Original Paper

Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep

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Brian J Piper[1,2,3], Rebecca M DeKeuster[4,12], Monica L Beals[5], Catherine M Cobb[4,6], Corey A Burchman[7,8], Leah Perkinson[9], Shayne T Lynn[9], Stephanie D Nichols[10] and Alexander T Abess[11]

Abstract

A prior epidemiological study identified a reduction in opioid overdose deaths in US states that legalized medical cannabis (MC). One theory to explain this phenomenon is a potential substitution effect of MC for opioids. This study evaluated whether this substitution effect of MC for opioids also applies to other psychoactive medications. New England dispensary members (n = 1,513) completed an online survey about their medical history and MC experiences. Among respondents that regularly used opioids, over three-quarters (76.7%) indicated that they reduced their use since they started MC. This was significantly ($p < 0.0001$) greater than the patients that reduced their use of antidepressants (37.6%) or alcohol (42.0%). Approximately two-thirds of patients decreased their use of anti-anxiety (71.8%), migraine (66.7%), and sleep (65.2%) medications following MC which significantly ($p < 0.0001$) exceeded the reduction in antidepressants or alcohol use. The patient's spouse, family, and other friends were more likely to know about their MC use than was their primary care provider. In conclusion, a majority of patients reported using less opioids as well as fewer medications to treat anxiety, migraines, and sleep after initiating MC. A smaller portion used less antidepressants or alcohol. Additional research is needed to corroborate these self-reported, retrospective, cross-sectional findings using other data sources.

Keywords

Marijuana, opioids, stigma

Introduction

Appreciation of the therapeutic potential of medical cannabis (MC) has undergone a substantial resurgence in the past two decades. Part of this has resulted from a pronounced increase of fundamental neurochemistry knowledge including the identification of the cannabinoid (CB_1 and CB_2) receptors, endogenous cannabinoid neurotransmitters, and the enzymes that control their production and elimination. CB_1 is found in the central nervous system structures important for pain (cerebral cortex), movement (globus pallidus, caudate/putamen, cerebellum), reward (substantia nigra), and memory (hippocampus) (Hamill et al., 2009) and also in fat, the liver, pancreas, and skeletal muscle (Mackie, 2008). CB_2 is localized to immune cells (B and T-lymphocytes and macrophages) and in the spleen, tonsils, gastrointestinal tract (Guzman, 2003), as well as some immune cells in the brain (Pertwee, 2009). There have also been indications for the existence of a CB_3 receptor (Fride et al., 2003; Morales and Jagerovic, 2016). These G-protein coupled receptors are activated by endocannabinoids, retrograde signaling molecules naturally produced by the mammalian body including anandamide and 2-ararchidonylglycerol.

CB receptors can also be activated by plant-based cannabis as well as synthetic cannabinoids. Although plant-based cannabis is federally banned in the United States (US), synthetic cannabinoids are produced and Food and Drug Administration (FDA)-approved for some indications. For example, dronabinol (synthetic tetrahydrocannabinol; THC) is approved for cachexia and anorexia in AIDS patients and nausea and vomiting in

[1]Department of Basic Sciences, Geisinger Commonwealth School of Medicine, Scranton, PA, USA
[2]Department of Basic Pharmaceutical Sciences, Husson University School of Pharmacy, Bangor, ME, USA
[3]Neuroscience Program, Bowdoin College, Brunswick, ME, USA
[4]Wellness Connection of Maine, Gardiner, ME, USA
[5]Department of Psychologcal Sciences, Northern Arizona University, Flagstaff, AZ, USA
[6]Center for Wellness Leadership, Portland, ME, USA
[7]Department of Anesthesiology and Perioperative Medicine, Geisel School of Medicine at Dartmouth, Lebanon, NH, USA
[8]Dartmouth Hitchcock Medical Center, Lebanon, NH, USA
[9]Champlain Valley Dispensary, Burlington, VT, USA
[10]Department of Pharmacy Practice, Husson University School of Pharmacy, Bangor, ME, USA
[11]Maine Medical Center, Portland, ME, USA
[12]Calyx Concepts LLC, Sidney, ME, USA

Corresponding author:
Brian J Piper, Department of Basic Sciences, Geisinger Commonwealth School of Medicine, Scranton, PA 18509, USA.
Email: psy391@gmail.com

chemotherapy patients. Nabilone, a synthetic analogue of THC, is approved for chemotherapy induced nausea and vomiting for patients that do not respond to other antiemetics. However, there is some controversy regarding the efficacy of dronabinol and nabilone for these indications (Aggarwal, 2013; Lutge et al., 2013; Todaro, 2012). Possible explanations for the limited utility of currently available synthetic cannabinoids is that they employ single substances or are administered orally. The combination of multiple biologically active agents (e.g. cannabidiol, cannabichromene, or cannabigerol), not just THC, that are present in the cannabis plant (El Sohly and Slade, 2005) may result in interactive or synergistic effects that are not present with dronabinol or nabilone. Vaporized or smoked cannabis is also likely to produce a more rapid onset of effects than with drugs administered orally.

New England, USA has been greatly impacted by the national opioid epidemic. There were enough opioids dispensed from Maine pharmacies in 2014 to supply every person in the state with a 16-day supply (Piper et al., 2016). On average, more than five people overdosed in Maine each week in 2015 with the majority involving opioids (Sorg et al., 2016). US states with MC laws, including Maine and Vermont, had a 25% lower mean opioid overdose mortality rate relative to states without these laws (Bachhuber et al., 2014). The mechanistic plausibility of this epidemiological result is supported by preclinical research showing cross-talk between the cannabinoid and opioid neurotransmitter systems (Fattore et al., 2004). A large preclinical and clinical literature has documented synergistic effects of cannabinoids and opioids (Cichewicz, 2004; Karst et al., 2010; Pertwee, 2009). Further, several investigations have examined whether this is a substitution effect with MC replacing other pharmaceutical or recreational drugs (Boehnke et al., 2016; Bradford and Bradford, 2016; Lucas et al., 2016; Mikuriya, 2004; Nunberg et al., 2011; Reiman, 2007; Zaller et al., 2015). Approximately two-thirds of San Francisco patients reported using cannabis as a substitute for 'prescription drugs' but which individual prescription agents or classes was not specified (Reiman, 2009). As patients use MC for a variety of indications including pain, anxiety, headaches and to improve sleep (Aggarwal, 2013; Rhyne et al., 2016), the primary goal of this investigation was to determine whether there is a substitution effect for opioids or other pharmacotherapies.

MC is quasi-legal in the US, in that it is condoned in different forms by half of the states but prohibited at a federal level. Although MC use is fairly prevalent with an estimated 650,000 registered users (Fairman, 2016), MC is also associated with some negative connotations. A qualitative study conducted with British Columbia dispensary patients identified several themes including that MC users were concerned that they are viewed as 'potheads' by society in general but also by their health care providers, that their health care providers believed that they were making up symptoms in order to procure MC, and that if their coworkers or employers were aware of their MC use that this would negatively impact their status. These perceptions regarding perceived stigma associated with MC could impact communication with health care providers. Therefore, a secondary objective of this study was to evaluate the extent that patients communicate with their primary care provider (PCP) and others about their use of MC.

Methods

Participants

The participants (n = 1513) for this convenience sample were members of dispensaries in New England, USA, primarily from Maine (66.1%) but also Vermont (24.2%), and Rhode Island (9.7%).

Procedures

The online survey (Supplemental Appendix I) was created based on discussions with dispensary staff, patients, and the peer-reviewed literature (Supplementary Table 1). The intended sample size (⩾1000) was selected with the hope that this would allow for sufficient sampling of diverse chronic pain types (e.g. neuropathic, post-surgery) with the expectation that a moderate number of volunteers would have incomplete surveys. The study strove for inclusive terminology most likely to be recognized by non-medical survey respondents. Quantitative and qualitative items were entered into *SurveyMonkey*. Data collection was completed in several phases starting with an extensive pilot (n = 151 which were included in the final sample) to test the functionality of the survey in August, 2015 with the patients in Maine. After this was completed, a handful of items were added or refined, and a new link was emailed to the remaining Wellness Connection of Maine dispensary members. The recruitment email is contained in Supplementary Appendix II and up to two weekly reminders were given. Almost half (47.4%) of individuals in Maine that received and opened the invitation email completed the survey. As the state laws including qualifying conditions, or the conditions an individual must be diagnosed with in order to enroll into a state's MC program vary, slightly different versions of the survey were constructed for Vermont and Rhode Island. A total of two-fifths (40.8%) of Vermont members with an active email address participated. Data collection was completed in April, 2016. The survey was open although the number of unique IP addresses were noted based on guidelines for online research (Eysenbach, 2004). Branch logic was applied such that an affirmative answer to select items, for example 'Do you regularly take opiate pain medications (such as oxycodone, hydrocodone, buprenorphine, methadone, or others)?', would result in follow-up items, such as 'Have you noticed a change in the amount of opiate medication you need for the same pain relief since you began using medical cannabis?', with options of 'a lot more', 'slightly more', 'no change', 'slightly less', or 'a lot less'. The substitution effect was further examined regarding anxiety medications with four benzodiazepine examples: agents for sleep with Ambien and Benadryl® as examples; drugs for depression with Celexa, Cymbalta, and Effexor as examples; migraine; and alcohol (see also Appendix I). Stage-by-stage feedback regarding the percent complete (25%, 50%, 75%) was provided. The only item where completion was mandatory was the consent. Participation in this study was voluntary and a subset (12.5%) of respondents did not complete all 77 items including 23 with an open-ended component, (1–10 items/ 31 pages, mean = 2.5 ± 0.4 items/page) but all data, including from incomplete questionnaires, was analyzed. The informed consent (Appendix I) indicated that participation would take about 15 min, that the purpose of the study was to learn more about the benefits and risks of MC, and that 'only

the investigators involved in this study will have access to survey responses'. This study was approved by the Institutional Review Boards of Husson University, USA (Protocol 15SP01) and Bowdoin College, USA (8/25/15).

Data analysis

Quantitative statistical analysis was completed with SPSS, version 23.0 (IBM, Chicago, IL) and Figures were constructed with GraphPad Prism, version 6.00 (Graphpad, La Jolla, CA). Items that asked about sensitive material (e.g. income) included a 'prefer not to disclose' option. Respondents that elected this item were excluded from those item analyses. A p-value of 0.05 was considered statistically significant although analyses that met more conservative alpha criteria were also noted. Variability was expressed as ± standard error of the mean (SEM). The substitution effect was evaluated by collapsing the percent of respondents that reduced their use of a family of substances 'slightly' or 'a lot' and comparing this with the reduction among patients that took antidepressants. Antidepressants were selected as the comparison group because their daily dosing was viewed as less amenable to modification because they are not used on an 'as-needed' basis. Qualitative analysis of open-ended responses (e.g. What do you like most/least about medical cannabis?) was completed with QSR NVivo 11 (QSR International, Melbourne, Australia) and images were constructed with the online tool Wordle (http://www.wordle.net/). Settings include a maximum of 100 words, prefer alphabetized, ignore common English words, and make all words lowercase.

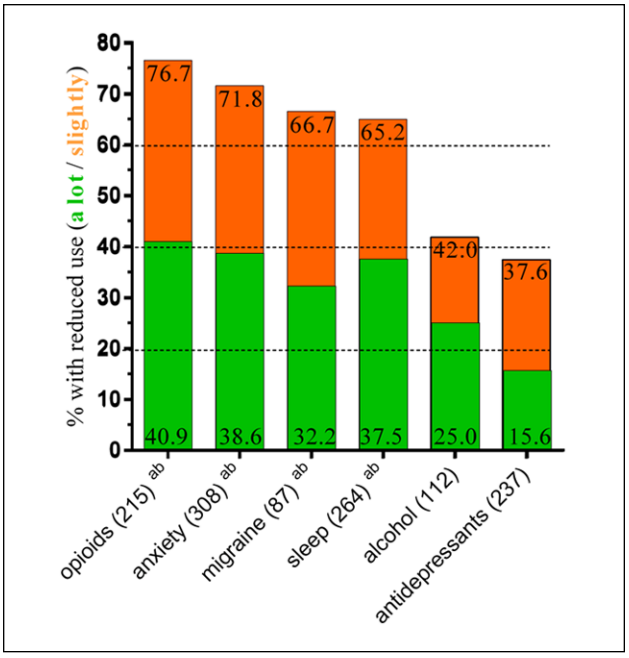

Figure 1. Percent of respondents with a reduction in opioid pain medications, agents for anxiety, migraine, drugs to improve sleep, alcohol consumption, and antidepressants. Total *N* that regularly used each group of drugs is in parentheses. Lower number on each bar is the % that reduced use 'a lot'. Upper number is the total that reduced use.
[a]$p \leqslant 0.0001$ versus antidepressants.
[b]$p \leqslant 0.0005$ versus alcohol.

Results

Participant characteristics

Most (95.6%) responses came from unique IP addresses. Slightly over half (52.9%) of respondents were female. The majority of members of the Maine dispensaries were male (60.0%) relative to only 46.3% of participants ($\chi^2(1) = 65.71$, $p < .0001$). Most (94.8%) respondents identified as white. In terms of educational attainment, 2.7% did not complete high school, 19.4% completed high school, 5.6% a vocational program, 32.6% had some college, 25.3% completed an undergraduate degree and 14.4% completed a professional or graduate degree. Approximately one-third (35.4%) were employed full-time, 27.3% were on disability, 14.0% were retired, 12.1% worked part-time, and over three-quarters (76.9%) were non-smokers of tobacco products. The average age was 48.0 ± 0.4 years (min = 18, max = 84), weight was 82.6 ± 0.6 kg, and body mass index (BMI) was 28.2 ± 0.2 (2.1% of respondents were underweight, 34.1% overweight, 31.8% obese). Certification to participate in their state's MC program was typically completed by a Doctor of Medicine (MD) (70.3%), doctor of osteopathic medicine (DO) (12.4%), or Nurse Practitioner (NP) (16.0%). The preferred delivery method was smoked joints for almost half (48.5%) followed by a vaporizer (22.3%), edibles (14.3%), tincture (10.8%), concentrates (3.4%), and topicals (0.7%). In response to 'How would you describe your use of cannabis?' with 11 options on a continuum from '100% recreational, 0% medical' to '0% recreational, 100% medical', the mean was 15.3 ± 0.5% recreational (or 84.7% medical) with respondents from Vermont (10.5 ± 0.9%) having lower ratings than Maine (16.5 ± 0.7%, $t(723.5) = 5.41$, $p < 0.0005$) or Rhode Island (18.9 ± 1.7%, $t(209.2) = 4.32$, $p < 0.0005$). Overall, two-thirds (63.6%) preferred *cannabis indica* dominant strains and the remainder (36.4%) *cannabis sativa* dominant strains.

Over two-thirds (70.4%) of patients in Maine and Rhode Island listed intractable or chronic pain followed by post-traumatic stress disorder (25.5%), severe muscle spasms (12.2%), or nausea (10.6%) as their qualifying condition. Although chronic pain was not a qualification to become a patient in Vermont's marijuana registry when the survey was administered, 69.0% of Vermont respondents indicated that they had been diagnosed by a medical professional with chronic pain. Among all patients with chronic pain, three-quarters (74.8%) had back/neck pain, one-third (34.5%) neuropathic, one-quarter (26.9%) reported pain following trauma or an injury, one-fifth (21.0%) with post-surgery or abdominal (17.7%) pain, while cancer (5.9%) and menstrual pain (4.2%) were less frequent. In response to 'How effective is medical cannabis in treating your symptoms or conditions?' with 11 options ranging from '0%, no relief at all' to '100%, complete relief', relief was greatest for the pain following trauma (77.9 ± 1.2%), followed by menstrual (77.5 ± 2.1%), abdominal (75.2 ± 1.2%), back/neck (73.0 ± 0.7%), neuropathic (72.3 ± 1.1%), cancer (75.8 ± 2.1%), and post-surgery (72.0 ± 1.3%).

Substitution effect

Among the subset of respondents that regularly used opioid pain medications (n = 215), Figure 1 shows that over three-quarters (76.7%) indicated that they reduced their use slightly or a lot

since they began using MC. This was significantly greater than the minority of patients that reduced their use of antidepressants (37.6%, $\chi^2(1) = 70.34$, $p \leqslant 0.0001$) or alcohol (42.0%, $\chi^2(1) = 70.34$, $p \leqslant 0.0001$). Approximately two-thirds or more of patients decreased their use of anti-anxiety, migraine, and sleep medications which significantly exceeded the decrease in antidepressants or alcohol (Figure 1). Note that more patients reported a reduction in depression medications (37.6%) than an increase (1.7%) following MC which was also true for alcohol (42.0% versus 0.0%; Supplemental Table 1).

Further analyses examined whether the substitution effect differed based on the type of chronic pain. Among the subset that used opioids, those that reduced their opioid medications 'slightly/a lot' was highest for pain following trauma/injury (89.5%), followed by neuropathic (81.5%), post-surgery (75.9%), back/neck (75.6%), and abdominal (70.0%) pain.

Communication

In response to 'How would you describe the way healthcare providers, in general, treat your use of medical cannabis?', a subset responded with 'unsupportive' (14.1%) or 'strongly unsupportive' (3.8%). Significantly fewer patients in Vermont felt unsupported or strongly unsupported (8.7%) than did those from Maine (21.2%, $\chi^2(1) = 26.17$, $p < 0.0001$) or Rhode Island (20.0%, $\chi^2(1) = 11.56$, $p < 0.001$). Over one-seventh (15.7%) of patient's PCPs were not informed of their use of MC although this was much lower in Vermont (3.9%) compared with either Rhode Island (16.2%, $\chi^2(1) = 20.82$, $p < 0.0001$) or Maine (20.9%, $\chi^2(1) = 48.40$, $p < 0.0001$). The PCP was less likely to know about their patient's MC use than was their spouse ($\chi^2(1) = 140.81$, $p < 0.0001$), immediate family ($\chi^2(1) = 7.38$, $p < 0.01$), or friends ($\chi^2(1) = 5.50$, $p < 0.05$) but more likely to know about MC than their employer ($\chi^2(1) = 440.91$, $p < 0.0001$, Figure 2).

Overall, one-quarter (24.5%) responded to 'Do you inform other healthcare providers (other specialists, pharmacists, clinics, etc.) of your medical cannabis use when providing information about other medications?' with 'sometimes' and one-seventh (15.5%) with 'no'. A greater portion of Vermont dispensary patients responded 'yes' about their communication (67.3%) with providers than did Maine (58.2%, $\chi^2(1) = 8.32$, $p < 0.005$) or Rhode Island (53.4%, %, $\chi^2(1) = 7.76$, $p \leqslant 0.005$) patients. Significantly fewer patients employed full-time (54.4%), compared with others (62.9%), consistently informed health care providers about their MC ($\chi^2(1) = 9.24$, $p < 0.005$). Less than half (42.7%) of unsupported patients consistently informed healthcare providers of their MC use versus two-thirds (64.8%) of patients that did not feel unsupported ($\chi^2(1) = 40.46$, $p < 0.0001$).

Qualitative

Figure 3(a) graphically represents what patients like most about MC and 'pain' and 'relief' were the most prominent words as well as sleep. Among 2549 responses, the theme medications emerged in 7.1%. Example responses included 'I have been able to drastically reduce my use of prescription opiates', 'It helps me cut down on pain meds', and 'Since I started using cannabis I came off of four psych meds'. Figure 3(b) depicts what patients like least about MC and economic factors ('cost', 'expense', 'price') followed by 'stigma' were the most frequent terms mentioned. Example responses included 'The cost is expensive for someone on a fixed income', 'The price, is pretty high (no pun intended)!', and 'I am made to feel like a criminal'.

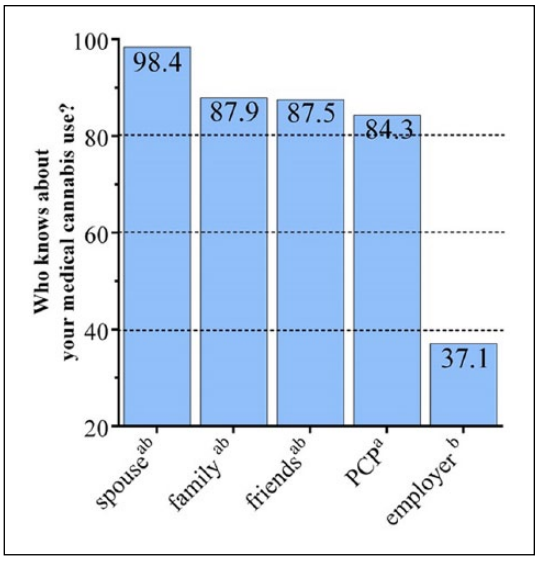

Figure 2. Percent of respondents whose spouse/significant other ($n = 1084$), immediate family ($n = 1311$), friends ($n = 1317$), PCP ($n = 1351$), or employer ($n = 606$) know about their use of medical cannabis.
[a]$p < 0.0001$ versus employer.
[b]$p < 0.05$ versus PCP.
PCP: primary care provider.

Discussion

The substitution effect has been a frequent topic of cross-sectional retrospective investigations of dispensary patients (Boehnke et al., 2016; Lucas et al., 2016; Mikuriya, 2004; Nunberg et al., 2011; Reiman, 2007, 2009; Zaller et al., 2015, Supplementary Table 1). This includes a sample of San Francisco area patients ($n = 130$) of which about three-quarters reported substitution of MC for 'prescription drugs, alcohol, or illicit drugs' (Reiman, 2007). A follow-up study from the same author but with a larger sample ($n = 350$) determined that two-thirds used cannabis as a substitute for 'prescription drugs' and 40% for alcohol (Reiman, 2009). The strengths of the present well-powered study are that the identified reduction in prescription and over the counter medications was robust and provided further detail on the multiple drug classes where patients report a decrease. These findings from our first objective corroborate a recent study of chronic pain patients in Michigan ($n = 183$) of which two-thirds discontinued their use of opioids, nonsteroidal anti-inflammatory drugs, or antidepressants among those that used these agents (Boehnke et al., 2016) and also an ecological report on opioid overdoses (Bachhuber et al., 2014). Together, these results suggest that MC may have efficacy for a variety of indications including not just pain control but also anxiety, sleep, decreasing alcohol consumption, and depression. Further clinical trials for these conditions is warranted.

Figure 3. Qualitative representation of responses to 'What do you like most (a) or least (b) about medical cannabis?'.

New England has been impacted by the national opioid epidemic (Simpatico, 2015; Sorg et al., 2016) and benzodiazepines use is extremely high, particularly among the elderly (Piper et al., 2016). While the overdose potential of opioids is well recognized, it is important to note that this risk is greatly magnified when combined with benzodiazepines (Dowell et al., 2016). The number needed to kill (NNK) secondary to opioid-related causes, after a mean of 2.6 years of opioid therapy, was found to be 550 (Frieden et al., 2016). Reduction of opioid daily dosage is important if complete opioid substitution cannot be attained. When patients were on 200 or more morphine mg equivalents (MMEs) per day, the NNK was 32 (Frieden et al., 2016). Therefore, on a population level, substitution of drugs with a more favorable adverse effect profile clearly has benefits. However, on an individual level, the addition of another psychotropic medication (cannabis) to an already complex regimen, may lead to additional and unpredictable efficacy and tolerability in a given patient. The relationship of cannabis therapeutics and its impact upon concurrent pharmacotherapies is an emerging science (Elikottil et al., 2009), especially as newer strains, concentrations, and modes of delivery of cannabis are developed and promulgated.

Importantly, the MC substitution effect was most pronounced for opioids, anxiolytics, migraine, and sleep promoting agents relative to antidepressants. This may be due to sample characteristics, in that the majority of participants had a history of chronic pain. Another factor is that agents for pain, anxiety, sleep, and headache may be taken on an as-needed basis whereas antidepressants are prescribed to be taken on an ongoing basis, often for an extended duration. Given that patients generally receive standing orders from their health care providers to take their antidepressants at a set daily dose, scaling back the dose may be impeded by the understanding that dosing changes with this particular class of medications needs to be overseen by the prescribing physician. As this MC substitution effect was identified with diverse drug classes and current evidence indicates that cannabinoids have a low risk of clinically significant drug interactions (Stout and Cimino, 2014), a pharmacokinetic explanation is unlikely and pharmacodynamic factors are much more plausible, particularly for opioids (Cichewicz, 2004; Karst et al., 2010; Pertwee, 2009). Future investigations should determine whether MC would allow for more effective taper and withdrawal from highly addictive opioid medications like heroin, oxycontin, or methadone (although see Epstein and Preston, 2015). Interestingly, there is evidence

indicating that cannabis may be useful to limit alcohol consumption (Mikuriya, 2004; Reiman, 2007, 2009, Supplementary Table 2) but this literature has been criticized for relying too heavily on retrospective designs and being susceptible to selection bias (Subbaraman, 2014). As existing pharmacotherapies for alcohol dependence produce only modest effects (Rösner et al., 2010a, 2010b), further preclinical and longitudinal clinical research examining MC combination therapies and MC in isolation for alcohol use disorders with a sample that is motivated to change their alcohol use is necessary. Similarly, some antidepressants, even those which are commonly utilized, have long therapeutic lags, and some have argued that their clinical significance is limited (Moncrieff and Kirsh, 2015; Stahl, 2013) so new pharmacotherapies, even those with small-to-moderate effect sizes, would be beneficial for nonresponders to other more standard interventions. The present findings should not be interpreted to indicate that the reduction in alcohol or antidepressants is insignificant. Importantly, states with MC laws showed a reduction in Medicare Part D spending of US$165.2 million per year. The number of doses filled each year per physician per day was reduced most prominently for pain (1826) followed by anxiety (562), nausea (541), seizures (486), sleep (362), with the least pronounced effects for depression (265) (Bradford and Bradford, 2016) which shows a broadly similar ranking as we identified. As pain, mood disorders, and sleep disruption are common comorbidities, these results may suggest a patient profile that may be most likely to benefit from MC or, at the very least, provide an impetus for further investigations with more rigorous experimental designs. Additional pharmacoeconomic research to identify the optimal MC dose, and route, which maximizes cost savings on other psychopharmacological agents is needed.

The dispensaries for MC distribution are largely disconnected from the rest of the healthcare infrastructure. They are not currently eligible to contribute data to prescription drug monitoring programs and information about MC is maintained outside the electronic medical records system. Although this is partially an understandable by-product of marijuana's current federal status as a Schedule I drug, there are clear implications of MC use for patient care and healthcare providers should be fully aware of which patients are using MC. There are stereotypes about marijuana users (Bottorff et al., 2013). A drug test that is positive for THC may have consequences for employment or driving privileges. Patients, especially those employed full-time, may be (rightfully or otherwise) concerned that disclosure of their MC to healthcare providers could be revealed to insurance companies and employers. Although patients were more likely to disclose their MC to their PCP than their employer, they were less likely to provide this information to their physician than to their spouse, family, or friends. If the legal status of cannabis changes (i.e. non-Schedule I), we are cautiously optimistic that this could facilitate communication regarding MC.

Some comments on the sample are noteworthy. There are certain groups where MC may not be appropriate including adolescents, pregnant women, and people with psychosis. As MC has been employed to stimulate appetite in HIV/AIDS patients, we were interested in the body weight of our primarily chronic pain participants. Perhaps surprisingly, our sample contained an equivalent portion with BMIs that met the criteria for overweight/obese (65.9%) as has been identified in the general adult US population (69.0%) (Ogden et al., 2014). Dispensary members are disproportionately male (Fairman, 2016) but the females slightly exceeded males as participants. Participants in this investigation were primarily (76.9%) non-smokers of cigarettes which is about the same as national data (79.2%) (Center for Behavioral Health Statistics and Quality, 2015). *Cannabis indica* strains generally have higher concentrations of THC, and THC to cannabidiol ratios, than *C. sativa* strains (Hillig and Mahlberg, 2004) and this sample preferred *C. indica* by a 2:1 ratio. This study was conducted with participants from three states, primarily Maine and Vermont but also including some from Rhode Island. As each state has their own MC system including their own qualifying conditions, samples obtained from one state (e.g. California) may not be to equivalent to those from another. Maine was the first state east of the Mississippi to legalize MC and recreational marijuana is condoned in a portion of the largest city in the state (South Portland). Even within New England, patients from Vermont believed their healthcare providers were more supportive of their decision to use MC and were more likely to share information about their MC use with other healthcare providers. One possibility for these state differences is that there have been more continuing education opportunities for providers regarding the risks and benefits of MC in Vermont. A retrospective design does not allow for inferences of causal relationship. It is possible that this self-selected patient group deciding to use MC may be motivated to live healthier. Therefore, the reported reduction in other pharmaceuticals and alcohol could be psychologically driven and not only, or exclusively, due to pharmacodynamic factors. Finally, MC patients were not queried about the substitution effect for specific agents (e.g. hydrocodone or buprenorphine) or doses. Additional prospective pharmacoepidemiological research (Haroutounian et al., 2015) employing electronic medical records is needed to provide this important information.

In conclusion, there are some limitations to this report and future directions. Some items that focused on the substitution effect targeted standard drug classes (e.g. pain and opioids, depression and antidepressants) whereas others, where multiple drug classes are commonly utilized (e.g. sleep and migraine), did not. The survey was designed to be interpretable by the general public and the data should be interpreted with this caveat in mind. Further research employing medical or pharmacy records is needed to further quantify changes following MC in the use of specific agents. This investigation identified a reduction in opioids when used primarily for chronic pain. Additional study is needed to determine whether the same magnitude of decrease would be identified in other populations (e.g. patients addicted to opioids attempting to wean off methadone or buprenorphine). Finally, this cross-sectional, retrospective online study is susceptible to a selection bias and these findings, although robust, may not generalize to patients outside of New England, who have limited internet access, or who procure their MC from outside of the dispensary systems and, although suggestive, should not form the basis for modifying clinical practice. Given the complex legal and cultural atmosphere surrounding this topic, further investigations on the substitution effect and medical communication which employ longitudinal designs could inform public policy.

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