American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 20, No 7 (July), 2019: pp 830–841
Available online at www.jpain.org and www.sciencedirect.com

Pills to Pot: Observational Analyses of Cannabis Substitution Among Medical Cannabis Users With Chronic Pain

Kevin F. Boehnke,* J. Ryan Scott,* Evangelos Litinas,† Suzanne Sisley,‡ David A. Williams,* and Daniel J. Clauw*

Anesthesiology Department, University of Michigan Medical School, Ann Arbor, Michigan., †Om of Medicine, Ann Arbor, Michigan., ‡Scottsdale Research Institute, Phoenix, Arizona.

Abstract: **Chronic pain is common, costly, and challenging to treat. Many individuals with chronic pain have turned to cannabis as an alternative form of pain management. We report results from an ongoing, online survey of medical cannabis users with chronic pain nationwide about how cannabis affects pain management, health, and pain medication use. We also examined whether and how these parameters were affected by concomitant recreational use, and duration of use (novice: <1 year vs experienced: ≥1 year). There were 1,321 participants (59% female, 54% ≥50 years old) who completed the survey. Consistent with other observational studies, approximately 80% reported substituting cannabis for traditional pain medications (53% for opioids, 22% for benzodiazepines), citing fewer side effects and better symptom management as their rationale for doing so. Medical-only users were older (52 vs 47 years old; $P < .0001$), less likely to drink alcohol (66% vs 79%, $P < .0001$), and more likely to be currently taking opioids (21% vs 11%, $P < .0001$) than users with a combined recreational and medical history. Compared with novice users, experienced users were more likely to be male (64% vs 58%; $P < .0001$), take no concomitant pain medications (43% vs 30%), and report improved health (74% vs 67%; $P = .004$) with use. Given that chronic pain is the most common reason for obtaining a medical cannabis license, these results highlight clinically important differences among the changing population of medical cannabis users. More research is needed to better understand effective pain management regimens for medical cannabis users.**

Perspective: This article presents results that confirm previous clinical studies suggesting that cannabis may be an effective analgesic and potential opioid substitute. Participants reported improved pain, health, and fewer side effects as rationale for substituting. This article highlights how use duration and intentions for use affect reported treatment and substitution effects.

Key words: *Cannabis, opioid substitute, chronic pain, side effects, pain management.*

Chronic pain affects >100 million Americans, and costs an estimated $635 billion dollars per year in the United States alone.[22] However, treating chronic pain is difficult, and many pharmacologic options only work in a subset of patients owing to inadequate pain relief or side effects that preclude use.[10,17] In the context of the ongoing opioid crisis, which claimed approximately 42,000 lives in 2016,[19] many individuals with chronic pain are seeking alternative medications for pain management. Cannabis is a promising analgesic for many chronic pain conditions, with recent meta-analyses of clinical trials suggesting that cannabis

Received October 18, 2018; Revised January 22, 2019; Accepted January 23, 2019.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Drs. Boehnke, Scott, and Williams declare no conflicts of interest. Dr. Clauw has consulted for Pfizer, Inc, Eli Lilly and Company, Tonix Pharmaceuticals, Aptinyx, Regeneron, IMC, and Intec. Dr. Litinas is Chief Medical Officer at and co-owner of Om of Medicine, a medical cannabis provisioning center in Ann Arbor, Michigan. Dr. Sisley has received funding from the Multidisciplinary Association for Psychedelic Studies and is a member of the Steering Committee/Entrepreneurship and Social Initiative Impact Advisor Board for the Lambert Center for the Study of Medicinal Cannabis and Hemp.

Address reprint requests to Kevin Boehnke, 24 Frank Lloyd Wright Drive, Ann Arbor, MI, 48106. E-mail: kboehnke@med.umich.edu

1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2019.01.010

or cannabinoids may be effective for chronic pain management,[46] although this effect was mostly seen in neuropathic pain.[30] Nationwide, medical cannabis legislation is associated with 25% fewer opioid overdose deaths in states with medical cannabis laws compared with those without,[2] with recent analyses suggesting that this effect is heavily driven by the presence of active medical cannabis dispensaries.[35] Further, states with medical cannabis laws have consistent decreases in opioid prescribing compared with those without, with this effect again strongest in states with active dispensaries.[6-8,45]

In 2016, we found that medical cannabis users in Michigan with chronic pain reported 64% lower opioid consumption, fewer side effects, and improved quality of life after using cannabis.[5] Other studies of medical cannabis users in the United States,[14,34,38,39] Canada,[4,25,26] and Israel[1,3,18] have found similar results, with users reporting improved pain, better quality of life, decreased opioid use, and in some cases, direct substitution of cannabis for opioids and other medications.[14,25,26,33] Although the rationale for substitution has been explored in 2 smaller studies[25,26] these studies have not focused on chronic pain. In addition, there are few reports of whether substitution patterns differ between subgroups of cannabis users. This finding is of special interest, given the rapidly changing cannabis landscape, in which there is increasing interest in cannabis among women and older individuals.[28]

In the present study, we build on this previous work, presenting results from an ongoing survey of medical cannabis patients throughout the United States. We queried whether medical cannabis patients substituted cannabis for other medications and their rationale for doing so, as well as whether pain or overall health had changed since using cannabis. We also examined differences between individuals who used cannabis solely for medical purposes versus those who used cannabis medically alone versus medically and recreationally, as well between individuals who had been using cannabis for <1 versus those who had been using cannabis for >1 year.

Methods

Adults (≥18 years old) who use cannabis for chronic pain in states with legal medical or recreational cannabis were invited to participate in an anonymous, online survey through the Qualtrics (Provo, UT) survey platform. Multiple dispensaries and cannabis certification clinics throughout the country sent this link to their client databases, as well as sharing the study information on social media. Participants were asked questions about the conditions and/or symptoms for which they used cannabis, health and pain changes since starting cannabis, current pain medication use, whether they had substituted cannabis for prescription pain medications (eg, opioids), alcohol use (nondrinker vs drinker), tobacco use (never, former, and current smoker), and sociodemographic information such as age, income, education, and relationship status. In addition, participants answered other questionnaires on cannabis use (administration routes, dosing frequency, etc), pain severity, anxiety, depression, and other measures that will be reported elsewhere. All surveys and study procedures were approved as an exempt study by the Institutional Review Board at the University of Michigan Medical School under protocol HUM00079724. Participants freely consented to participate in the study, were not compensated for participating, and were able to drop out at any time.

Participants and Eligibility

A total of 1,697 participants submitted responses. All submissions with missing demographic data were excluded (n = 322). Seven participants identified as transgender 7 (<1%) and were excluded from analysis owing to this extremely small sample size. Two subset analyses were conducted, where the population was split into 2 independent groups according to specific categorization (novice vs experienced cannabis users and medical only users vs combined medical and recreational users) based on responses to survey questions (described elsewhere in this article). Participants with missing responses to these grouping variables were excluded (n = 30) and discussed in detail elsewhere in this article. After all exclusions (n = 358, 21%), 1,321 participants were eligible for analysis.

Design and Categorization

The groupings of interest are described; in addition to these planned analyses, a post hoc analysis was performed and included an assessment of differences between those who substituted cannabis for a pain medication and those who did not.

Medical Cannabis Experience: Novice Versus Experienced Users

Participants were asked, "How long ago did you start using medical cannabis?" and were able to select: "less than 1 month ago; 1, 2, ...11 months ago; 1, 2, ...10 years ago; or more than 10 years ago." Participants were divided into 2 groups, namely, 1) those who had used medical cannabis for <1 year (n = 489 [37%]) and 2) those who started medical cannabis ≥1 year ago (n = 832 [63%]). Those who reported starting medical cannabis use within the past year were labeled novice cannabis users and those who had used for a year or more were considered experienced users. These labels are used throughout this article for ease of reading.

Type of Cannabis Use Over the Past Year: Medical-Only Versus Combined Medical and Recreational Use

Participants were asked about their cannabis use during the previous year and were given the following options: Did not use at all (n = 24 [2%]), recreationally only (n = 27 [2%]), medically only (designated MED;

n = 715 [52%]), or a combination of medically and recreationally (designated MEDREC; n = 606 [44%]). Participants who selected used recreationally only (n = 27), who did not answer 1 of the 2 categorization questions (n = 2), or who selected did not use but failed to indicate how long ago they started medical cannabis (n = 23) were all excluded from analyses.

Concomitant pain medications. Concomitant pain medications were assessed by asking participants to select all pain drug classes that they currently used, including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs, serotonin norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), gabapentanoids, benzodiazepines, or other medications. If participants selected other, they were directed to a free text question in which they could type the name of the other medication.

Alcohol and tobacco use. Participants were asked about whether they had ever used cigarettes, and were invited to choose from options that included, "I never smoke and have never smoked," "I used to smoke cigarettes, but I no longer do," "I smoke cigarettes some days," and "I smoke cigarettes every day." For alcohol consumption, participants were asked "How often do you have a drink containing alcohol?" Response options included: never, monthly or less, 2 to 4 times a month, 2 to 3 times a week, and ≥4 times a week. Those who never drank were categorized on nondrinkers, and those who ever drank were categorized as drinkers.

Substitution. Participants were asked whether they had substituted cannabis for any drug classes of pain medication. Substitution rationale was assessed by asking participants to rank their most important reasons for substituting cannabis for medication.[25] Participants could choose from the following: fewer adverse effects, fewer withdrawal effects, the ability to obtain cannabis versus (drug), greater social acceptance of cannabis, better symptom management with cannabis, and other. If other was selected as one of their choices, they were directed to a free text entry in which they could describe their substitution rationale.

Covariates

Age was reported as a continuous variable and used to report group mean ages. Owing to the large range of ages and for consistency with previous research,[21,24] age was converted to categorical groups. Also collected was annual household income, highest education level, relationship status, alcohol use, and smoking status. Concomitant pain medications were converted to a dichotomous (yes/no) for assessment as a covariate.

Statistical Analysis

Histogram and quantile−quantile plots were used to assess normality of continuous variable distribution. Univariate and multiple logistic regression were used to calculate unadjusted odds ratios (OR) and adjusted ORs (AOR), respectively, for the odds of substituting and for meeting group categorization (eg, experienced vs novice, and medical vs MEDREC user). Relevant statistically significant confounding variables were controlled for in multiple logistic regression (eg, sex, age, relationship status, income, education, smoking, alcohol use). The Pearson χ^2 test was used to assess differences in proportions for categorical variables and are reported as frequency (percent). Between-group differences in continuous variables were assessed by independent samples t-tests, which included Levine's test for assessment of variances for equality; the Mann−Whitney *U* test was used as a nonparametric alternative for ordinal and highly skewed data. Continuous variables are reported as mean ± standard deviation or median ± standard error. All tests were 2-tailed and significance was set at $P < .05$. All analysis was performed using IBM SPSS 24 (SPSS, Inc, Armonk, NY).

Results

This study population included 1,321 medical cannabis users (59% female) with a mean age of 50 ± 14 years (Table 1). The sample had greatest representation from California (20%), Maine (18%), Arizona (10%), and New Hampshire (9%). Nearly all participants (86%) reported having an associate's degree, some college or higher; one-half (49%) were married, and 62% reported an annual household income of <than $70,000. Of the respondents, 37% reported starting medical cannabis <1 year ago, compared with 63% who started >1 year ago. Participants also reported using cannabis for a large number of pain-related symptoms and mood disorders (n = 4,876 of 5,449 conditions/symptoms listed), which are detailed in Table 2. These include broad symptoms (eg, chronic pain), specific diagnoses (eg, rheumatoid arthritis), chronic pain conditions that fall under the definition of chronic overlapping pain conditions (eg, fibromyalgia), and mood disorders that are often comorbid with pain (eg, anxiety). More than one-half of the sample population reported using cannabis for anxiety (52%).

Participants reported current concomitant pain medications (Table 3): opioid analgesics (16%), benzodiazepines (13%), NSAIDs (31%), gabapentanoids (12%), disease-modifying antirheumatic drugs (3%), SNRIs (9%), SSRIs (12%), and other medications (16%, free-text entry). Of the participants, 38% reported no concomitant medication use. Eighty percent reported substituting cannabis for other medications, with a mean (standard deviation) of 2.0 ± 1.4 substitutions (range = 0−7, n = 2,136 total substitutions) per user. Among substitutors, females reported a significantly greater number of medication substitutions than males (t = 2.3, $P = .02$).

Substituting participants were asked to report how their medication consumption changed since they began using cannabis medically. A high rate of users reported complete cessation of medication since initiating cannabis use: opioids (72%), benzodiazepines (68%), NSAIDs (44%), gabapentanoids (74%), disease-modifying antirheumatic drugs (80%), SNRIs (78%), and

Table 1. Study Population and Demographics

	Total (N = 1,321)	Male (N = 540 [41%])	Female (N = 781 [59%])	χ^2	P Value
Age, y					
Mean ± SD	49.8 ± 13.9	49.1 ± 14.4	50.43 ± 13.5	1.7	.084
18–25	56 (4.2)	20 (3.7)	36 (4.6)	14.7	.005
26–34	164 (12.4)	83 (15.4)	81 (10.4)		
35–49	385 (29.2)	161 (29.9)	224 (28.7)		
50–64	501 (38.0)	178 (33.1)	323 (41.4)		
≥65	213 (16.1)	96 (17.8)	117 (15.0)		
Annual household income ($U.S.)					
<10,000	97 (7.5)	38 (7.2)	59 (7.7)	2.9	.723
10,000–39,999	393 (30.4)	156 (29.4)	237 (31.1)		
40,000–69,999	312 (24.1)	132 (24.9)	180 (23.6)		
70,000–99,999	237 (18.3)	96 (18.1)	141 (18.5)		
100,000–149,999	145 (11.2)	57 (10.7)	88 (11.5)		
>150,000	109 (8.4)	52 (9.8)	57 (7.5)		
Education (highest completed)					
Less than high school degree	12 (.9)	8 (1.5)	4 (.5)	9.5	.091
High school or GED	170 (12.9)	77 (14.3)	93 (11.9)		
Associates degree, technical school, or some college	576 (43.7)	235 (43.6)	341 (43.7)		
Bachelor's degree	324 (24.6)	138 (25.6)	186 (23.8)		
Master's degree	165 (12.5)	56 (10.4)	109 (14.0)		
Professional or doctoral degree	72 (5.5)	25 (4.6)	47 (6.0)		
Relationship status					
Single	233 (17.7)	98 (18.2)	135 (17.3)	9.7	.084
Married	651 (49.4)	276 (51.2)	375 (48.1)		
Living together	187 (14.2)	76 (14.1)	111 (14.2)		
In a relationship but not living together	67 (5.1)	27 (5.0)	40 (5.1)		
Divorced	137 (10.4)	54 (10.0)	83 (10.7)		
Widowed	43 (3.3)	8 (1.5)	35 (4.5)		
Alcohol intake					
Nondrinker	319 (27.9)	114 (24.3)	205 (30.5)	5.4	.021
Drinker	823 (72.1)	356 (75.7)	467 (69.5)		
Smoking history					
Never smoker	390 (34.1)	157 (33.3)	233 (34.7)	.5	.790
Former smoker	554 (48.5)	234 (49.7)	320 (47.6)		
Current smoker	199 (17.4)	80 (17.0)	119 (17.7)		
Residence					
California	274 (20.2)	99 (18.3)	175 (22.5)	23.8	.206
Maine	235 (17.8)	103 (19.1)	132 (16.9)		
Arizona	134 (10.1)	57 (10.6)	77 (9.9)		
New Hampshire	120 (9.1)	51 (9.4)	69 (8.9)		
Pennsylvania	99 (7.5)	48 (8.9)	51 (6.5)		
Nevada	62 (4.7)	27 (5.0)	35 (4.5)		
Canada	35 (2.6)	19 (3.5)	16 (2.1)		
Other states	362 (27.9)	136 (25.2)	226 (28.7)		
Experienced user (>1 year of use)	832 (63.0)	362 (67.0)	470 (60.2)	6.4	.011
Combined medical and recreational use (MEDREC)	606 (45.9)	285 (52.8)	321 (41.1)	17.5	<.0001

SD, standard deviation.
NOTE. Values are n (%) unless otherwise indicated.

SSRIs (80%). No more than 3% of substituting users in each medication class reported their medication use had increased either a little or a lot except DMARDs (5%) (Fig 1). The top reasons for medication substitution across medication classes were 1) fewer adverse effects from cannabis and 2) better symptom management with cannabis. Participants also reported significant improvements in pain (Fig 2) and health (Fig 3), with 88% reporting that their pain had improved a lot or a little, and 71% reporting that their health had improved a lot or a little since starting cannabis.

Participants who reported substituting were significantly younger (49.4 ± 13.6 years vs 52.1 ± 14.8 years; $P = .004$), and more likely to be female (61% vs 54%; $P = .025$) than nonsubstituting users. Females were 30% more likely to report substituting than males, although not significantly so (adjusted for: age, alcohol use, concomitant medication; AOR = 1.30, 95% CI = .88–1.94, $P = .085$). A significantly greater proportion of nonsubstituting cannabis users reported concomitant medication use (52% vs 34%; $P < .0001$). Since starting cannabis use medically, a significantly greater proportion of substitutors reported that pain had

Table 2. Types of Chronic Pain Conditions and Pain-Related Symptoms in the Study Population

Conditions or symptoms	*n (%)*
Acute pain	530 (40.1)
Severe and chronic pain	899 (68.1)
Chronic overlapping pain conditions	
Back pain	763 (57.8)
Migraine	282 (21.3)
Fibromyalgia	199 (15.1)
Irritable bowel disease or Crohn's disease	183 (13.8)
Temporomandibular joint disorder	84 (6.4)
Osteoarthritis	269 (20.4)
Rheumatoid arthritis	129 (9.8)
Comorbid mood disorders	
Anxiety	689 (52.2)
Post-traumatic stress disorder	324 (24.5)
Depression	525 (39.7)

NOTE. Although the entire population identified as having chronic pain of some kind, reported are the chronic pain conditions, symptoms, and mood disorders in the study population. The percentages add up to far greater than 100%, because participants reported using cannabis to manage or treat on average 4.5 conditions or symptoms.

decreased either a little or a lot ($\chi^2 = 12.4$, $P = .002$) and that their health had improved either a little or a lot ($\chi^2 = 8.7$, $P = .012$), compared with nonsubstituting users.

Novice Versus Experienced Cannabis Users

A significantly greater proportion of novice users were female than experienced users (64% vs 58%; $P = .005$; Table 4). Groups differed significantly in relationship status ($P = .023$), but did not differ by age ($P = .409$), education ($P = .06$), or income ($P = .64$). There were no differences in alcohol or tobacco consumption between groups ($P = .28$ and $P = .18$, respectively). Novice users were represented mostly by California (15%), Pennsylvania (17%), and New Hampshire (17%), and experienced users were represented by California (24%) and Maine (25%).

A significantly greater proportion of experienced users reported no concomitant pain medication use (43% vs 30%; $P < .0001$; Table 3). Novice users reported a significantly higher rate of concomitant opioids (22% vs 13%; $P < .0001$), benzodiazepines (17% vs 10%; $P < .0001$), gabapentanoids (16% vs 10%; $P < .0001$), NSAIDs (35% vs 28%; $P = .02$), and SNRIs (14% vs 7%; $P < .0001$) compared with experienced users. A significantly greater proportion of experienced users reported their health had improved since they had started medical cannabis (74% vs 67%; $P = .004$), although changes in pain ($P = .74$) did not differ significantly between groups.

The odds of substitution did not differ between novice and experienced users: (OR = 1.06, 95% CI = .73 - 1.52, $P = .71$) and (AOR = 1.05, 95% CI = .71 - 1.56, $P = .74$). However, among substitutors, experienced users reported a greater number of substitutions than novice users (mean $\pm$ standard deviation = 2.11 $\pm$ 1.43 vs 1.85 $\pm$ 1.43, respectively; $P = .001$). Experienced users reported a significantly higher rate of substitution for benzodiazepines (24% vs 17%; $P = .001$), NSAIDs (43% vs 37%; $P = .02$), and SSRIs

Table 3. Concomitant Medication Use Among the Study Population, Novice Versus Experienced Users and MED Versus MEDREC Users

Medication class	*Total (N = 1,321)*	*Male (N = 540)*	*Female (N = 781)*	χ^2	P *Value*	*Novice (N = 489)*	*Experienced (N = 832)*	χ^2	P *Value*	*MED (N = 715)*	*MEDREC (N = 606)*	χ^2	P *Value*
Opioid	207 (16.2%)	88 (16.9%)	119 (15.8%)	.2	.660	102 (21.7%)	105 (13.0%)	16.6	<.0001	141 (20.6%)	66 (11.2%)	20.4	<.0001
Benzodiazepine	163 (12.8%)	55 (10.5%)	108 (14.3%)	4.0	.045	81 (17.3%)	82 (10.2%)	13.4	<.0001	101 (14.7%)	62 (10.5%)	5.0	.025
NSAID	393 (30.8%)	165 (31.6%)	228 (30.3%)	.3	.613	163 (34.8%)	230 (28.5%)	5.4	.020	230 (33.5%)	163 (27.7%)	5.1	.024
Gabapentanoid	154 (12.1%)	51 (9.8%)	103 (13.7%)	.9	.332	77 (16.4%)	77 (9.6%)	13.2	<.0001	100 (14.6%)	54 (9.2%)	7.6	.006
DMARD	39 (3.1%)	7 (1.3%)	32 (4.2%)	4.8	.029	15 (3.2%)	24 (3.0%)	.1	.734	22 (3.2%)	17 (2.9%)	.1	.740
SNRI	118 (9.3%)	37 (7.1%)	81 (10.8%)	4.9	.026	64 (13.6%)	54 (6.7%)	17.5	<.0001	69 (10.1%)	49 (8.3%)	1.1	.285
SSRI	160 (12.5%)	41 (7.9%)	119 (15.8%)	17.8	<.0001	64 (13.6%)	96 (11.9%)	.8	.367	96 (14.0%)	64 (10.9%)	2.8	.093
Other	202 (15.8%)	80 (15.3%)	122 (16.2%)	.2	.674	73 (15.6%)	129 (16.0%)	.1	.836	112 (16.3%)	90 (15.3%)	.3	.610
No concurrent meds	500 (38.0%)	219 (41.0%)	281 (36.0%)	3.8	.053	142 (29.8%)	353 (43.4%)	23.4	<.0001	239 (34.3%)	256 (43.2%)	10.8	.001

Abbreviation: DMARD, disease-modifying antirheumatic drug.

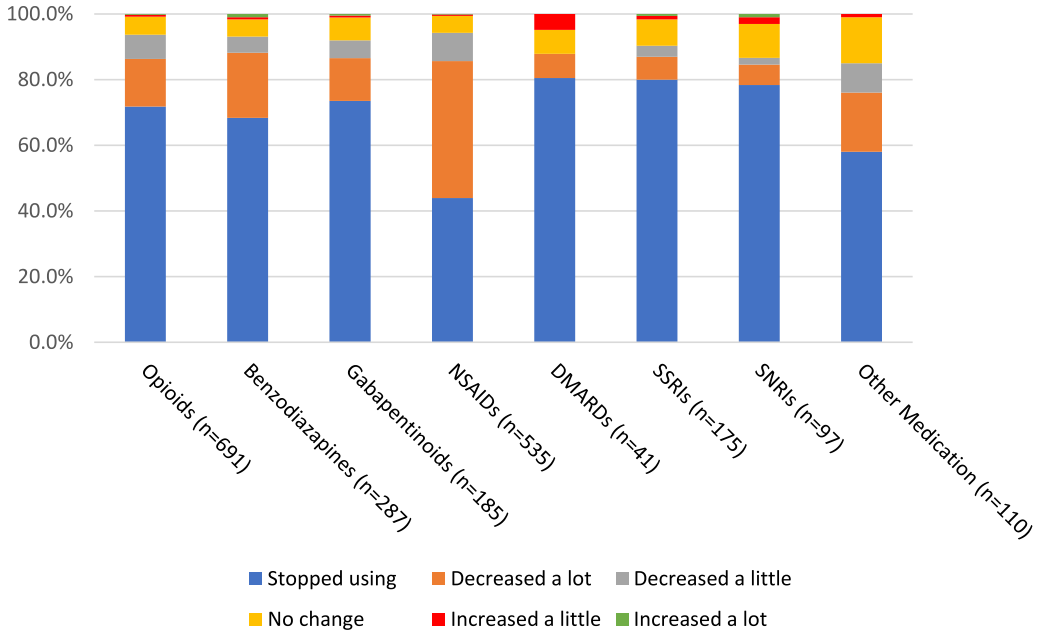

Fig 1. Substitution of cannabis for pain medication.

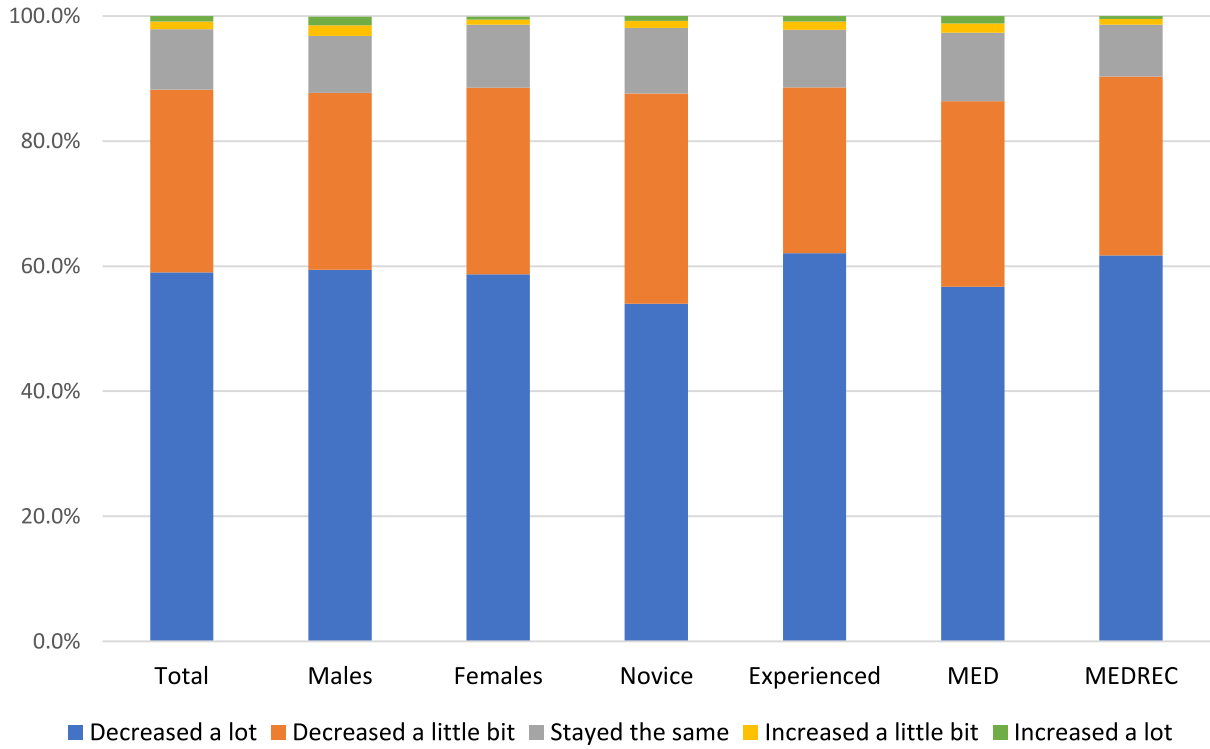

Fig 2. Changes in pain since starting cannabis.

(16% vs 8%; $P < .0001$) compared with novice users. As before, the top reasons for substitution for both groups were 1) fewer adverse side effects from cannabis and 2) better symptom management with cannabis than from (medication), for both groups and all medication classes.

Concomitant Recreational Use (MED vs MEDREC)

MEDREC users were significantly younger than nonrecreational users (46.9 ± 14.2 vs 52.3 ± 13.0 years; $\chi^2 = 7.1$, $P < .0001$; Table 4). The MEDREC group had a higher proportion of experienced users compared with the MED group (73.1% vs 54.4%; $P < .0001$). A significantly larger proportion of females were MED users compared with MEDREC users (64% vs 53%; $\chi^2 = 20.2$, $P < .0001$). Compared with males, females were 35% less likely to be MEDREC users: OR = .62 (95% CI = .47-.84, $P < .0001$); adjusted for age category and drinking status, and concomitant medication: AOR = .66 (95% CI = .48–.92, $P = .001$). Relationship status differed significantly ($P < .0001$), with MEDREC users reporting a

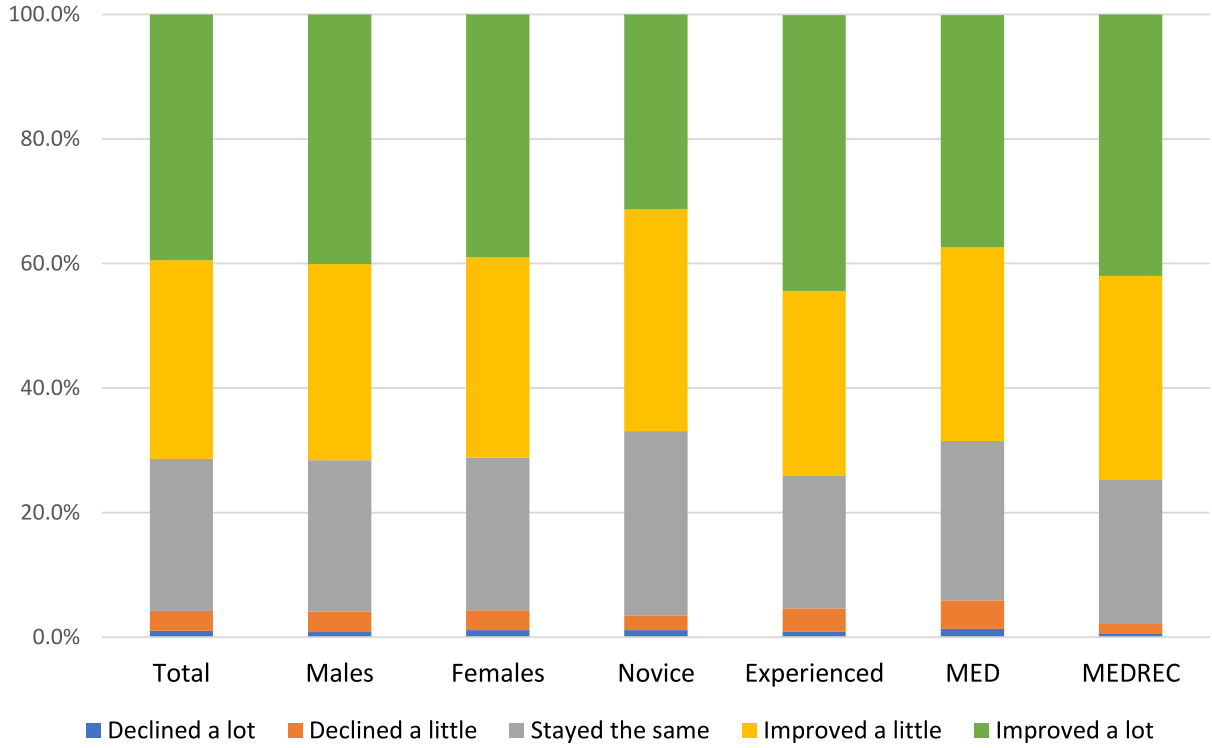

Fig 3. Changes in health since starting cannabis.

lower rate of marriage (43% vs 55%); education ($P = .22$) and income ($P = .15$) did not differ. A significantly greater proportion of MEDREC users reported alcohol use (79% vs 66%; $P < .0001$) as well as a higher proportion of never smokers (37% vs 30%) that did not attain statistical significance ($P = .054$). Geographically, MED users were represented mainly by California (17.8%), Maine (17%), New Hampshire (13%), and Arizona (17%), whereas MEDREC users were predominately from California (24%) and Maine (19%).

Compared with MED users, MEDREC users reported using fewer concomitant medications, both overall and in multiple medication classes including opioids, benzodiazepines, NSAIDS, and gabapentanoids (Table 3). There were no statistically significant differences between the number of medication substitutions between MED and MEDREC users ($P = .16$). After controlling for sex, age, relationship status, alcohol use, and smoking status, MED users were found to be 34% less likely to report substituting than MEDREC users (AOR = .66, 95% CI = .44-.98, $P = .006$). Compared with MED users, a significantly greater proportion of MEDREC users reported substituting overall ($\chi^2 = 5.7$; $P = .017$), as well as a greater proportion reporting substituting cannabis for opioids (57% vs 48%; $P = .002$) and gabapentanoids (17% vs 10%; $P < .0001$). A slightly higher proportion of MEDREC users reported a lot of improvement in their health (42% vs 37%; $P = .007$) compared with MED users, although the groups did not differ in changes in pain.

Discussion

Consistent with our previous report,[5] but with a much larger sample size (n = 1,321 vs n = 185), we found that medical cannabis users with chronic pain reported substituting cannabis for opioids and other pain medications, as well as reporting decreased pain and improved health after using cannabis. The 2 most common reasons for substitution were improved symptom management and fewer adverse side effects. These findings closely replicate findings in Canada, where Lucas et al[25] reported that 63% of 270 medical cannabis users substituted cannabis for prescription drugs, including opioids (32%) and benzodiazepines (16%) for similar reasons. Although other studies did not capture substitution rationale, their results have been remarkably consistent.[14,34,38,39,41] For example, 97% (n = 841) of medical cannabis users in California reported decreasing opioid consumption[38] and 77% of medical cannabis users with pain reporting reduced opioid use since starting medical cannabis.[33]

Longitudinal studies in Israel and New Mexico further our findings of cannabis being opioid sparing and reducing pain. In Israel, 3 recent open-label studies followed cannabis users for 6 months in clinical settings.[1,3,18] In the first, 176 participants using cannabis for intractable chronic pain reported significantly decreased pain and pain interference, and 32 of 73 had discontinued opioids at 6 months.[18] In the second, of 344 elderly individuals with cancer who used opioids at baseline, 36% discontinued use and 9.9% decreased their dosage.[3] In the third, conducted among 901 elderly individuals with mixed conditions, 114 discontinued opioid use and 29 reduced their dosage.[1] Participants reported a median 4-point decrease in pain on a 0- to 10-point visual analog scale, exceeding the typical 2-point threshold for clinically significant improvement.[16] This pattern of discontinuing or decreasing opioid use was also reported among habitual opioid

Table 4. Characteristics of Novice Versus Experienced Users and MED Versus MEDREC Users

	Novice (N = 489)	*Experienced (N = 832)*	χ^2	P *Value*	*MED (N = 715)*	*MEDREC (N = 606)*	χ^2	P *Value*
Sex, female	331 (64.0%)	481 (57.8%)	12.7	.0004	459 (64.0%)	321 (53.0%)	17.1	<.0001
Age, y								
Mean ± SD	50.2 (13.4)	49.6 (14.1)	.8	.409	52.3 (13.0)	46.9 (14.2)	7.1	<.0001
18–25	18 (3.7%)	38 (4.6%)	5.5	.244	11 (1.5%)	45 (7.4%)	56.7	<.0001
26–34	54 (11.1%)	110 (13.2%)			69 (9.7%)	95 (15.7%)		
35–49	151 (30.9%)	234 (28.2%)			193 (27.0%)	192 (31.7%)		
50–64	196 (40.2%)	305 (36.7%)			305 (42.7%)	196 (32.4%)		
≥65	69 (14.1%)	144 (17.3%)			136 (19.0%)	77 (12.7%)		
Annual household income ($U.S.)								
<10,000	37 (7.7%)	60 (7.4%)	3.4	.642	55 (7.9%)	42 (7.0%)	8.0	.154
10,000–39,999	137 (28.7%)	256 (31.4%)			207 (29.8%)	186 (31.1%)		
40,000–69,999	118 (24.7%)	194 (23.8%)			174 (25.0%)	138 (23.1%)		
70,000–99,999	85 (17.8%)	152 (18.7%)			136 (19.6%)	101 (16.9%)		
100,000–149,999	53 (11.1%)	92 (11.3%)			64 (9.2%)	81 (13.5%)		
>150,000	48 (10.0%)	61 (7.5%)			59 (8.5%)	50 (8.4%)		
Education (highest completed)								
Less than high school degree	7 (1.4%)	5 (.6%)	10.4	.065	7 (1.0%)	5 (0.8%)	7.0	.22
High school or GED	77 (15.8%)	93 (11.2%)			97 (13.6%)	73 (12.0%)		
Associates technical school or some college	207 (42.4%)	369 (44.4%)			317 (44.5%)	259 (42.7%)		
Bachelor's	107 (21.9%)	217 (26.1%)			156 (21.9%)	168 (27.7%)		
Master's	65 (13.3%)	100 (12.0%)			93 (13.0%)	72 (11.9%)		
Professional or doctoral	25 (5.1%)	47 (5.7%)			43 (6.0%)	29 (4.8%)		
Relationship status								
Single	83 (17.0%)	150 (18.1%)	13.1	.023	108 (15.2%)	125 (20.6%)	30.6	<.0001
Married	267 (54.6%)	384 (46.3%)			389 (54.6%)	262 (43.2%)		
Living together	55 (11.2%)	132 (15.9%)			84 (11.8%)	103 (17.0%)		
In a relationship but not living together	19 (3.9%)	48 (5.8%)			27 (3.8%)	40 (6.6%)		
Divorced	46 (9.4%)	91 (11.0%)			73 (10.3%)	64 (10.6%)		
Widowed	19 (3.9%)	24 (2.9%)			31 (4.4%)	12 (2.0%)		
Alcohol intake								
Nondrinker	132 (29.7%)	187 (26.8%)	1.2	.281	210 (33.7%)	109 (21.0%)	22.4	<.0001
Drinker	312 (70.3%)	511 (73.2%)			413 (66.3%)	410 (79.0%)		
Smoking history								
Never smoker	161 (36.3%)	229 (32.8%)	3.42	.181	231 (37.1%)	159 (30.5%)	5.8	.054
Former smoker	200 (45.0%)	354 (50.6%)			291 (46.8%)	263 (50.5%)		
Current smoker	83 (18.7%)	116 (16.6%)			100 (16.1%)	99 (19.0%)		
Residence								
California	72 (14.8%)	202 (24.3%)	292	<.0001	126 (17.8%)	148 (24.4%)	54.3	<.0001
Maine	29 (5.9%)	206 (24.8%)			118 (16.7%)	115 (19.0%)		
Arizona	46 (9.4%)	88 (10.6%)			89 (12.6%)	45 (7.4%)		
New Hampshire	84 (17.2%)	36 (4.3%)			90 (12.7%)	30 (5.0%)		
Pennsylvania	83 (17.0%)	16 (1.9%)			49 (6.9%)	49 (8.1%)		
Nevada	23 (4.7%)	39 (4.7%)			31 (4.4%)	30 (5.0%)		
Canada	9 (1.8%)	26 (3.1%)			16 (2.3%)	18 (3.0%)		
Other states	143 (29.2%)	219 (26.3%)			196 (26.6%)	171 (28.1%)		
Experienced user: duration of ≥1 year					389 (54.4%)	443 (73.1%)	49.2	<.0001
MEDREC	163 (33.3%)	443 (53.2%)	49.2	<.0001				

Abbreviation: SD, standard deviation.

users with chronic pain in New Mexico who enrolled in the state medical cannabis program.[42]

The current study and the consistent nature of these observational findings provide additional nuance to the ongoing debate about cannabis's analgesic value for chronic pain, as well as a potential substitute for opioids or other drugs. Indeed, they add granularity to the ecological associations between medical cannabis laws and opioid overdose decreases, highlighting a specific behavioral mechanism (intentionally substituting cannabis for opioids and other medications) that may be driving these statewide trends. Further, the noted differences between the subgroups (novice vs experienced, MEDREC vs MED) suggest distinct demographic and behavioral patterns that may reflect the changing nature of cannabis use nationwide, at least among users with chronic pain.

Our sample population had a higher proportion of females (59%) and older adults (54% over the age of 50). With the exception of the study in New England,[33] our sample population is quite different from other U.S.

studies on substitution, in which the populations were generally male and younger.[14,38,41] These differences likely reflect the focus of this study on chronic pain, which affects women and the elderly at a higher rate than other populations.[11,22] It may also reflect the changing demographics of medical cannabis users. As more states have legalized cannabis over time, perceptions of cannabis safety and its medical value have increased, and more seniors are interested in cannabis as a potential pain management tool when recommended by doctors.[23,28] In our sample, MED users tended to be older and female compared with MEDREC users. This finding is consistent with a recent analysis of a national sample, although that study aggregated users by medical use versus recreational use, rather than medical versus combined medical and recreational use.[24] Respondents who used cannabis medically in the national sample also had lower past year alcohol abuse,[24] similar to our study in which participants who used cannabis medically alone were more likely to not drink alcohol at all.

Our findings that MED users were both more likely to report substituting cannabis for pain medications and to currently take multiple concomitant medications suggest several potentially overlapping interpretations. These include: 1) intentional medical use and harm reduction by deliberately trying to improve health outcomes, as reflected in the substitution rationale; 2) the potential for polysubstance abuse (adding cannabis to several other medications), 3) higher medication requirements among MED users owing to more serious medical issues, reflecting an inability to stop taking certain medication classes, and 4) MED users are likely to be new to cannabis, so they have not had as much time to taper other medications. With regard to experience with cannabis, novice users were more likely than experienced users to be female and to take concomitant medications. This finding is consistent with trends of higher historical rates of recreational cannabis use among men than women,[12] suggesting that women may be a new and growing group of medicinal cannabis users. The higher concomitant medication use also makes intuitive sense, because it likely takes time to figure out a successful dosing regimen that would allow individuals to taper off medications. Although future longitudinal studies will help to parse out these differences, our reported association between medication substitutions and improved pain and health suggests that, within our cohort, many medical cannabis users with chronic pain are finding better pain management outcomes with cannabis than traditional pain medications.

We acknowledge the importance of approaching our substitution findings with caution, both because cannabis use carries numerous health risks (eg, respiratory issues from smoking, cognitive issues, impaired driving)[43,44] and because substitution trends have been contended. Olfson et al[32] examined longitudinal data on cannabis and opioid use from the National Epidemiologic Survey on Alcohol and Related Conditions, which conducted surveys from 2001 to 2002 (wave 1) and follow-up between 2004 and 2005 (wave 2). Cannabis use at wave 1 was associated with a 2.62 higher odds of nonmedical opioid use, as well as a 2.18 higher odds of opioid use disorder at wave 2. Nonmedical opioid use was amplified among individuals with pain. Similarly, a recent longitudinal study of individuals with chronic pain who were prescribed opioids in Australia also found that cannabis use was associated with more pain severity, pain interference, and anxiety, as well as no evidence of cannabis substitution for opioids.[9] Unfortunately, these studies were lacking in several critical ways. They did not distinguish between medical and recreational cannabis use—an important distinction, given that medical and recreational users exhibit different drug use characteristics, with medical users reporting lower prevalence of drug and alcohol use/abuse (excluding cannabis).[24] Further, the medical cannabis landscape in these studies is incongruent with the current cannabis environment, because medical cannabis was only recently legalized in Australia, and U.S. laws have changed substantially since the National Epidemiologic Survey on Alcohol and Related Conditions was conducted in 2005. Twenty-two additional states have legalized medical cannabis, and 9 have legalized recreational cannabis.[36] There are a wide variety of available cannabis products,[23] increasing education opportunities for physicians and patients,[27] and a much larger patient base (estimated to be >2.1 million),[37] as well as the ongoing opioid crisis, which has placed stricter guidelines on opioid prescribing practices[15] and led patients to seek alternatives. All that said, as with any analgesic, it is likely that cannabis is not appropriate to use in some individuals owing to the risk of addiction and abuse, as well as because it is not always effective for pain management. Determining which populations are most at risk as well as those who stand to benefit the most from cannabinoid therapies remains an important and ongoing research topic.

A logical next step would be to examine whether these substitution findings hold up in clinical trials, which would more rigorously test their validity. Unfortunately, to our knowledge no trials have been conducted that directly examine cannabis as an opioid substitute, although preclinical and a small, double-blind study suggested that cannabidiol may attenuate craving.[20] A recent systematic review also reported that preclinical (but not human) studies consistently showed synergistic analgesic effects between tetrahydrocannabinol and opioids.[29] Since that review was published, a clinical trial in healthy individuals showed that combining subanalgesic doses of oxycodone with smoked cannabis increased pain thresholds and pain tolerance.[13] This finding suggests that individuals using cannabis with opioids may be able to lower their opioid dosage to achieve the same analgesic effect and represents a potential mechanism for how individuals are finding similar pain relief while lowering their opioid dose.

It is also possible that participants are using cannabis to manage affective aspects of chronic pain or opioid tapering—such as anxiety or pain-related distress—that lead to perceptions of improved symptom management. Indeed, many participants in our survey frequently reported that they were using cannabis to manage anxiety, depression, and post-traumatic stress

disorder. Although there is little peer-reviewed evidence suggesting that cannabis is useful for these mood disorders (with some studies suggesting that cannabis use may worsen anxiety and depression among individuals with chronic pain),[40] there are currently multiple ongoing clinical trials to better understand cannabis's potential therapeutic value in this context.[31]

Limitations

Our study has several limitations. First, the cross-sectional design leaves us unable to examine changes over time, and we are forced to make inference based on retrospective self-report data. Second, our self-selected sample likely over-represents those who have found cannabis to be useful as medicine, because individuals who tried cannabis and found it to be unhelpful likely would not respond to this survey. Third, we are unable to know how many people were informed about this survey via the various recruitment methods, so we cannot accurately estimate the response rate. Fourth, we were unable to distinguish specific mechanisms or protocols of how medical cannabis users tapered off of opioids and other drugs. In this same vein, we did not analyze administration routes, cannabinoid preferences, or cannabinoid content of products that might be related to medication substitution as these are beyond the scope of this current investigation. Fifth, given the increased scrutiny applied to opioid prescribing in the context of the current opioid crisis, it is possible that tightened prescription standards lowered accessibility to opioids and thus contributed to the decreased opioid use reported in this study. However, it is unlikely that such standards were the chief driver behind the effect, because participants had a consistent rationale (reduced side effects, symptom management) for substituting cannabis for opioids. Sixth, we are uncertain whether participants who reported substituting cannabis for pain medications eventually went back to using those medications. Seventh, we acknowledge that our classification of cannabis users as MED versus MEDREC is limited, because definitions of recreational use may vary among individuals and because it is possible that one can use a substance medically but still obtain recreational effects (ie, the high from cannabinoids).

Conclusions

Cannabis's plausibility as an opioid substitute has been documented extensively in the observational literature, and our current study provides additional support for this hypothesis. However, rigorous trials that test reproducible tapering protocols or guidelines are lacking. Given that cannabis remains a Schedule I substance under the Controlled Substances Act, it is unlikely that many cannabis clinical trials will fill in this gap in the near future. However, there are many such protocols currently available but untested in the scientific literature (eg, Healer.com.). Most follow similar guidelines, including starting at low doses and slowly increasing until desired pain relief is achieved, combining use of cannabidiol and tetrahydrocannabinol, and using different administration routes for breakthrough pain/craving and long-term pain relief. Rigorous, randomized observational studies using standardized, validated measures of pain (such as the Brief Pain Inventory) should follow participants using such protocols to establish dosing targets for effective cannabis analgesia and substitution.

Acknowledgments

We are extremely grateful to the medical cannabis patients who generously donated their time to participate in this study. We also are grateful for the many clinics (especially OMNI Medical Services), physicians (especially Dustin Sulak, MD, of Healer.com), and the many cannabis dispensaries who aided with study recruitment. Finally, we thank David Koyle, Louis Johnson, Ryan Lakin, and Adrian Devitt-Lee for their thoughtful contributions to this study.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.01.010.

References

1. Abuhasira R, Schleider LB, Mechoulam R, Novack V: Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. Eur J Intern Med 49:44-50, 2018

2. Bachhuber MA, Saloner B, Cunningham CO, Barry CL: Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med 174:1668-1673, 2014

3. Bar-Lev Schleider L, Mechoulam R, Lederman V, Hilou M, Lencovsky O, Betzalel O, Shbiro L, Novack V: Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. Eur J Intern Med 49:37-43, 2018

4. Baron EP, Lucas P, Eades J, Hogue O: Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain 19:37, 2018

5. Boehnke KF, Litinas E, Clauw DJ: 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, 2016

6. Bradford AC, Bradford WD: Medical marijuana laws reduce prescription medication use in Medicare Part D. Health Aff (Millwood) 35:1230-1236, 2016

7. Bradford AC, Bradford WD: Medical marijuana laws may be associated with a decline in the number of pre-

scriptions for Medicaid enrollees. Health Aff (Millwood) 36:945-951, 2017

8. Bradford AC, Bradford WD, Abraham A, Bagwell Adams G: Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. JAMA Intern Med 178:667-672, 2018

9. Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, Nielsen S, Cohen M, Chan G, Mattick RP, Blyth F, Shanahan M, Dobbins T, Farrell M, Degenhardt L: Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: Findings from a 4-year prospective cohort study. Lancet Public Health 3:E341-E350, 2018

10. Clauw DJ: Pain management: Fibromyalgia drugs are 'as good as it gets' in chronic pain. Nat Rev Rheumatol 6:439-440, 2010

11. Clauw DJ: Fibromyalgia: A clinical review. JAMA 311:1547-1555, 2014

12. Compton WM, Han B, Jones CM, Blanco C, Hughes A: Marijuana use and use disorders in adults in the USA, 2002-14: Analysis of annual cross-sectional surveys. Lancet Psychiatr 3:954-964, 2016

13. Cooper ZD, Bedi G, Ramesh D, Balter R, Comer SD, Haney M: Impact of co-administration of oxycodone and smoked cannabis on analgesia and abuse liability. Neuropsychopharmacology 43:2046-2055, 2018

14. Corroon Jr. JM, Mischley LK, Sexton M: Cannabis as a substitute for prescription drugs - a cross-sectional study. J Pain Res 10:989-998, 2017

15. Dowell D, Haegerich TM, Chou R: CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA 315:1624-1645, 2016

16. Farrar JT, Young Jr. JP, LaMoreaux L, Werth JL, Poole RM: Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94:149-158, 2001

17. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M: Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 14:162-173, 2015

18. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, Davidson E: The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: A prospective open-label study. Clin J Pain 32:1036-1043, 2016

19. Hedegaard H, Warner M, Minino AM: Drug overdose deaths in the United States, 1999-2016. NCHS Data Brief (294):1-8

20. Hurd YL, Yoon M, Manini AF, Hernandez S, Olmedo R, Ostman M, Jutras-Aswad D: Early phase in the development of cannabidiol as a treatment for addiction: Opioid relapse takes initial center stage. Neurotherapeutics 12:807-815, 2015

21. Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert AS, Walton M, Blow FC: Characteristics of adults seeking medical marijuana certification. Drug Alcohol Depend 132:654-659, 2013

22. Institute of Medicine. Relieving pain in America: A blueprint for transforming prevention, care, education, and research. Washington, DC: The National Academies Press, 2011

23. Keyhani S, Steigerwald S, Ishida J, Vali M, Cerda M, Hasin D, Dollinger C, Yoo SR, Cohen BE: Risks and benefits of marijuana use: A national survey of U.S. adults. Ann Intern Med 169:282-290, 2018

24. Lin LA, Ilgen MA, Jannausch M, Bohnert KM: Comparing adults who use cannabis medically with those who use recreationally: Results from a national sample. Addict Behav 61:99-103, 2016

25. Lucas P, Walsh Z: 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, 2017

26. Lucas P, Walsh Z, Crosby K, Callaway R, Belle-Isle L, Kay R, Capler R, Holtzman S: Substituting cannabis for prescription drugs, alcohol and other substances among medical cannabis patients: The impact of contextual factors. Drug Alcohol Rev 35:326-333, 2016

27. MacCallum CA, Russo EB: Practical considerations in medical cannabis administration and dosing. Eur J Intern Med 49:12-19, 2018

28. Malani P, Singer D, Solway E, Kirch M, Clark S: Older adults' perspectives on medical marijuana. University of Michigan National Poll on Healthy Aging. April 2018. Available at: http://hdl.handle.net/2027.42/143211

29. Nielsen S, Sabioni P, Trigo JM, Ware MA, Betz-Stablein BD, Murnion B, Lintzeris N, Khor KE, Farrell M, Smith A, Le Foll B: Opioid-sparing effect of cannabinoids: A systematic review and meta-analysis. Neuropsychopharmacology 42:1752-1765, 2017

30. Nugent SM, Morasco BJ, O'Neil ME, Freeman M, Low A, Kondo K, Elven C, Zakher B, Motu'apuaka M, Paynter R, Kansagara D: The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. Ann Intern Med 167:319-331, 2017

31. O'Neil ME, Nugent SM, Morasco BJ, Freeman M, Low A, Kondo K, Zakher B, Elven C, Motu M, Paynter R: Benefits and harms of plant-based cannabis for posttraumatic stress disorder. Ann Intern Med 167:332-340, 2017

32. Olfson M, Wall MM, Liu SM, Blanco C: Cannabis use and risk of prescription opioid use disorder in the United States. Am J Psychiatry 175:47-53, 2018

33. Piper BJ, Beals ML, Abess AT, Nichols SD, Martin MW, Cobb CM, DeKeuster RM: Chronic pain patients' perspectives of medical cannabis. Pain 158:1373-1379, 2017

34. Piper BJ, DeKeuster RM, Beals ML, Cobb CM, Burchman CA, Perkinson L, Lynn ST, Nichols SD, Abess AT: Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. J Psychopharmacol 31:569-575, 2017

35. Powell D, Pacula RL, Jacobson M: Do medical marijuana laws reduce addictions and deaths related to pain killers. J Health Econ 58:29-42, 2015

36. Available at: Procon.org. 31 legal medical marijuana states and DC. 2018. Accessed October 22, 2018

37. Available at: Procon.org. Number of legal medical marijuana patients. 2018. Accessed October 22, 2018

38. Reiman A, Welty M, Solomon P: Cannabis as a substitute for opioid-based pain medication: Patient self-report. Cannabis Cannabinoid Res 2:160-166, 2017

39. Sexton M, Cuttler C, Finnell JS, Mischley LK: A cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. Cannabis Cannabinoid Res 1:131-138, 2016

40. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, (DC): National Academies Press, 2017

41. Troutt WD, DiDonato MD: Medical cannabis in Arizona: Patient characteristics, perceptions, and impressions of medical cannabis legalization. J Psychoactive Drugs 47:259-266, 2015

42. Vigil JM, Stith SS, Adams IM, Reeve AP: Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. PLoS One 12, 2017. e0187795-e0187795

43. Volkow ND, Baler RD, Compton WM, Weiss SR: Adverse health effects of marijuana use. N Engl J Med 370:2219-2227, 2014

44. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R, Bloomfield MAP, Curran HV, Baler R: Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: A review. JAMA Psychiatry 73:292-297, 2016

45. Wen H, Hockenberry JM: Association of medical and adult-use marijuana laws with opioid prescribing for Medicaid enrollees. JAMA Intern Med 178:673-679, 2018

46. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J: Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 313:2456-2473, 2015