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Predictors of Response to Medical Cannabis for Chronic Pain: A Retrospective Review of Real-Time Observational Data

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ABSTRACT

Objective: People living with chronic pain increasingly use medical cannabis for symptom relief. We conducted a retrospective cohort study examining cannabis for chronic pain relief using anonymous archival data obtained from the medicinal cannabis tracking app, Strainprint®. **Method:** We acquired cannabis utilization data from 741 adults with chronic pain and used multilevel modeling to examine the association of age, sex, type of pain (muscle, joint or nerve pain), cannabis formulation (high CBD, balanced CBD:THC, or high THC), route of administration (inhaled or ingested), cannabis use before vs. during the COVID-19 pandemic, and duration of cannabis use, with pain relief. **Results:** Most patients were female (n = 464; 63%), with a mean age of 39 (SD = 11), and our cohort had completed a total of 83,622 tracked cannabis sessions through Strainprint. The majority of sessions reported use of inhaled cannabis products (78%), typically with high tetrahydrocannabinol (THC; 64%) versus high cannabidiol (CBD; 15%) or balanced THC:CBD (21%) products. The median change in pain scores across sessions was -3.0 points on a 10-point numeric rating scale (NRS; IQR -4.5 to -2.0). In our adjusted model, greater pain relief was associated with male vs. female sex (-0.69 points on a 10-point NRS; 95%CI -0.46 to -0.91). We found statistically significant, but trivial associations with joint pain (-0.05 points), balanced THC:CBD products in the long term (-0.003 points), and cannabis use during the pandemic (0.18 points). **Conclusions:** We found that people living with chronic pain report important pain relief when using cannabis for medical purposes, and that men may achieve greater pain relief than women.

Key words: = cannabis; marijuana; chronic pain; mobile application; cohort; Strainprint

Approximately one in five adults suffer from chronic pain globally (Goldberg & McGee, 2011). The severity of symptoms and functional limitations are variable and have been associated with underlying pathology, age, sex, and mental health status (Reyes Velez et al., 2021; Treede et al., 2015). Medical cannabis is an increasingly popular treatment for chronic pain, however, clinical trials typically evaluate a narrow range of products consumed through one route of administration (ingestion; Busse et al., 2021) which has uncertain generalizability to the wide range of products available to patients.

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Although medical cannabis has been found to provide modest relief from chronic pain, pooled estimates across trials show substantial unexplained heterogeneity (Wang et al., 2021), suggesting the possibility that effectiveness may vary depending on patient or product characteristics. For example, a prospective cohort study of 551 people living with chronic pain and using cannabis for medical purposes found that achieving ≥30% reduction in pain at 1-year was positively associated with lower body mass index, long to normal sleep duration, and lower depression scores at baseline, and negatively associated with neuropathic pain (Aviram et al., 2021). Another cohort study of 2,987 individuals using cannabis products to manage chronic pain found that higher tetrahydrocannabinol (THC) products were associated with both greater pain relief and increased risk of side effects (Li et al., 2019).

Clinical trials typically randomize patients to a single type of cannabis product that they adhere to for the duration of the study, whereas in practice patients may alter their method or frequency of consumption, or change products based on response. Although observational data is unable to establish causality, patient data in naturalistic conditions can help inform practical patterns of use that may identify promising interventions for clinical trials (United States Food and Drug Administration (FDA), 2018). We conducted a retrospective study of medical cannabis use among people living with chronic pain to evaluate the different types of products in use, associations with pain relief, and factors that may influence treatment effects.

METHODS

We conducted a retrospective cohort study examining cannabis use for chronic pain with anonymous archival data obtained from the medicinal cannabis tracking app, Strainprint (https://strainprint.ca/). Strainprint is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the Personal Information Protection and Electronic Documents Act (PIPEDA), and the Personal Health Information Protection Act (PHIPA), and individuals who register on the app sign a Consent to Collection and Use of Data form for research purposes. We adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Vandenbroucke et al., 2007) for our study, which was approved by the Hamilton Health Sciences-McMaster Research Ethics Board (project no. 10562).

Upon initial use of the Strainprint app (Strainprint Technologies Inc., 2020), individuals are prompted to enter demographic information, such as date of birth and sex, plus the conditions and symptoms on a pulldown menu that they hope to address with cannabis. Users are then prompted to rate the severity of each symptom on a 0 to 10-point numeric rating scale (NRS) prior to cannabis use. Higher scores indicate greater pain on the 10-point NRS, and the minimally important difference is -1.5 points (Wang et al., 2023). Next, they select the cannabis product they are using (i.e., flower, oil, capsule, edible, vape pen cartridge, concentrate), route of administration (i.e., vape, oil, smoke, edible, pill, tincture, spray, concentrate, dab bubble, dab portable, topical), and dose (i.e., mgs for soft gel, mls for oils, puffs for inhaled products) for each session. Strainprint records the cannabis product used, linked to a certificate of analysis confirming the levels of THC and cannabidiol (CBD).

After an onset period that is defined by the chosen route of administration (e.g., 10 minutes for inhalation, 60 minutes for ingestion), users are prompted with a push notification to complete their session by rating their post-use symptom severity on the same 10-point numeric scale. For each session, a change score is generated by subtracting the initial symptom severity from the symptom severity after cannabis use. Since some users have multiple sessions per day, we used the average change score for each day of cannabis use to calculate the daily average change score for all users.

Inclusion Criteria

All individuals (Canadian adults ≥18 years of age) who entered session data into Strainprint regarding use of cannabis for relief from muscle, joint or nerve pain, from February 2017 to November 2020, were included in our study. We only included data from individuals that inhaled or ingested medical cannabis, as other methods (e.g., topical) were rarely endorsed. We attempted to exclude individuals using cannabis for acute

pain or non-pain complaints by removing those with less than 30 days of cannabis use (i.e., less than 30-days between their first and last recorded cannabis sessions), or who reported mild pain or less at baseline (i.e., < 4 on a 0 to 10-point NRS for pain). We excluded patients that recorded sessions with cannabis products that did not have an accompanying certificate of analysis to confirm THC:CBD composition. Individuals with missing data for age or sex were also excluded.

Cannabis Chemotypes

We used the classification system proposed by Jikomes & Zoorob (Jikomes & Zoorob, 2018) to classify cannabis products in the dataset as either high THC, high CBD, or a balanced ratio of THC:CBD (Table 1).

Table 1. *Cannabis Chemotypes Defined by the Ratio of THC to CBD*

Chemotype	THC:CBD Ratio
High THC (Chemotype I)	5:1 or greater
Balanced THC:CBD (Chemotype II)	Less than 5:1 and greater than 1:5
High CBD (Chemotype III)	1:5 or lower

Data Analysis

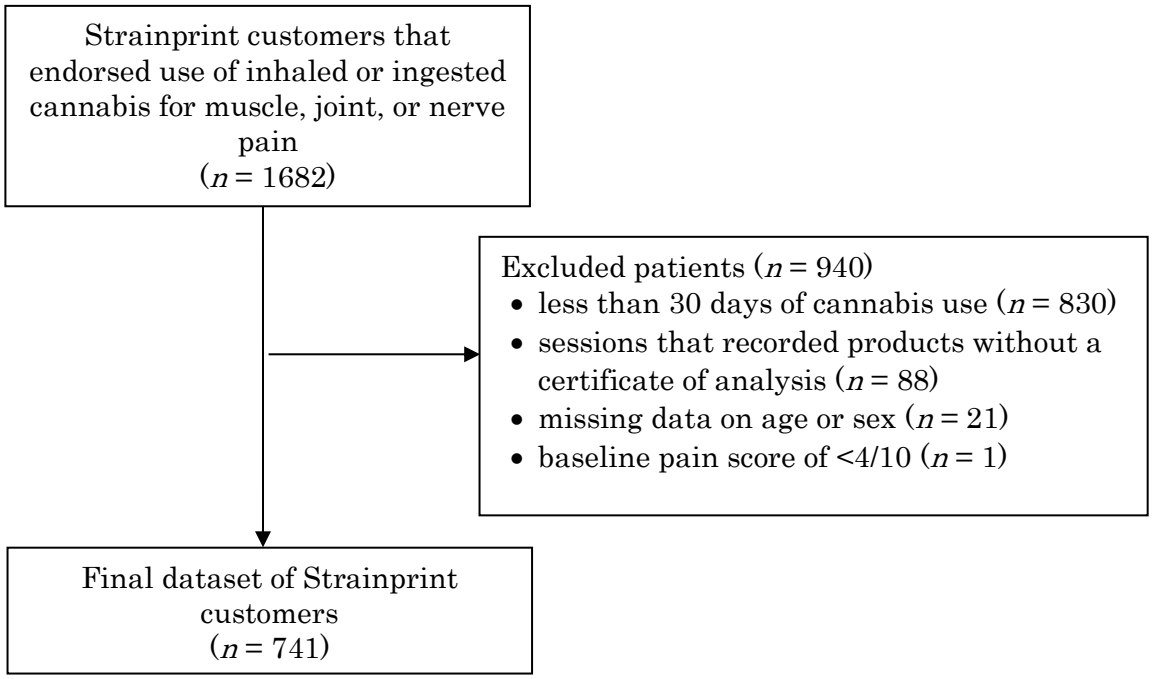
We used descriptive statistics to summarize demographic information. We reported categorical data as proportions, and continuous data as means and standard deviations (*SD*s) if normally distributed and as medians and interquartile ranges (*IQR*s) if not. We defined a product change when patients switched from one cannabis product to another (high CBD, balanced ratio of THC:CBD, high THC), and added up the number of changes for each patient. We constructed a multilevel linear mixed effects model to explore the associations of age, sex, type of pain (i.e., muscle, joint, or nerve pain), cannabis formulation (high CBD, balanced CBD:THC, or high THC), route of administration (inhaled or ingested), duration of medical cannabis use, and cannabis use before vs. during the COVID-19 pandemic, with change in pain scores after treatment.

A linear mixed effects model allows for examination of change in pain score by considering both within- and between-subject variability despite differences in the number of observations across individuals. It estimates time-variant slope variables at the within-subject level that are then used to predict change at the between-subject level. Our model included fixed effect terms for age at baseline (for every 10-year increase), sex (female vs. male), and type of chronic pain (muscle vs. joint vs. nerve pain). We also included an interaction term (cannabis*duration) to account for possible interactions between cannabis formulation and duration of use. We modelled our independent factors and outcome (pain change scores) as functions of time/sessions at the within-subjects level, and used the slopes of these regressions (i.e., regression coefficients) to test for between-subjects level effects. We conducted covariance structure modeling for our linear mixed model, which combines factor analysis, path analysis, and multiple regression to model the relationships between observed and unobserved variables. Selection of a covariance structure that is too simple leads to the loss of precision in parameter estimates, whereas choosing one that is too complex can result in the loss of parsimony and efficiency. There are several covariance structures that can be tested to identify a best fit for model data (e.g., autoregressive, compound symmetry, unstructured, variance components; Kaplan, 1990). We found an unstructured covariance matrix for perceived stress most optimized the fit statistics (Akaike's Information Criterion, Bayesian Information Criterion) to predict changes in pain severity over time. Negative coefficients indicate reduction in pain. All statistical analyses were performed with Stata 15.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Our cohort was comprised of 741 individuals that used cannabis for chronic pain and entered a total of 83,622 Strainprint sessions. (Figure 1). The median age of participants was 39 years (*IQR* 31 to 46), and approximately two thirds of Strainprint users were female (63%). Treatment sessions most often targeted joint pain (41%) or muscle pain (40%), with nerve pain being the focus for 19% of total sessions (Table 2).

Figure 1. *Participant Flow Diagram*



Inhaled products were used for 78% of treatment sessions, with 45% delivered by vaporizer and 32% by smoking. The remaining 22% of treatment sessions involved ingesting cannabis products, mostly (21%) by consumption of cannabis oil. Two-thirds of treatment sessions (65%) involved high THC cannabis products, 21% used products with a balanced THC:CBD ratio, and only 15% involved high CBD products. Participants recorded a median of 24 sessions (*IQR* 9 to 93), and the median duration for use of the Strainprint app was 214 days (*IQR* 85 to 490). Participants changed products a median of 2 times (*IQR* 0 to 11) over the course of their recorded cannabis use (Table

Table 2. *Participant and Product Characteristics (n = 741 participants, 83,622 sessions)*

Age, mean (SD)	38.9 years (11.1)
Gender, *n* (%)	
Female	464 (63%)
Male	277 (37%)
Type of pain treated per session, *n* (%)	
Joint pain	34,202 (41%)
Muscle pain	33,736 (40%)
Nerve pain	15,684 (19%)
Route of administration per session, *n* (%)	
Ingested*	
Oil	17,698 (21%)
Sublingual oil	606 (0.7%)
Sublingual tincture	43 (0.1%)
Inhaled	
Vaporized	37,303 (45%)
Smoked	26,738 (32%)
Concentrate	1,104 (1%)
Dab bubbler	100 (0.1%)
Dab portable	30 (0.04%)
Cannabis chemotype per session, *n* (%)	

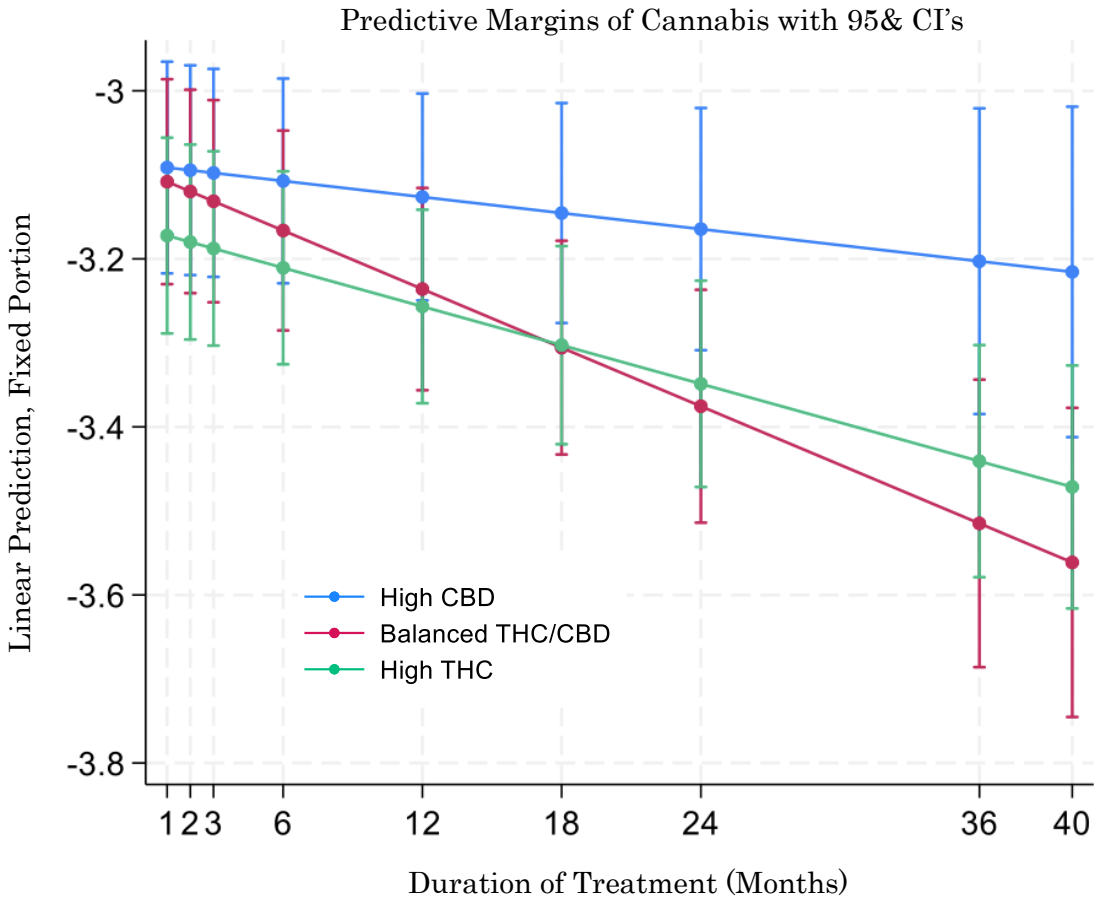
High THC	
Balanced THC:CBD	
High CBD	
No. of treatment sessions, median (*IQR*)	24 (9 to 93)
Treatment duration, median (*IQR*)	214 days (85 to 490)
No. of product changes during treatment, median (*IQR*)†	2 (0 to 11)

Note. * Oil products are either oil-filled capsules that are swallowed, or liquid cannabis-infused oil that is taken orally with a dropper. Sublingual oil is administered under the tongue for faster absorption.
†The total number of changes from one product to the other.

Impact on Pain

The median reported change in pain scores across treatment sessions for participants was -3.0 points on a 10-point NRS (*IQR* -4.5 to -2.0). Our linear mixed model found that male sex was associated with greater pain relief versus female sex (-0.69 points, 95%CI -0.91 to -0.46). Other factors showed either no significant association, or associations that were statistically significant but trivial. Specifically, joint pain was associated with a -0.05-point reduction in pain vs. muscle pain, cannabis products with a balanced ratio of THC:CBD at longer term use showed a -0.01-point reduction in pain vs. high CBD products at shorter term use, and cannabis use during the COVID-19 pandemic was associated with a 0.18-point increase in pain severity (Figure 2, Table 3).

Figure 2. *Predictive Margins for Three Types of Cannabis and Duration of Treatment*



Note. *Negative values represent pain reduction on a 10-point numeric rating scale for pain.

Table 3. *Linear Mixed Effect Model for Pain Reduction*

Factors		beta coefficient (95%CI)	*p*-value.
Age	every 10-year decrease	-0.006 (-0.10 to 0.09)	.90
Sex	Female	reference	
	Male	-0.69 (-0.91 to -0.46)	<.001
Symptom	Muscle pain	reference	
	Joint pain	-0.05 (-0.08 to -0.01)	.01
	Nerve pain	-0.03 (-0.08 to 0.02)	.22
Chemotype	High CBD	reference	
	Balanced THC/CBD	-0.01 (-0.08 to 0.06)	.82
	High THC	-0.08 (-0.14 to -0.01)	.02
Route of Administration	Inhaled	reference	
	Ingested	-0.04 (-0.10 to 0.007)	.09
Duration of treatment (months)	every 1-month increase	-0.003 (-0.008 to 0.002)	.20
Cannabis x Duration	High CBD at shorter term	reference	
	Balanced THC/CBD at longer term	-0.003 (-0.008 to -0.003)	.004
	High THC at longer term	-0.004 (-0.01 to 0.001)	.08
COVID-19 pandemic	Before pandemic	reference	<.001
	During pandemic†	0.18 (0.12 to 0.25)	

Note. * Negative values represent pain reduction on a 10-point numeric rating scale for pain.
† The World Health Organization declared COVID-19 viral disease a pandemic on March 11, 2020.

DISCUSSION

Our study of a consecutive cohort of 741 individuals using cannabis for relief from chronic pain found the majority were seeking to address joint or muscle-related pain with inhaled products, most often administered with a vaporizer. Two thirds of all recorded treatment sessions involved high THC products, and participants changed products a median of 2 times over the course of their recorded cannabis use. On average, participants reported large reductions in pain across treatment sessions with a median reduction that was double the minimally important difference, and male sex was associated with greater pain relief versus female sex.

Relevant Literature

Our findings are aligned with previous observational reports of cannabis use for chronic pain (Lee et al., 2023; Li et al., 2019; Tait et al., 2023); however, the reductions in pain we observed (median of -3 points on a 0-10 point NRS) was much larger than randomized trials have reported when accounting for non-specific effects

(weighted mean difference of -0.5cm on a 10cm VAS; Cuttler et al., 2022; Li et al., 2019; Wang et al., 2021). The most recent clinical practice guideline made a conditional recommendation for the use of non-inhaled medical cannabis for chronic pain due to the close balance between benefits and harms along with high variability in patient preferences (Busse et al., 2021).

The state of the evidence on sex dependant differences in pain reduction after the administration of cannabinoids is limited, and preclinical evidence has shown mixed results. Female rodents may exhibit greater reductions in pain after acute treatment with cannabinoids relative to male rodents; however, these differences may attenuate or even show larger benefits in male rodents with repeated cannabis administration (Cooper & Haney, 2016; Craft et al., 2013). An experimental study that looked at pain responses after the administration of a cold-pressor test found that men had decreased pain sensitivity after they consumed THC while women had no decrease (Cooper & Haney, 2016). Further, a prior observational study of 1249 chronic pain patients using vaporized THC found no difference in pain relief between men and women, but also suffered from a 47% loss to follow-up that may have introduced bias.(Aviram et al., 2023) Whether men or women benefit more from using medical cannabis for pain relief remains uncertain and further research is needed to address this knowledge gap.

We found cannabis use during the COVID-19 pandemic was slightly less effective for pain relief. This is unlikely to be due to reduced access, as cannabis sales in general increased during the pandemic;(MacKillop et al., 2021) however, 78% of cannabis consumed by participants in our cohort was inhaled and respiratory infection due to COVID-19 may have resulted in reduced intake. We also found that cannabis products with balanced ratios of THC:CBD were slightly more effective than high CBD products at longer term use, and cannabis was slightly more effective for joint vs. muscle pain. While these findings are consistent with prior cohort studies (Aviram et al., 2023; Li et al., 2019), the associations we found were statistically significant but clinically trivial. Our findings highlight the importance of presenting associations in absolute terms to facilitate interpretation (Busse et al., 2015).

The way that individuals consumed cannabis in our dataset was diverse and we found that switching products was common. A likely explanation for this behaviour could be attempts by patients to improve symptom relief, reduce adverse effects, or both. Additional factors which could result in switching products may include lack of availability or price changes. Our findings are in-line with a prior study wherein, over a 12-month period, 86% of medical cannabis patients changed the type of product they were using (Kalaba et al., 2021). Additionally, some researchers have found that medical cannabis users may administer multiple products and different routes of administration to relieve different symptoms, a practice termed "dose layering" (Boehnke et al., 2019).

Limitations

There are several limitations to this study. First, all the data used in our study is self-reported and users may not accurately report the product or dose they used. Second, Strainprint does not require users to distinguish between acute and chronic pain. We did remove participants from our dataset that used cannabis for less than 30 days to focus on chronic pain, and the median duration of cannabis use among our participants was 214 days (*IQR* 85 to 490) which suggests most pain complaints were chronic. Third, the lack of a control group was another important limitation that introduced non-specific effects. Further, patients that find benefit from cannabis may be more likely to continue use, while those that do not benefit may not. Therefore, our data may over-represent individuals that derive benefit from using medical cannabis.

Conclusion

Our analysis of observational data from chronic pain patients who use medical cannabis found large reductions in pain, and that men were more likely to experience greater pain relief than women. Our findings require confirmation in rigorously conducted randomized trials that include a placebo control to account for non-specific effects. Future trials should also consider allowing participants to modify their cannabis product after randomization, based on response, to reflect real-world practices.

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