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The effectiveness of self-directed medical cannabis treatment for pain

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ABSTRACT

The prior medical literature offers little guidance as to how pain relief and side effect manifestation may vary across commonly used and commercially available cannabis product types. We used the largest dataset in the United States of real-time responses to and side effect reporting from patient-directed cannabis consumption sessions for the treatment of pain under naturalistic conditions in order to identify how cannabis affects momentary pain intensity levels and which product characteristics are the best predictors of therapeutic pain relief. Between 06/06/2016 and 10/24/2018, 2987 people used the ReleafApp to record 20,513 cannabis administration measuring cannabis' effects on momentary pain intensity levels across five pain categories: musculoskeletal, gastrointestinal, nerve, headache-related, or non-specified pain. The average pain reduction was –3.10 points on a 0–10 visual analogue scale (SD = 2.16, d = 1.55, $p < .001$). Whole *Cannabis* flower was associated with greater pain relief than were other types of products, and higher tetrahydrocannabinol (THC) levels were the strongest predictors of analgesia and side effects prevalence across the five pain categories. In contrast, cannabidiol (CBD) levels generally were not associated with pain relief except for a negative association between CBD and relief from gastrointestinal and non-specified pain. These findings suggest benefits from patient-directed, cannabis therapy as a mid-level analgesic treatment; however, effectiveness and side effect manifestation vary with the characteristics of the product used.

1. Introduction

Chronic pain afflicts more than 20% of adults[1,2] and is the most financially burdensome health condition faced by Western societies; exceeding, for example, the combined direct and indirect costs (e.g., sick leaves and early retirement) of treating heart disease *and* cancer in the United States (U.S.), and by more than three times, the costs devoted to the prevention and treatment of diabetes.[3–6] The over-prescribing of opioid medications has compounded this burden due to the prevalence and severity of adverse side effects,[7] unintended interactions with other medications,[8] rates of misuse,[9–11] and risk of overdose, which currently takes the lives of roughly 115 Americans a day.[12–14]

Medical cannabis is rapidly gaining popularity as a mid-level analgesic and promising substitute for prescription opioids for treating various chronic pain conditions.[15,16] Unfortunately, historical federal regulatory barriers to assessing the *Cannabis* plant's potential therapeutic effects have largely limited research to clinical investigations of the pharmacodynamics of synthetic analogue medications or cannabis-derived formulates neither widely used nor generalizable to the extensive range of products currently sold in state-legal medical cannabis dispensaries.[17,18] Aggregate state-level and region-specific analyses and large correlational survey studies suggest that many patients substitute legal medical cannabis for prescription opioids in vivo.[19–24] While potentially offering greater external validity than clinical experiments, these studies cannot sufficiently rule out certain confounds (e.g., memory biases, social desirability responses, selection bias, and unrelated omitted correlates) to measuring cannabis' effects on individual-level pain experiences. More importantly, no previous studies adequately account for the range of products available at medical cannabis dispensaries or the complexity of patients' treatment decisions when pain is actually experienced. According to the National Academies of Sciences, Engineering, and Medicine 2017 Committee on the Health Effects of Marijuana,

> "While the use of cannabis for the treatment of pain is supported by well-controlled clinical trials … very little is known about the

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efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States".[17]

We fill this void in the scientific literature by using the largest database of real-time cannabis administration sessions in the U.S. to examine how common cannabis product characteristics affect self-reported pain relief and side effect manifestation. The mobile software application, Releaf App™,[25]was designed to help patients navigate the variable nature of cannabis-based products available to the general public by recording cannabis usage at the actual session-level, including product types, routes of administration, labeled product characteristics, and major cannabinoid contents, along with a wide array of potential symptoms, changes in symptom severity levels, and experienced side effects of cannabis usage in real time. While some product characteristics, such as the distinction between "*C. indica"* versus "*C. sativa"* plant strains, may not accurately represent the actual chemovars and phytocannabinoid-terpene-terpenoid synergy or "entourage effect" that people experience from using whole, natural *Cannabis* plants,[26–30] we take advantage of the opportunity to measure the relative associations between the most common product characteristics available to consumers and hence the characteristics which patients often make product decisions. The current analyses used data from people who consumed cannabis therapeutically for immediate to short-term relief (within 4 h) of pain intensity falling within one of several possible pain categories. Users recorded subjective pain intensity levels prior to and following normative cannabis consumption, along with information on a wide range of side effects as experienced by the patients under typical in vivo conditions.

2. Methods

2.1. Study design

The Institutional Review Board at the University of New Mexico approved the study design. Anonymized data were obtained through the owner of the Releaf App™, MoreBetter, Ltd., and are subject to an investigator confidentiality agreement. The Releaf App™ mobile software was designed to record real-time effects of consuming cannabis for any given user-defined session (enabling recording of multiple symptoms and multiple symptom levels per session). In each user-administered session, the patient specifies the symptoms to be treated along with a battery of user-described and other potentially available (e.g., labeled) product characteristics, reports a starting symptom intensity level, consumes the cannabis product, updates the symptom level, records side effects, and ends the dosing session.[31],[32] The Releaf App™ includes 11 pain-related symptoms and 47 side effects (called "feelings" in the user interface) crowd-sourced among Releaf App™ developers, beta testers, dispensaries, and patients. Each user-administered session can include tracking relief across multiple symptoms, but only one side effect profile recording is available (i.e., indicated side effects are submitted one time per session). The study sample includes treatment sessions with a pain symptom reported, starting pain intensity levels greater than 0 (on a 0–10, 11-point visual analogue scale), and ending pain intensity levels reported within 4 h (as well as robustness checks using sessions that ended within one to three hours.) The final analysis sample includes 2987 users who completed 20,513 cannabis administration sessions, including starting and ending symptom levels, between 06/06/2016 and 10/24/2018. The analysis sample consists of 53.5% of total users (5588) and 34.3% of total sessions (59,997) recorded within the Releaf App™ between those dates with exclusion primarily due to non-recording of a final symptom level within four hours.

2.2. Study outcomes

The study objective is to estimate changes in pain severity (pain relief) and the prevalence of side effects associated with cannabis consumption, and whether these effects differ by product characteristics. We measure pain relief by subtracting the ending pain intensity level from the starting pain intensity level, resulting in pain relief outcomes ranging between -10 (maximum pain relief) and 9 (minimum pain relief/maximum increase in pain severity). The 47 possible side effects are categorized as 17 negative side effects, 19 positive side effects, and 11 context-specific side effects (see Supplemental Table S1). We convert these categories of side effects into dummy variables indicating if the user reported any of the side effects in the category and continuous variables measuring the share, or proportion, of total side effects in each category that the user selected. The most commonly reported negative side effects are dry mouth (31%) and feeling foggy (21%), the most frequent positive side effects are feeling relaxed (61%) and peaceful (50%), and the most common context-specific side effects are feeling high (41%) and thirsty (30%).

2.3. Statistical analysis

We use means comparisons to estimate the change in pain intensity levels resulting from cannabis consumption. Mixed-effects models are then used to analyze the effects of product characteristics on pain relief and the prevalence of side effects. We regress pain relief on the product characteristics separately. For the cannabinoid analyses and side effect outcomes, we include all the product characteristics and focus on the most common type of cannabis products, combustibles (dried natural flower and concentrates). Potency levels were the least reported product characteristics due to variability in product origins (e.g., private or commercial retail) and labeling practices throughout the U.S. To facilitate comparison across pain categories, we aggregate the eleven reported pain symptoms across the five categories: Gastrointestinal (abdominal, cramping, gastrointestinal, or menstrual pain), Musculoskeletal (back, joint, or muscle pain), Headache (headache or migraine), Nerve (nerve pain) and Other (other/non-specified pain). Starting pain level is included in all regressions because it is a strong predictor of symptom relief.[31],[32] To estimate the mixed-effects model, all estimates of slopes and intercepts were allowed to vary randomly by user, and standard errors are clustered at the user level to account for heteroscedasticity and arbitrary correlation at the user level. Analyses were conducted using Stata 15.1.

3. Results

Table 1 presents the numbers of users who entered each type of information, descriptive statistics for the product characteristics at the session-symptom level (e.g., % out of all the total symptoms and session recordings), the average starting and ending pain intensity levels (at the symptom level), and the prevalence of side effects (at the session level). The sample size changes due to non-reporting of product characteristics (Supplemental Fig. 1 depicts the starting and ending pain intensity and pain relief for each of the five different pain categories). Table 2 shows the results from regressing the change in pain level on product characteristics with each column representing a separate regression. Column 1 presents the effect of product type on pain relief. Sessions involving the use of flower resulted in similar pain relief to that experienced in sessions using the use of concentrates and topicals while sessions involving edibles, pills, and tinctures resulted in less pain relief relative to those involving flower. Column 2 indicates that strains labeled as "*C. sativa"* are associated with less pain relief than "hybrid" plants while Column 3 suggests that pain relief does not vary with combustion method. Column 4 shows that when other product characteristics are not controlled for, THC and CBD levels are not statistically significant predictors of pain relief. Column 5 includes all predictor variables for flower and concentrates, the most commonly used product types, and shows that, after controlling for product type, labeled plant phenotype and combustion method, higher THC levels are

Table 1
Descriptive statistics.

	Mean	Std. Dev.
Panel A: Product Type (20,513 user-sessions, 2987 users)		
Concentrate	0.26	0.44
Edible	0.06	0.24
Dried Flower	0.58	0.49
Pill	0.00	0.05
Tincture	0.08	0.27
Topical	0.01	0.09
Panel B: Labeled Plant Phenotype (16,703 user-sessions, 2579 users)		
"Hybrid"	0.48	0.50
"C. indica"	0.32	0.47
"C. sativa"	0.20	0.40
Panel C: Combustion Method (14,314 user-sessions, 2568 users)		
Joint	0.09	0.29
Pipe	0.35	0.48
Vape	0.56	0.50
Panel D: THC (7803 symptom-sessions, 1237 users)		
Average THC%	29.50	23.59
THC < 10%	0.17	0.37
THC 10-19%	0.27	0.45
THC 20-34%	0.33	0.47
THC 35%+	0.23	0.42
Panel E: CBD (6048 user-sessions, 1014 users)		
Average CBD%	12.04	17.48
CBD < 1%	0.21	0.41
CBD 1-9%	0.40	0.49
CBD 10-34%	0.29	0.45
CBD 35%+	0.10	0.30
Panel F: Outcome and Control Variables (20,513 user-sessions, 2987 users)		
Average Starting Pain Level	5.87	1.99
Average Ending Pain Level	2.77	2.02
Average Pain Intensity Change	−3.10	2.16
Panel G: Pain categories (20,513 user-sessions, 2987 users)		
Gastrointestinal	0.12	0.32
Musculoskeletal	0.58	0.49
Headache	0.12	0.33
Nerve	0.09	0.29
Other	0.09	0.29
Panel H: Side Effects (11,705 user-sessions, 2501 users)		
Any Negative Side Effect	0.67	0.47
% of Negative Side Effects	0.10	0.11
Any Positive Side Effect	0.94	0.24
% of Positive Side Effects	0.23	0.17
Any Context-Specific Side Effect	0.78	0.41
% of Context-Specific Side Effects	0.19	0.17

Notes: The averages for THC and CBD potency, and starting, ending, and change in pain intensity levels across the sessions are shown. Mean and SD values for the product characteristics, pain conditions, and side effects are also at the symptom level, and indicate the frequencies and dispersion across all the total symptom sessions. The eleven pain symptoms are grouped into five pain categories: Gastrointestinal (abdominal, cramping, gastrointestinal, or menstrual pain), Musculoskeletal (back, joint, or muscle pain), Headache (headache or migraine), Nerve (nerve), and Other (other). Nineteen positive, seventeen negative, and eleven context-specific side effects were available for selection.

the strongest independent predictors of greater pain relief while higher CBD levels are generally associated with lower pain relief. In all columns, a higher starting pain level is associated with greater pain relief. Regressions analyzing user sessions that ended within one to three hours showed similar patterns of findings (see Supplemental Table S2).

Table 3 presents regressions of side effects on product characteristics, including all product characteristics for flower and concentrates. Use of concentrates is associated with less reporting of positive side effects and weakly associated with more reporting of negative side effects. Vaping is associated with reduced reporting of context-specific side effects. *C. indica*-labeled products appear to be weakly associated with more reporting of negative side effects and less reporting of positive effects, but not associated with context-specific side effects. Higher THC is associated with increased reporting of positive and context-specific side effects, while there is also suggestive evidence that higher CBD levels are associated with decreased reporting of negative and context-specific side effects. Given that concentrates can have THC levels higher than 35% while flower cannot, we repeat the analyses of pain relief and side effects including only sessions involving the use of *Cannabis* flower to ensure uniformity. The results are similar to those reported in Tables 2 and 3 (see Supplemental Table S3 for detailed results).

Table 4 compares the effect of product characteristics on pain relief across pain categories, again limited to flower and concentrates, and including all the product characteristics. For users with headache or migraine pain, labeled plant phenotype and combustion method were predictors of pain relief; products labeled as *"C. indica"* are associated with less reported pain relief relative to "hybrid" products, and using a pipe and vaping are associated with less pain relief compared to smoking a joint. As shown in Fig. 1, THC and CBD levels affect pain relief differently across pain categories. The positive association between high THC and pain relief in the overall results is driven by users with back, joint, or muscle pain, users with headache or migraine, and users with non-specified pain. For users with abdominal pain, cramping, gastrointestinal pain, or menstrual pain, a 10–14% THC level is weakly associated with less symptom relief relative to THC levels below 10%. The negative association between CBD level and symptom relief is only prevalent among users with abdominal pain, cramping, gastrointestinal pain, or menstrual pain and users in the non-specified pain category. For users in the musculoskeletal, headache and migraine, and nerve pain categories, CBD levels had neither a positive or negative independent effect on pain relief, after controlling for THC levels and other product characteristics.

4. Discussion

Randomized clinical trials cannot adequately take into consideration the many contexts in which pain is experienced and myriad factors that influence in vivo pain experiences and patient treatment decisions, including tissue stress and damage (e.g., physical disease and injury) and peripheral and central nociception (i.e., afferent input and brain processing), as well as mental thoughts (e.g., memories), emotions, situational circumstances, and social settings.[33–37] This is the first study to measure how consumption of the wide variety of cannabis-based products used under natural conditions affects real-time changes in momentary pain intensity and experienced side effects. We use data from the Releaf App™, a publicly available software program that allows people to record the short-term effectiveness of self-managed medical cannabis treatment and thus is creating the largest repository of measurements of patient-reported pain intensity levels prior to and following consumption of commercially available cannabis-based products in the U.S. In our sample, we observed an average pain reduction of roughly 3 points on a standard 0 to 10 visual analogue pain scale, consistent with its application as a mid-level analgesic. The mobile software technology was designed to help solve a significant practical, medical, and scientific challenge to pharmaceutical applications of the *Cannabis* plant: the ability to monitor and measure therapeutic and side effects across the vast range of products available at medical cannabis dispensaries, which vary by plant phenotype, consumption method, and major cannabinoid contents. Though limited in absolute experimental control (e.g., double-blinded randomization and use of a placebo intervention), which is typically enhanced by making the research environments, methods of patient interactions, and clinical interventions themselves more *artificial*, the current observational research design maximizes the external validity and generalizability of the findings through assessments of patients' actual medical treatment decisions and the experienced effects of those decisions, all in real time.

In addition to the general clinical effectiveness of patient-managed cannabis use as a mid-level analgesic treatment, we found subtleties in

Table 2
Effects of product characteristics on pain relief.

Outcome = Pain Change (Ending Pain Level - Starting Pain Level)					
	(1)	(2)	(3)	(4)	(5)
Panel A: Product Type, omitted category = Dried Flower					
Concentrate	0.071				0.025
	(0.049)				(0.154)
Edible	0.222***				
	(0.079)				
Pill	0.463**				
	(0.188)				
Tincture	0.468***				
	(0.089)				
Topical	−0.103				
	(0.189)				
Panel B: Labeled Plant Phenotype, omitted category = "Hybrid"					
"C. indica"		−0.030			0.028
		(0.040)			(0.087)
"C. sativa"		0.091**			0.032
		(0.044)			(0.089)
Panel C: Combustion Method, omitted category = Joint					
Pipe			0.067		0.266
			(0.067)		(0.163)
Vape			0.058		0.231
			(0.069)		(0.160)
Panel D: THC and CBD, omitted categories = THC < 10% and CBD < 1%					
THC 10-19%				−0.036	−0.138
				(0.092)	(0.099)
THC 20-34%				−0.037	−0.232**
				(0.097)	(0.103)
THC 35%+				−0.097	−0.248*
				(0.097)	(0.144)
CBD 1-9%				0.059	0.113
				(0.096)	(0.097)
CBD 10-34%				0.063	0.181**
				(0.096)	(0.084)
CBD 35%+				0.200	0.197
				(0.148)	(0.173)
Starting Pain Level	−0.607***	−0.622***	−0.602***	−0.602***	−0.591***
	(0.010)	(0.011)	(0.010)	(0.019)	(0.021)
Constant	0.296***	0.366***	0.231***	0.298**	0.079
	(0.054)	(0.061)	(0.076)	(0.139)	(0.208)
Number of sessions	20,513	16,637	16,703	5,301	4,603
Number of users	2,987	2,579	2,568	888	760

Notes: Columns 1–5 represent separate equations regressing change in pain intensity level on different types of product characteristics, comparing each product type to an omitted category. All regressions are estimated using a mixed effects model. Standard errors, clustered at the individual user level, are shown in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

the association between cannabis use and symptom relief by types of products and the contents of the cannabis consumed. Among the limited number of product characteristics that are typically made available to consumers, we found that consumption of whole, natural *Cannabis* flower was associated with greater anesthetic potential than were most other types of products. Use of concentrates was also associated with fewer positive and slightly more negative side effect experiences relative to use of flower. This is likely due to the introduction of solvents and other additives, alongside the removal of most terpenoids, terpenes, and flavonoids, as occurs with common methods used to produce high THC concentrates in the U.S. However, among all the measured product characteristics, THC potency levels emerged as the strongest independent predictors of pain relief and experienced side effects, with higher potency levels generally offering the greatest therapeutic potential for musculoskeletal, headache-related, and the "other/non-specified" pain categories; in contrast, lower levels of THC may be more therapeutic for gastrointestinal/abdominal-related pain. CBD potency, however, was generally not predictive of pain relief, except for a negative therapeutic effect on the cramping/abdominal and non-specific pain categories. Patients were more likely to experience positive rather than negative side effects, with higher THC levels increasing the probability of experiencing a positive side effect seemingly without affecting the likelihood of experiencing a negative side effect. Although not predictive of pain relief, CBD potency levels did appear to be associated with a decreased probability of side effects, particularly negative or context-specific side effects, i.e., side effects which may be positive or negative depending on the context in which the cannabis is consumed.

The omnibus finding that THC potency is the strongest independent predictor of pain relief in the current dataset, while CBD contents may detract from relief has several possible explanations. In practical terms, fraudulent CBD products have flooded U.S. commercial markets.[38] Due, in part to CBD's reputation as "non-psychoactive," inexperienced users may have difficulty evaluating the legitimacy of purchased products. Another possibility is that CBD has a much longer latency to effect relative to THC, and any potential analgesic effects from CBD use could not be captured by voluntary entry of the four-hour sessions composing our data.

Experientially, one of the major mechanisms likely underlying cannabis' quick-acting analgesic effects is the role of THC on the regulation of cognizant and perceptual (e.g., attention-directing) components of the human endocannabinoid system (ECS[39–42]). Often

Table 3
Effects of product characteristics on side effects.

Outcomes:	(1) Negative	(2) % of Negative	(3) Positive	(4) % of Positive	(5) Context-Specific	(6) % of Context-Specific
Concentrate	0.012	0.017*	−0.047**	−0.042**	−0.047	0.003
	(0.041)	(0.010)	(0.023)	(0.018)	(0.040)	(0.014)
"C. indica"	0.050*	0.011*	0.005	−0.019***	0.024	0.016**
	(0.026)	(0.006)	(0.011)	(0.006)	(0.020)	(0.008)
"C. sativa"	0.027	0.000	−0.002	−0.002	−0.007	−0.003
	(0.020)	(0.005)	(0.011)	(0.009)	(0.024)	(0.007)
Pipe	0.013	−0.002	0.008	−0.018	−0.037	−0.008
	(0.041)	(0.009)	(0.018)	(0.013)	(0.038)	(0.014)
Vape	0.006	−0.012	−0.006	−0.018	−0.075**	−0.029**
	(0.044)	(0.009)	(0.017)	(0.013)	(0.038)	(0.014)
THC 10-14%	0.014	0.015**	0.025*	0.026***	0.090**	0.046***
	(0.033)	(0.007)	(0.014)	(0.010)	(0.038)	(0.007)
THC 15-34%	0.007	0.008	0.023*	0.035***	0.067*	0.048***
	(0.032)	(0.007)	(0.013)	(0.012)	(0.038)	(0.010)
THC 35%+	0.083	0.016	0.073**	0.057***	0.144***	0.061***
	(0.053)	(0.011)	(0.030)	(0.017)	(0.049)	(0.015)
CBD 1-9%	−0.050*	−0.011	−0.016*	−0.022**	−0.097***	−0.029***
	(0.028)	(0.006)	(0.009)	(0.011)	(0.026)	(0.008)
CBD 10-34%	−0.056**	−0.011*	0.000	−0.006	−0.086***	−0.023***
	(0.027)	(0.006)	(0.009)	(0.010)	(0.027)	(0.008)
CBD 35%+	−0.063*	−0.017**	−0.037	−0.000	−0.098**	−0.052***
	(0.038)	(0.008)	(0.029)	(0.016)	(0.045)	(0.015)
Starting Pain Level	0.005	0.001	−0.002	−0.005***	0.002	0.000
	(0.006)	(0.001)	(0.003)	(0.002)	(0.005)	(0.002)
Constant	0.608***	0.083***	0.962***	0.285***	0.816***	0.167***
	(0.061)	(0.012)	(0.024)	(0.020)	(0.060)	(0.017)
Observations	2,877	2,877	2,877	2,877	2,877	2,877
N Users	652	652	652	652	652	652

Notes: All regressions are estimated using a mixed effects model. Concentrate is relative to Flower, "*C. indica*" and "*C. sativa*" are relative to "Hybrid," THC categories are relative to THC between 0 and 10%, and CBD categories are relative to 0% CBD, and Pipe and Vape are relative to Joint. Standard errors, clustered at the individual user level, are shown in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

Table 4
Effects of product characteristics on pain relief by different pain categories.

	Gastrointestinal	Musculoskeletal	Headache	Nerve	Other
Concentrate	−0.135	−0.144	0.388	−0.309	0.513*
	(0.211)	(0.158)	(0.389)	(0.332)	(0.275)
"C. indica"	0.330	−0.086	0.480**	−0.052	0.084
	(0.290)	(0.104)	(0.219)	(0.087)	(0.125)
"C. sativa"	0.109	0.065	−0.272	0.159	0.025
	(0.133)	(0.106)	(0.248)	(0.190)	(0.216)
Pipe	0.078	0.107	1.026***	0.003	−0.357
	(0.296)	(0.143)	(0.275)	(0.546)	(0.238)
Vape	0.333	0.105	0.670**	−0.208	0.005
	(0.293)	(0.171)	(0.297)	(0.481)	(0.241)
THC 10-14%	0.495**	−0.134	−0.877***	0.068	−0.274**
	(0.236)	(0.106)	(0.289)	(0.303)	(0.137)
THC 15-34%	0.290	−0.245**	−0.228	−0.112	−0.523***
	(0.239)	(0.121)	(0.316)	(0.308)	(0.182)
THC 35%+	0.046	−0.075	−0.775**	−0.522	−1.236***
	(0.288)	(0.136)	(0.363)	(0.402)	(0.226)
CBD 1-9%	0.287	0.059	0.076	−0.215	0.511**
	(0.326)	(0.116)	(0.269)	(0.202)	(0.209)
CBD 10-34%	0.215	0.128	0.163	−0.123	0.457*
	(0.325)	(0.101)	(0.282)	(0.199)	(0.242)
CBD 35%+	0.928**	0.196	0.167	0.270	0.917***
	(0.468)	(0.146)	(0.446)	(0.505)	(0.261)
Starting Pain Level	−0.608***	−0.583***	−0.601***	−0.666***	−0.607***
	(0.045)	(0.024)	(0.045)	(0.085)	(0.050)
Constant	−0.947**	0.310	−0.487	1.277**	0.304
	(0.471)	(0.204)	(0.458)	(0.589)	(0.340)
Observations	389	2,622	505	558	529
N Users	157	529	187	131	133

Notes: All regressions are estimated using a mixed effects model. Concentrate is relative to Flower, "*C. indica*" and "*C. sativa*" are relative to "Hybrid," THC categories are relative to THC between 0 and 10%, and CBD categories are relative to 0% CBD, and Pipe and Vape are relative to Joint. The eleven pain symptoms are grouped into five pain categories: Gastrointestinal (abdominal, cramping, gastrointestinal, or menstrual pain), Musculoskeletal (back, joint, or muscle pain), Headache (headache or migraine), Nerve (nerve), and Other (other). Standard errors, clustered at the individual user level, are shown in parentheses. *** $p < 0.01$, ** $p < 0.05$, * $p < 0.10$.

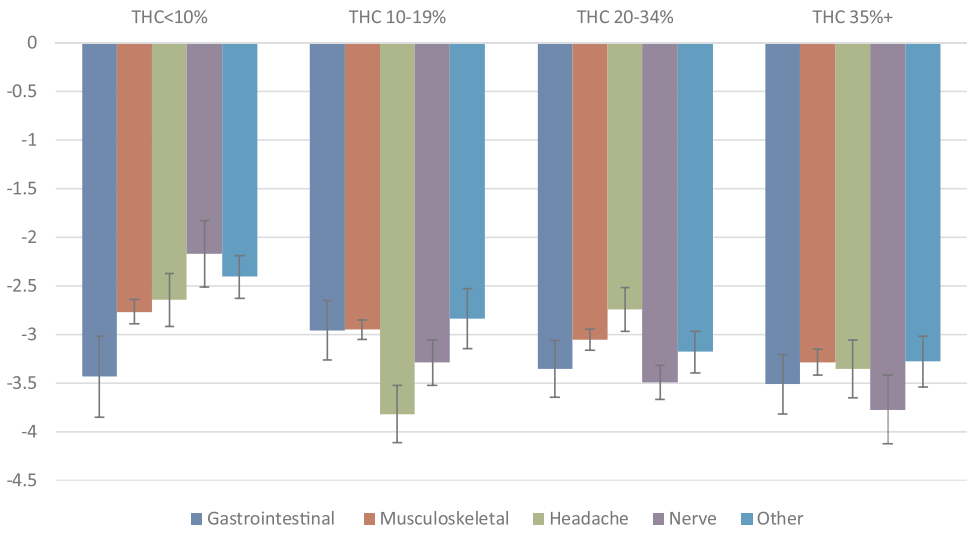

Fig. 1. Average pain relief by type of pain and THC levels.
Notes: Adjusted pain relief refers to covariate-adjusted change in pain severity, obtained from a mixed effects model controlling for product type, plant phenotype, combustion method, CBD categories, and starting symptom level. The eleven pain symptoms are grouped into five pain categories: Gastrointestinal (abdominal, cramping, gastrointestinal, or menstrual pain), Musculoskeletal (back, joint, or muscle pain), Headache (headache or migraine), Nerve (nerve), and Other (other). 95% confidence intervals are included.

described as a masterwork of coordinated chemical signals, the ECS consists of natural ligands (e.g., anandamide and 2-AG) and receptors (e.g., CB1 and CB2) responsible for the homeostatic regulation of wide-ranging bodily functions, including sleep, feeding (e.g., gut permeability and adipogenesis), libido and fertility, pain perception, motivation, happiness, anxiety, learning and memory, social cognitive functioning, autoimmune responses, cellular redox, and cancer pathophysiology.[32,43–58] THC is a partial agonist of CB1 and CB2 receptors, collectively the most abundant G-protein-coupled 7-transmembrane receptors in the human brain. CB1 and CB2 receptors reciprocally interact and are co-localized with μ opioid receptors in CNS tissue structures (e.g., nucleus accumbens, hippocampus, neocortex, and amygdala) responsible for attention, behavioral motivations, learning, and nociception.[59–64] CBD instead has very low affinity for CB1 and CB2 receptors,[65] and appears to allosterically down-regulate CB1 receptor activity, resulting in inverse effects from THC exposure.[17,66] Pharmacologically, CBD lacks the intoxicating properties of THC and likely plays an inverse role on the ability to experience the analgesic shifts in attentional demands and mental percepts produced by THC exposure. Related research has explored the use of THC as a potential adjuvant for common neuropathic pain medications such as gabapentin,[67,68] though few studies to date have directly compared the *relative* (non-additive) effectiveness of self-directed cannabis use against any other pharmaceutically-derived medication for the treatment of pain or any other health condition, either for momentary symptom relief or as a long-term treatment.

While novel and practical, the observational nature of the research design had unavoidable drawbacks, most notably the absence of a comparison group; which could have resulted in overestimation of the effectiveness of cannabis if unsatisfied users chose not to use the Releaf App™, or underestimation of cannabis' effectiveness if, for example, users under-utilized the app for already satisfactory product choices and their effects. Another major limitation is the absence of measurements of other cannabinoid chemicals and terpenes, which undoubtedly contribute to the therapeutic outcomes of cannabis products used in vivo, and especially dried natural *Cannabis* flower, which contains the fullest range of natural chemicals and remains the most popular form of cannabis consumed in the U.S. More research is therefore needed on the effectiveness and influence of the various distinct chemotypic properties of the *Cannabis* plant[26–29] and of an ever broadening range of consumption technologies (e.g., water bongs, non-combusting vaporizers, topicals) that can cause different chemical reactions (e.g., hydrolysis and thermolysis effects) that lead to distinct combinations of phytocannabinoid, terpenoid, and flavonoid exposure. Finally, the study was limited in the amount of information obtained by Releaf App™ users and did not include detailed demographic characteristics, pre-app experience using cannabis, verified accuracy of product labeling,[69] and concurrent use of other pain medications, which would have enabled direct comparison of the effectiveness of and interactions among different classes of medications (including *Cannabis*) used to treat pain and other health conditions.

In conclusion, although cannabis has well-established clinical drawbacks, including the potential for dependence and addiction and an increased risk of motor vehicle accidents, psychedelic or psychotic experiences, and short-term cognitive impairment,[17,70] these side effects are relatively less severe than the more serious medical and societal problems caused by misused prescription and nonprescription opioids. While some studies show an association between illegal cannabis use and increased risk of opioid misuse,[71,72] an amassing body of literature suggests that the *legal* ability to use cannabis in the U.S., which gives law-abiding people access to a wide variety of cannabis-based products, tends to result in a reduction in and often even cessation of prescription opioid use among chronic pain patients.[15,16] One recent clinical experiment also shows that cannabis reduces the symptoms of withdrawal and opioid cravings for people with heroin addictions.[73] The current findings show that self-directed medical cannabis treatment, especially among users of higher THC products, is associated with significant improvements in at least short-term pain relief, perhaps a major reason why cannabis has become one of the most widely used medications in the United States.

Author contributions

JMV, SSS, and XL conceived the study. FB, KK, BH independently designed and developed the Releaf App™ and server infrastructure as part of their effort to help create an education tool for medical cannabis patients. XL conducted the analyses. JMV, SSS, and XL drafted the manuscript. All authors contributed substantially to its intellectual content and revision.

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Declaration of Competing Interest

FB, KK, and BH are employed by MoreBetter, Ltd. Dr. Vigil is Director of the University of New Mexico Medical Cannabis Research

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.07.022.

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