicines [70,71], and it is consistently shown as causing less individual and societal damage than alcohol, cigarettes, and several illicit and legally used substances (e.g., cocaine, amphetamines, and opiates) [62,69]. However, absent adequate evidence of the therapeutic efficacy of cannabis for treating other conditions independent of pain, i.e., anxiety [11], caution is warranted as there is caution that cannabis may exacerbate some symptoms [12].

Notwithstanding the stated concerns, limiting prescription benzodiazepines, opioids, and their combined use in therapy may reduce overall risk if significant displacement toward cannabis occurs. Cannabis addiction does not result in fatal overdoses or engender many of the other deleterious consequences associated with other substances. Recent research reveals, for instance, that medical cannabis legalization may lessen the unfavorable consequences linked with opioid use, such as overdose mortality [13]. However, findings on this point are inconsistent. Nevertheless, cannabis legalization may be one strategy to tackle these prescription drug epidemics without expanding the use of illegal drugs beyond cannabis for recreational purposes [49]. More time is needed to determine the utility of medicinal cannabis. If patients with complicated medical management demands find medical cannabis ineffective or lose its perceived efficacy, like other medications, patients may return to benzodiazepines and/or opioids. Such concerns have yet to be thoroughly vetted.

4.2. Limitations and future research

Despite our merits, several limitations are present. Measurement error may have entered the equations since not all MMLs were enacted or implemented during the preceding year of a matched survey year (the time period of the dependent variables). Yet, only a modest number of states established laws during the research years, resulting in a relatively small amount of error. Notably, limitations would also imbue studies using the MML enactment date [72] because such dates do not capture any lag or variation that might occur across and within jurisdictions, e.g., prohibitive hardship for some physicians, patients, and medicinal cannabis availability was limited. Nonetheless, the present method subsumes the observed difference in medical cannabis legislation through aggregation. Further, if the aforementioned differences impacted cannabis use, there would be no expectation that MMLs would significantly impact benzodiazepine and/or opioid use or misuse. Such an impact was observed here and is a testament to the robustness of the findings given the current methods, as the findings complement others' work discussed earlier.

Another limitation of the current work concerns the opioid use variable, which displays minimum variation that is consistent with past work [14,49] and is not unexpected given that survey questions concerning criminal activity can create biased answers, such as social desirability bias. The variables for benzodiazepines and the combined variable (necessarily) present a similar issue. This problem can arise in therapeutic settings if people are reluctant to reveal their drug usage. Only successive blood and urine samples from individuals might overcome this constraint; however, a large-scale study of risk factors, laws, and regulations would be cost prohibitive. The proposed methodology is also limited to examining static time periods. As more states legalize medicinal cannabis, a longitudinal strategy that can capture more years than this study might help future research better establish a link between cannabis legalization and benzodiazepine and/or opioid use and misuse.

Finally, little is known about substance use behaviors among aging Americans despite a greater susceptibility to pain-related conditions [22,23], and for which benzodiazepines and other drugs, such as opioid analgesics, are commonly prescribed for management. This situation is troubling because those represented in the age category of 50 years and older account for over 70 million people, and clear answers can be derived from examining this population related to the opioid epidemic and ancillary harms and what some are referring to as the benzodiazepine epidemic [2,5]. The findings reported here demonstrate the higher demand for benzodiazepines, opioids, and combined use as the respondent's age increased, whereas those in the 50- to 64-year-old age category peaked in their use of these drugs compared to the youngest adults in the study. Misuse was less apt to occur in the older than younger population. Future work should therefore focus on the conditioning effect of age. Since older populations are more prone to have pain-related conditions, the benefits and costs from any shift from benzodiazepines and/or opioids toward medicinal cannabis may concentrate among them. However, this effect may be diminished as anxiety in younger people has been on the rise [24], and some patients rely on benzodiazepines for therapy. In the aggregate, the differences in conditions by age can consequently serve to flatten any effect seen. Irrespective, this is an area ripe for further investigation.

4.3. Conclusions

In sum, although research demonstrates that the main psychoactive component of cannabis, tetrahydrocannabinol, is comparable to pharmaceutical analgesics for pain management its side effects,

such as mental cloudiness and sedation, substance use disorder, lung disease, and any ancillary social costs have raised concerns [53,65]. Nonetheless, cannabis does not have the same hazardous substance use profile as benzodiazepines and/or opioids [73]. Considering these results and concerns, additional study into cannabis as a line of treatment for medical management is sorely needed, especially as more states seek to legalize it.

Use of AI tools declaration

The authors declare that they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

All authors declare no conflicts of interest in this paper.

References

1. Alamanda VK, Wally MK, Seymour RB, et al. (2020) Prevalence of opioid and benzodiazepine prescriptions for osteoarthritis. *Arthritis Care Res* 72: 1081–1086. https://doi.org/10.1002/acr.23933
2. Chen J, Are benzodiazepines the new opioids? The USA Yale Medicine, 2019. Available from: https://www.yalemedicine.org/news/benzodiazepine-epidemic
3. Bachhuber MA, Hennessy S, Cunningham CO, et al. (2016) Increasing benzodiazepine prescriptions and overdose mortality in the United States, 1996–2013. *Am J Public Health* 106: 686–688. https://doi.org/10.2105/AJPH.2016.303061
4. Lembke A, Papac J, Humphreys K (2018) Our other prescription drug problem. *N Engl J Med* 378: 693–695. https://doi.org/10.1056/NEJMp1715050
5. Limandri BJ (2018) Benzodiazepine use: the underbelly of the opioid epidemic. *J Psychosoc Nurs Ment Health Serv* 56: 11–15. https://doi.org/10.3928/02793695-20180521-03
6. Wright SL (2020) Limited utility for benzodiazepines in chronic pain management: A narrative review. *Adv Ther* 37: 2604–2619. https://doi.org/10.1007/s12325-020-01354-6
7. Dowell D, Haegerich TM, Chou R (2016) CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA* 315: 1624–1645. https://doi:10.1001/jama.2016.1464
8. Kowalski-McGraw M, Green-McKenzie J, Pandalai SP, et al. (2017) Characterizing the interrelationships of prescription opioid and benzodiazepine drugs with worker health and workplace hazards. *J Occup Environ Med* 59: 1114–1126. https://doi.org/10.1097/JOM.0000000000001154
9. Maust DT, Kales HC, Wiechers IR, et al. (2016) No end in sight: benzodiazepine use in older adults in the United States. *J Am Geriatr Soc* 64: 2546–2553. https://doi.org/10.1111/jgs.14379
10. Abrams DI, Couey P, Shade SB, et al. (2011) Cannabinoid opioid interaction in chronic pain. *Clin Pharmacol Ther* 90: 844–851. https://doi.org/10.1038/clpt.2011.188
11. National Academies of Sciences, Engineering, and Medicine (2017) The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research, Washington: The National Academies Press. https://doi.org/10.17226/24625

12. Hill KP (2015) Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA* 313: 2474–2483. https://doi.org/10.1001/jama.2015.6199
13. Bachhuber MA, Saloner B, Cunningham CO, et al. (2015) Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Intern Med* 174: 1668–1673. https://doi.org/10.1001/jamainternmed.2014.4005
14. Flexon JL, Stolzenberg L, D'Alessio SJ (2019) The effect of cannabis laws on opioid use. *Int J Drug Policy* 74: 152–159. https://doi.org/10.1016/j.drugpo.2019.09.013
15. Sarvet AL, Wall MM, Keyes KM, et al. (2018) Self-medication of mood and anxiety disorders with marijuana: higher in states with medical marijuana laws. *Drug Alcohol Depend* 186: 10–15. https://doi.org/10.1016/j.drugalcdep.2018.01.009
16. Whiting PF, Wolff RF, Deshpande S, et al. (2015) Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 313: 2456–2473. https://doi.org/10.1001/jama.2015.6358
17. Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health Public Use File, Codebook. The USA Substance Abuse and Mental Health Services Administration, 2022. Available from: https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health
18. Hemmelgarn B, Suissa S, Huang A, et al. (1997) Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA* 278: 27–31. https://doi.org/10.1001/jama.1997.03550010041037
19. National Institute on Drug Abuse, Drug overdose death rates. The USA National Institute on Drug Abuse, 2023. Available from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates
20. Simon LS (2011) Relieving pain in America: a blueprint for transforming prevention, care, education and research. *J Pain Palliat Care* 26: 197–198. https://doi.org/10.3109/15360288.2012.678473
21. Reuben DB, Alvanzo AA, Ashikaga T, et al. (2015) National Institutes of Health Pathways to prevention workshop: the role of opioids in the treatment of chronic pain. *Ann Intern Med* 162: 295–300. https://doi.org/10.7326/M14-2775
22. Johannes CB, Le TK, Zhou X, et al. (2010) The prevalence of chronic pain in United States adults: results of an internet-based survey. *J Pain* 11: 1230–1239. https://doi.org/10.1016/j.jpain.2010.07.002
23. Volkow ND, McLellan AT (2016) Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med* 374: 1253–1263. https://doi.org/10.1056/NEJMra1507771
24. Goodwin RD, Weinberger AH, Kim JH, et al. (2020) Trends in anxiety among adults in the United States, 2008–2018: rapid increases among young adults. *J Psychiatr Res* 130: 441–446. https://doi.org/10.1016/j.jpsychires.2020.08.014
25. Terlizzi EP, Villarroel MA, Symptoms of generalized anxiety disorder among adults: United States, 2019. The USA National Center for Health Statistics NCHS Data Brief, No. 378, 2020. Available from: https://www.cdc.gov/nchs/data/databriefs/db378-H.pdf
26. Nuckols TK, Anderson L, Popescu I, et al. (2014) Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Ann Intern Med* 160: 38–47. https://doi.org/10.7326/0003-4819-160-1-201401070-00732
27. Jones CM, The latest prescription trends for controlled prescription drugs. The USA Food and Drug Administration, 2015. Available from: https://archives.nida.nih.gov/sites/default/files/cjonesnida-bhccprescriptiontrendsslides.pdf

28. Volkow ND, Baler RD, Compton WM, et al. (2014) Adverse health effects of marijuana use. *N Engl J Med* 370: 2219–2227. https://doi.org/10.1056/NEJMra1402309
29. Mallow PJ, Belk KW, Topmiller M, et al. (2018) Geographic variation in hospital costs, payments, and length of stay for opioid-related hospital visits in the USA. *J Pain Res* 11: 3079–3088. https://doi.org/10.2147/JPR.S184724
30. National Institute on Drug Abuse, Drug Overdose Death Rates. The USA National Institute on Drug Abuse, 2019. Available from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates (updated to 2023)
31. Chen Q, Larochelle MR, Weaver DT, et al. (2019) Prevention of prescription opioid misuse and projected overdose deaths in the United States. *JAMA Netw Open* 2: e187621. https://doi.org/10.1001/jamanetworkopen.2018.7621
32. Martell BA, O'Connor PG, Kerns RD, et al. (2007) Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Ann Intern Med* 146: 116–127. https://doi.org/10.7326/0003-4819-146-2-200701160-00006
33. Jann M, Kennedy WK, Lopez G (2014) Benzodiazepines: A major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract* 27: 5–16. https://doi.org/10.1177/0897190013515001
34. Carico R, Zhao X, Thorpe CT, et al. (2018) Receipt of overlapping opioid and benzodiazepine prescriptions among veterans dually enrolled in Medicare Part D and the Department of Veterans Affairs: A cross-sectional study. *Ann Intern Med* 169: 593–601. https://doi.org/10.7326/M18-0852
35. Gellad WF, Zhao X, Thorpe CT, et al. (2017) Overlapping buprenorphine, opioid, and benzodiazepine prescriptions among veterans dually enrolled in Department of Veterans Affairs and Medicare Part D. *Subst Abus* 38: 22–25. https://doi.org/10.1080/08897077.2016.1267071
36. Boehnke KF, Gangopadhyay S, Clauw DJ, et al. (2019) Qualifying conditions of medical cannabis license holders in the United States. *Health Aff* 38: 295–302. https://doi.org/10.1377/hlthaff.2018.05266
37. Boehnke KF, Litinas E, Clauw DJ (2016) Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. *J Pain* 17: 739–744. https://doi.org/10.1016/j.jpain.2016.03.002
38. Corroon Jr JM, Mischley LK, Sexton M (2017) Cannabis as a substitute for prescription drugs—A cross-sectional study. *J Pain Res* 10: 989–998. https://doi.org/10.2147/JPR.S134330
39. Lucas P (2012) Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. *J Psychoactive Drugs* 44: 125–133. https://doi.org/10.1080/02791072.2012.684624
40. Lucas P, Walsh Z (2017) Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy* 42*:* 30–35. https://doi.org/10.1016/j.drugpo.2017.01.011
41. Piper BJ, DeKeuster RM, Beals ML, et al. (2017) Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. *J Psychopharmacol* 31: 569–575. https://doi.org/10.1177/0269881117699616
42. Reiman A, Welty M, Solomon P (2017) Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res* 2: 160–166. https://doi.org/10.1089/can.2017.0012

43. Socias ME, Wood E, Lake S, et al. (2018) High-intensity cannabis use is associated with retention in opioid agonist treatment: A longitudinal analysis. *Addiction* 113: 2250–2258. https://doi.org/10.1111/add.14398
44. Burns TL, Ineck JR (2006) Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother* 40: 251–260. https://doi.org/10.1345/aph.1G217
45. Lau N, Sales P, Averill S, et al. (2015) A safer alternative: cannabis substitution as harm reduction. *Drug Alcohol Rev* 34: 654–659. https://doi.org/10.1111/dar.12275
46. Center for Behavioral Health Statistics and Quality, Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health, (HHS Publication No. SMA 16-4984, NSDUH Series H-51). The USA Substance Abuse and Mental Health Services Administration, 2016. Available from: http://www.samhsa.gov/data/
47. Bruce D, Brady JP, Foster E, et al. (2018) Preferences for medical marijuana over prescription medications among persons living with chronic conditions: alternative, complementary, and tapering uses. *J Altern Complement Med* 24: 146–153. https://doi.org/10.1089/acm.2017.0184
48. Powell D, Pacula RL, Jacobson M (2018) Do medical marijuana laws reduce addictions and deaths related to pain killers?. *J Health Econ* 58: 29–42. https://doi.org/10.1016/j.jhealeco.2017.12.007
49. Wen H, Hockenberry JM, Cummings JR (2015) The effect of medical marijuana laws on adolescent and adult use of marijuana, alcohol, and other substances. *J Health Econ* 42: 64–80. https://doi.org/10.1016/j.jhealeco.2015.03.007
50. Bradford AC, Bradford WD (2016) Medical marijuana laws reduce prescription medication use in Medicare part D. *Health Aff* 35: 1230–1236. https://doi.org/10.1377/hlthaff.2015.1661
51. Bradford AC, Bradford WD (2017) Medical marijuana laws may be associated with a decline in the number of prescriptions for Medicaid enrollees. *Health Aff* 36: 945–951. https://doi.org/10.1377/hlthaff.2016.1135
52. Wen H, Hockenberry JM (2018) Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. *JAMA Intern Med* 178: 673–679. https://doi.org/10.1001/jamainternmed.2018.1007
53. Kroenke K, Cheville A (2017) Management of chronic pain in the aftermath of the opioid backlash. *JAMA* 317: 2365–2366. https://doi.org/10.1001/jama.2017.4884
54. National Center of State Legislatures, State Medical Cannabis Laws. The USA National Center of State Legislatures, 2023. Available from: https://www.ncsl.org/health/state-medical-cannabis-laws
55. IBM Corp (2021) IBM SPSS Statistics for Windows, Version 28.0.0, Armonk, NY: IBM Corp. Available from: https://www.ibm.com/docs/en/spss-statistics/28.0.0
56. Substance Abuse and Mental Health Services Administration, Results from 2013 national survey on drug use and health: Summary of national findings. The USA Substance Abuse and Mental Health Services Administration, 2014. Available from: https://www.samhsa.gov/data/report/results-2013-national-survey-drug-use-and-health-summary-national-findings
57. Khatapoush S, Hallfors D (2004) "Sending the wrong message": Did medical marijuana legalization in California change attitudes about and use of marijuana?. *J Drug Issues* 34: 751–770. https://doi.org/10.1177/002204260403400402

58. Schuermeyera J, Salomonsen-Sautela S, Price RK, et al. (2014) Temporal trends in marijuana attitudes, availability and use in Colorado compared to non-medical marijuana states: 2003–2011. *Drug Alcohol Depend* 140: 145–155. https://doi.org/10.1016/j.drugalcdep.2014.04.016
59. Wall MM, Poh E, Cerda M, et al. (2011) Adolescent marijuana use from 2002 to 2008: higher in states with medical marijuana laws, cause still unclear. *Ann Epidemiol* 21: 714–716. https://doi.org/10.1016/j.annepidem.2011.06.001
60. Stolzenberg L, D'Alessio SJ, Dariano D (2016) The effect of medical cannabis laws on juvenile cannabis use. *Int J Drug Policy* 27: 82–88. https://doi.org/10.1016/j.drugpo.2015.05.018
61. Kalant H (2015) Cannabis control policy: no rational basis yet for legalization. *Clin Pharmacol Ther* 97: 538–540. https://doi.org/10.1002/cpt.112
62. Rehm J, Fischer B (2015) Cannabis legalization with strict regulation, the overall superior policy option for public health. *Clin Pharmacol Ther* 97: 541–544. https://doi.org/10.1002/cpt.93
63. Timko C, Cucciare MA (2018) Commentary on Socias et al. (2018): Clinical research perspectives on cannabis use in opioid agonist treatment. *Addiction* 113: 2259–2260. https://doi.org/10.1111/add.14432
64. MacCallum CA, Russo EB (2018) Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 49: 12–19. https://doi.org/10.1016/j.ejim.2018.01.004
65. Häuser W, Finnerup NB, Moore RA (2018) Systematic reviews with meta-analysis on cannabis-based medicines for chronic pain: A methodological and political minefield. *Pain* 159: 1906–1907. https://doi.org/10.1097/j.pain.0000000000001295
66. Lachenmeier DW, Rehm J (2015) Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. *Sci Rep* 5: 8126. https://doi.org/10.1038/srep08126
67. Nutt DJ, King LA, Phillips LD (2010) Drug harms in the UK: A multicriteria decision analysis. *Lancet* 376: 1558–1565. https://doi.org/10.1016/S0140-6736(10)61462-6
68. van Amsterdam J, Opperhuizen A, Koeter M, et al. (2010) Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population. *Eur Addict Res* 16: 202–207. https://doi.org/10.1159/000317249
69. Lake S, Socías ME, Milloy MJ (2020) Evidence shows that cannabis has fewer relative harms than opioids. *CMAJ* 192: E166–E167. https://doi.org/10.1503/cmaj.74120
70. Gable RS (1993) Toward a comparative overview of dependence potential and acute toxicity of psychoactive substances used nonmedically. *Am J Drug Alcohol Abuse* 19: 263–281. https://doi.org/10.3109/00952999309001618
71. Gable RS (2004) Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction* 99: 686–696. https://doi.org/10.1111/j.1360-0443.2004.00744.x
72. Pacula RL, Boustead AE, Hunt P (2014) Words can be deceiving: A review of variation among legally effective medical marijuana laws in the United States. *J Drug Policy Anal* 7: 1–19. https://doi.org/10.1515/jdpa-2014-0001
73. Walker JM, Huang SM (2002) Cannabinoid analgesia. *Pharmacol Ther* 95: 127–135. https://doi.org/10.1016/S0163-7258(02)00252-8

AIMS Press