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Cannabis Use Preferences and Decision-making Among a Cross-sectional Cohort of Medical Cannabis Patients with Chronic Pain

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ABSTRACT: Cannabis is commonly used to manage chronic pain, but cannabis use patterns among individuals with chronic pain, has not been well-characterized. We report cannabinoid, administration route, and product selection preferences among medical cannabis users with chronic pain from an ongoing, online survey. We also examined whether these preferences are affected by differences in sex, intentions behind use (medical only [MED] vs medical + recreational [MEDREC]), and experience with cannabis (novice: <1 year vs experienced: ≥1 year). The survey was completed by 1,321 participants (59% female) 76.5% of whom used cannabis every day. 93.4% used 2 or more administration routes and 72.5% used 3 or more. Female, MED, and novice users were less likely to smoke or vaporize (all $P < .0001$), but more likely to rank edibles, tinctures, and topicals as a first-choice administration route than their counterparts. Female and MED users also preferred low THC: high cannabidiol ratios significantly more than their counterparts. Overall, only 2.6% of participants selected cannabis products with input from a medical professional, although 54.9% relied on advice from dispensary employees. More male, MEDREC, and experienced users selected products based on factors that reflected greater comfort with cannabis (eg, smell, visual properties, cannabis variety). The wide variability in cannabis use among these different groups indicates the need for further research to investigate how specific use routines relate to clinical outcomes.

Perspective: Medical cannabis users with chronic pain show distinct differences in cannabinoid preferences and administration associated with user sex, intentions behind use, and experience with cannabis. This article highlights the wide variability in cannabis preferences among medical cannabis users with chronic pain, which may be relevant for clinical outcomes.

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Key words: Cannabis, cannabis use routine, CBD, THC, administration route.

Since 1996, the legality of cannabis in the United States has changed dramatically. While it remains a Schedule I substance (i.e., no accepted medical use, high risk of abuse) under the Controlled Substances Act, cannabis is now legal in 33 states and Washington DC for medical purposes, as well as in 10 states and Washington DC for recreational use.[39] According to estimates from state medical cannabis registry data, there are now >2.1 million legal medical cannabis patients nationwide,[40] and we recently reported that 62% of qualifying conditions in medical cannabis state registries are for chronic pain.[4] This is

unsurprising, given that ~100 million Americans have chronic pain,[27] and that many drugs for chronic pain have limited efficacy and challenging side effect profiles.[18,23,27] Ecological studies have reported associations between the presence of medical cannabis legislation and a variety of outcomes, including decreased opioid overdose deaths,[2,38] hospitalizations,[45] and pain medication prescriptions,[8-10] with these effects enhanced by the presence of active, operating cannabis dispensaries. Similarly, observational studies conducted in many states in the US[5,15,16,37,41,44,48,52,53] as well as in Canada[3,30,31] and Israel[1,21,43] have complemented these findings, with medical cannabis users reporting improved pain, decreased side effects, and substituting cannabis for opioids and other medications.

However, much uncertainty remains about *how* medical cannabis patients use for pain management. This question is of special importance, given increasing use of cannabis for pain despite underwhelming results from cannabinoid clinical trials for chronic pain, in which participants typically report mild and clinically insignificant pain relief but significant side effects.[34,49,59] However, the rigidity of clinical trial dosing does not reflect the reality of medical cannabis patients, who often have access to numerous cannabis products, making it difficult to make practical inference from clinical trial data.[47]

A recent nationally representative survey demonstrated that cannabis users use multiple administration routes; 14.6% of the population used cannabis, with 12.9% smoking, 6% using edibles, 4.7% vaporizing, 1.9% taking concentrates, and 0.8% using topically applied products.[46] However, this study was not focused on medical cannabis users, and whether such variability occurs in medical users is unknown. To our knowledge, no studies on medical cannabis users have comprehensively examined cannabis use preferences, although some collected data on the most commonly used administration route,[37,44] cannabis variety preferences (eg, indica vs sativa),[7,13] or cannabinoids preferences (ie, tetrahydrocannabinol [THC] and cannabidiol [CBD]).[44] This last point is of special importance due to the greatly disparate effects of these cannabinoids. While known to have analgesic properties, THC is psychoactive and thought to be responsible for most of the abuse/addiction potential of cannabis.[34,54] In contrast, CBD has little abuse potential, reflected by the consistently favorable safety profile reported in clinical studies[26] and the recent classification of Epidiolex (a CBD-based product) as Schedule V by the Drug Enforcement Administration. In addition, CBD may increase THC's therapeutic window and decrease adverse side effects, so we would expect to see differences in use patterns between individuals seeking the cannabis "high" versus those seeking medical effects.[32]

Thus, the objective of the current study was to provide a fuller characterization of cannabis use and decision-making around cannabis products among an ongoing nationwide cross-sectional survey of medical cannabis users with chronic pain. We asked participants questions related to cannabinoid and cannabis variety preferences, frequency of use, administration routes, and decision about product choices. Consistent with our previous report from this cohort, we examined differences in use patterns between: 1) males and females; 2) participants who used cannabis solely for medical purposes (MED) and those who used cannabis both medically and recreationally (MEDREC); and 3) novice (<1 year of use) and experienced (≥1 year of use). We hypothesized that females, MED participants, and novice participants would be less likely to smoke and would prefer products with more CBD than males, MEDREC participants, and experienced participants.

Methods

Design and Categorization

Adults (≥18 years old) who use cannabis medically for chronic pain in states with legal medical or recreational cannabis were invited to participate in an uncompensated, anonymous, online survey using a password protected link through the Qualtrics (Provo, UT) survey platform between January and August 2018. Dispensaries and cannabis certification clinics throughout the country sent the survey link and password to their client databases or shared study information on social media platforms. All study procedures were approved under protocol HUM00079724 by the Institutional Review Board at the University of Michigan Medical School. Participants freely consented to participate and could drop out at any time.

Subgroups

As in our previous analysis,[6] we assessed differences between men and women, individuals who used cannabis solely for medical purposes in the past year (designated MED, n = 715, 54%) and those who used cannabis both recreationally and medically in the past year (designated MEDREC, n = 606, 46%). Significant clinical, behavioral, and cannabis consumption differences have been reported between MED and MEDREC users elsewhere in the scientific literature, so we chose to use these categories here as well.[6,29,50,55] We also assessed differences between novice (<1 year of use, n = 489, 37%) and experienced participants (≥1 year of use, n = 832, 63%).

Measures

Frequency of Cannabis Use

We asked participants about cannabis use frequency, both in days per week (1−7 days) and times per day (once, twice, three, four, five or more times).

Cannabinoid Content, Cannabis Variety

1) To determine preferred cannabis variety, participants were asked, "What kind of cannabis do you

typically use to treat your condition?", with the options of indica, sativa, sativa/indica blends, and "don't know," Indicas are typically described as having relaxing or sedating effects, while sativas are often characterized as being "uplifting and energetic."[36]

2) To gauge cannabinoid preferences, participants were asked the following question: "Cannabis contains multiple active ingredients, such as THC (Tetrahydrocannabinol) and CBD (Cannabidiol). Do you prefer a certain ratio of THC to CBD?" If yes was selected, participants were asked to choose from a list of cannabinoid ratios, including high THC: low CBD, high THC: high CBD, low THC: high CBD, low THC: low CBD, only THC, only CBD, or other. If participants selected "Other," they were directed to a free-text entry window. Our interpretation of the responses was as follows: selection of high THC: high CBD indicates that the participant uses a large (subjective) quantity of both THC and CBD, selection of low THC: high CBD indicates that the participant uses a large (subjective) quantity of CBD and a low (subjective) quantity of THC, etc...

Administration Routes

Participants ranked cannabis administration routes from 1 to 6 (1 most used, 6 least used), with options including smoking, vaporizing, edible/eating, topical applications, tinctures, and other methods. If participants selected "other," they were directed to a free-text entry window. We asked participants to only rank those administration routes that they used. We used these data to examine the rates of single and multiple administration method utilization.

Product Selection Factors

To determine how participants chose cannabis products, we asked: "How do you select which cannabis products to use?" Participants were invited to select all that applied from a list that included: recommendations from a dispensary employee, recommendations from a friend, smell, visual properties (for example, density, size of buds, color, etc...), described effects, THC or other cannabinoid content, cannabis variety (indica vs sativa), name, or other. If participants selected "other," they were directed to a free-text entry window.

Statistical Analysis

We performed subgroup descriptive analyses, and present results as frequency, n (%) and mean ± standard deviation (SD) or median ± standard error, for categorical and continuous variables, respectively. We used Pearson's chi-square test to assess differences in categorical variables. The Median rank tests were used for nonparametric and highly-skewed data. All analysis was performed using IBM SPSS 25 (Armonk, NY).

Results

Study Population

Our study population consisted of n = 1,321 medical cannabis patients, which was 59.1% female. See supplementary Tables 1 and 2 for a full demographic characterization of this cohort and the associated conditions for which participants use medical cannabis.

Daily cannabis intake of 76.5% was reported by the participants. Frequency of use per day was evenly distributed (Table 1). 59.6%, 28.7%, and 11.8% of the study population reported a preference for indica/sativa blends, indica and sativa, respectively. Seventy percent indicated a specific preference for a specific THC: CBD ratio, with 70.7% preferring either high THC: high CBD (37%) or low THC: high CBD (33.7%) (Table 2). Only 17% preferred high THC: low CBD, and <5% preferred low THC: low CBD, only THC, or only CBD, respectively.

Most of the study population reported using at least 2 (93.4%) or 3 (72.5%) administration routes (Table 3). Vaporizing (74.5%) was the most commonly used administration route, followed by edibles (71.2%), smoking (68.9%), tinctures (56.8%), topical applications (49.9%) and other administration routes (5.3%). Smoking was the most common first-choice administration route (39.4%), followed by vaporizing (29%), tinctures (13.7%), edibles (12.2%), topical applications (4.1%), and other (1.6%) (Fig 1).

Selection of cannabis products was most attributed to THC or cannabinoid content (62.2%), dispensary employee recommendations (54.9%), described effects (52.0%), and cannabis variety (51.9%) (Table 4). Only 2.6% indicated that they had consulted with a medical professional about choosing cannabis products.

Sex Differences

There were no sex differences with regards to preference for cannabis varieties and frequency of use, and history of recreational cannabis use (all P > .168) (Table 1). Females reported significantly greater preference for low THC: high CBD (40.8% vs 23.4%, P < .0001) (Table 2). In contrast, males had a greater preference for high THC: high CBD (43.6% vs 32.4%, P < .0001). Females reported significantly lower rates of vaporizing and smoking (P = .008 and P < .0001, respectively), and higher rates of using of tincture and topical applications (P = .0003 and P < .0001, respectively) (Table 3). Rankings for smoking, vaporizing, topical application, and tincture administration routes also differed between sex (all P < .023). A lower percentage of females than males ranked smoking and vaporizing as a first or second choice administration route, while a higher percentage of females ranked topicals and tinctures as a first, second, or third choice administration route (Fig 1). Compared to females, a higher proportion of males selected cannabis products based on cannabinoid content, cannabis variety, visual properties, and smell (all P < .041) (Table 4). Among those who indicated that they had consulted with a medical professional about choosing cannabis products (P = .015), 3.5% were females versus 1.3% males.

Table 1. Cannabis use Frequency in Days per Week and Times per day Across Groups

	Total (N=1,292)	Male (N=529)	Female (N=763)	X2 (DF)	P-value	MED (N=699)	MEDREC (N=593)	X2 (DF)	P-value	Novice (N=477)	Experienced (N=815)	X2 (DF)	P-value
Days/week				2.1 (6)	.907			17.1 (6)	.009	477 (100.0%)	815 (100.0%)	9.3 (6)	.158
1	20 (1.5%)	6 (1.1%)	14 (1.8%)			17 (2.4%)	3 (0.5%)			9 (1.9%)	11 (1.3%)		
2	23 (1.8%)	9 (1.7%)	14 (1.8%)			14 (2.0%)	9 (1.5%)			10 (2.1%)	13 (1.6%)		
3	52 (4.0%)	18 (3.4%)	34 (4.5%)			34 (4.9%)	18 (3.0%)			27 (5.7%)	25 (3.1%)		
4	51 (3.9%)	22 (4.2%)	29 (3.8%)			27 (3.9%)	24 (4.0%)			20 (4.2%)	31 (3.8%)		
5	84 (6.5%)	34 (6.4%)	50 (6.6%)			47 (6.7%)	37 (6.2%)			37 (7.8%)	47 (5.8%)		
6	73 (5.7%)	31 (5.9%)	42 (5.5%)			29 (4.1%)	44 (7.4%)			26 (5.5%)	47 (5.8%)		
7	989 (76.5%)	409 (77.3%)	580 (76.0%)			531 (76.0%)	458 (77.2%)			348 (73.0%)	641 (78.7%)		
Times/day				5.7 (4)	.223			22.7 (4)	<.0001			20.4 (4)	<.0001
1	182 (14.1%)	65 (12.3%)	117 (15.3%)			111 (15.9%)	71 (12.0%)			69 (14.5%)	113 (13.9%)		
2	333 (25.8%)	140 (26.5%)	193 (25.3%)			205 (29.3%)	128 (21.6%)			150 (31.4%)	183 (22.5%)		
3	300 (23.2%)	113 (21.4%)	187 (24.5%)			152 (21.7%)	148 (25.0%)			110 (23.1%)	190 (23.3%)		
4	162 (12.5%)	72 (13.6%)	90 (11.8%)			89 (12.7%)	73 (12.3%)			60 (12.6%)	102 (12.5%)		
5+	315 (24.4%)	139 (26.3%)	176 (23.1%)			142 (20.3%)	173 (29.2%)			88 (18.4%)	227 (27.9%)		

Most participants used cannabis multiple times every day. MEDREC and experienced users used cannabis more frequently each day than their counterparts.

Table 2. Preferred Cannabinoid Ratios Among Study Population, Males versus Females, MED versus MEDREC Users, and Novice versus Experienced Users

	Total (N=925)	Male (N=376)	Female (N=549)	X2 (DF)	P-value	MED (N=507)	MEDREC (N=418)	X2 (DF)	P-value	Novice (N=335)	Experienced (N=590)	X2 (DF)	P-value
High THC: low CBD	157 (17.0%)	74 (19.7%)	83 (15.1%)	32.9 (6)	<.0001	68 (13.4%)	89 (21.3%)	40.6 (6)	<.0001	67 (20.0%)	90 (15.3%)	13.4 (6)	.037
High THC: high CBD	342 (37.0%)	164 (43.6%)	178 (32.4%)			165 (32.5%)	177 (42.3%)			99 (29.6%)	243 (41.2%)		
Low THC: high CBD	312 (33.7%)	88 (23.4%)	224 (40.8%)			208 (41.0%)	104 (24.9%)			123 (36.7%)	189 (32.0%)		
Low THC: low CBD	34 (3.7%)	14 (3.7%)	20 (3.6%)			17 (3.4%)	17 (4.1%)			15 (4.5%)	19 (3.2%)		
Only THC	13 (1.4%)	8 (2.1%)	5 (0.9%)			7 (1.4%)	6 (1.4%)			5 (1.5%)	8 (1.4%)		
Only CBD	21 (2.3%)	8 (2.1%)	13 (2.4%)			18 (3.6%)	3 (0.7%)			9 (2.7%)	12 (2.0%)		
Other	46 (5.0%)	20 (5.3%)	26 (4.7%)			24 (4.7%)	22 (5.3%)			17 (5.1%)	29 (4.9%)		

There were significant differences in cannabinoid preferences between groups. Females, MED, and novice users preferred low THC: high CBD ratios significant more than their counterparts, who tended to prefer high quantities of THC.

Table 3. Type and Number of Cannabis Administration Routes Employed Across Groups

	Total (N=1,276)	Male (N=524)	Female (N=752)	X2 (DF)	P-VALUE	MED (N=686)	MEDREC (N=590)	X2 (DF)	P-VALUE	Novice (N=471)	Experienced (N=805)	X2 (DF)	P-VALUE
Administration route (any ranking)													
Smoking	879 (68.9%)	404 (77.1%)	475 (63.2%)	28.0 (1)	<.0001	367 (53.5%)	512 (86.8%)	163.9 (1)	<.0001	251 (53.3%)	628 (78.0%)	29.2 (1)	<.0001
Vaporizing	951 (74.5%)	411 (78.4%)	540 (71.8%)	7.1 (1)	.008	465 (67.8%)	486 (82.4%)	35.6 (1)	<.0001	333 (70.7%)	618 (76.8%)	5.84 (1)	.016
Edible	908 (71.2%)	376 (71.8%)	532 (70.7%)	0.2 (1)	.69	448 (65.3%)	460 (78.0%)	24.8 (1)	<.0001	293 (62.2%)	615 (76.4%)	29.2 (1)	<.0001
Topical	637 (49.9%)	193 (36.8%)	444 (59.0%)	60.9 (1)	<.0001	350 (51.0%)	287 (48.6%)	0.7 (1)	.4	185 (39.3%)	452 (56.1%)	33.8 (1)	<.0001
Tinctures	725 (56.8%)	266 (50.8%)	459 (61.0%)	13.3 (1)	.0003	416 (60.6%)	309 (52.4%)	8.8 (1)	.003	254 (53.9%)	471 (58.5%)	2.5 (1)	.11
Other	68 (5.3%)	25 (4.8%)	43 (5.7%)	0.5 (1)	.46	43 (6.3%)	25 (4.2%)	2.6 (1)	.107	33 (7.0%)	35 (4.3%)	0.9 (1)	.36
Use multiple methods													
Two or more	1192 (93.4%)	482 (92.0%)	710 (94.4%)	3.0 (1)	.08	624 (91.0%)	568 (96.3%)	14.5 (1)	.0001	425 (90.2%)	767 (95.3%)	12.3 (4)	.0004
Three or more	925 (72.5%)	371 (70.8%)	554 (73.7%)	1.3 (1)	.26	452 (65.9%)	473 (80.2%)	32.4 (1)	<.0001	288 (61.1%)	637 (79.1%)	48.2 (1)	<.0001
Four or more	484 (37.9%)	183 (34.9%)	301 (40.0%)	3.4 (1)	.06	208 (30.3%)	276 (46.8%)	36.5 (1)	<.0001	111 (23.6%)	373 (46.3%)	65.4 (1)	<.0001
Five or more	267 (20.9%)	108 (20.6%)	159 (21.1%)	0.05 (1)	.82	108 (15.7%)	159 (26.9%)	24.1 (1)	<.0001	49 (10.4%)	218 (27.1%)	49.9 (1)	<.0001
Six or more	28 (2.2%)	7 (1.3%)	21 (2.8%)	3.0 (1)	.08	13 (1.9%)	15 (2.5%)	0.5 (1)	.43	8 (1.7%)	20 (2.5%)	0.9 (1)	.36

Most individuals used at least 2 administration routes, with over 70% using 3. Females, MEDREC, and Experienced users utilized more administration routes. Males, MEDREC, and Experienced users were more likely to employ smoking, vaporizing, and take edibles as an administration route (any ranking), while females and MED users were more likely to use tinctures and topicals.

MED versus MEDREC Differences

Both groups had a high proportion of everyday cannabis users, although MEDREC users typically used cannabis more frequently, both in terms of days per week and times per day, ($P = .009$ and $P < .0001$, respectively) (Table 1). MEDREC and MED participants reported greatest preference for indica/sativa blends, followed by indica and sativa. MED users preferred different cannabinoid ratios than MEDREC users ($P < .0001$) with the biggest differences between low THC: high CBD (41.0% vs 24.9%, respectively) (Table 2). MEDREC users employed more administration routes than MED users (all $P \leq .0001$). MEDREC users were most likely to smoke (86.8%) or vaporize (82.4%), while MED users were most likely to vaporize (67.8%) and consume edibles (65.3%) (Table 3). Administration route rankings differed significantly between MEDREC and MED users (all $P < .0001$). MEDREC users ranked smoking (52.7%) and vaporizing (30.3%) as their most preferred administration route, whereas MED users ranked smoking (28%), vaporizing (27.8%), and tinctures (19.4%), and edibles (16.5%) as their top choice (Fig 1).

A greater proportion of MEDREC users reported selecting cannabis based on THC or cannabinoid content, cannabis variety, described effects, visual properties, smell, recommendation from friends, and the product name (all $P < .019$) (Table 4). MED users were more likely to select based on recommendations from dispensary employees ($P = .025$). Among MED users, 4.1% indicated that they had consulted with a medical professional about choosing cannabis products, compared to 0.8% of MEDREC users ($P = .0002$).

Duration of Medical Cannabis Use (Novice vs Experienced)

There were no differences in weekly use between novice and experienced users, though experienced users reported more frequent daily use (Table 1). There were no difference in preference for cannabis varieties ($P = .754$). Both groups reported greatest preference for high CBD ratios, although a greater proportion of novice users preferred low THC: high CBD while experienced users preferred high THC: high CBD ($P = .037$) (Table 2).

Compared to novice users, experienced users were more likely to administer cannabis via smoking, vaporizing, edible, and topical applications (all $P < .016$), and used significantly more administration routes (all $P \leq .0004$) (Table 3). Groups also differed significantly in preference ranking for all administration methods (all $P < .034$). Novice users ranked vaporizing highest (34.8%), followed by smoking (26.1%), tinctures (18.5%), and edibles (14.2%) while experienced users ranked smoking highest (47.2%) followed by vaporizing (25.6%), edibles (11.1%), and tinctures (10.9%) (Fig 1).

Novice users were more likely to select a cannabis product based on dispensary recommendations, while experienced users chose products based on nearly all other
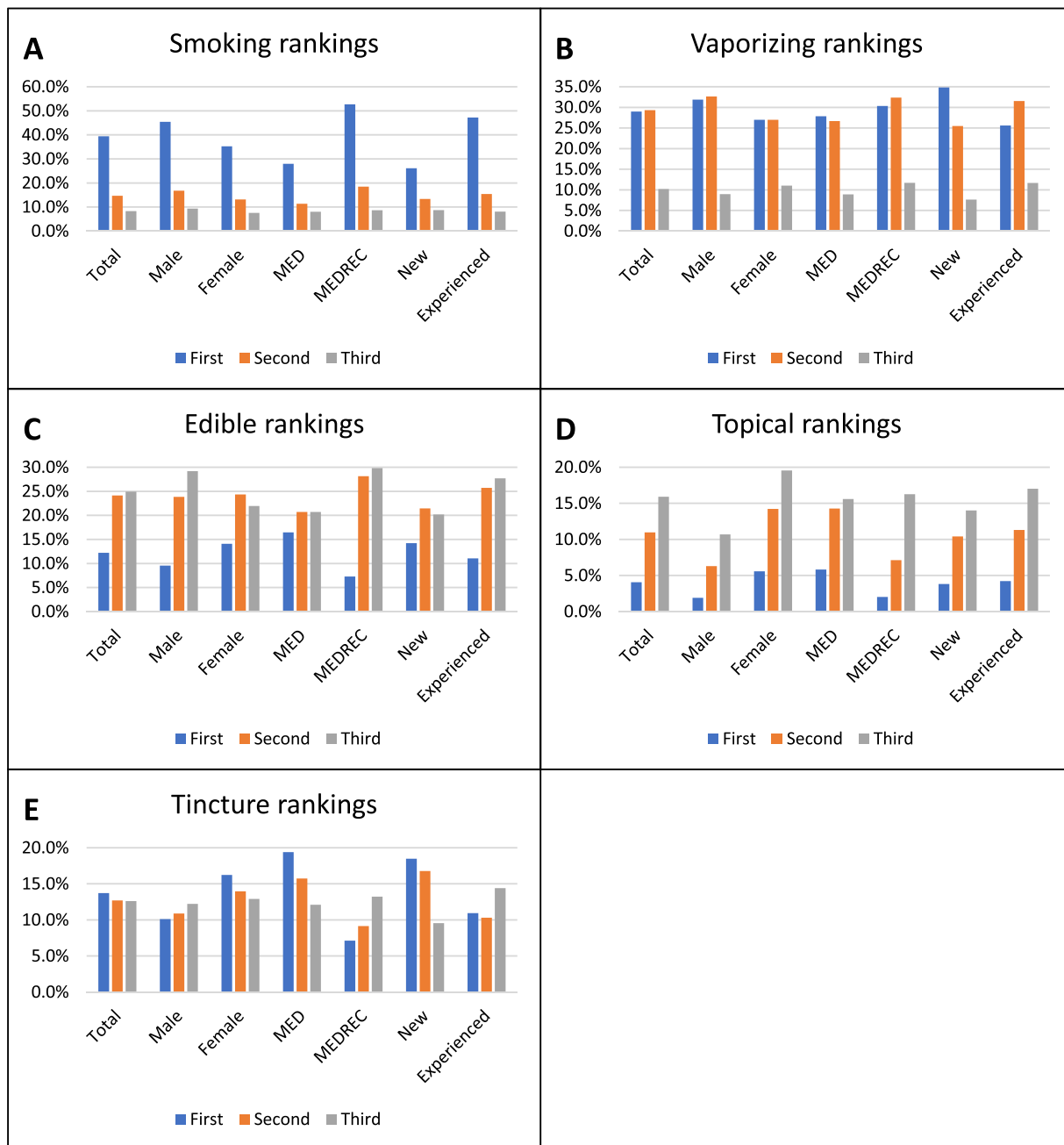
Figure 1. Top 3 administration route rankings among study population and each subgroup.
First, second, and third choice administration routes are displayed as blue, orange, and grey, respectively. Smoking is the top ranked choice among all groups except novice users. Abbreviations: MED, individuals who only use cannabis medically; MEDREC, individuals who use cannabis both medically and recreationally.

selection factors (all $P < .006$) (Table 4). Among novice users, 4.3% indicated that they had consulted with a medical professional about choosing cannabis products, compared to 1.6% of experienced users ($P = .002$).

Discussion

Our results demonstrate wide variability in use strategies and decision-making around cannabis products among medical cannabis users with chronic pain. Consistent with other studies of medical cannabis users, most participants in our survey use cannabis daily, with many

using several times per day.[44,58] There are several patterns that emerge from the data.

Cannabinoid Preferences Differed by Gender and Intentions for Use

Overall, 70.7% of participants with a preferred cannabinoid ratio preferred high THC: high CBD or low THC: high CBD. Our inference is that someone who used a "high" quantity of THC likely is experiencing psychoactive effects of THC, while someone used a "low" quantity of THC likely is experiencing minimal psychoactivity. With this interpretation, our results reflect the growing

Table 4. Participant Decision-Making Around Cannabis Product Selection by Group

	Total (N = 1,315)	Male (N = 538)	Female (N = 777)	X2	P-value	MED (N = 712)	MEDREC (N = 603)	X2	P-value	Novice (N = 486)	Experienced (N = 829)	X2	P-value
Dispensary employee	722 (54.9%)	287 (53.3%)	435 (56.0%)	0.9	.34	411 (57.7%)	311 (51.6%)	5.0	.025	325 (66.9%)	397 (47.9%)	44.6	<.0001
Friend	307 (23.3%)	128 (23.8%)	179 (23.0%)	0.1	.75	138 (19.4%)	169 (28.0%)	13.6	.0002	93 (19.1%)	214 (25.8%)	7.6	.006
Smell	337 (25.6%)	162 (30.1%)	175 (22.5%)	9.6	.002	126 (17.7%)	211 (35.0%)	51.2	<.0001	69 (14.2%)	268 (32.3%)	52.8	<.0001
Visual properties	346 (26.3%)	177 (32.9%)	169 (21.8%)	20.4	<.0001	131 (18.4%)	215 (35.7%)	50.1	<.0001	68 (14.0%)	278 (33.5%)	60.4	<.0001
Described effects	684 (52.0%)	271 (50.4%)	413 (53.2%)	1.0	.32	349 (49.0%)	335 (55.6%)	5.6	.018	252 (51.9%)	432 (52.1%)	0.008	.93
Cannabinoid content	818 (62.2%)	356 (66.2%)	462 (59.5%)	6.1	.01	406 (57.0%)	412 (68.3%)	17.7	<.0001	275 (56.6%)	543 (65.5%)	10.4	.001
Cannabis variety	682 (51.9%)	297 (55.2%)	385 (49.5%)	4.1	.04	327 (45.9%)	355 (58.9%)	21.9	<.0001	227 (46.7%)	455 (54.9%)	8.2	.004
Name	187 (14.2%)	77 (14.3%)	110 (14.2%)	0.006	.94	77 (10.8%)	110 (18.2%)	14.8	.0001	47 (9.7%)	140 (16.9%)	13.1	.0003
Other	315 (24.0%)	126 (23.4%)	189 (24.3%)	0.1	.71	182 (25.6%)	133 (22.1%)	2.2	.14	114 (23.5%)	201 (24.2%)	0.1	.75
Medical professional	34 (2.6%)	7 (1.3%)	27 (3.5%)	6.0	.02	29 (4.1%)	5 (0.8%)	13.6	.0002	21 (4.3%)	13 (1.6%)	9.2	.002

Values represent frequency (n), percent (%), X^2, Chi-square test; P-value. All groups differed significantly across multiple product selection criteria. Only 2.6% were advised by medical professionals, compared to 54.9% by dispensary employees.

interest in CBD as a wellness product and pain-reliever. Indeed, a recent survey of n = 2,409 cannabidiol users reported common use for pain, anxiety, depression, and sleep issues.[15] Additionally, participants reported distinct cannabinoid preferences, which were significantly influenced by gender and intentions behind use (MED vs MEDREC). We found that males were more likely than females to prefer cannabis products with high levels of THC, and females were more likely to prefer products with low THC: high CBD ratios. This may be due to the generally higher rates of cannabis use in males,[14,20] and thus greater familiarity with and tolerance of THC-containing products. Similarly, MED users were significantly more likely to prefer low THC: high CBD ratios compared to MEDREC users. This may indicate concern about THC effects, an attempt to mitigate THC's psycho-activity with CBD, or greater comfort with CBD as a non-intoxicating product.[32,42] MED participants may also prefer less THC because high doses of THC may actually increase pain, as has been seen in clinical trials with vaporized cannabis.[56,57]

Administration Routes and Preferences

The vast majority of our study population employed at least 2 to 3 administration routes, with 21% using 5 or more. This diversity of administration routes highlights a key difference between real-life medical cannabis use and clinical trials, showcasing consumer interest in the plethora of available cannabis products. This result is consistent with nationally representative data showing similar overlap in administration routes, but places it in a more medicalized context.[46] Although most other studies report primary administration routes and sometimes listed more than one,[1,15,16,37,43,44,58] we are unaware of other studies that have catalogued and ranked preferences for multiple administration routes.

Compared to MED and novice users, a higher proportion of MEDREC and experienced users employed multiple administration routes. Such patterns are consistent both with greater familiarity with cannabis (which may lead to greater knowledge of administration routes) and desire for cannabis's nonmedical effects, which may lead toward experimentation with a variety of administration routes. Smoking and/or vaporizing were the first, second, or third choice methods among all groups. This overwhelming dominance of inhaled cannabis is consistent with other individual and national studies of cannabis use patterns.[37,44,46] However, we also found that administration route preferences appear to be strongly influenced by both duration of and intention (MED vs MEDREC) behind use. Novice and MED users in our population reported a significantly lower likelihood of smoking compared to experienced and MEDREC users. We posit that these trends may be driven by novice and MED users seeking symptom relief rather than intoxication. Seen through this lens, it makes sense that MED users would prefer noninhalation administration routes such as tinctures, edibles, and topicals, which avoid the hazards of smoking as well as having slower onset, less euphoria, and longer-lasting effects.[24,32]

Similar to our results, an observational study conducted in Israel found that significantly more medical users vaporized or ingested cannabis compared to recreational users.[50] Licensed medical users were also significantly less likely to smoke cannabis than either of the other groups.

Cannabis Product Selection

Among all participants, the most common reasons for selecting cannabis products were cannabinoid content, recommendations from a dispensary employee, described effects, and cannabis variety. Only 2.6% of the entire population indicated that they had received advice from a medical professional, indicating a deep disconnection between current medical practice and cannabis product selection. This could be due to our recruitment through dispensaries, or may reflect physician discomfort with cannabis products, as well as legal concerns about recommending or advocating use of a Schedule I substance.[11] The number of participants who received advice on selecting cannabis products from a medical practitioner may also be artificially low, as responses were collected from the "other" category rather than being a prespecified choice. Compared to MED and novice users, MEDREC and experienced users were considerably more likely to select products based on cannabinoid content, variety (indica vs sativa), and smell. While many scientists have openly questioned the value of indica versus sativa as being related to chemical composition or medicinal effects,[36] these designations are still clearly important for consumers. Product selection among MEDREC and experienced users may also reflect greater experience or comfort with cannabis, as well as less discernment or concern about side effects. In contrast, MED and novice users were significantly more likely to rely on recommendations from a dispensary employee, suggesting less comfort and familiarity with making decisions about cannabis products. The overall reliance upon dispensary employee recommendations highlights the need for better understanding and standardization of how such employees are trained. However, this practice is also concerning, as it cedes medical guidance to dispensary employees who may lack necessary training: one study reported that only 55% of dispensary staff had any formal training of any kind, 20% of which was medical in nature.[22]

These results complement our previous findings regarding differences between MED/MEDREC and novice/experienced cannabis users, showing how these distinctions reflect not only demographic differences (eg, age, gender), changes in pain and overall health, and medication substitution behaviors,[6] but also choices made around products, administration routes, and cannabinoid content.

Clinical Implications

We are left with one glaring question: why, and how, do medical cannabis users employ multiple administration routes and cannabinoids? We hypothesize that medical cannabis users target different symptoms by using variable administration routes and formulations, which can have significantly different pharmacokinetics, active ingredients, and effects. We refer to this practice as *dose layering*. Though we have not seen this reported in the scientific literature, we have encountered it in our personal interactions with numerous patients and dispensary employees. The rationale behind dose layering is analogous to using multiple medications to address different symptoms. For example, a person with chronic pain may have pain flares throughout the day, as well as comorbid anxiety and sleep problems. That individual might be prescribed a daily extended release pain medication, while also using a fast-acting pain reliever for breakthrough pain, a sleep aid, and an anti-anxiety medication. We believe that a similar philosophy could partly explain the variable cannabinoid use strategies in our study.

In practice, dose layering depends on both pharmacokinetics and cannabinoid mechanisms of actions. Pharmacokinetically, smoking, and vaporizing effects onset quickly (5−10 minutes) and last for a 2 to 4 hours, edibles take 1 to 3 hours to onset and last for 6 to 8 hours, and tinctures typically onset in 15 to 45 minutes and last 6 to 8 hours.[32] Mechanistically, CBD is nonintoxicating,[32] analgesic (in preclinical studies),[12,19,33,35] exerts mild antianxiety effects,[17,33] and may attenuate the psychoactivity and adverse event profile of THC.[32] (Although there is little clinical evidence to suggest that CBD is analgesic in humans, a large, recent observational study showed that the most common indications for which people use CBD oil are pain and arthritis.[15]) By contrast, THC is psychoactive, analgesic, induces somnolence, and may reduce the unpleasantness of pain.[28,51] By combining multiple administration routes and cannabinoid formulations, it is plausible that patients could tailor usage to their specific needs. For example, one could imagine a hypothetical patient with chronic pain ingesting a high CBD: low THC edible to avoid intoxication while providing long-term pain relief during the day, ingesting a THC-dominant edible to help with sleep, and using vaping or tinctures as needed to treat other symptoms such as breakthrough pain or anxiety.

Limitations

As with our previous analyses of these data, the cross-sectional design prevents us from prospectively examining these trends, and our inference is further limited by recall bias as many participants had been using cannabis for over a year. Our results are likely skewed by selection bias, as many participants were recruited through medical cannabis dispensaries or medical cannabis clinics, and we do not know how many participants received the survey but chose not to participate. Further, our focus on individuals with chronic pain means that we may not be capturing important cannabis use and decision-making behavior regarding other medical conditions. However, as chronic pain accounts for 62% of qualifying conditions for which medical cannabis licenses are obtained nationwide,[4] we believe our results are still quite meaningful.

Although our data show that participants utilize multiple administration routes, we do not know how this is actually reflected in real-life use patterns. For example, we have no sense how frequently second or third choice administration routes get used (e.g., daily vs monthly). Our questions on cannabinoid preferences were also limited by our broad categories of CBD: THC ratios, which do not give the opportunity for participants to select specific ratios, eg, 20:1 CBD: THC. We also acknowledge that this question may have led to subjective interpretation that could conflate quantity of cannabinoids consumed and preferred ratios. However, we believe that this still provides valuable information about how participants viewed their use of CBD and THC. Finally, we did not analyze use routines, so we acknowledge that our proposed dose layering paradigm remains hypothetical, given the dearth of information on CBD, its related metabolites,[25] and the unknowns about the pharmacokinetics of variable administration routes now employed by medical cannabis users.

Conclusions

In this study, we report that many medical cannabis users with chronic pain use administration routes other than smoking (such as vaporizing, tinctures, and edibles), and frequently use multiple administration routes to ingest cannabis products. Our findings also reflect the fast-growing interest in CBD, as >70% preferred products with high levels of CBD. Novice and MED users tend to rely on dispensary employees to choose cannabis products, and very few seek advice from medical professionals about selecting such products.

As barriers to cannabis research continue to loosen, the varieties of cannabis products − both cannabinoid formulations and administration routes − will continue to grow. As such, it is vitally important for researchers to improve dosing approaches in clinical studies as well as better measure effects of CBD and other cannabinoid metabolites to better understand different cannabinoid combinations and administration routes. Adequately capturing the multi-modal effects of these dosing strategies and synchronizing them with pain mechanisms in future clinical studies will better reflect the reality of cannabis dosing and help resolve controversies around the utility of cannabinoids for pain.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2019.05.009.

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