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High frequency medical cannabis use is associated with worse pain among individuals with chronic pain

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Abstract

Cannabis is widely used for chronic pain. However, there is some evidence of an inverse dose-response relationship between cannabis effects and pain relief which may negatively affect analgesic outcomes. In this cross-sectional survey, we examined whether daily cannabis use frequency was associated with pain severity and interference, quality of life measures relevant to pain (e.g., anxiety and depressive symptoms), and cannabis use preferences (administration routes, cannabinoid ratio). Our analysis included 989 adults who used cannabis every day for chronic pain. Participant use was designated as light, moderate, and heavy (1-2, 3-4, and 5 or more cannabis uses per day, respectively). The sample was also sub-grouped by self-reported medical only use (designated MED, n=531, 54%) vs. medical use concomitant with a past-year history of recreational use (designated MEDREC, n=458, 46%). In the whole sample, increased frequency of use was significantly associated with worse pain intensity and interference, and worse negative affect, although high frequency users also reported improved positive affect. Subgroup analyses showed that these effects were driven by MED participants. Heavy MED participant consumption patterns showed greater preference for smoking, vaporizing, and high THC products. In contrast, light MED participants had greater preference for tinctures and high CBD products. Selection bias, our focus on chronic pain, and our cross-sectional design likely limit the generalizability our results. Our findings suggest that lower daily cannabis use frequency is associated with better clinical profile as well as lower risk cannabis use behaviors among MED participants. Future longitudinal studies are needed to examine how high frequency of cannabis use interacts with potential therapeutic benefits.

Keywords

medical cannabis; tetrahydrocannabinol; cannabidiol; use frequency

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INTRODUCTION

Cannabis use is becoming increasingly widespread as more states legalize cannabis for medical and recreational states purposes. There are an estimated >2.1 million people with medical cannabis licenses[51] in the 33 states with legalized medical cannabis,[50] and we recently showed that chronic pain accounts for 62% of patient qualifying conditions for medical cannabis licenses nationwide.[6] Coupled with the common lack of physician knowledge on cannabis[26] and reports of decreased opioid and other pain medication prescribing in states with legalized medical cannabis,[11–13,70] this finding may indicate dissatisfaction with current pain medications – many of which have significant side effects and only work in a subset of the population.[18,25] Indeed, many medical cannabis patients report substituting cannabis for opioids and other pain medications due to better symptom management and fewer side effects. [3,9,38,39]

However, cannabis comes with various risks, including acute cognitive dysfunction, worsening of mood and substance use disorders, addiction, cyclical vomiting in cannabis hyperemesis syndrome,[28] and higher risk of motor vehicle accidents.[30,63,64] Further, the lack of cannabis use guidelines coupled with the increasing potency of medical cannabis products[24] may increase the likelihood that individuals seeking cannabis medically may be exposed to products that contain high levels of tetrahydrocannabinol (THC), which causes most of cannabis's negative side effects, including increased risk of psychosis and addiction potential.[63,64] Indeed, Colorado, which has legalized both recreational and medical cannabis, has reported increases in the number of cannabis-related hospitalizations, both generally and in pediatric populations.[68]

One reason that high THC products might be problematic is because cannabinoid effects may not follow a linear dose-response curve for a variety of symptoms, including pain and anxiety.[37,41,49,66,72] Practically, this means that there can be diminishing returns as doses increase past an optimal point, resulting in worsening symptom control at higher doses. For example, in a large, 5-week long clinical trial among cancer patients using sublingual 1:1 THC:CBD for pain management, individuals using a lower dose (1-4 sprays/day) reported decreased pain and fewer side effects than those using 6-10 or 11-16 sprays/day.[49] Similarly, a study of smoked cannabis on capsaicin-induced pain found increased pain with cannabis containing 8% THC, but decreased pain with 4% THC cannabis.[66]

However, the acknowledged shortcomings of cannabinoid clinical trials have contributed to a mismatch between clinical trial and observational findings of medical cannabis efficacy.[59,71] These shortcomings include limited indications tested, small sample size, unrepresentative dosing paradigms[57,58], and the use of pharmaceutical-grade cannabinoids (which contain solely THC analogs, THC, or THC and CBD) vs. whole plant extracts which contain numerous minor cannabinoids, terpenes, and flavonoids.[52] We believe that this mismatch may also be partially explained by both pharmacokinetic and cannabinoid mechanisms. Pharmacokinetically, smoking and vaporizing cannabis causes rapid onset of effects which taper off quickly, while sublingual and oral ingestion tend to have slower onset and longer lasting effects.[31,40] As such, smoking likely has a higher risk of dependence or addiction than oral ingestion, analogous to injecting heroin vs. orally ingesting methadone.

Mechanistically, THC is psychoactive and intoxicating, but also can cause analgesia and induce somnolence.[45,63] By contrast, CBD is non-intoxicating, exerts anti-inflammatory and analgesic effects in preclinical studies of arthritis,[29,41,47] and has also been shown to have anxiolytic effects in small clinical trials in human.[21,72] In a recent small trial (n=7), CBD also reduced pain following kidney transplant.[22] Therefore, cannabinoid and administration preferences may predict differences in cannabinoid effectiveness for chronic pain management.

In the current study, we assessed associations between daily frequency of cannabis use, cannabis-related characteristics, and patient-reported outcomes in a sample of daily medical marijuana users from an ongoing cross-sectional cohort. We hypothesized that more uses of cannabis per day would be associated with worse pain and associated symptoms (e.g., anxiety). We also examined cannabis use patterns (e.g., administration routes, cannabinoid preferences), hypothesizing that less frequent use would be associated with CBD-dominant products and non-smoking administration routes.

METHODS

Individuals ≥18 years old who self-reported use of cannabis for chronic pain were invited to participate in an online, anonymous survey using the Qualtrics survey platform between January and August 2018. The anonymous survey link was sent to cannabis dispensary patrons, patrons of clinics that certify medical cannabis patients, and social media. This study was approved by the Institutional Review Board (IRB) at the University of Michigan under protocol HUM00079724. Participants freely consented to participate and could to drop out at any time. As previously described,[9] n=1,321 individuals completed surveys. We selected the subset of individuals who used cannabis daily, providing an eligible sample of n=989.

Prior recreational use

Participants categorized their cannabis use in the past year as medical only, recreational only, or a combination of medical and recreational. Recreational only participants were excluded. Participants who reported only medical use in the past year are referred to as MED (n=531), while those who reported medical and recreational use in the past year are referred to as MEDREC (n=458). Significant clinical, behavioral, and cannabis consumption differences have been frequently reported between MED and MEDREC participants, so we chose to use these categories here as well.[36,60,65]

Cannabis use frequency

Participants were asked to report the frequency of their daily cannabis use and were categorized as light (1–2 times), moderate (3–4 times), and heavy (5 or more times). Use frequency was used as a proxy of dose. This was done for several reasons. First, there is a great deal of inter-individual variation in cannabis effects, which depend on familiarity with and tolerance of cannabis effects, as well as underlying physiological differences.[40] This means that individuals likely use cannabis until the desired effect is achieved, rather than choosing a specific dose (e.g. 5mg). Second, to our knowledge, there is no validated medical

cannabis dosing questionnaire which adequately accounts for the variety of administration routes and cannabinoid formulations available to medical cannabis users. Third, there is a great deal of variability in quality control and standardization across available medical cannabis products,[10,53,62] so even if a product label says 20mg THC, it might contain something vastly different. Fourth, while some studies have asked participants about the number of grams of cannabis used per day,[61] this categorization may not be useful if participants are using concentrates, edibles, or other non-flower cannabis products. Thus, while frequency of use is not a perfect proxy, we believe that it is still a valuable measure of dose.

Administration routes, cannabis variety, and cannabinoid preferences

Participants were asked to rank their preferred administration routes (smoking, vaporizing, eating, tinctures, topicals, or other), and select their preferred THC:CBD ratio (high THC : low CBD, high THC : high CBD, low THC : high CBD, low THC : low CBD, CBD alone, THC alone, other). Our inference from the latter question was that someone who selected high THC : high CBD is indicating that they use a large (subjective) quantity of both THC and CBD.[8] Participants were also asked about their preferred cannabis variety, and 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”. Indica strains are often characterized as having relaxing or sedating effects, compared to sativa strains which are described as “uplifting and energetic”.[48]

Socio-demographic characteristics

Sex, state of residence, highest education level completed, and annual household income (US$) were reported categorically, while age (years) was reported as both continuous and categorical. Cigarette smoking (current, former or never smoker), alcohol intake (yes/no) and concomitant opioid analgesic and benzodiazepine use (yes/no) were taken into account due to known effects on chronic pain symptoms.[55]

Clinical measures

Pain—Pain severity and pain-related interference in daily activities was assessed by using a modification of questions from the Brief Pain Inventory.[19] Pain severity was assessed using the average of two, zero to ten scalar questions (worst and average pain in the past 7 days) with scores ranging 0-10. Pain interference is the average of seven questions with scores ranging 0-10. Higher scores indicate worse symptoms.

Physical function, fatigue and sleep—Patient Reported Outcome Measurement Information System (PROMIS) physical function, fatigue, and sleep were measured using standardized 8-item questionnaires.[16] For each questionnaire, scores were summed for a raw total score which is converted to a standardized t-score, on a scale of 0-100 with a standard deviation of 10 and median of 50. Higher scores on the functional measure were indicative of better physical function, while higher scores for sleep and fatigue indicated greater difficulties for these domains.

Anxiety and depressive symptoms—Anxiety and depressive symptoms were measured using the Generalized Anxiety and Depression (GAD-7) scale and the Patient Health Questionnaire (PHQ9). The GAD-7 is a seven-item, Likert scale with scores ranging from 0-21, with higher scores indicating greater anxiety severity.[56] The PHQ-9 includes 9 items with scores ranging from 0-27 with higher scores indicating higher depression severity.[35]

Cognition—The multidimensional inventory of subjective cognitive impairment (MISCI) is a 10-item, 5-point Likert-style patient reported measure of cognitive dysfunction.[34] Scores were summed, ranging 10-50, with higher scores indicating better subjective impression of cognitive function.

Affect—Positive and negative affect were measured with the Positive and Negative Affect Schedule (PANAS), a 20-item scale with alternating positive and negative affect questions.[69] Scores were summed, ranging from 10-50 for both the positive and negative affect scales, where higher scores indicated higher positive affect and higher negative affect, respectively.

Statistical Analysis

Descriptive statistics were used to describe demographics, cannabis use (preferred cannabinoid ratios and administration), and alcohol, tobacco, and pain medication use. The population was sub-grouped by cannabis use frequency (light, moderate, heavy) and by MED vs. MEDREC. Categorical variables (e.g. sex, education, cannabinoid preferences) were analyzed by Pearson's Chi-square (X^2) test. Univariate differences between cannabis intake and continuous variables (e.g., age) were assessed via student's t-test and one-way analysis of variance (ANOVA).

Pain and other patient-reported outcomes among subgroups were assessed using analysis of covariance (ANCOVA). Post hoc pairwise differences were assessed using Bonferroni's test. Potential confounders were analyzed as independent variables via chi-square test, t-test or ANOVA for between-group differences. Variables that were significantly associated ($p < 0.05$) with a clinical measure (i.e., age, sex, income, education, smoking, alcohol use, opioid use, benzodiazepine use) were considered potential confounders and included as covariates in that measure-specific ANCOVA model. Age was used as a continuous rather than categorical variable in ANCOVA models due to increased model fit. Adjusted scores are represented as estimated marginal mean ± standard error (SE). All tests were two-tailed and statistical significance set at $p<0.05$. Analysis was conducted using SPSS 25. (Armonk, New York)

RESULTS

Participants (n=989, female 59%) were 49.6 ± 13.7 years. Other demographic information is reported in table 1. Sixty-one percent reported concomitant pain-related medication use, with 15% and 13% reporting current opioids and benzodiazepines, respectively. Participants were from 20 states with legalized medical cannabis (as well as n=23 from Canada), with the highest proportion from Maine (19%), California (18%), Arizona (10%) and New Hampshire (10%).

The study population were sub-grouped by frequency of daily cannabis use: light (1-2 uses/day, n=307, 31.0%), moderate (3-4 uses/day, n=382, 38.6%) and heavy (5 or more uses/day, n=300, 30.4%). Age, household income, and education level showed significant inverse associations with frequency of cannabis use, while rates of cigarette smoking increased with cannabis use frequency (Table 1). Opioid and benzodiazepine use, sex (male), and age were associated with significant differences on most clinical measures, thus, these variables were included as covariates in most models. Unadjusted outcomes (estimated marginal mean) showed significant differences in pain, pain interference, anxiety, depression, positive affect, and negative affect between use categories (Appendix Table 1). Adjusted scores (estimated marginal mean) showed that light use participants reported significantly lower pain than heavy or moderate use participants, and significantly lower pain interference, negative affect, and positive affect than heavy use participants (Table 2).

Frequency groups reported significant differences in preferred THC:CBD ratios and administration routes (Appendix Table 2). Heavy use participants preferred high THC: high ratios CBD (57.2% vs. 26.9% of light and 39.1% of moderate use participants) while light use participants preferred low THC: high CBD products (44.7% vs. 29.0% of moderate and 12.4% of heavy participants). Frequency groups also reported significant differences in administration use preferences, with a significantly larger proportion of light use participants preferring edibles and tinctures as their top ranked administration routes.

MED vs. MEDREC participants

Consistent with our previous report, MED participants were more likely to be older, female, and currently using opioids and benzodiazepines, but were less likely to drink or smoke (Appendix Table 2). MED participants also showed greater preference for low THC: high CBD ratios and tinctures, while MEDREC participants showed greater preference for high THC: high CBD ratios and smoking/vaporizing. In univariate analyses, MEDREC participants reported significantly lower pain severity, pain interference, sleep disturbance, fatigue, depressive symptoms, and cognitive dysfunction than MED participants (all $p<0.003$).

Clinical measures and cannabinoid preferences among MED Participants

Among MED participants, heavy use participants were younger, had lower income, less education, and were more likely to smoke cigarettes than light or moderate use participants (Appendix Table 3). Light use participants were more likely to take concomitant pain medications (though not opioids or benzodiazepines). In pairwise analysis, light use participants reported significantly lower pain severity scores than moderate or heavy use participants (5.4 vs. 6.2 and 6.2, respectively, $p<0.0001$) and lower pain interference lower scores than moderate or heavy use participants (4.4 vs. 5.4 and 5.5, respectively, $p<0.0001$). Light use participants also reported lower positive affect (23.5 vs. 25.2, $p=0.037$) and negative affect (24.7 vs. 26.8, $p=0.011$) than heavy use participants (Table 3).

Frequency groups had significantly different preferences for THC:CBD ratio ($X^2=46.0$, $p<0.0001$) (Table 4). Heavy use participants preferred high THC: high CBD ratios (60.9% vs. 27.5% and 33.6%), while light use participants preferred low THC: high CBD ratio

(46.5% vs. 35% moderate and 18.5% heavy use participants, respectively). Heavy use participants were also more likely than light use participants to rank smoking and vaporizing as their most preferred administration routes, and light use participants were more likely to prefer edibles and tinctures as their most preferred administration route. Moderate use participant top ranked preferences fell between light and heavy participants on all administration routes except edibles.

Clinical measures and cannabinoid preferences among MEDREC Participants

Heavy MEDREC participants were less educated, more likely to be a current or former smoker, and more likely to be currently taking opioid analgesics than moderate or light participants (Appendix Table 3). Moderate MEDREC participants were more likely to be female than light or heavy participants. There were no clinical differences between use groups, except that light use participants had significantly worse physical function than moderate use participants (Table 3).

Frequency groups had significantly different preferences for THC:CBD ratio (X^2=46.0, p<0.0001) (Table 4). Heavy use participants preferred high THC: high CBD ratios (54.1% vs. 46.1% and 25% for moderate and light use participants, respectively), while light use participants preferred low THC: high CBD ratio (39.7% vs. 22% moderate and 7.2% heavy use participants, respectively). Heavy use participants were also more likely than light use participants to rank smoking and vaporizing as their most preferred administration routes, and light use participants were more likely to select edibles and tinctures as their most preferred administration route. Top ranked preferences for moderate use participants fell between light and heavy use participants on all administration routes except edibles.

DISCUSSION

We report an inverse relationship between frequency of cannabis use and clinical pain and pain interference among MED individuals with chronic pain. However, this relationship was not seen with other characteristics (e.g., anxiety and depression) that often go with chronic pain. Compared to heavy use MED participants, light use MED participants reported lower pain severity, pain interference, and negative affect after adjustment for numerous relevant covariates (sex, age, income, education, and concomitant opioid and benzodiazepine use). Light use MED participants were also more likely than heavy or moderate use MED participants to report consumption patterns that were consistent with safer use of cannabis products, including greater preference for administration routes with slower onset and longer effects (e.g., edibles, tinctures) and for low THC: high CBD ratios.[40] While clinical measures did not differ among light, moderate, and heavy use MEDREC participants (excepting in physical function), these *consumption preferences* remained consistent as well.

While other studies have documented differences between frequency of use or dosing and other characteristics, we are unaware of any studies that have characterized the relationship between frequency of use and pain severity. Our results are consistent with a recent Canadian study of individuals using cannabis for anxiety, in which those who use higher quantities of cannabis (>3 grams per day) had more severe clinical symptoms than those who used ≤3 grams per day.[61] Our results are also congruent with other studies examining

trends in clinical differences between individuals who use medical vs. recreational cannabis, in which medical only use is associated with worse health. A study using nationally representative data found that medical cannabis use was associated with older age, higher likelihood of reporting daily cannabis use, unemployment, and fair/poor health compared to recreational use.[36] Similarly, Wall et al. reported that medical only cannabis use (n=82) as associated with a higher prevalence of evidence-based medical reasons for using cannabis than combined medical and recreational use (n=362), but lower odds of anxiety.[65]

Consistent with these findings, in our study we found that MED participants tended to be more clinically compromised across an array of clinical measures than MEDREC participants. This makes intuitive sense, as MED participants likely have a higher disease burden, reflected by their greater use of medications (See Appendix Table 2).[15] We postulate that the inverse relationship between frequency and clinical symptoms may be confined to MED participants in our population because this lower baseline of health may amplify the negative effects of cannabis overuse and harmful administration routes like smoking. Similarly, it is possible that heavy use among MED participants reflects a worse baseline clinical phenotype than those with light cannabis use. Another possibility is that since these light use MED participants preferred high CBD: low THC ratios, they might be deriving more potential benefit from CBD than those preferring high THC levels, which may be associated with more negative side effects from THC. Indeed, the frequent co-morbidity of mood disorders in chronic pain may mean that the anxiolytic[21,37,72] and anti-psychotic effects of CBD,[32] as well as CBD's potentially antagonistic effects on THC-related psychoactivity might mean that CBD-dominant products have a better therapeutic profile. It is also possible that higher doses of THC may induce hyperalgesia. Indeed, a small clinical trial of capsaicin-induced pain among healthy volunteers showed that individuals who smoked 8% THC cannabis had increased evoked pain compared to those who smoked placebo cannabis.[66] However, these effects were not replicated in a subsequent trial among individuals with painful diabetic neuropathy,[67] suggesting that these effects may differ between healthy and clinical populations.

Our results also resemble trends seen among chronic daily opioid users with chronic pain, in which individuals using low, stable opioid doses tend to report better symptom management, lower pain scores,[43] and lower symptoms of depression than those who use high doses.[42] Our reported association between higher cannabis use and worsened negative affect is consistent with this trend, and is supported by a recent naturalistic study of cannabis users in which symptoms of negative affect were reduced in the short term but depressive symptoms worsened over time.[23] Such a trend is troubling, as it is similar to how daily, high doses of opioids result in off-target effects that dysregulate mood, social bonding, and other key functions of the endogenous opioid system.[2,17] We hypothesize that we may be seeing an analogous impact on the endocannabinoid system, which is similarly connected with a wide variety of complex behaviors.[46] More research into the interactions between these systems is warranted, since preclinical studies show analgesic synergism between cannabinoids and opioids that do not translate smoothly into human studies.[20,44] Further, such research may provide a better understanding of why some studies report participants being able to effectively substitute cannabis for opioids,[3,7,9,38] while others show increased opioid use or requirements among individuals using cannabis.[4,14,15] It is worth noting that the non-

medicalized context of the latter studies (e.g., Campbell et al, 2018) may have affected participant's ability to access appropriate clinical care and education about cannabis.

While heavy cannabis use does not come with the same risk profile as opioids (i.e., no overdose mortality risk), we believe it is important to consider strategies to modify cannabis use to reduce harm and maximize benefit. Just as tapering opioid doses among individuals who use chronically and daily may result in equivalent or improved pain control without negatively affecting other symptoms,[27] it is possible that tapering cannabis doses among individuals with heavy, daily cannabis use may have similar results. As we argue in a recent commentary, we support the development of guidelines that focus on harm reduction, including features such as independent verification of safety and potency testing, use of CBD-dominant products that add THC only when necessary, and on using slower onset, longer acting formulations like edibles and tinctures with proper medical guidance.[5] (Such guidelines could also mention the availability of FDA-approved cannabinoid pharmaceuticals (e.g., dronabinol, Epidiolex, and nabilone), which could be used off-label for pain.) While titration is more difficult with these longer acting products, increasing standardization and clinical guidelines would make it possible to avoid the intoxication and increased ER visits that are associated with ingesting high doses of THC.[68] Such guidelines should account for cannabis use disorder and other substance use disorders, and draw from standardized reporting protocols for other drugs[40,54] as well as existing legal structures in Canada and other countries with better regulated medical cannabis.[33]

Limitations

As with previous analyses of this cohort, inference is limited temporally by our cross-sectional study design, so it is possible that heavy users are using cannabis more frequently because they have worse clinical symptoms and thus need more medication to treat their symptoms. However, this argument is weakened by our finding that heavy users were far more likely to smoke and use high THC products than light users, which may suggest problematic use that could contribute to less adequate pain control. Our inference is also limited by selection bias due to recruitment through medical cannabis dispensaries and clinics that approve cannabis licenses, and we are also uncertain of how many people were exposed to our survey and chose not to take it. This selection bias ties into expectancy bias, especially with CBD products in which the scientific literature surrounding its use in pain is relatively weak but the hype in popular culture is omnipresent. Further, our analyses rely on the assumption that daily use frequency accurately reflects dose, which may not be the case as we did not capture quantities of active ingredients (e.g., mg of THC) consumed daily. Indeed, some individuals using cannabis once or twice a day may consume a large quantity, while others using cannabis 5 or more times per day may consume small amounts each time. However, there is great inter-individual variation in cannabis dosing effects, which depends on familiarity with/tolerance of cannabis and underlying physiological differences, so we believe that frequency of use may be a better indicator than quantity consumed.[40] While we noted distinct preferences of light use participants for long acting administration routes and low THC: high CBD products compared to moderate and heavy use participants, we did not adjust for these in our statistical modeling as our sample population was not adequately powered to account for these effects. Further, such ratios can be difficult to verify, as product

testing at dispensaries and of CBD products generally are often unreliable and product potency may vary between batches.[10,62] In addition, we did not investigate the prevalence of cannabis use disorder or other substance use disorders among our study population, which may affect participant perceptions about cannabis use and pain management. Finally, we do not account for medication interactions outside of opioids and benzodiazepines, which may limit our results as our study population reported numerous concomitant pain medications,[9] and THC may have synergistic interactions with opioids[20,44] and gabapentin.[1]

CONCLUSION

Our results show robust associations between increased frequency of daily cannabis use and worse clinical pain and associated symptoms among medical cannabis patients with chronic pain. The trend of these effects is similar to that of frequent, daily opioid use among individuals with chronic pain. These findings highlight the need for publicized cannabis use guidelines that are focused on harm reduction and delineate between cannabinoid effects and the pros and cons of different administration routes. Future prospective longitudinal studies that adequately characterize dosing are needed to examine whether and how these trends hold in individuals using medical cannabis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Greater daily frequency of cannabis use was linked with higher pain severity.
- Smoking, vaporizing, and high levels of THC were associated with heavy use.
- Tinctures, topicals, edibles, and CBD were associated with light daily use.
- Medical only cannabis use was associated with a higher symptom burden.
- Medical+recreational cannabis use was linked with a lower symptom burden.

Perspective:

Our findings suggest that lower daily cannabis use frequency is associated with better clinical profile as well as safer use behaviors (e.g., preference for CBD and non-inhalation administration routes). These trends highlight the need for developing cannabis use guidelines for clinicians to better protect patients using cannabis.

Table 1.

Demographics

	Total n=989 (100%)	Light n=307 (31%)	Moderate n=382 (38.6%)	Heavy n=300 (30.3%)	X2 or F	p
Female (%)	580 (59.0%)	183 (59.6%)	230 (60.2%)	167 (55.7%)	1.6	0.449
Age: mean ± SD	49.6 ± 13.7	52.4 ± 14.0	49.4 ± 13.6	46.9 ± 13.0	41.5	**<0.0001**
Age category					25.0	**<0.0001**
18-25	40 (4.0%)	13 (4.2%)	15 (3.9%)	12 (4.0%)		
26-34	131 (13.3%)	24 (7.8%)	51 (13.4%)	56 (18.7%)		
35-49	291 (29.5%)	89 (29.0%)	115 (30.2%)	87 (29.0%)		
50-64	379 (38.4%)	108 (35.2%)	150 (39.4%)	121 (40.3%)		
65+	147 (14.9%)	73 (23.8%)	50 (13.1%)	24 (8.0%)		
Marital status					18.5	**0.048**
Single	182 (18.5%)	48 (15.7%)	74 (19.4%)	60 (20.0%)		
Married	485 (49.2%)	169 (55.4%)	190 (49.9%)	126 (42.0%)		
Living together	145 (14.7%)	34 (11.1%)	53 (13.9%)	58 (19.3%)		
In a relationship but not living together	42 (4.3%)	12 (3.9%)	17 (4.5%)	13 (4.3%)		
Divorced	98 (9.9%)	27 (8.9%)	37 (9.7%)	34 (11.3%)		
Widowed	34 (3.4%)	15 (4.9%)	10 (2.6%)	9 (3.0%)		
Education					19.7	**0.003**
High school / GED or less	10 (1.0%)	35 (11.4%)	60 (15.7%)	56 (18.7%)		
Associates / some college, no degree	141 (14.3%)	119 (38.9%)	171 (44.9%)	142 (47.3%)		
Bachelors	432 (43.8%)	86 (28.1%)	93 (24.4%)	67 (22.3%)		
Masters/ Doctoral/ Professional	246 (24.9%)	66 (21.6%)	57 (15.0%)	35 (11.7%)		
Household Income ($US)					20.9	**0.022**
Less than $10,000	84 (8.7%)	20 (6.7%)	35 (9.4%)	29 (9.8%)		
$10,000 - $39,999	307 (31.7%)	79 (26.5%)	128 (34.4%)	100 (33.7%)		
$40,000 - $69,999	229 (23.7%)	70 (23.5%)	78 (21.0%)	81 (27.3%)		
$70,000 - $99,999	167 (17.3%)	60 (20.1%)	66 (17.7%)	41 (13.8%)		
$100,000 - $149,999	109 (11.3%)	37 (12.4%)	39 (10.5%)	33 (11.1%)		
More than $150,000	71 (7.3%)	32 (10.7%)	26 (7.0%)	13 (4.4%)		
Drinker (yes/no)	609 (69.8%)	197 (73.0%)	231 (69.8%)	181 (66.5%)	2.65	0.266
Cigarette intake					33.7	**<0.0001**
Never smoker	283 (32.4%)	119 (44.1%)	105 (31.8%)	59 (21.6%)		
Former smoker	427 (48.9%)	117 (43.3%)	159 (48.2%)	151 (55.3%)		
Current Smoker	163 (18.7%)	34 (12.6%)	66 (20.0%)	63 (23.1%)		
% not taking concomitant pain medications	383 (38.8%)	112 (36.5%)	144 (37.8%)	127 (42.5%)	2.6	0.278
Opioid analgesics (% yes)	147 (15.0%)	42 (13.8%)	59 (15.6%)	46 (15.5%)	0.5	0.780

	Total n=989 (100%)	**Light n=307 (31%)**	**Moderate n=382 (38.6%)**	**Heavy n=300 (30.3%)**	**X2 or F**	**p**
Benzodiazepines (% yes)	126 (12.9%)	41 (13.5%)	46 (12.1%)	39 (13.2%)	0.3	0.857

Table 1. Values represent frequency (n), percent (%) and mean ± standard deviation (SD). Differences assessed via Chi-square test and one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively. Tests were two tailed, with significance set at $p < 0.05$. Significant p values are bold.

Table 2.

Patient reported outcomes among frequency groups (adjusted)

N=989	Light n=307 (31%)	Moderate n=382 (38.6%)	Heavy n=300 (30.3%)	F	P
Pain severity	5.2 ± 0.1 n=288	5.6 ± 0.1 n=360	5.6 ± 0.1 n=283	3.13	**0.044**
Pain interference	4.2 ± 0.2 n=287	4.7 ± 0.2 n=360	4.7± 0.2 n=283	3.73	**0.024**[b]
Physical function	38.5 ± 0.15 n=279	39.0 ± 0.1 n=349	39.0 ± 0.1 n=277	2.86	0.058
Sleep disturbance	50.7 ± 0.5 n=280	50.8 ± 0.5 n=349	51.4 ± 0.5 n=279	0.55	0.578
Fatigue	52.7 ± 0.8 n=281	53.8 ± 0.7 n=355	52.9 ± 0.8 n=279	0.59	0.553
Depression	5.7 ± 0.3 n=284	6.1 ± 0.3 n=357	6.5 ± 0.3 n=282	1.30	0.272
Anxiety	5.5 ± 0.3 n=272	6.2 ± 0.3 n=336	6.2 ± 0.3 n=273	1.38	0.253
Cognitive function	37.0 ± 0.6 n=269	36.5 ± 0.5 n=331	36.7 ± 0.6 n=270	0.19	0.825
Positive affect	23.9 ± 0.4 n=274	24.8 ± 0.3 n=339	25.2 ± 0.4 n=276	3.25	**0.039**[b]
Negative affect	25.1 ± 0.4 n=274	26.0 ± 0.3 n=339	26.7 ± 0.4 n=276	4.84	**0.008**[b]

Table 2. Light = 1-2 uses per day, Moderate = 3-4 uses per day, Heavy =5 or more uses per day. Values represent estimated marginal mean ± standard error (SE). Adjusted for age, sex, and concomitant opioid and benzodiazepine use. Post hoc pairwise differences obtained using Bonferroni's test with paired differences in marginal means labeled a: light < moderate, b: light < heavy. Tests are two-tailed, and significance considered $p < 0.05$. Significant p values are bold.

Table 3.

Patient reported outcomes among MED and MEDREC participants by daily use frequency

	MED (n = 531)					MEDREC (n = 458)				
Subgroup	**Light n=200 (38%)**	**Moderate n=197 (37%)**	**Heavy n=134 (25%)**	**F**	**P**	**Light n=107 (23%)**	**Moderate n=185 (40%)**	**Heavy n=166 (36%)**	**F**	**P**
Pain severity	5.4 ± 0.2 n=186	6.2 ± 0.2 n=190	6.2 ± 0.2 n=127	9.1	**<0.0001**[ab]	5.2 ± 0.2 n=102	5.0 ± 0.2 n=170	5.0 ± 0.2 n=156	0.3	0.76
Pain interference	4.43 ± 0.2 n=185	5.44 ± 0.2 n=190	5.5 ± 0.2 n=127	7.8	**<0.0001**[ab]	3.9 ± 0.3 n=102	3.8 ± 0.2 n=170	3.9 ± 0.22 n=156	0.1	0.87
Physical Function	39.0 ± 0.2 n=179	39.2 ± 0.2 n=187	39.4 ± 0.2 n=126	1.0	0.372	37.8 ± 0.2 n=100	38.7 ± 0.2 n=162	38.4 ± 0.2 n=152	3.5	**0.03**[a]
Sleep Disturbance	51.3 ± 0.6 n=179	51.9 ± 0.63 n=187	52.7 ± 0.7 n=126	0.9	0.41	48.5 ± 0.8 n=101	49.3 ± 0.7 n=162	50.1 ± 0.7 n=153	1.2	0.31
Fatigue	54.5 ± 1.1 n=180	56 ± 1.1 n=189	55.2 ± 1.3 n=126	0.5	0.617	49.9 ± 1.2 n=101	51.8 ± 1.0 n=166	51.27 ± 1.0 n=153	0.8	0.45
Depression	5.9 ± 0.4 n=182	6.7 ± 0.4 n=190	7.5 ± 0.5 n=127	2.7	0.067	5.8 ± 0.6 n=102	5.6 ± 0.4 n=167	5.7 ± 0.4 n=155	0.0	0.95
Anxiety	5.6 ± 0.43 n=174	6.3 ± 0.4 n=179	7.18 ± 0.50 n=124	2.8	0.059	5.4 ± 0.5 n=98	5.9 ± 0.4 n=157	5.3 ± 0.4 n=149	0.6	0.55
Cognitive function	37.2 ± 0.8 n=174	35.0 ± 0.8 n=180	34.9 ± 0.9 n=123	2.6	0.071	37.0 ± 0.9 n=95	38.2 ± 0.7 n=151	38.0 ± 0.7 n=147	0.6	0.54
Positive Affect	23.5 ± 0.4 n=176	24.6 ± 0.4 n=181	25.2 ± 0.5 n=124	3.3	**0.037**[b]	24.6 ± 0.6 n=98	25.0 ± 0.5 n=158	25.2 ± 0.5 n=151	0.3	0.71
Negative Affect	24.7 ± 0.5 n=176	26.1 ± 0.4 n=181	26.8 ± 0.6 n=125	4.5	**0.011**[b]	25.9 ± 0.6 n=97	25.9 ± 0.5 n=158	26.7 ± 0.5 n=151	0.9	0.40

Table 3. Light = 1-2 uses per day, Moderate = 3-4 uses per day, Heavy =5 or more uses per day. Values represent estimated marginal mean ± standard error (SE). Adjusted for age, sex, and opioid and benzodiazepine. Post hoc pairwise differences obtained using Bonferroni's test with paired differences in marginal means labeled a: light < moderate, b: light < heavy. Tests are two-tailed and significance considered $p < 0.05$. Significant p values are bold.

Table 4.

Cannabinoid preferences of MED vs. MEDREC users.

	MED users					MEDREC users				
	Light n=200 (38%)	**Moderate n=197 (37%)**	**Heavy n=134 (25%)**	**X2**	**p**	**Light n=107 (23%)**	**Moderate n=185 (40%)**	**Heavy n=166 (36%)**	**X2**	**p**
Cannabis strain used										
Indica	66 (37.5%)	53 (29.4%)	42 (32.3%)	3.92	0.417	24 (24.2%)	40 (22.6%)	47 (28.5%)	3.16	0.531
Sativa	15 (8.5%)	24 (13.3%)	15 (12.3%)			14 (14.1%)	18 (10.2%)	21 (12.7%)		
Hybrid	95 (54.0%)	103 (57.2%)	72 (55.4%)			61 (61.6%)	119 (67.2%)	97 (58.8%)		
Ratio preference (% yes)	141 (70.5%)	138 (70.1%)	91 (67.9%)	1.8	0.410	67 (62.6%)	138 (74.6%)	110 (66.3%)	5.5	0.063
Preferred THC:CBD ratio				46.0	**<0.0001**				37.5	**<0.0001**
High THC : low CBD	14 (9.9%)	24 (17.1%)	13 (14.3%)			16 (23.9%)	29 (21.0%)	33 (30.0)%)		
High THC : high CBD	39 (27.7%)	45 (32.6%)	55 (60.4%)			17 (25.4%)	63 (45.7%)	60 (54.5%)		
Low THC : high CBD	66 (46.8%)	49 (35.5%)	17 (18.7%)			27 (40.3%)	31 (22.5%)	8 (7.3%)		
Low THC : low CBD	4 (2.8%)	7 (5.1%)	0 (0.0%)			2 (3.0%)	6 (4.3%)	1 (0.9%)		
Only THC	4 (2.8%)	1 (0.7%)	1 (1.1%)			1 (1.5%)	3 (2.2%)	2 (1.8%)		
Only CBD	9 (6.4%)	3 (2.2%)	1 (1.1%)			1 (1.5%)	2 (1.4%)	0 (0.0%)		
Other	5 (3.5%)	9 (6.5%)	4 (4.4%)			3 (4.5%)	4 (2.9%)	6 (5.5%)		
Administration routes (% answered)	186 (93%)	194 (98.5%)	130 (97.0%)			104 (97.2%)	183 (98.9%)	164 (98.8%)		
Smoking	79 (42.5%)	111 (57.2%)	97 (74.6%)	31.8	**<0.0001**	86 (82.7%)	159 (86.9%)	156 (95.1%)	19.4	**0.0007**
Rank 1 and 2	57 (30.6%)	83 (42.8%)	80 (61.5%)	35.6	**<0.0001**	64 (61.5%)	139 (76.0%)	136 (82.9%)	8.6	**0.01**
Vaporizing	101 (54.3%)	133 (68.6%)	110 (84.6%)	31.6	**<0.0001**	83 (79.8%)	145 (79.2%)	143 (87.2%)	4.7	0.32
Rank 1 and 2	84 (45.2%)	111 (57.2%)	79 (60.8%)	39.3	**<0.0001**	65 (62.5%)	111 (60.7%)	107 (65.2%)	0.36	0.83
Edible	116 (62.4%)	121 (62.4%)	92 (70.8%)	2.7	0.256	82 (78.8%)	140 (76.5%)	131 (79.9%)	0.61	0.739
Rank 1 and 2	82 (44.1%)	59 (30.4%)	46 (35.4%)	16.8	**0.002**	39 (37.5%)	58 (31.7%)	58 (35.4%)	1.4	0.84
Topical application	98 (52.7%)	98 (50.5%)	66 (50.8%)	0.1	0.932	46 (44.2%)	88 (48.1%)	88 (53.7%)	2.4	0.298
Rank 1 and 2	38 (20.4%)	41 (21.1%)	16 (12.3%)	5.8	0.21	11 (10.6%)	19 (10.4%)	8 (4.9%)	9.3	0.053
Tincture	115 (61.8%)	117 (60.3%)	79 (60.8%)	0.0	0.979	57 (54.8%)	89 (48.6%)	82 (50.0%)	1.0	0.594

	MED users					MEDREC users				
	Light n=200 (38%)	**Moderate n=197 (37%)**	**Heavy n=134 (25%)**	**X2**	**p**	**Light n=107 (23%)**	**Moderate n=185 (40%)**	**Heavy n=166 (36%)**	**X2**	**p**
Rank 1 and 2	81 (43.5%)	65 (33.5%)	31 (23.8%)	18.9	**0.0008**	24 (23.1%)	31 (16.9%)	8 (4.9%)	22.7	**0.0001**

Table 4. Values represent frequency (n), percent (%) and mean ± standard deviation (SD) for categorical and continuous variables, respectively. Differences assessed via Chi-square test. Tests were two tailed, with significance set at $p < 0.05$. Significant p values are bold.