Cannabis- Based Reduction in Opioid-Related Harms: Population-Based Observational Meta-Analysis

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Research

Abstract

Background. Rhetoric abounds about harms associated with easier access to cannabis. Yet, surveys of medical marijuana patients and recreational users in Canada and the USA observed that they prevalently substitute cannabis for alcohol, opioids and other drugs. This synthetic study focused on arguably the most harmful substance, opioids, and hypothesized reduced harms with medical and recreational cannabis legalization.

Methods. Broad keyword searches of interdisciplinary research databases, peer-reviewed and gray, between 2010 and 2020 retrieved 11 studies. Their outcomes were synthesized with a sample-weighted meta-analysis that compared opioid-related outcomes before and after marijuana legalization in states that legalized marijuana versus those that had not.

Results. All but one of the primary studies supported the marijuana protection or harm reduction hypothesis. In aggregate and controlling for typically eight state-level covariates, risks associated with opioid use diminished by 7% (RR = 0.93, 95% CI 0.92, 0.94) after legalization; 7% after medical marijuana and 35% after recreational marijuana legalization ($p < .05$). Opioid prescriptions decreased by 8% and opioid overdose mortality diminished by 25% after medical marijuana legalization. Both were further diminished after recreational marijuana was legalized.

Conclusions. Their potential public health significances is clear, suggesting that such legislation profoundly affects the behaviors of physicians, patients and addicts in protective ways. However, all the studies, thus far, have been state-level, ecological analyses. Further multilevel and clinic-based analyses in ought to be accomplished to systematically replicate (or refute) this study's harm reduction estimates and to put them into clinical practice where indicated.

Background

Political rhetoric has abounded with equivocal evidence-based support to suggest that cannabis is a gateway to the use and ultimate, misuse and abuse of harder drugs [1–3]. Moreover, observational studies have suggested that cannabis use may be associated with the development of certain psychosocial and cognitive problems, particularly among youthful users [4–5]. Others have argued an alternative, marijuana protection hypothesis [6–7]. They theorize that primarily through informal substitutions of much less harmful cannabis (less dangerous withdrawal and essentially no overdose risk) [8] for myriad other substances, licit (alcohol, prescription opioids and other psychotropic drugs) and illicit (opioids and others), the harms of these harder drugs and alcohol are significantly reduced. This synthetic study aims to test this marijuana protection or substitution hypothesis.

A qualitative San Francisco-based study of 97 baby boomers, respectively, one-third and two-thirds of whom were medical or recreational cannabis users, provided developmental support for the substitution hypothesis [9]. In life history interviews participants prevalently reported substituting cannabis for alcohol, pharmaceuticals and illicit drugs. Their rationales included: "cannabis' low addiction risk," "less

adverse side effects" and even "its greater effectiveness in relieving symptoms like chronic pain." In preliminarily planning this study we engaged in a scope of the research on such substitutions [10], finding 12 quantitative surveys that all cross-validated the qualitative study. Their descriptive characteristics and outcomes are displayed in Table 1 [11–22]. They consistently found that medical marijuana patients and recreational users in Canada and the USA prevalently (approximately 25–50%) substituted cannabis for alcohol, opioids and other drugs. The pooled cannabis-opioid substitution prevalence estimate was the largest observed (53.2%). Additionally, opioids are arguably the most potentially harmful of these substances, and our preliminary scoping review found ample such evidence to synthesize. Therefore, this meta-analytic study will focus on marijuana protections from opioid-related harms.

Opioids are one of the most commonly prescribed drugs in America, their prescription rates having increased four-fold since 2000 [23–24]. Horrifyingly, nearly a million Americans have died from drug overdoses since then, seven of every ten of them due to opioids, and the per capita Canadian loss of life due to opioid overdoses have, tragically, been quite similar [25–26]. Contemporaneously, about half of the states and Canada legalized medical marijuana and more recently a few states and Canada legalized recreational marijuana. Such presents a naturalistic policy laboratory for testing the marijuana protection hypothesis. A research question is clearly implied: Are there significantly fewer opioid-related harms, morbid and mortal, in states and provinces that have legalized marijuana, ostensibly, where cannabis products are more readily available? Notwithstanding the historical difficulty of doing marijuana trials in North America, evidence has accumulated that marijuana is at least somewhat effective in alleviating the suffering associated with a host of illnesses both physical and mental [27–29]. It makes colloquial sense then that people with illnesses ranging from cancer or multiple sclerosis to anxiety or posttraumatic stress disorders would do all that they can to alleviate their own suffering, some perhaps using an available and relatively safe substance, indeed medicine, such as cannabis.

It is important to note two previous systematic reviews of the research on cannabis-based reductions of opioid-related harms [30–31]. These provided an important scholarly service as they systematically replicated a probable association. However, neither included a meta-analytic component. As this field's primary research is necessarily observational, observing associations between cannabis use and diminished opioid-related harms, we think an observational meta-analysis would add a very useful interpretive adjunct [32]. It will allow not only for the testing of cannabis use-opioid harm correlations, but also for the estimation of their sizes. Additionally, the previous reviews only assessed the effects of medical cannabis legalization. This meta-analytic review, therefore, will temporally update and analytically enhance the previous reviews while incorporating the effects of both medical and recreational cannabis legalization. It hypothesizes reduced opioid-related harms with medical and recreational cannabis legalization.

Methods

Selection of Studies

The following research or gray literature databases were searched between January 1, 2010 and January 1, 2020: *PubMed, Medline, CINAHL Complete, ProQuest Nursing and Allied Health Database, Social Services Abstracts, ProQuest Sociology Collection, EconLit, ProQuest Dissertations and Theses, Conference Proceedings Citation Indexes—Science and Social Sciences & Humanities*, and *Google Scholar*. Detailed keyword search schemes are summarized as follows: (cannabis or marijuana) and (medical or recreational) and (prescription or illicit opioids) and (legalization or laws or policies). Any longitudinal study of any opioid-related outcome that was accomplished anywhere on Canada or the USA was included. Also, the typically time series or similarly designed studies had to have provided some measure of control for potentially confounding variables through any type of mathematical or regression model. Searches were augmented with bibliographic reviews of retrieved studies. Searches of their authors were also performed. Two reviewers, with the support of an experienced academic librarian, independently searched for eligible studies and consensus decisions were reached after discussion. Eleven studies were so selected [33–43]

Meta-Analysis

Rate ratios, odds ratios or similar measures of association estimated primate study risk ratios or relative risks. Study associations (natural logarithm of their relative risks [RR] were weighted by their inverse variances, computed from estimated standard errors ($1/SE^2$) so that larger, more precise studies, weighed more. Such precision-weighted associations were then pooled using a weighted meta-regression model. Each study could contribute only once to the meta-analysis. If a primary study provided multiple interrelated cannabis-opioid outcomes, they would be pooled so that that study contributed one data point for the meta-analysis. Pooled RRs within 95% confidence intervals (CI) were calculated from primary study regression statistics as was a test of heterogeneity (c^2) and the planned comparison between medical and recreational cannabis legalization (z) [44–46]. The primary study outcomes were observed to be significantly heterogeneous; c^2 (10) = 185.88, $p < .05$. Therefore, the potential moderation of cannabis use-opioid harm associations by medical versus recreational cannabis legalization was tested and other potential moderations by study population or research design characteristics were explored. Study characteristics were abstracted independently from full primary study manuscripts by two reviewers, and after discussion their agreement was 100%. Meta-analytic hypotheses were independently tested and cross-validated by two analysts. Finally, for ease of interpretation, all RRs less than 1.00 indicate harm reductions while those greater than 1.00 indicate harm increments.

Results

Sample Description

Descriptive characteristics and outcomes of the 11 studies retrieved for this meta-analysis are displayed in Table 2. Respective, studies of medical and recreational marijuana legalization are displayed in the top and bottom of the table. Single, multiple and pooled opioid-related outcomes along with a select outcome among a specifically, most vulnerable population are displayed in the table's furthest right column. All

sampled USA populations between 1997 and 2017. Also, all were state-level or ecological analyses of generally, very large samples. The most typical time series or similarly designed studies used repeated measurements, at least one each prior to and after legalization, in states where marijuana was legalized compared to states where marijuana remained illegal. All the studies used multivariable mathematical or regression models to control the potential confounding influence of between 3 and 18 state-level covariates (median = 8). These were demographic and socioeconomic characteristics as well other drug or alcohol-relevant policies (e.g., prescription drug monitoring programs, medical marijuana dispensaries, pain management clinics, alcohol tax rates, etc.). Finally, it can be seen in the reference list that only one of the studies was an unpublished or gray literature report [41], while the remainder were peer-reviewed, published articles.

Meta-Analytic Findings

All except one [35] of the 11 primary studies supported the marijuana protection hypothesis, that is, they observed that marijuana legalization was associated with significant opioid-related harm reductions. In aggregate, risks associated with opioid use diminished by 7% (RR_{pooled} = 0.93, 95% CI 0.92, 0.94) after legalization; 7% after medical marijuana (RR_{pooled} = 0.93, 95% CI 0.92, 0.94) and 35% after subsequent recreational marijuana legalization (RR = 0.65, 95% CI 0.59, 0.73); z = 6.25, p < .05. No other population or research design characteristic was significantly moderating. Excluding the single counter-hypothetical finding, select pooled analyses suggested that opioid prescriptions decreased by 8% and opioid overdose mortality diminished by 25% after medical marijuana legalization, and that both were even further diminished after recreational marijuana use was legalized. Additionally, such significant and substantial harm reductions were replicated across other diverse outcomes: opioid-related motor vehicle crash fatalities (diminished by 21% overall and by 50% among drivers aged 21 to 40) and hospitalizations related to opioid dependence or abuse (decreased by 23%).

Adjunct Findings

In systematically searching for this meta-analysis' studies of opioid outcomes we serendipitously found some others of alcohol, other prescription medication and marijuana outcomes post-medical marijuana legalization. Alcohol-related crash fatalities were observed to decrease significantly (OR = 0.85) as did prescriptions for medications used for conditions most amenable to adjuvant cannabis treatment (ORs of 0.54 among Medicare and 0.91 among Medicaid enrollees) [47–49]. It is of no surprise that marijuana legalization is associated with more prevalent marijuana use, but any in-kind harms due to the more prevalent use of marijuana seem minuscule [50]. For example, only a 1% increase in marijuana-dependent hospitalizations were observed in Colorado after legalization (RR = 1.01, 95% CI 1.00, 1.02) [51]. Finally, even suggestive evidence of diminished homicides and suicides post-legalization has been observed [52–53].

Discussion

This meta-analysis found much support for the marijuana protection hypothesis [30–31] Consistent with previous systematic reviews, this meta-analytic review observed consistent inverse associations between cannabis legalization and opioid-related harms. Ten of the 11 primary studies analyzed, in fact 14 of 15 of their outcomes, supported the hypothesis. Such is based on the theory that with increased availability of legalized marijuana, and through formal and informal substitutions by physicians, patients, addicts and others, opioid related harms are reduced. The evidence in support of the marijuana protection hypothesis remains correlational, but we think that this study bolstered confidence in is causal interpretation in several ways. First, it systematically replicated the findings of two previous synthetic research groups. Second, ten primary research groups replicated significant cannabis use-opioid harm reduction correlations across diverse opioid-related outcomes: prescriptions, hospitalizations, motor vehicle crash fatalities and ultimately, overdose mortality. Third, the primary studies provided some measure control for potential time-dependent and numerous other confounds though their longitudinal designs and regressions. Fourth, it was systematically replicated by peer-reviewed published and unpublished or gray literature research so it probably cannot be explained by publication bias. Fifth and most importantly, this meta-analytic study was able to characterize the size of the observed cannabis-opioid harm reduction correlations. For example, it allowed for the central estimates that opioid prescription rates and overdose mortality rates decreased, respectively, by approximately 10% and 25% post-marijuana legalization. Given the commonness of opioid prescribing in North America as well as the horrible consequent loss of life due to opioid-related overdoses, such holds the promise of saving hundreds of thousands of lives over the next generation. At the population level, the cannabis-opioid correlations observed here and the preventive impacts that they represent may, we think, be deemed huge.

The marijuana protection hypothesis was not unequivocally supported, however. In fact, one study's findings were distinctly counter-hypothetical. Having extended this field's cohort to 2017, it observed a pattern of null findings, culminating in the estimation of an approximate 25% increase in opioid overdoses in 2017 [35]. Certainly, such an outlier cannot merely be dismissed. It extended a previous study's cohort by seven years [33], but did not otherwise "use the same methods" as claimed. Notably, the most recent, but counter-hypothetical study, attempted to control for more potential confounds than did the earlier study. One of these covariates was whether the states had legalized recreational marijuana (in assessing the impact of medical marijuana legalization). Given this study's finding of the incremental harm-reducing impact of recreational marijuana, typically after medical marijuana legalization, we think that such an adjustment may have overcontrolled for the key predictor—increased cannabis use consequent to its greater availability. We also think that the single counter-hypothetical finding of increased overdose mortality in 2017 could be explained by the contemporaneous prevalent intrusion of illicitly manufactured fentanyl into communities across North America [54–57]. That substance may have been so unpredictable and dangerous as to overwhelm any cannabis-based protections among prescription opioid patients and or vulnerable people such as addicts aiming to curb their abuse of opioids other than fentanyl. For now, we think the preponderance of correlational evidence supports the marijuana protection hypothesis. Clearly, better controlled designs that ultimately randomize some aspect of cannabis availability and use will be needed to resolve the debate.

Potential Limitations and Future Research Needs

As this field's primary studies measured their critical variables at the state-level (e.g., binary cannabis legalization and adjusted mortality rates) they are legitimately vulnerable to criticism related to the ecological fallacy. Admittedly, because their central unit of analysis was states they did not actually measure the specific behaviors of specific individuals. A now well-known epidemiologic principle contextualizes this criticism. "Perils are posed not only by the ecological fallacy, but also by the individualistic fallacy" [58]. In other words, personal behaviors are probably critically important here, but so too are social forces like the marijuana policies studied so far. This field's next generation seems to call logically for the multilevel study of personal behavior by social force interactions.

Relatedly, it has been noted that a number of interrelated policies have not been well accounted for yet among this field's primary studies [59]. They are other progressive or liberal policies that might also reduce opioid-related harms: methadone and buprenorphine made available to assist in the treatment of opioid dependence, more liberal treatment (other than imprisonment) of opioid users, and the ready community distribution of naloxone. These are policies that tend to be internally consistent and along with marijuana legalization generally fit a progressive political world view; views that are generally found in so-called blue, rather than red states. Because of their strong, perhaps nearly perfect intercorrelations, each of their specific independent effects may not be knowable. Still it would be very instructive to better understand the aggregate protective effects of such progressive policies. Future individual-state multilevel research might be even further advanced by incorporating the blue-red state dichotomy.

This meta-analytic study may have also been limited by its inability to specifically target vulnerable populations who may stand to benefit most from cannabis substitutions. For example, five of its primary studies sampled special populations such as Medicare or Medicaid enrollees or young people, but six of its primary studies were of the general population of adults. As one might expect the greatest cannabis-based reductions in opioid-related harms among such vulnerable populations as patients and or addicts seeking solutions, this study's observed associations indicative of harm reductions among the general population may be underestimates of the truth among vulnerable populations [60]. Alternatively, it stands to reason that cannabis is not only not a panacea for all medical ills, physical and mental, its more ready availability through legalization may increase harms among certain populations (e.g., young nonusers or addicts not seeking treatment). For example, one of the studies we previously cited as reporting the substitution of cannabis for their prescribed opioid medications (41%) also indicated that some of them used both, and nearly one of every ten such patients (8%) reported that they consequently increased their opioid usage.[22] Future research ought to more specifically link patient, addict and general population characteristics to outcomes, to better understand who stands to benefit or to be harmed most by cannabis legalization.

Relatedly and finally, we do not think it premature to consider cannabis-based harm reduction clinical interventions. The population-based evidence seems suggestive enough to begin explorations and ultimately trials perhaps among the most vulnerable people for whom other extant treatments have not

worked well: opioid addicts or chronic alcoholics who have experienced multiple treatment failures and or perhaps for whom traditional, abstinence-based treatments do not seem a good fit. We are unaware of a single systematic review of rigorously evaluated interventions, suggesting that little such clinical experimentation has yet been accomplished. We hope that the substantially loosened legal restrictions across Canada and parts of the USA will open the door to such a novel and potentially groundbreaking clinical research agenda.

Conclusions

The potential public health significance of cannabis legalization is clear. This synthesis strongly suggests that such legislation may profoundly affect the behaviors of certain physicians, patients and addicts in protective ways. However, all the studies, thus far, have been state-level, ecological analyses. Multilevel and clinic-based analyses in Canada and the USA are needed to systematically replicate (or refute) this study's opioid-related harm reduction estimates and to use them in practice when indicated with vulnerable populations who may benefit most.

Declarations

Ethics approval and consent to participate

This research did not involve human participants and was thus exempt from institutional board review.

Consent for publication

Not applicable

Availability of data and materials

Not Applicable

Competing Interests

The authors declare no competing interests

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Authors Contributions

I.K. MacMillan originated the study, led the writing and contributed to all aspects of the article.

K.M. Gorey contributed to the analysis and interpretation of the findings as well as the writing.

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