American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 00, No 00 (), 2019: pp 1–9
Available online at www.jpain.org and www.sciencedirect.com

Original Reports

Short- and Long-Term Effects of Cannabis on Headache and Migraine

Carrie Cuttler,*,† Alexander Spradlin,* Michael J. Cleveland,‡ and Rebecca M. Craft*,†

*Department of Psychology, Washington State University, Pullman, Washington, †Translational Addiction Research Center, Washington State University, Pullman, Washington, ‡Department of Human Development, Washington State University, Pullman, Washington

Abstract: **Use of cannabis to alleviate headache and migraine is relatively common, yet research on its effectiveness remains sparse. We sought to determine whether inhalation of cannabis decreases headache and migraine ratings as well as whether gender, type of cannabis (concentrate vs flower), delta-9-tetrahydrocannabinol, cannabidiol, or dose contribute to changes in these ratings. Finally, we explored evidence for tolerance to these effects. Archival data were obtained from Strainprint, a medical cannabis app that allows patients to track symptoms before and after using different strains and doses of cannabis. Latent change score models and multilevel models were used to analyze data from 12,293 sessions where cannabis was used to treat headache and 7,441 sessions where cannabis was used to treat migraine. There were significant reductions in headache and migraine ratings after cannabis use. Men reported larger reductions in headache than women and use of concentrates was associated with larger reductions in headache than flower. Further, there was evidence of tolerance to these effects.**

Perspective: ***Inhaled cannabis reduces self-reported headache and migraine severity by approximately 50%. However, its effectiveness appears to diminish across time and patients appear to use larger doses across time, suggesting tolerance to these effects may develop with continued use.***

Key Words: *Medical marijuana, delta-9-tetrahydrocannabinol, cannabidiol, headache, migraine.*

Use of cannabis to treat headache dates back hundreds to thousands of years,[15,23] and is currently widespread among medical cannabis users.[2,26] Nearly 36% of medical cannabis users reported using cannabis to treat headache/migraine; moreover, they retrospectively reported an average 3.6-point decrease (on a 10-point scale) in headache severity after cannabis use.[26] Similarly, 40% of patients for whom medical cannabis was recommended for migraine reported a positive effect, with a decrease in migraine frequency from 10.4 to 4.6 migraines/month.[22] Moreover, another study found that approximately two-thirds of cannabis users indicated slight to substantial decreases in use of other migraine medications after initiating medical cannabis use.[21] These studies suggest that many individuals are using cannabis to treat headache and migraine, and that users experience some therapeutic effects. To date, however, there has only been 1 randomized, double-blind study of cannabinoid treatment for headache or migraine. Conducted in 30 outpatients with medication overuse headache, this study showed that nabilone (a synthetic cannabinoid) was more effective than ibuprofen in reducing pain intensity, reducing intake of other analgesics, and increasing quality of life.[20]

Preclinical studies also suggest that cannabinoids may be effective for migraine. Using a rat model of migraine (in which dural inflammation suppresses wheel-running), sumitriptan, morphine, and delta-9-

Received June 14, 2019; Revised October 25, 2019; Accepted November 1, 2019.
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors
Conflict of Interest: None of the authors have any conflicts of interest.
Data Statement: Data are available upon request (carrie.cuttler@wsu.edu).
Address reprint requests to Carrie Cuttler, PhD, Department of Psychology, Washington State University, P.O. Box 644820, Pullman, WA 99164-4820 E-mail: carrie.cuttler@wsu.edu
1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2019.11.001

tetrahydrocannabinol (THC) each prevented migraine-suppressed wheel-running.[12,13] However, rats given morphine repeatedly showed tolerance to morphine's antimigraine effect and increased sensitivity to further migraine induction,[12] echoing the tolerance and medication overuse headache phenomena observed in human migraineurs.[25,28] In contrast, rats did not develop tolerance to THC's antimigraine effect.[12] THC likely acts similarly to the endocannabinoid anandamide, which inhibits vasodilation of dural blood vessels and decreases release of calcitonin gene-related peptide from trigeminal neurons, 2 of the many mechanisms that are known to contribute to migraine.[1] The fact that patients with chronic migraine have been found to be anandamide-deficient further suggests that an under-responsive endocannabinoid system contributes to migraine susceptibility.[10]

In the present study, we used a large archival dataset obtained from the medical cannabis app Strainprint to address questions regarding the perceived efficacy of cannabis in medical cannabis users who used the app to track changes in headache or migraine from before to after cannabis use. The primary objective of the present study was to examine whether inhaled cannabis would decrease headache and migraine severity ratings. The second objective was to explore factors that predict such decreases, including gender, type of cannabis, cannabidiol (CBD) and THC content, and dose. Based on preclinical studies showing greater antinociceptive sensitivity to cannabinoids in females compared to males,[6] we predicted that the perceived analgesic efficacy of cannabis would be greater in women than men. Given that CBD enhancement of THC-induced antinociception has been found in animals,[4,5,14] and suggestions that the ratio of THC to CBD modulates some cannabis effects,[24,29] we also explored interactions between THC and CBD in predicting change in headache and migraine severity ratings.

The third objective was to investigate the development of tolerance to the putative effects of cannabis on headache and migraine, and to examine change in baseline headache/migraine severity ratings as a function of the repeated use of cannabis to manage these symptoms. We included this objective because tolerance to cannabis among chronic cannabis users has been well-documented,[9,19] and the phenomenon of medication overuse headache, which occurs in approximately 15% of migraine patients,[28] may be related to the development of tolerance to migraine medications.

Method

Procedure

Archival data from Strainprint were obtained. This free medical cannabis app provides individuals with a means of tracking changes in symptom severity as a function of different doses and strains of cannabis. During the initial set-up period, individuals enter basic demographic information (gender [male, female, other] and date of birth) as well as their medical conditions and symptoms. Subsequently, individuals open the app immediately prior to using cannabis to manage their conditions/symptoms. They first select the condition/symptom for which they are about to use cannabis to manage. They are then prompted to enter the strain of cannabis that they are about to use by selecting from a list of over 1,000 strains sold by licensed medical cannabis distributors and cannabis concentrate producers in Canada. The THC and CBD content for each of these strains is prepopulated in the app and was obtained by analyses conducted by one of Health Canada's licensed dealers, with the exception of the cannabis concentrate content data which were obtained from the concentrate manufacturers' websites. Health Canada enforces strict production guidelines, quality control guidelines and mandatory lab testing from all ministry approved licensed dealers. This mandatory lab testing includes 5 stages of processing: preparation, chromatography, general spectrometry, heavy metal spectrometry, and microbial analysis. Strainprint app users may also enter additional strain names and cannabinoid content (%THC, %CBD) for products that are not prepopulated in the app, but we did not include session data that had user-generated cannabinoid content. Users track their medical cannabis sessions by: 1) rating the severity of each symptom/condition on a scale of 0 (none) to 10 (extreme) before using cannabis, 2) identifying their method of administration (smoke, oil, vape, dab bubbler, dab portable, edible, pill, spray, transdermal, tincture), and 3) indicating the dose (eg, number of puffs). Twenty minutes after cannabis use, individuals are prompted (via a push notification) to re-rate the severity of their symptom(s)/condition(s).

For the present study, we obtained anonymous data from medical cannabis users who used the app to track the effectiveness of cannabis to treat headache and/or migraine. Specifically, we obtained data on these individuals' anonymous ID codes; cannabis treatment session numbers; gender; age; symptoms; self-reported headache/migraine severity before each tracked session of medical cannabis use; self-reported headache/migraine severity after each tracked session of medical cannabis use; cannabinoid content (%THC, %CBD) for the cannabis used in each session; the method of obtaining the cannabinoid content data (ie, licensed dealer vs user-generated); as well as the method of administration and dose for each session. As part of the app terms of use, individuals agree that the data may be used for any purpose deemed appropriate by Strainprint. The Office of Research Assurances at Washington State University determined that this anonymous archival study was exempt from the need for IRB review.

Inclusion/Exclusion Criteria

As depicted in Fig 1, data were obtained from 1,876 cannabis users who collectively used the app 22,491 times to track changes in their headache severity, and from 1,019 users who together used the app 14,091 times to track changes in migraine severity over a 16-month period (February 2017 to June 2018). Given

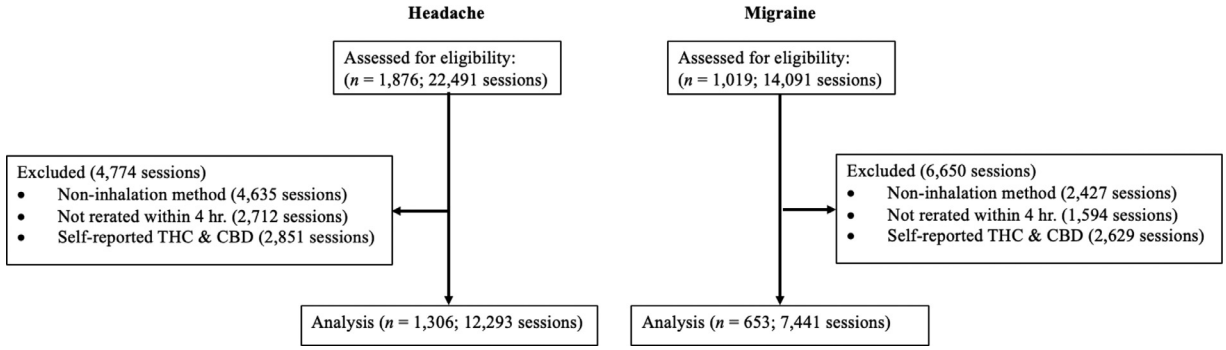

Figure 1. Flow chart showing number of headache and migraine sessions excluded and analyzed.

potential differences in onset and efficacy among different routes of administration (eg, oral vs inhaled), only tracked sessions in which individuals indicated administering cannabis via inhalation methods (smoking, vaping, concentrates, dab bubbler, dab portable) were selected (n = 17,856; 79.4% of headache data and n = 11,664; 82.8% of migraine data). Tracked sessions that involved cannabis administration via other methods (eg, tincture, edibles) were excluded from the present study. As the acute subjective effects of inhaled cannabis peak at about 10 to 30 minutes and taper off after 3 to 4 hours,[11,17] only tracked inhalation sessions for individuals who re-rated their symptoms within 4 hours were included (n = 15,144 tracked headache sessions and n = 10,070 tracked migraine sessions). Finally, we excluded tracked sessions for which THC and CBD values were entered by users due to concerns with the validity and reliability of those data.

Participants

The final sample comprised 1,306 medical cannabis users who used the app 12,293 times to track changes in headache and 653 medical cannabis users who used the app 7,441 times to track changes in migraine severity. Descriptive statistics on the samples, the THC and CBD concentrations in the cannabis used, and the number of tracked sessions for headache and migraine are shown in Table 1.

Data Analysis

The percentage of tracked sessions in which a reduction in severity, an increase in severity, and no change in severity were reported following cannabis use were computed separately for headache and migraine. Gender differences in these percentages were then examined using chi-square analyses.

For each headache or migraine episode, we used a 2-time points latent change score (LCS) model to examine changes between the severity ratings from before to after the tracked session of medical cannabis use. LCS models use a within-subjects approach to examine changes within people over time.[16] The LCS model is specified using a structural equation modeling (SEM) approach to model the change between "before" and "after" cannabis use as a latent factor. Within the context of SEM, the latent change factor (ΔRATING), is measured by the "after" cannabis use severity rating with a factor loading fixed to 1. This creates a latent factor that captures the change between the "before" and "after" cannabis use severity ratings (see Fig 2).

Specifying the LCS model in an SEM framework allows 3 important questions to be addressed. First, the mean of the latent change factor (Δ RATING) provides an estimate of the average change over time. A negative mean of the LCS factor suggests that, on average, participants' severity ratings decreased from before to after the cannabis use session. Second, the LCS model also estimates the variance of the latent change factor, which indicates the heterogeneity across participants regarding the average difference (ie, the extent to which individuals differed in their change in ratings from before to after cannabis use). Third, the covariance between severity scores from before cannabis use and the latent change factor (Δ RATING) indicates the extent to which the change in severity is proportional to severity scores before cannabis use.

Conditional LCS models allow for the addition of predictors to the latent change factor. Estimates for each

Table 1. Descriptive Statistics

Symptom	*Gender*	*Age*	*# Sessions*	*THC Content*	*CBD Content*
Headache	n = 812 (62.2%) W;	Range 18–74	Range 1–985	Range 0–77%	Range 0–50.7%
	n = 485 (37.1%) M;	M = 34.39	M = 79.53	M = 14.49%	M = 2.58%
	n = 9 (.7%) ?	SD = 8.64	SD = 159.51	SD = 7.14%	SD = 4.91%
Migraine	n = 424 (64.9%) W;	Range 18–65	Range 1–599	Range 0–77%	Range 0–34%
	n = 225 (34.5%) M;	M = 33.00	M = 80.85	M = 14.88%	M = 2.49%
	n = 4 (.6%) ?	SD = 8.97	SD = 111.28	SD = 6.91%	SD = 4.67%

Abbreviations: n, sample size; W, woman; M, man; ?, unknown; M, mean; SD, standard deviation.

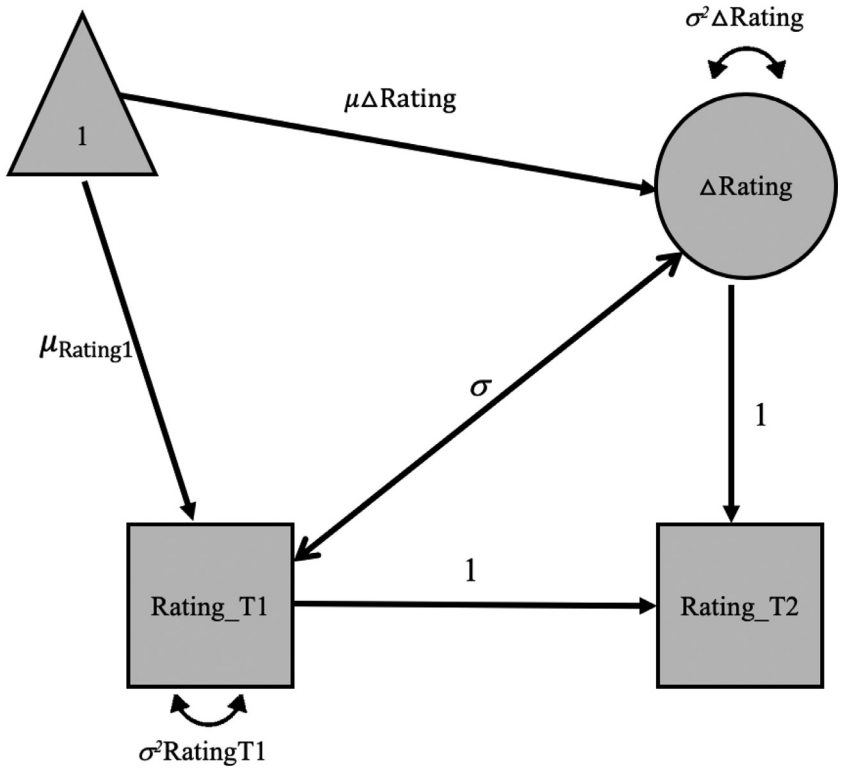

Figure 2. The basic univariate LCS model, with the commonly used symbols in SEM. The variable 'Rating' represents severity ratings and is measured at 2 time points (Rating_T1 and Rating_T2). Change (ΔRating) between the 2 timepoints is modeled as a latent variable. The model shown is just identified, which means there are as many estimated parameters as there are pieces of information from the data provided. Thus, model fit indices are not available.

predictor can be interpreted as beta coefficients that estimate the effect of the predictor variable on the change. When a LCS is positive it indicates that higher values on the predictor variable are associated with less of a decrease in severity ratings from before to after cannabis use, while negative estimates indicate higher values on the predictor variable are associated with more of a decrease in ratings. All LCS models were estimated using Mplus (version 8.2;[18]) with maximum likelihood with robust standard errors to account for nesting of repeated measures within participants.

Univariate LCS models were estimated to test the first 2 study objectives. A baseline model without any predictor variables was first estimated to describe the nature of change in severity ratings from before to after cannabis use (objective 1). Next, 2 conditional models were estimated that added predictor variables to the baseline model (objective 2). Model 1 estimated the effects of time/cannabis use session, gender, type of cannabis (flower = 0 vs concentrate = 1), THC concentration, CBD concentration, and dose on the latent change factor. Model 2 included the same predictor variables and also estimated the interaction of THC X CBD on the latent change factor.

Finally, to address our third objective, for each type of episode (headache/migraine), multilevel modeling (MLM) with repeated measures was used to describe 1) changes in baseline severity ratings across time/cannabis use sessions, and 2) changes in cannabis doses as a function of time/number of sessions. In these unconditional models, cannabis use session was centered at Time 1 so that the intercept (Time 0) represented the first session in each model. The fixed and random linear effects of time/cannabis use session were first estimated. Additional models added fixed and random quadratic effects of time/cannabis use session. All multilevel models were fit using SAS Proc Mixed, with maximum likelihood estimation and incomplete data treated using missing at random assumptions.

Results

Objective 1: Overall Change in Severity

Headache

As shown in Table 2, initial analyses revealed that headache ratings decreased in the vast majority of tracked sessions. Examining changes by gender, we found that significantly more sessions involving headache reduction were reported by men than by women (Men = 90.9% vs Women = 89.1%), $\chi^2(1) = 10.87$, $P = .001$, and significantly more sessions involving headache exacerbation (ie, worsening of symptoms) were reported by women than by men (Women = 2.9% vs Men = 1.8%), $\chi^2(1) = 16.28$, $P < .001$. There were no gender differences in the percentage of cannabis use sessions in which users reported no change in headache severity (Women = 8.1% vs Men = 7.4%), $\chi^2(1) = 2.03$, $P = .15$.

Table 2. Changes in Symptom Severity

Symptom	% Sessions Symptom Reduction	% Sessions Symptom Exacerbation	% Sessions No Symptom Change	Baseline Severity Rating	Postcannabis Use Severity Rating
Headache	89.9%	2.4%	7.7%	M = 5.79 SD = 1.81	M = 2.74 SD = 1.88
Migraine	88.1%	3.1%	8.8%	M = 6.65 SD = 2.08	M = 3.30 SD = 2.43

Abbreviation: M, mean; SD, standard deviation.

Migraine

As shown in Table 2, migraine ratings also decreased in the vast majority of tracked sessions. A similar percentage of men and women reported symptom reduction (Men = 87.3% vs Women = 88.6%), $\chi^2(1) = 2.47$, $P = .12$, and exacerbation (Men = 2.9% vs Women = 3.2%), $\chi^2(1) = .62$, $P = .43$. Significantly more men than women reported no change in severity (Men = 9.9% vs Women = 8.2%), $\chi^2(1) = 5.50$, $P = .02$.

Objective 2: Predictors of Change in Severity

Headache

As shown in Table 2 and Fig 3, headache ratings were reduced by 47.3% following cannabis use. In line with this, results of the baseline LCS model indicated that the mean of the latent change factor was negative and statistically significant ($\mu_\Delta = -3.06$, $SE = 0.18$, $P < .001$), suggesting a significant reduction in headache severity from before to after using cannabis. The variance parameter of the latent change factor was statistically significant (estimate = 4.74, $P < .001$), which indicates that there were significant individual differences in reductions in headache severity. There was also a significant covariance between the headache severity ratings before using cannabis and the latent change factor (estimate = −2.24, $P < .001$), indicating that more severe headache episodes are associated with greater reductions in headache severity.

The results of the conditional LCS models are displayed in Table 3. Both models suggest that reduction in headache severity ratings were associated with time/cannabis use session, gender, and type of cannabis used

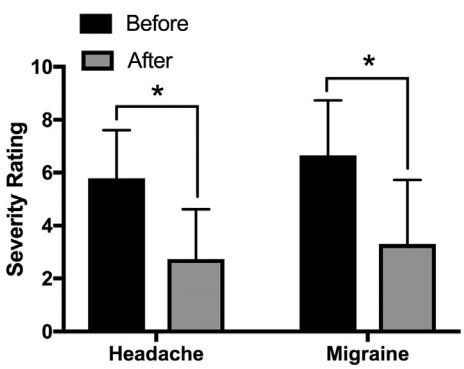

Figure 3. Each bar represents the mean with standard error bars representing standard deviations. Severity ratings could range from 0 (none) to 10 (extreme), * indicates significant difference, $P < .001$.

Table 3. LCS Models Predicting Change in Headache Severity Ratings

Predictor	Model 1		Model 2	
	b	*SE*	*b*	*SE*
Time/Cannabis Use Session	.13*	.05	.13*	.05
Gender (women = 1)	.12*	.05	.12*	.05
Type† (concentrate = 1)	−.09**	.02	−.09**	.02
THC (centered)	.02	.03	.03	.03
CBD (centered)	.02	.03	.06	.04
Dose (centered)	−.03	.04	−.03	.04
THC X CBD	–	–	.03	.03

*$P < .05$.
**$P < .001$.
†concentrate vs flower.

(flower vs concentrate). Specifically, later headache episodes were associated with less of a decrease in symptoms following cannabis use compared to earlier episodes ($\beta = .13$, $SE = .05$, $P = .010$), indicating that some tolerance to the effects of cannabis on headache reduction may occur as a function of repeated use. Further, women (coded 1) reported less of a decrease in headache severity than men ($\beta = .12$, $SE = .05$, $P = .010$). Moreover, sessions in which a concentrate was used were associated with a greater reduction in headache ratings than sessions in which flower was used ($\beta = -.09$, $SE = .02$, $P < .001$). There were no main effects of THC concentration, CBD concentration, or dose on headache reduction in any of the models. Model 2 further indicated no THC X CBD interaction on headache reduction.

Migraine

As shown in Table 2 and Fig 3, mean migraine ratings were reduced by 49.6%, following cannabis use. Further, results of the baseline model for migraine episodes indicated that the mean of the latent change factor was negative and statistically significant ($\mu_\Delta = -3.35$, $SE = .33$, $P < .001$), suggesting a significant reduction in migraine severity from before to after cannabis use. The variance parameter of the latent change factor was significant (estimate = 7.06, $P < .001$), which indicates that there were significant individual differences in reductions in migraine severity ratings. There was a significant covariance between the severity ratings before cannabis use and the latent change factor (estimate = −2.75, $P < .001$), indicating that more severe migraine episodes were associated with greater reductions in migraine ratings. The results of the conditional LCS models are displayed in Table 4. Contrary to the

Table 4. LCS Models Predicting Change in Migraine Severity Ratings

Predictor	Model 1		Model 2	
	b	*SE*	*b*	*SE*
Time/Cannabis Use Session	−.08	.06	−.08	.05
Gender (women = 1)	.11	.11	.11	.10
Type† (concentrate = 1)	.04	.04	.04	.04
THC (centered)	.12	.07	.08	.07
CBD (centered)	.002	.08	−.13	.14
Dose (centered)	−.11	.06	−.11	.07
THC X CBD	–	–	−.12	.08

*$P < .05$.
**$P < .01$.
***$P < .001$.
†concentrate vs flower.

results of the headache models, they revealed no significant predictors of reductions in migraine severity ratings.

Objective 3. Changes in Baseline Severity and Dose Across Time

Headache

The results of a MLM predicting change in baseline headache ratings as a function of time/cannabis use sessions revealed no significant change (b = .002, *SE* = .003, *P* = .415. Polynomial terms were also estimated but did not reveal significant quadradic effects. Moreover, independent examinations of sessions involving the use of flower and sessions involving the use of concentrates revealed that baseline headache ratings remained static across time/cannabis use sessions for each type of cannabis.

A second MLM revealed a significant increase in dose across time/cannabis use sessions (b = .04, *SE* = .009, $P < .001$). Given the significant effect of cannabis type in predicting change in headache severity, additional exploratory analyses were conducted to examine changes in dose across time/cannabis use sessions for flower and concentrates separately. The results indicated that dose increased across time/cannabis use sessions involving flower (b = .04, *SE* = .009, $P < .001$). In contrast, dose deceased significantly across time/cannabis use sessions involving use of concentrates (b = −.01, *SE* = .003, $P < .001$).

Migraine

Consistent with the results of the headache analyses, the results of a MLM predicting change in baseline migraine severity as a function of time/cannabis use sessions revealed no significant change in baseline migraine ratings (b = .0004, *SE* = .002, *P* = .770). Polynomial terms were also estimated but did not reveal significant quadradic effects. Once again, independent examinations of sessions involving the use of flower and sessions involving the use of concentrates revealed that baseline migraine ratings remained static across time/cannabis use sessions for each type of cannabis. Finally, a second MLM revealed a significant increase in dose across time/cannabis use sessions (b = .04, *SE* = .01, *P* = .001).

Discussion

Objective 1. Overall Change in Severity

The primary objective of this study was to examine effects of inhaled cannabis on headache and migraine severity. Results revealed that for the vast majority of cannabis use sessions, patients reported reductions in headache (89.9%) and migraine severity (88.1%). Moreover, a 47.3% decrease in headache severity and a 49.6% decrease in migraine severity were reported following cannabis use. These results suggest that inhaled cannabis reduces the perceived severity of headache and migraine by nearly 50%.

Objective 2. Predictors of Change in Severity

Gender, type of cannabis (flower vs concentrate), and time/cannabis use session predicted change in headache ratings. In contrast, none of the predictors accounted for a significant portion of change in migraine severity ratings. While the failure to detect predictors of change in migraine ratings was somewhat surprising, power was substantially higher to detect significant predictors using the headache session data (12,293 sessions) than the migraine session data (7,441 sessions). Nevertheless, the null results indicate that cannabis reduces migraine severity regardless of the type, dose, THC or CBD content.

Comparisons of men and women revealed that more women than men reported headache exacerbation, and more men than women reported headache reduction, following cannabis use. Moreover, men reported larger reductions in headache severity following cannabis use than did women. While these findings contradict our hypothesis, they corroborate previous findings demonstrating that smoked cannabis produced greater analgesia in men than women.[7] Nevertheless, the size of the gender differences in the present study are quite small, with differences of only 1.1% and 1.8% in the percentage of men and women who reported headache exacerbation and reduction, respectively. Similarly, the regression coefficient of 0.12 for gender indicates that the size of reduction in headache between men and women differs by only 0.12/10 units. A similarly sized coefficient for gender (b = .11) predicting change in migraine severity was detected but was not statistically significant, likely because there were substantially fewer migraine episodes to analyze. Therefore, while gender was found to moderate some of the headache results, the size of these effects may limit their practical value.

While use of cannabis flower was associated with significant reductions in headache ratings, use of

concentrates was associated with significantly larger reductions in these ratings. To date, almost no research has examined the health effects of concentrates and as such this finding is entirely novel. Given that concentrates are far more potent than flower, it is tempting to think that this effect may reflect their potency. However, the absence of significant dose effects argues against this explanation. Alternatively, it is possible that the cannabis concentrate findings are less reliable given that they represented a minority of the complete dataset (3.4% of headache episodes). Given that concentrates are becoming increasingly popular and available,[27] future research on their health effects is urgently needed.

Results of analyses examining THC and CBD contradicted our hypothesis that THC and CBD would interact to predict the perceived analgesic effects of cannabis. Given the high degree of power afforded by the extremely large datasets and the use of validated THC and CBD content information, these results argue against differences in the efficacy of cannabis with varying concentrations of THC and CBD in reducing headache/migraine. Moreover, these results converge with previous research demonstrating no impact of cannabis strain on therapeutic effect[3] and no significant difference in preference among strains with differing THC and CBD content in patients using cannabis for headache and migraine.[2] It is also important to note that cannabis contains hundreds of other phytocannabinoids besides THC and CBD, plus terpenes and flavonoids that may contribute to its medicinal properties. Unfortunately, documentation of other cannabis constituents was too sparse in the present dataset for us to conduct analyses exploring their therapeutic potential. Nevertheless, our findings indicate that medical cannabis patients can use factors other than THC and CBD content to guide their cannabis selection

Results also revealed no effects of dose of inhaled cannabis on change in headache/migraine severity. These results may reflect the tendency for cannabis users to self-titrate once optimal effects are achieved, and the possibility that users who differ in experience with cannabis and/or body mass require different doses to achieve those same optimal effects.

Objective 3. Changes in Baseline Severity and Dose Across Time

We also investigated long-term consequences of using cannabis to treat headache and migraine. First, we examined evidence for change in perceived efficacy of cannabis over time in an attempt to explore whether tolerance or sensitization to its effects develops. The results revealed that reductions in headache ratings diminished as a function of time/cannabis use sessions, suggesting that tolerance may develop with repeated use of the drug. In contrast, time/cannabis use sessions were unrelated to change in migraine ratings, which is consistent with previous research[12] and suggests cannabis remains an effective treatment for migraines with repeated use.

Another index of tolerance is the need for larger quantities of the drug to achieve the same effects. Consistent with this, results of the MLM examining change in dose indicate that increased doses were used across time/cannabis use sessions for both headache and migraine. This indicates that patients are using larger doses to achieve smaller therapeutic effects on headache across time and similar therapeutic effects on migraine across time. However, further exploratory analyses indicate that these dose escalations may be specific to cannabis flower, as dose of concentrate used to treat headache *decreased* across time/cannabis use sessions. The latter finding is surprising given that one might expect tolerance to develop more quickly with higher potency concentrates. However, there is evidence that other phytocannabinoids and terpenes present in cannabis flower are reduced in some concentrates and that these additional components may buffer effects of ingested cannabis flower.[8] This means that the effects we observed may not be indicative of tolerance development but rather a differential "dialing in" process between those who use flower and those who use concentrates. Nonetheless, given that only a minority of sessions involved concentrate use, this result should be interpreted cautiously until further systematic research has been conducted.

Finally, we examined changes in baseline symptom ratings (ie, ratings of headache/migraine severity before each cannabis use session) across time/cannabis use sessions to explore whether repeated use of cannabis to manage headache/migraine would result in medication overuse headache. Results revealed no significant changes in baseline severity of headaches or migraines across cannabis use sessions. This was true for flower sessions, concentrate sessions, and both types of sessions combined. These findings are encouraging given that medication overuse headache occurs in approximately 15% of migraine patients taking conventional medications.[25,28]

Limitations and Strengths

Limitations of the study include possible sampling bias and the lack of a placebo control group. Concretely, the sample likely over-represents individuals who find cannabis effective in reducing headache/migraine severity, as those who do not find it effective would be unlikely to continue to use cannabis and the Strainprint app. Further, it is unclear what percentage of the samples represented new users vs experienced users. As such, the degree to which users in our samples have already developed tolerance to cannabis is unclear. Moreover, it was not possible to obtain a placebo control group. Thus, it is likely that some of the efficacy of cannabis in reducing headache and migraine severity can be attributed to expectancy effects. Nevertheless, our results demonstrating beneficial effects of cannabis on headache and migraine are consistent with the results of 1

randomized, double-blind study showing that nabilone (a synthetic cannabinoid) was effective in reducing headache intensity.[20] Regardless, additional double-blind, placebo-controlled studies are required to corroborate these findings.

These limitations are offset by several strengths. First, the data were obtained from a large sample of medical cannabis patients using a wide variety of cannabis strains in their natural environment. As such, the results have high ecological validity and should translate to other cannabis patients inhaling various strains of cannabis in their own environment to treat these conditions. Moreover, the Strainprint app was developed to aid medical cannabis patients in identifying the strains and doses of cannabis that optimally reduce their symptoms and the vast majority of users were likely unaware that their data are being used for scientific investigation. This would reduce explicit response bias stemming from some medical cannabis patients' desire to portray cannabis as an effective medicine to the scientific community.

Conclusions

The present study indicates that inhaled cannabis reduces headache and migraine severity ratings by approximately 50%. Repeated use of cannabis is associated with tolerance to its effects, making tolerance a risk factor for the use of cannabis to treat headache and migraine. However, cannabis does not appear to lead to the medication overuse headache that is associated with other conventional treatments, meaning that use of cannabis does not make headaches or migraines worse over time. Future double-blind, placebo controlled clinical trials are warranted and will help to rule out placebo effects and provide a more controlled examination of dose, type of cannabis, THC, CBD, and THC x CBD interactions.

Acknowledgments

We thank the creators of Strainprint for freely and openly providing the data used in this study.

References

1. Akerman S, Kaube H, Goadsby PJ: Anandamide is able to inhibit trigeminal neurons using an in vivo model of trigeminovascular-mediated nociception. J Pharmacol Exp Ther 309:56-63, 2003

2. Baron EP, Lucas P, Eades J, Hogue O: Patterns of medicinal cannabis use, strain analysis, and substitution effects among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain 19:37-64, 2008

3. Brunt TM, van Genugten M, Honer-Snoeken K, van de Velde MJ, Niesink RJM: Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. J Clin Psychopharm 34:344-349, 2014

4. Burstein S: Cannabidiol and its analogs: A review of their effects on inflammation. Bioorg Med Chem 23:1377-1385, 2016

5. Casey SL, Atwal N, Vaughan CW: Cannabis constituent synergy in a mouse neuropathic pain model. Pain 158:2452-2460, 2017

6. Cooper ZD, Craft RM: Sex-dependent effects of cannabis and cannabinoids: A translational perspective. Neuropsychopharmacology 43:34-51, 2017

7. Cooper ZD, Haney M: Sex-dependent effects of cannabis-induced analgesia. Drug Alcohol Depen 167:112-120, 2016

8. Gallily R, Yekhtin Z, Hanuš L: Overcoming the bell-shaped dose-response of cannabidiol by using cannabis extract enriched in cannabidiol. Pharmacol Pharm 6:75-85, 2015

9. Gorelick DA, Goodwin RS, Schwilke E, Schwope DM, Darwin WD, Kelly DL, McMahon RP, Liu F, Ortemann-Renon C, Bonnet D, Huestis MA: Tolerance to effects of high-dose oral Δ^9-tetrahydrocannabinol and plasma cannabinoid concentrations in male daily cannabis smokers. J Anal Toxicol 37:11-16, 2013

10. Greco R, Demartini C, Zanaboni AM, Piomelli D, Tassorelli C: Endocannabinoid system and migraine pain: An update. Front Neurosci 12:1-7, 2018

11. Grotenhermen F: Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 42:327-360, 2003

12. Kandasamy R, Dawson CT, Hilgendorf TN, Morgan MM: Medication overuse headache following repeated morphine, but not Δ9-tetrahydrocannabinol administration in the female rat. Behav Pharmacol 29:469-472, 2018

13. Kandasamy R, Lee AT, Morgan MM: Depression of home cage wheel running: A reliable and clinically relevant method to assess migraine pain in rats. J Headache Pain 18:5-13, 2017

14. King KM, Myers AM, Soroka-Monzo AJ, Tuma RF, Tallarida RJ, Walker EA, Ward SJ: Single and combined effects of Δ^9-tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. Br J Pharmacol 174:2832-2841, 2017

15. Lochte BC, Beletsky A, Samuel NK, Grant I: The use of cannabis for headache disorders. Cannabis Cannabinoid Res 2.1:61-71, 2017

16. McArdle JJ: Latent variable modeling of differences and changes with longitudinal data. Ann Rev Psychol 60:577-605, 2009

17. Menkes DB, Howard RC, Spears GF, Cairns ER: Salivary THC following cannabis smoking correlates with subjective intoxication and heart rate. Psychopharmacology 103:277-279, 1991

18. Muthén LK, Muthén BO: Mplus User's Guide, 8th ed.Los Angeles, Muthén & Muthén, 1998-2017.

19. Newmeyer MN, Swortwood MJ, Abulseoud OA, Huestis MA: Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration. Drug Alcohol Depend 175:67-76, 2017

20. Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M: Nabilone for the treatment of medication overuse headache: Results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain 13:677-684, 2012

21. Piper BJ, DeKeuster RM, Beals ML, Cobb CM, Burchman XA, Perkinson L, Lynn ST, Nicholas SD, Abess AT: Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. J Psychopharmacol 31:569-575, 2017

22. Rhyne DN, Anderson SL, Gedde M, Borgelt LM: Effects of medical marijuana on migraine headache frequency in an adult population. Pharmacotherapy 36:505-510, 2016

23. Russo E: Cannabis for migraine treatment: The once and future prescription? An historical and scientific review. Pain 76:3-8, 1998

24. Russo E, Guy GW: A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Med Hypoth 66:234-246, 2006

25. Schwedt TJ, Alam A, Reed ML, Fanning KM, Munjal S, Buse DC, Dodick DW, Lipton RB: Factors associated with acute medication overuse in people with migraine: Results from the 2017 migraine in America symptoms and treatment (MAST) study. J Headache Pain 19:38-47, 2018

26. Sexton M, Cuttler C, Finnell JS, Mischley LK: Cross-sectional survey of medical cannabis users: Patterns of use and perceived efficacy. Cannabis Cannabinoid Res 1:131-138, 2016

27. Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G: Variation in cannabis potency and prices in a newly legal market: Evidence from 30 million cannabis sales in Washington State. Addiction 112:2167-2177, 2017

28. Vikelis M, Spingos KC, Rapoport AM: A new era in headache treatment. Neurol Sci 39(Suppl 1):547-558, 2018

29. Zuardi AW, Hallak JEC, Crippa JAS: Interaction between cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC): Influence of administration interval and dose ratio between the cannabinoids. Psychopharmacology 219:247-249, 2012