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Original Research Article

Alleviative effects of *Cannabis* flower on migraine and headache

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ABSTRACT

Objective: Few studies to date have measured the real-time effects of consumption of common and commercially available *Cannabis* products for the treatment of headache and migraine under naturalistic conditions. This study examines, for the first time, the effectiveness of using dried *Cannabis* flower, the most widely used type of *Cannabis* product in the United States, in actual time for treatment of headache- and migraine-related pain and the associations between different product characteristics and changes in symptom intensity following *Cannabis* use.

Methods: Between 06/10/2016 and 02/12/2019, 699 people used the Releaf Application to record real-time details of their *Cannabis* use, including product characteristics and symptom intensity levels prior to and following self-administration; data included 1910 session-level attempts to treat headache- (1328 sessions) or migraine-related pain (582 sessions). Changes in headache- or migraine-related pain intensity were measured on a 0–10 scale prior to, and immediately, following *Cannabis* consumption.

Results: Ninety-four percent of users experienced symptom relief within a two-hour observation window. The average symptom intensity reduction was 3.3 points on a 0–10 scale (standard deviation = 2.28, Cohen's d = 1.58), with males experiencing greater relief than females ($P < 0.001$) and a trend that younger users (< 35 years) experience greater relief than older users ($P = 0.08$). Mixed effects regression models showed that, among the known (i.e., labeled) product characteristics, tetrahydrocannabinol levels 10% and higher are the strongest independent predictors of symptom relief, and this effect is particularly prominent in headache rather than migraine sufferers ($P < 0.05$), females ($P < 0.05$) and younger users ($P < 0.001$). Females and younger users also appear to gain greater symptom relief from flower labeled as "*C. indica*" rather than "*C. sativa*" or other hybrid strains.

Conclusion: These results suggest that whole dried *Cannabis* flower may be an effective medication for treatment of migraine- and headache-related pain, but the effectiveness differs according to characteristics of the *Cannabis* plant, the combustion methods, and the age and gender of the patient.

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1. Introduction

Nearly 40 million people in the United States (U.S.) or one in seven adults (with even higher rates among certain demographic groups, such as women) are affected by recurrent migraines and other chronic headache-related conditions, rendering them the third most prevalent medical condition in the U.S. [1–3]. Chronic migraine suffering can lead to decreased performance, socialization and overall quality of life [4] and presents an increased risk for numerous comorbidities and reciprocal disturbances, such as sleep disorders, behavior problems, depression and anxiety [5,6]. Conventional pharmaceutical treatments for severe headaches are often unsuccessful [7] and have historically consisted of a variety of drug classes (including acetaminophen and nonsteroidal anti-inflammatory drugs, triptans, ergot alkaloids, antiemetics, glucocorticoids, β-receptor blockers, calcium channel blockers, angiotensin II blockers, tricyclic antidepressants, opioids, anticon-

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vulsants, antiseizure medications, isometheptene and botulinum toxin), each with their own sets of potential risks, negative side effects and dangerous polypharmaceutical drug interactions [8]. Chronic headache sufferers report high rates of dissatisfaction with conventional pharmaceutical treatments [9,10], leading many to experiment with complementary and alternative treatment options [11–14].

Medical *Cannabis* is becoming a popular alternative to several major classes of conventional pharmaceutical drugs that are commonly used to treat headaches, including sedatives, opioids and antidepressants [15–18]. This is due, in part, to rapidly changing marijuana laws and increased availability throughout the country; nevertheless, the federal government has restricted research on patient outcomes for common and commercially available *Cannabis*-based products, including products used by millions of people every day [19,20]. The clinical literature [16,18,20–24] suggests that *Cannabis* is commonly used and may be effective for treating a multitude of health conditions, including chronic pain disorders and several chronic headache conditions. For instance, in one study among migraine sufferers authorized to use *Cannabis*, patients reported a decrease in migraine headache frequency from 10.4 to 4.6 per month [25]. However, we are aware of few studies that have measured the real-time effects of *Cannabis* on headache and migraine pain intensity levels. Likewise, no study to date has measured the relative effects of the two major cannabinoids, tetrahydrocannabinol (THC) and cannabidiol (CBD), for treating headache in real-life settings.

In this study we document, for the first time, the real-time effectiveness of dried *Cannabis* flower, the most widely used *Cannabis* product in the U.S., for the treatment of headache- and migraine-related pain; further we correlate *Cannabis* product characteristics with changes in symptom intensity following *Cannabis* consumption.

2. Methods

2.1. Study design

An analytic observational research design was used to examine the research questions of how *Cannabis* consumption affects the intensity of headache- and migraine-related pain sensations, and whether labeled product characteristics are associated with changes in pain severity.

2.2. Setting

We operationalize our research question using a mobile educational software application called Releaf Application (App) (MoreBetter Ltd., U.S.) [26], which has collected the largest dataset of real-time patient reports of self-directed medical *Cannabis* use in the U.S. The App enables documentation of product characteristics, including labeled phenotype, route of administration, primary cannabinoid contents and the headache- or migraine-related pain intensity user experienced prior to and following *Cannabis* administration, as well as the myriad possible side effects of using *Cannabis* in a real-life setting. The genus *Cannabis* (family Cannabaceae) consists of the species *C. sativa* and *C. indica*, based on the phenotypic descriptions of Lamarck in 1785 [27,28], and many medical *Cannabis* products are labeled as derivatives or hybrids of these two species. The App further allows users to record the gender and age of a patient, factors yet unstudied with respect to *Cannabis* usage, providing preliminary information on how the effects of using *Cannabis* may differ across user subgroups. The current data were supplied by the Releaf App, subject to a confidentiality agreement. The Releaf App is freely available and voluntarily downloaded by users onto their cell phones, designed to assist patients in navigating the wide range of products available in medical *Cannabis* dispensaries. Users select one or several symptoms from 50 possible selections (including migraine and headache) and voluntarily provide demographic information, such as age and gender. For each unique product tracked within the App, the user can select multiple product dimensions, including those studied in this paper, i.e., labeled plant phenotype (*C. indica*, *C. sativa*, or hybrid), combustion method (joint, pipe, or vaporizer), and reported THC and CBD concentrations. All state-level medical *Cannabis* programs and regions in which recreational *Cannabis* use is legal in the U.S. require THC and CBD potency analyses and labeling. Although the App collects data on other products, e.g., processed concentrates and edibles, we focused on flower in this study because it is the most widely used type of marijuana in the U.S., and offers relatively homogeneous product dimensions, including THC and CBD potency levels, relative to other types of products (e.g., concentrates and edibles), which may contain many different types of non-phytochemical compounds such as solvent residues and other additives. The University of New Mexico Institutional Review Board approved the use of these data.

2.3. Participants

Case reports used in this study were from individuals who reported using *Cannabis* flower to treat headache- or migraine-related pain through the Releaf App between 06/10/2016 and 02/12/2019. To be included, case reports also had to contain self-reported symptom intensity levels at the beginning of treatment and within a two-hour window after treatment.

2.4. Variables

This paper focuses on symptom relief. We compared starting symptom levels (1 to 10) against the last symptom level reported within a two-hour period after flower consumption; this resulted in a range of possible symptom relief values from –10 to 9, with more negative numbers indicating greater symptom relief, 0 indicating no change, and more positive numbers indicating worsening of symptoms. The main outcome variable, change in symptom intensity, is calculated continuously as the ending level minus the starting symptom level. Symptom being treated, plant species (*C. indica*, *C. sativa*, or hybrid), combustion method (joint, pipe and vaporizer), cannabinoid potency, and user gender and age (younger or older than 35 years) are treated as categorical variables. Symptom intensity starting level is used as a covariate.

2.5. Data measurement

Changes in headache- and migraine-related symptom intensity are measured on a visual analogue scale (VAS) from 0 to 10, where 0 is no pain and 10 is the worst pain ever felt. At the start of each *Cannabis* use-session, the App user enters a starting symptom level between 0 and 10; at the end of each session, the user enters an ending symptom level. Users are free to enter additional symptom levels throughout the *Cannabis* use-session. Plant species and cannabinoid potency levels are indicated on the product labels, and combustion method and demographic characteristics (gender and age) are reported by users. For gender, we restrict our analysis to only those identifying as female or male, due to the small sample size (n = 17) of non-binary identities.

2.6. Bias

Peak symptom relief can vary following *Cannabis* consumption but may not be sustained. We therefore use the last symptom level

within 2 hours to conservatively represent a more enduring level of symptom relief. Cannabinoid potency levels exceeding 35% of dried plant mass were deemed unrealistic and excluded from the analyses.

2.7. Statistical analysis

In order to determine how product characteristics affect changes in symptom levels, we regress our symptom relief outcome against the (dummy-coded) product characteristics using a linear mixed model and allowing intercepts to vary randomly by user with an unstructured variance covariance matrix. We also control for starting symptom levels, which mechanistically affect how much symptom relief a user can report [29,30]. Standard errors are clustered at the user level to control for heteroskedasticity and arbitrary correlation within users. Because reporting of product characteristics is voluntary and THC and CBD levels require product labeling or access to laboratory tests, we have substantially fewer cases reporting THC and CBD than other product characteristics. Therefore, to maximize the sample size, we ran our regressions separately by product type before running the complete model, which included all product characteristics. In addition to running regressions on the full sample, we conducted subgroup analyses by symptom type (migraines and headaches), gender (female and male) and age group (34 and below or 35 and above 35 years of age in line with a mean age in the sample of 34). We first test for differences across subgroups using *t*-tests to conduct mean comparisons of starting and ending symptom levels and symptom relief (ending minus starting symptom level) by subgroup, before running the complete regression model including all product characteristics separately by subgroup. We conduct postestimation *F*-tests of the equivalence of coefficients within regressions and run regressions interacting the subgroup variables with the product characteristic variables to test for equivalence in the effects across subgroups. The full sample regressions are robust enough to include a random slope parameter for starting symptom level with or without allowing for an unstructured covariance matrix, but we do not have enough power to do so in the model broken out by subgroup. As an additional exploratory exercise, we run chi-squared tests and *t*-tests of the prevalence of each product characteristic across subgroups to identify differences in product usage patterns. We used STATA 15.1 (Stata corporation, U.S.) to conduct our analyses.

3. Results

3.1. Participants

In total, 1910 *Cannabis* use-sessions, recorded by 699 users treating headaches (n = 493) or migraines (n = 280), were included in the analyses; some users applied *Cannabis* to treat both headaches and migraines. Because reporting of demographic information and product characteristics was not required by the Relief App, some analyses have fewer observations and user counts. For example, 22% (n = 419) of the sessions using *Cannabis* flower to treat headache- or migraine-related pain included both THC and CBD potency analyses, which we capped at 35% due to the biological limitations of the plant. Potency may be omitted from use-sessions either because a user did not elect to report it, or because the information was not included in the product packaging; potency information is typically only available for *Cannabis* purchased from dispensaries. Home cultivated, caregiver provided, or illegally acquired *Cannabis* is unlikely to include potency information. The average user entered 21 sessions (median = 5 sessions) over 125 days (median = 65 days), with new users continuing to subscribe through the last day of the sample period on 02/02/2019. Demographic information was available for users who chose to report it: 353 users (1216 sessions) reported gender (32% male, 68% female) and 343 users (1,194 sessions) reported age (mean ± standard deviation [SD] = [34.0 ± 9.1] years). Table 1 provides descriptive statistics for product characteristics. "*Sativa*" strains were the least commonly used (16%) with "hybrid" strains the most commonly used (54%). As for combustion method, 14% of sessions involved joints, while pipes and vapes were used in 46% and 40% of sessions, respectively. Average THC levels were 17.61% (SD = 8.45%) and CBD levels averaged 7.73% (SD = 8.57%). In our subgroups by symptom, gender and age, 30% of sessions were recorded by migraine suffers, 67% of sessions were recorded by females, and 57% of sessions were recorded by people under age 35.

3.2. Symptom relief in response to Cannabis use

Average symptom relief in the sample is –3.28 (SD = 2.28) with the mean starting symptom level of 5.79 (SD = 2.06) and a mean ending level of 2.51 (SD = 2.10). In 94% of sessions, users reported symptom relief (ending – starting symptom level < 0). On a per-session basis, users reported no symptom relief or worsening symptoms in 4% and 2% of sessions, respectively. On a per-user basis, 8% of users reported unchanged symptom levels and 4% of users reported worse symptoms in at least one session in the sample.

Table 2 presents results from regressions of symptom relief against the product characteristics for each product category separately and then jointly. The separate regressions in model one through four do not indicate any statistically significant differences in symptom relief by product characteristic, except for a decrease in symptom relief associated with higher CBD products. A regression of all product characteristics together in model five suggests

Table 1
Descriptive characteristics of flower products and symptom relief.

Variable	Percentage of sessions	Sessions (n)	Users (n)
Plant species: 634 users, 1678 sessions			
Hybrid	54%	903	377
C. indica	30%	504	250
C. sativa	16%	271	169
Combustion method: 663 users, 1830 sessions			
Joint	14%	261	146
Pipe	46%	840	349
Vape	40%	729	238
THC level: 287 users, 741 sessions			
0%–9%	21%	154	69
10%–19%	36%	268	139
20%–35%	43%	319	144
CBD level: 206 users, 542 sessions			
0%	29%	155	62
1%–9%	34%	184	93
10%–35%	37%	203	94
Symptom relief: 699 users, 1910 sessions			
Symptom improved	94%	1789	670
Symptom unchanged	4%	41	52
Symptom worsened	2%	80	30

All sessions used *Cannabis* flower. Symptoms treated include migraines and headaches. Patients selected from 19 positive, 17 negative and 11 context-specific side effects. For categorical variables, the percent of sessions, the number of sessions, and the number of users responding affirmatively to that sub-category are reported. Because some users used more than one type of product during our sample period, the number of users summing across sub-categories will be greater than the number of users who report for that category overall. For example, 634 users ever report a plant sub-species, but some of those users report using more than one plant sub-species during our sample period. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

Table 2
Symptom relief by product characteristic.

Model	Intercept	Coefficient	95% confidence interval	*P* value
Model 1: subtype (hybrid as reference)	0.202		−0.088, 0.492	0.171
C. indica		0.058	−0.121, 0.238	0.524
C. sativa		0.524	−0.071, 0.356	0.191
Starting symptom level		−0.662	−0.717, −0.608	< 0.001
Model 2: combustion method (joint as reference)	0.002		−0.365, 0.368	0.993
Pipe		0.176	−0.097, 0.449	0.206
Vape		0.206	−0.151, 0.461	0.322
Starting symptom level		−0.632	−0.687, −0.577	< 0.001
Model 3: THC levels (THC 0%–9% as reference)	0.188		−0.359, 0.734	0.500
THC 10%–19%		−0.108	−0.531, 0.314	0.615
THC 20%–35%		0.615	−0.638, 0.152	0.228
Starting symptom level		−0.622	−0.705, −0.539	< 0.001
Model 4: CBD level (CBD 0% as reference)	−0.544		−1.097, 0.009	0.054
CBD 1%–9%		0.279	−0.211, 0.768	0.264
CBD 10%–35%		0.537	0.085, 0.989	0.020
Starting symptom level		−0.543	−0.641, −0.446	< 0.001
Model 5: all product characteristic	−0.606		−1.677, 0.464	0.267
C. indica		−0.048	−0.495, 0.399	0.833
C. sativa		0.228	−0.260, 0.715	0.360
Pipe		0.719	0.132, 1.306	0.016
Vape		0.366	−0.319, 1.052	0.295
THC 10%–19%		−0.727	−1.288, −0.166	0.011
THC 20%–35%		−0.709	−1.300, −0.117	0.019
CBD 1%–9%		0.479	−0.209, 1.167	0.173
CBD 10%–35%		0.383	−0.343, 1.110	0.301
Starting symptom level		−0.543	−0.659, −0.426	< 0.001

Each model represents a separate regression. Regressions are based on a linear mixed effects model including patient-level random intercepts with an unstructured covariance matrix. The coefficients for the product characteristics, which are all categorical variables, measure the effect relative to the reference category. Starting symptom level is a non-categorical variable, and therefore, does not have a reference category. Standard errors are clustered at the patient level to adjust for heteroskedasticity and arbitrary correlation within patients. Reference categories are hybrid, joint, THC 0%–9% and CBD 0%. The outcome is symptom relief, with negative coefficients indicating greater symptom relief. Model 1 includes 1678 sessions and 634 patients; model 2 includes 1830 sessions and 663 patients; model 3 includes 741 sessions and 287 patients; model 4 includes 542 sessions and 206 patients; model 5 includes 353 sessions and 151 patients. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

that THC levels are driving symptom relief, while individuals using pipes may experience less symptom relief. The coefficient on the highest CBD level still is negative (indicating less symptom relief) but it is no longer statistically significant. The treatment outcome is the change in symptom intensity level on a VAS, over the 2 hours following treatment (ending – starting symptom level); an outcome with a negative sign indicates improved symptoms, while a positive-signed outcome indicates worsening symptoms.

3.3. Other analyses

Table 3 shows mean comparisons of the outcomes across the three subgroups by symptom type (migraine versus headache), gender (female versus male) and age (< 35 versus ≥ 35). Comparisons by "symptom type" shows that, although starting and ending symptom levels are statistically significantly different between migraine and headache users ($P < 0.001$), with migraine sufferers reporting higher starting and ending symptom levels, the symptom relief experienced is the same across the two groups (−3.3 on a 0–10 VAS). Between the two sexes, greater symptom relief was reported among males driven by lower ending symptom levels ($P < 0.001$). Younger users experienced lower ending symptom levels ($P = 0.008$), but this did not translate into statistically significantly greater symptom relief.

Fig. 1 shows regression coefficient estimates with 95% confidence intervals. Zero indicates no symptom relief; values below zero indicate improved symptoms, while values above zero indicate worsening symptoms. The THC categories are relative to THC < 10%; the CBD categories are relative to CBD = 0%; the species names are relative to "hybrid;" the combustion methods are relative to "joint" and the starting symptom ranges in value from 1 to 10. The results for migraines were based on a sample of 284 users and 606 sessions, while the results for headaches were based on a sample of 509 users and 1409 sessions. The underlying regressions that generated the results in Fig. 1 used linear mixed effects regression models with random intercepts at the user level and clustered standard errors.

Table 3
Mean comparisons of symptom relief by subgroup.

Subgroup panel	Symptom relief (within 2 hours)	Starting symptom level	Ending symptom level
Symptom type			
Migraine (n = 582)	−3.30 ± 0.10	6.44 ± 0.09	3.14 ± 0.09
Headache (n = 1328)	−3.27 ± 0.06	5.51 ± 0.05	2.24 ± 0.05
P value	0.831	< 0.001	< 0.001
Gender			
Female (n = 820)	−2.85 ± 0.07	5.58 ± 0.07	2.73 ± 0.08
Male (n = 396)	−3.69 ± 0.11	5.78 ± 0.10	2.10 ± 0.09
P value	< 0.001	0.116	< 0.001
Age (years)			
Age < 35 (n = 687)	−3.22 ± 0.09	5.60 ± 0.08	2.38 ± 0.08
Age ≥ 35 (n = 507)	−3.00 ± 0.09	5.70 ± 0.09	2.70 ± 0.09
P value	0.081	0.386	0.008

Categorical variables are compared using chi-squared tests, while continuous variables are compared using two-sided *t*-tests. "*n*" refers to the number of sessions. Symptom relief is calculated as the ending symptom level minus the starting symptom level. Data are shown as mean ± standard deviation.

The regressions underlying Fig. 1 are shown in Table 4. Perhaps partly due to a lack of power in the migraine subsample, none of the coefficients for the product characteristics nor the intercepts are statistically significantly different from zero. Headache sufferers appear to be driving the main effect, and indicated greater symptom relief with levels of THC 10% or higher; they also may

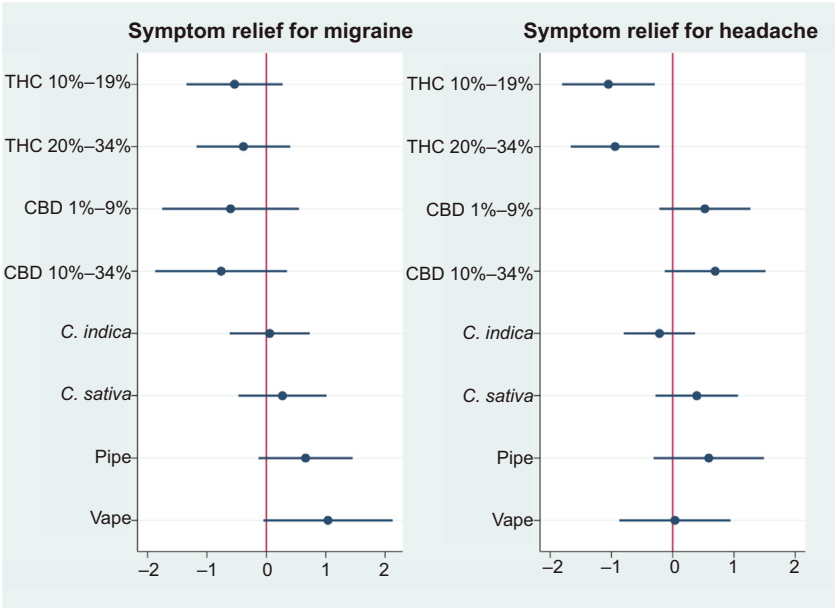

Fig. 1. Regression coefficients by symptom. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

Table 4
Regressions by symptom type.

Model	Intercept	Coefficient	95% confidence interval	*P* value
Model 1: migraine	0.055		−1.527, 1.637	0.946
C. indica		0.057	−0.616, 0.731	0.867
C. sativa		0.272	−0.470, 1.014	0.473
Pipe		0.661	−0.131, 1.454	0.102
Vape		1.038	−0.052, 2.128	0.062
THC 10%–19%		−0.535	−1.344, 0.274	0.195
THC 20%–35%		−0.386	−1.174, 0.403	0.338
CBD 1%–9%		−0.602	−1.754, 0.550	0.306
CBD 10%–35%		−0.761	−1.870, 0.348	0.179
Starting symptom level		−0.525	−0.680, −0.370	< 0.001
Model 2: headache	−0.683		−1.916, 0.550	0.277
C. indica		−0.215	−0.796, 0.366	0.468
C. sativa		0.393	−0.279, 1.065	0.252
Pipe		0.589	−0.312, 1.489	0.200
Vape		0.037	−0.871, 0.946	0.936
THC 10%–19%		−1.05	−1.806, −0.293	0.007
THC 20%–35%		−0.94	−1.663, −0.216	0.011
CBD 1%–9%		0.525	−0.216, 1.267	0.165
CBD 10%–35%		0.693	−0.130, 1.516	0.099
Starting symptom level		−0.505	−0.644, −0.367	< 0.001

Each model represents a separate regression by symptom type. Regressions are based on a linear mixed effects model including patient-level random intercepts with an unstructured covariance matrix. The coefficients for the product characteristics, which are all categorical variables, measure the effect relative to the reference category. Starting symptom level is a non-categorical variable, and therefore, does not have a reference category. Standard errors are clustered at the patient level to adjust for heteroskedasticity and arbitrary correlation within patients. Reference categories are hybrid, joint, THC 0%–9% and CBD 0%. The outcome is symptom relief, with negative coefficients indicating greater symptom relief. Model 1 includes 152 sessions and 67 patients, and model 2 includes 201 sessions and 95 patients. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

be experiencing less symptom relief with CBD levels 10% and above. *F*-tests of the differences in the reported coefficients by category indicate no statistically significant differences between the reported coefficients by category except for pipe and vape. In particular, pipe and vape had a distinct effect among those suffering from headaches, with pipes offering less relief than vapes, although neither pipes nor vapes offered statistically significantly different levels of relief relative to joints. *F*-tests supported the overall finding that the benefits of higher THC were nonlinear and plateaued above 10% among both subgroups.

The coefficients are similar across the two conditions except for the coefficients for the higher THC categories, which are larger and statistically significantly more negative (greater symptom relief) for headache suffers. However, testing for differences in coefficients across the subgroups using interaction terms indicated that (data not shown) only CBD levels differed statistically in their effect across subgroups, with headache sufferers experiencing less symptom relief from high CBD products than migraine sufferers. *F*-tests did not indicate differences in the coefficients for THC and CBD among those suffering from migraines, but did suggest statistically significant and opposing effects (THC increases symptom relief; CBD decreases symptom relief) among those with headaches ($P < 0.05$). A comparison of the prevalence of certain product characteristics in Table 5 suggested that users may be aware of these

differences, with headache users more likely to buy products with 0% CBD ($P = 0.009$). Mean comparisons of the prevalence of product characteristics in each group are shown in Table 5.

Subgroup analyses of mean comparisons extended to gender are reported in Table 3, and regressions by subgroup are reported in Table 6. The mean comparisons in Table 3 show that the greater symptom relief reported by males and by those under 35 is driven by lower ending symptom levels in these two subgroups. In Table 6, the results of separate regressions for females and males suggest opposing effects not identified in the aggregate regression. The sample sizes are small and regressions using interaction terms to directly test for differences by gender indicate no statistical differences across groups (data not shown). *F*-tests of the differences in the reported coefficients within categories suggested that females benefited most from *C. indica*. Although males benefitted more from pipes than from joints, no statistically significant differences existed between pipes and vapes, based on *F*-tests of the equivalence of the coefficients on pipe and vape within males. While the regressions indicate higher THC levels may be more beneficial, *F*-tests again suggest a plateauing effect; although THC greater than 10% offered more symptom relief than lower levels of THC, no statistically significant difference existed between medium and high levels of THC in either group.

Comparisons of the means by gender are shown in Table 7 and suggested that users may be aware of some of the differences identified in our regression analysis, with females choosing pipes more often than males. Table 7 suggests different purchase patterns by gender, with males seemingly more likely to consume joints and higher THC products, although the regression analysis suggests that the effects of these product characteristics do not differ across genders. In particular, females may benefit from THC purchasing patterns more similar to those of males.

In the regressions by age group (< or ≥ 35 years; Table 8), both subgroups benefitted from using products with THC greater than 10%, but with a plateau in the effect at higher THC levels. More specifically, *F*-tests of the equivalence of the coefficients for the THC categories within subgroups do not indicate a statistically significant difference between the higher THC levels in either subgroup. Among younger users, *C. indica*-labeled products are associated with greater symptom relief than either hybrid or *C. sativa*-labeled products, based on the regression results and *F*-tests of the difference between *C. indica* and *C. sativa* products. Regressions using interaction terms (data not shown) indicate that younger patients benefit more than older patients from 0% CBD, relative to products containing CBD; however, other differences in the coefficients between the two subgroups are not statistically significant.

In Table 9, mean comparisons suggest that younger users may be more likely to choose THC levels below 10% and CBD levels above 19% although both are associated with reduced symptom relief among younger patients.

Table 5
Mean and ratio comparisons of product characteristics between migraines and headaches.

Product characteristic	Migraine	Headache	*P* value
Plant phenotype (constituent ratio)			
Hybrid	0.55	0.53	0.450
C. indica	0.27	0.31	0.085
C. sativa	0.18	0.15	0.261
Combustion method (constituent ratio)			
Joint	0.15	0.14	0.711
Pipe	0.47	0.45	0.534
Vape	0.38	0.41	0.370
THC level (mean ± SD; constituent ratio in subgroups)	17.29 ± 0.54	17.75 ± 0.38	0.497
0%–9%	0.20	0.21	0.755
10%–19%	0.35	0.39	0.307
20%–35%	0.44	0.41	0.462
CBD level (mean ± SD; constituent ratio in subgroups)	8.42 ± 0.60	7.27 ± 0.46	0.127
0%	0.22	0.33	0.009
1%–9%	0.37	0.32	0.194
10%–35%	0.40	0.35	0.240

Categorical variables (plant sub-species, combustion method, and THC and CBD levels) are compared using chi-squared tests, while the continuous variables (THC and CBD) are compared using two-sided *t*-tests. THC: tetrahydrocannabinol; CBD: cannabidiol; SD: standard deviation; *C.*: *Cannabis*.

Table 6
Symptom relief by gender.

Model	Intercept	Coefficient	95% confidence interval	*P* value
Model 1: female	0.529		−1.659, 2.716	0.636
C. indica		−0.816	−1.554, −0.078	0.030
C. sativa		0.219	−0.522, 0.959	0.562
Pipe		0.399	−0.987, 1.786	0.572
Vape		0.137	−1.279, 1.554	0.850
THC 10%–19%		−0.955	−1.808, −0.102	0.028
THC 20%–35%		−1.151	−2.109, −0.193	0.018
CBD 1%–9%		0.322	−0.681, 1.324	0.530
CBD 10%–35%		0.352	−0.813, 1.516	0.554
Starting symptom level		−0.620	−0.823, −0.417	< 0.001
Model 2: male	−1.466		−3.126, 0.194	0.084
C. indica		0.108	−1.095, 1.312	0.860
C. sativa		−0.576	−1.630, 0.477	0.284
Pipe		1.141	0.116, 2.166	0.029
Vape		−0.017	−1.340, 1.306	0.980
THC 10%–19%		−0.832	−2.017, 0.352	0.168
THC 20%–35%		−0.785	−1.556, −0.014	0.046
CBD 1%–9%		0.437	−0.686, 1.560	0.446
CBD 10%–35%		0.121	−0.958, 1.200	0.826
Starting symptom level		−0.359	−0.552, −0.167	< 0.001

Each model represents a separate regression by gender. Regressions are based on a linear mixed effects model including patient-level random intercepts with an unstructured covariance matrix. The coefficients for the product characteristics, which are all categorical variables, measure the effect relative to the reference category. Starting symptom level is a non-categorical variable, and therefore, does not have a reference category. Standard errors are clustered at the patient level to adjust for heteroskedasticity and arbitrary correlation within patients. Reference categories are hybrid, joint, THC 0%–9%, and CBD 0%. The outcome is symptom relief, with negative coefficients indicating greater symptom relief. Model 1 includes 155 sessions and 59 patients, and model 2 includes 64 sessions and 28 patients. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

Table 7
Mean and ratio comparisons of product characteristics by gender.

Product characteristic	Female	Male	*P* value
Plant phenotype (constituent ratio)			
Hybrid	0.54	0.60	0.058
C. indica	0.29	0.25	0.170
C. sativa	0.17	0.15	0.377
Combustion method (constituent ratio)			
Joint	0.13	0.23	< 0.001
Pipe	0.47	0.34	< 0.001
Vape	0.40	0.43	0.452
THC level (mean ± SD; constituent ratio in subgroups)	16.26 ± 0.50	18.41 ± 0.35	0.013
0%–9%	0.28	0.15	0.002
10%–19%	0.31	0.46	0.001
20%–35%	0.41	0.38	0.524
CBD level (mean ± SD; constituent ratio in subgroups)	7.62 ± 0.55	8.51 ± 0.82	0.397
0%	0.34	0.24	0.084
1%–9%	0.30	0.27	0.581
10%–35%	0.36	0.49	0.031

Categorical variables (plant sub-species, combustion method, and THC and CBD levels) are compared using chi-squared tests, while the continuous variables (THC and CBD) are compared using two-sided *t*-tests. THC: tetrahydrocannabinol; CBD: cannabidiol; SD: standard deviation; *C.*: *Cannabis*.

4. Discussion

To date, the exact causes of migraine and headache are incompletely understood, but likely involve complex neuronal and hormonal mechanisms, genetic and epigenetic associations [31,32], common mental and physical comorbidities, and other heterogeneous characteristics by patient subgroup. For example, women have a one in four chance of experiencing a migraine at some point in their life and represent roughly 85% of all chronic migraine sufferers [23]. In this study, all groups experienced symptom relief primarily associated with THC levels 10% and over, with joints potentially offering more relief than pipes. The analgesic effects of *Cannabis* varied primarily with age, with younger patients experiencing greater benefits in general. The only statistically significant difference across groups by product characteristics was that higher CBD levels were associated with less symptom relief among those suffering from headaches and younger users.

Although the majority (94%) of *Cannabis* consumers in the current study experienced reductions in headache- or migraine-related pain intensity, other studies have shown that headaches can be caused by substance use, including *Cannabis* [33]. Unfortunately, federal regulatory barriers have restricted clinical research on the effects of commonly consumed medical *Cannabis* products, and particularly, *Cannabis* flower with high THC content [19,20]. The result has been a general lack of a comprehensive understanding of the mechanisms through which *Cannabis* may affect migraine and other headache-related pain experience. One possibility, based on the "dopamine pathway hypothesis," suggests that various migraine symptoms, such as hypotension, hyperactivity, nausea, vomiting, yawning and irritability, may be associated with dopaminergic stimulation [34,35]. Dopamine antagonists have been reported to be very effective at relieving migraine attacks [2,8], and most antipsychotic medications and antiemetics are used for headache relief, due to their antidopaminergic properties. Evidence suggests that THC may exacerbate psychotic symptoms in schizophrenic patients, and in animal models, and that THC increases dopamine synthesis and release, as well as dopaminergic cell firing [36]. However, the effects of THC on the dopaminergic pathways in humans seem to be complex and dose-dependent; lower doses of THC appear to raise dopamine levels by increasing the conversion of tyrosine to dopamine, while higher doses of THC lead to decreased dopamine synthesis [36].

Another mechanism of action that headache and migraine medications have in common with *Cannabis* is that they reduce glutamate plasma levels [37]. Amitriptyline, memantine, dextromethorphan and ketamine are examples of N-methyl-D-aspartate (NMDA) receptor antagonists that reduce glutamate plasma levels and are used to treat headaches [38]. Because magnesium levels tend to be low during headaches and migraines, one potential explanation for these relationships could be the role of glutamate in magnesium absorption in the brain. Extracellular

Table 8
Symptom relief by age subgroup.

Model	Intercept	Coefficient	95% confidence interval	*P* value
Model 1: age < 35 years	−2.289		−3.688, −0.891	0.001
C. indica		−1.102	−2.216, 0.012	0.053
C. sativa		0.280	−0.375, 0.935	0.402
Pipe		1.181	0.374, 1.988	0.004
Vape		1.470	0.468, 2.471	0.004
THC 10%–19%		−1.639	−2.367, −0.911	< 0.001
THC 20%–35%		−1.166	−1.987, −0.345	0.005
CBD 1%–9%		1.658	0.839, 2.478	< 0.001
CBD 10%–35%		1.691	0.912, 2.469	< 0.001
Starting symptom level		−0.339	−0.462, −0.215	< 0.001
Model 2: age ≥ 35 years	0.872		−1.673, 3.417	0.502
C. indica		−0.083	−0.962, 0.796	0.852
C. sativa		−0.013	−1.013, 0.987	0.980
Pipe		−0.314	−2.301, 1.673	0.757
Vape		−0.592	−2.665, 1.482	0.576
THC 10%–19%		−0.818	−1.721, 0.085	0.076
THC 20%–35%		−1.487	−3.089, 0.114	0.069
CBD 1%–9%		−0.004	−1.262, 1.254	0.995
CBD 10%–35%		−0.717	−1.684, 0.250	0.146
Starting symptom level		−0.534	−0.721, −0.347	< 0.001

Each model represents a separate regression by age group. Regressions are based on a linear mixed effects model including patient-level random intercepts with an unstructured covariance matrix. The coefficients for the product characteristics, which are all categorical variables, measure the effect relative to the reference category. Starting symptom level is a non-categorical variable, and therefore, does not have a reference category. Standard errors are clustered at the patient level to adjust for heteroskedasticity and arbitrary correlation within patients. Reference categories are hybrid, joint, THC 0%–9%, and CBD 0%. The outcome is symptom relief, with negative coefficients indicating greater symptom relief. Model 1 includes 115 sessions and 42 patients, and model 2 includes 89 sessions and 39 patients. THC: tetrahydrocannabinol; CBD: cannabidiol; *C.*: *Cannabis*.

Table 9
Mean and ratio comparisons of product characteristics by age group.

Product characteristic	Age < 35 years	Age ≥ 35 years	*P* value
Plant phenotype (constituent ratio)			
Hybrid	0.57	0.57	0.859
C. indica	0.26	0.28	0.478
C. sativa	0.17	0.15	0.539
Combustion method (constituent ratio)			
Joint	0.17	0.15	0.335
Pipe	0.44	0.41	0.248
Vape	0.39	0.44	0.059
THC level (mean ± SD; constituent ratio in subgroups)	16.35 ± 0.60	17.38 ± 0.53	0.213
0%–9%	0.29	0.18	0.005
10%–19%	0.29	0.45	< 0.001
20%–35%	0.41	0.36	0.283
CBD level (mean ± SD; constituent ratio in subgroups)	8.40 ± 0.59	6.45 ± 0.73	0.049
0%	0.29	0.36	0.207
1%–9%	0.27	0.31	0.399
10%–35%	0.44	0.33	0.048

Categorical variables (plant sub-species, combustion method, and THC and CBD levels) are compared using chi-squared tests, while the continuous variables (THC and CBD) are compared using two-sided *t*-tests. THC: tetrahydrocannabinol; CBD: cannabidiol; SD: standard deviation; *C.*: *Cannabis*.

magnesium ions are able to bind to specific sites on the NMDA receptor, blocking the passage of other cations, ultimately suppressing glutamatergic activity [39]. This may explain how NMDA antagonism and the supplementation of magnesium can be effective as a prophylactic and treatment for headache- and migraine-related pain [40].

Excitotoxicity—when neurons are literally excited to death—and inflammatory mechanisms associated with glutamatergic activity may also be involved in headache and migraine pathogenesis [41]. Lamotrigine is used to treat epilepsy and is also known to have antiglutamatergic effects, as well as to be effective for treating migraines with aura via protection against excitotoxicity [41,42]. Excitotoxicity and enhanced glutamatergic signaling may also explain why monosodium glutamate and aspartame produce headaches in sensitive individuals [43]. Hence, consistent with our results, THC may be effective at treating migraine and headache pain (and offer additional neuroprotective benefits) by inducing presynaptic inhibition of glutamate release [44–46] and reducing excitatory neurotransmission [47,48]. Finally, and in addition to its effects on dopamine synthesis and glutamate suppression, THC may affect headache- and migraine-related pain by modulating cognizant perceptions and attentional demands [23,49–51]. CB1 and CB2 receptors, to which THC is a partial agonist, are the most abundant G-protein-coupled 7-transmembrane receptors in the human brain; they reciprocally interact and are co-localized with μ opioid receptors in brain structures (e.g., nucleus accumbens, hippocampus, neocortex and amygdala) that play a role in the psychological concomitants (e.g., emotional, learning, social experience) of pain perception [52–57].

While practical and statistically powerful, the current observational/quasi-field experimental research design has unavoidable limitations, including the lack of a control group, the potential for a placebo effect, and the voluntary adoption of Releaf App use. These factors could have resulted in either: a) overestimation of the effectiveness of *Cannabis* if users with negative experience decided to not use the App; or b) underestimation of *Cannabis*'s effectiveness if users decided not to use the App due to current satisfaction with product choices and their effects. Another limitation was the inability to incorporate measurements of more cannabinoids (e.g., cannabinol, cannabigerol and cannabichromene), the large number of known terpenes, and users' neurohormonal profiles, which likely interact synergistically with CBD and THC to produce *Cannabis*' unique effects across individuals, plant strains and usage contexts. Future research will benefit from the incorporation of these factors, as well as evaluation of the effectiveness and potential health risks associated with *Cannabis*-based products other than whole dried *Cannabis* flower, such as tinctures, edibles and topicals, which are typically produced using extraction methods that rely on solvents that can be toxic for human consumption [58]. Additionally, such products may be metabolized differently, involve different mechanisms of action, and would typically contain noncannabinoid chemicals that have their own clinical effects. More generally, longer term studies are required to evaluate whether the apparent significant short-term effectiveness of *Cannabis* flower for treating migraines and headaches persists in the long-run and outweighs potential risks from both short- and long-term use.

In conclusion, the medical effectiveness of *Cannabis* for treating a wide range of conditions, including migraines and headaches, as documented herein, must be weighed against not just its risks but also the effectiveness-risk profile of conventional treatments. It seems possible that the use of *Cannabis* flower, combined with other behavioral modifications, might offer some patients a natural, safer and more effective treatment regimen, compared to the use of some conventional prescription pharmaceuticals. Symptom relief appears likely to arise from how cannabinoids modulate and interact with many pathways inherent in migraine and headache production, including the same triptan mechanisms of action and opiate pathways targeted by many conventional pharmaceutical medications. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for new classes of medications [22,23]. Alternatively, *Cannabis* flower may be a natural substitute for pharmaceutical treatments. According to the current results, *Cannabis* flower appears to be effective at reducing headache- and migraine-related pain intensity for most people that choose to use it.

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Authors' contributions

JV and SS conceived the study. FB, KK, and 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. SS conducted the analyses. JV, SS, JD, and SL drafted the manuscript. All authors contributed substantially to its intellectual content and revision. All authors had access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Conflicts of interest

The authors FB, KK and BH were employed by company MoreBetter Ltd. The remaining authors declare that the research

was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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