Medication Overuse Headache in Chronic Migraine Patients Using Cannabis: A Case-Referent Study

Niushen Zhang (nzhang5@stanford.edu)
Stanford University School of Medicine https://orcid.org/0000-0002-8869-7732
Yohannes W Woldeamanuel
Stanford University School of Medicine

Research article

Keywords: migraine, chronic migraine, medication overuse headache, cannabis, case-referent study

Posted Date: February 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-185874/v1

Medication Overuse Headache in Chronic Migraine Patients Using Cannabis: a Case-Referent Study

Niushen Zhang[1*], MD; Yohannes W. Woldeamanuel[1*], MD

[1]Department of Neurology & Neurological Sciences, Stanford University School of Medicine, Palo Alto, CA, USA
*Both authors have made equal contribution.

Corresponding Author:
Niushen Zhang, MD
211 Quarry Road, Suite 206
Palo Alto, California, 94304 USA
E-mail: nzhang5@stanford.edu
Telephone: 405-880-4957

Contributing Authors:
Yohannes W. Woldeamanuel, MD—E-mail: ywoldeam@stanford.edu

Statistical analysis completed by Yohannes W. Woldeamanuel, MD

Manuscript: 2463 words
Abstract: 245 words
Title: 94 characters (with spaces)
References: 38
Tables: 2
Figures: 4
Supplemental table: 1

Search Terms: migraine, chronic migraine, medication overuse headache, cannabis, case-referent study

Author disclosures:

Dr. Niushen Zhang reports no relevant disclosures
Dr. Yohannes Woldeamanuel reports no relevant disclosures

No funding or sponsorship was received in connection with this manuscript.

Abstract

Objective: To examine whether cannabis use predicts medication overuse headache (MOH) in chronic migraine (CM) patients.

Methods: Electronic chart review was conducted by combining the terms "chronic migraine", "medication overuse", "cannabis", "CBD", "THC" for patients seen at our headache clinics from 2015 to 2019. Of 729 charts identified, 368 (150 using cannabis; 218 not using cannabis) met our inclusion criteria, i.e., adult CM patients with ≥ 1-year CM duration. The following variables were extracted from each patient's chart: MOH diagnosis as dependent variable, and predictor variables as age, sex, migraine frequency, current CM duration, current cannabis use duration, overused acute migraine medications, current MOH duration, and types of cannabis products used. Logistic regression was employed to identify variables predicting MOH while controlling for remaining predictors. Agglomerative hierarchical clustering (AHC) was conducted to explore natural clusters using all predictor variables.

Results: There were 212 CM patients with MOH (*cases*) and 156 CM patients without MOH (*referents*). Current cannabis use statistically significantly predicted cases with MOH – odds ratio 6.0 (3.45, 10.43), $p < 0.0001$. Current cannabis use, opioid use, and MOH were significantly associated. AHC revealed two major natural clusters. Cluster I patients were younger with less migraine frequency, higher MOH burden, more current cannabis and opioid users than cluster II.

Conclusion: Cannabis use significantly contributes to the prevalence of MOH in CM. Bidirectional cannabis-opioid association was observed – use of one

increased use of the other. Advising CM patients with MOH to reduce cannabis use may help treat MOH effectively.

Introduction

Medication overuse headache (MOH) is a consequence of regular overuse of acute headache medications in patients with pre-existing primary headache disorders, such as migraine (ICHD-3). MOH presents as either a new headache or worsening of a pre-existing headache[1]. Prevalence of MOH in the general population is 0.5-2.6%; among patients with chronic daily headache, the prevalence of MOH is estimated to be 11-70%[2]. The Nord-Trøndelag Health Survey (Helseundersøkelsen i Nord-Trøndelag: HUNT), a community-based study from Norway involving nearly 50,000 participants, showed that 54% of chronic migraine patients had comorbid MOH[3]. A study from Latin American countries reported that up to 95% of MOH patients have migraine[4]. Treatment of MOH requires tapering and discontinuing the offending medication, and, typically, the addition of preventive treatment[5]. However, withdrawal of the offending medication can be challenging because of the initial increase in pain and other withdrawal side effects[6].

Cannabis is the most widely used drug in the world, with an estimated 192 million adults who used cannabis globally in 2018 (3.9% of people aged 15-64)[7]. Cannabis dependence is the second most common drug use disorder after opioid dependence afflicting 22.1 million people worldwide in 2016. It affects the endocannabinoid system in the brain, which plays a role in pain processing[8–10]. There is moderate evidence to support the use of cannabis or cannabinoids for the treatment of chronic pain in adults[11–13] and as opioid-sparing agents[14–16].

However, other studies show cannabis use to be a risk factor for abuse or dependence of prescription opioids and other drugs[17–19]. There is currently limited evidence suggesting that cannabis could be helpful for treatment of migraine[20]. There are no randomized controlled clinical trials that support this hypothesis. However, there is emerging anecdotal clinical evidence that use of cannabis may lead to medication overuse[17,21]. Based on clinical observation, patients with chronic migraine and MOH appear to be concomitantly using cannabis products.

Our study is the first of its kind to assess the risk of MOH in chronic migraine patients who use cannabis. In addition, we sought to utilize unsupervised data reduction methods to explore data-driven as well as clinically meaningful natural clusters of chronic migraine patients based on variables such as MOH comorbidity, use of cannabis and opioids, age, migraine frequency, duration of chronic migraine and MOH. These approaches allowed us to gain in-depth insight into the MOH risk and other related variables associated with cannabis use. Furthermore, we explored whether there was opioid-sparing effect of cannabis use in chronic migraine with or without MOH. The findings contribute to the growing body of work that will help guide physician recommendations for chronic migraine patients who are already self-medicating with cannabis.

Methods

Electronic Chart Search

This research used data provided by STARR, “STAnford medicine Research data Repository” (STARR), a clinical data warehouse containing live Epic data from Stanford Health Care (SHC), the Stanford Children’s Hospital (SCH), the University Healthcare Alliance (UHA) and Packard Children's Health Alliance (PCHA) clinics and other auxiliary data from Hospital applications such as radiology picture archiving and communication system (PACS). STARR platform is developed and operated by Stanford Medicine Research IT team and is made possible by Stanford School of Medicine Research Office. Using the Stanford Research Repository Cohort Discovery Tool (part of the STARR platform), we created a cohort for the chronic migraine patients. Our search terms included “chronic migraine”, “medication overuse”, “cannabis”, “CBD”, “THC”, and “marijuana.” We reviewed electronic charts of patients seen from January 1, 2015 to January 1, 2019. Two headache specialists (NZ, YWW) reviewed the charts and labeled each chart as included, excluded, or undecided. The undecided charts were reviewed by both authors, and disagreements were resolved by discussion.

Inclusion and Exclusion Criteria

We included adult chronic migraine patients aged 18 and above with a minimum of one-year chronic migraine duration, using and *not* using cannabis products at time of clinic visit. We excluded children under the age of 18 years, patients with

episodic migraine, chronic migraine shorter than one-year duration, secondary headache disorders (such as post-traumatic headache).

Data Extraction

The data that was extracted included age, sex, diagnosis of chronic migraine, average number of headache days per month during the last 3 months, duration of chronic migraine in years, cannabis use at the time of encounter, duration of last cannabis use in months, type of cannabis used, diagnosis of medication overuse headache, and abortive medications causing the medication overuse headache.

Ethical approval

The study received full ethics approval from the institutional review board at Stanford University (Protocol 50215). De-identified data was stored securely in Stanford encrypted server. Our study is in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies[22].

Power Analysis and Sample Size Estimation

Sample size was estimated using logistic regression 2-tailed test whether a dichotomous variable (*use* or *no use* of cannabis) was a significant predictor of a binary outcome (presence of absence of MOH), with other covariates (e.g. age, sex, monthly migraine frequency, duration of current CM) – at an α error

probability of 0.05, a 1–β error probability of 80% (power), low squared multiple correlation coefficient (R^2) of 0.04 between the main predictor (cannabis use) and other covariates, and an estimated 50% proportion of cannabis users. The null hypothesis that probability of MOH when a chronic migraine patient is *not* using cannabis was estimated to be 0.54 based on the HUNT study[3]. We estimated for our alternative hypothesis that probability of MOH when a chronic migraine patient is using cannabis to be 0.68 (odds ratio = 1.90). Based on these assumptions, there is 80% chance of correctly rejecting the null hypothesis that a particular category of the main predictor variable (using cannabis) is not associated with the value of the outcome variable (MOH), with 345 patients. After adjusting for an assumed 7% of missing data, our final sample size was made 368 patients. Sample size estimation was conducted on G*Power 3.1.9.6[23,24].

Statistical Analysis

Data were summarized using descriptive statistics. Differences in variables between cases and referents were analyzed using Welch's *t*-tests and chi-squared tests with Yates correction. Logistic regression was employed to identify variables predicting CM patients with MOH (*cases*) from CM patients without MOH (*referents*). Predictor variables (age, sex, monthly migraine frequency, duration of current CM, current use of cannabis, opioid, butalbital, benzodiazepine) were tested in one block to determine their predictive capacity by examining their adjusted odds ratio (OR) statistics. Opioid, butalbital, benzodiazepine use was included in predictor variables as these are

dependence causing drugs that are sometimes prescribed in migraine management. The regression model's goodness-of-fit was tested using Cox & Snell R-square[25], Nagelkerke R-square[26], and Hosmer and Lemeshow test[27]. Correlogram based on Spearman rank correlation was used to assess the associations among all variables. Sex (female, male), current use of cannabis (yes, no), opioid, butalbital, and benzodiazepine were dummy coded as "1" and "0" for analysis. Significance threshold was set at *p*-value of 0.05. Missing data were excluded from analysis.

Additionally, unsupervised data-driven agglomerative hierarchical clustering (AHC) analyses was performed to explore MOH-consistent natural clusters within the total patient population using all predictor variables (age, sex, monthly migraine frequency, duration of current CM, current use of cannabis, opioid, butalbital, benzodiazepine). Clustering analysis was performed using Ward's agglomeration method with Squared Euclidean distance metric as measure of dissimilarity. A dendrogram was created to visualize the AHC clustering and select the major clusters. Statistical analyses were done using Statistical Package for Social Sciences (version 21.0; SPSS Inc, Chicago IL) and XLSTAT 2020 (Addinsoft).

Data Availability Statement

The data that support the findings of this project are available from the contributing author, YWW, upon reasonable request.

Results

Of the 729 charts reviewed, a total of 368 patients (212 cases and 156 referents) were included in the study. The remaining 361 patients were excluded as per our aforementioned exclusion criteria. Clinical characteristics of included patients are displayed in Table 1. There were no statistically significant differences in age, sex ratio, monthly migraine frequency, and duration of current CM. There was 3 times greater number of cases (CM patients with MOH) currently using cannabis than referents (CM patients without MOH) (p = 0.00001; chi-squared test). On average, cases were using cannabis about 4 times longer than referents (19 versus 5 months). In cases and referents, overused acute migraine medications included triptans (sumatriptan, rizatriptan), non-steroidal anti-inflammatory medications (ibuprofen, naproxen, ketorolac), acetaminophen, combination medications (acetaminophen/aspirin/caffeine, acetaminophen/codeine, butalbital/acetaminophen/caffeine, butalbital/aspirin/caffeine), opioid medications (tramadol, oxycodone, oxycodone/acetaminophen, hydrocodone, hydrocodone/acetaminophen, hydromorphone, morphine), and benzodiazepines (alprazolam, lorazepam, clonazepam, diazepam). The median duration of MOH in cases was 2 years. The different forms of cannabis products used by cases included, inhalation products (joints, electronic vaping devices), orally ingested products (cookies, tablets, gummies, tinctures, mints), topical products (oils, ointments, creams, patches). Cases exhibited a significantly higher usage of inhaled and ingested cannabis products compared to referents (Figure 1, Table 1). There was 5% of missing data in the following datasets: duration of current

cannabis use and duration of current MOH. Missing data were excluded from analysis.

Logistic regression (Figure 2, Table 2) showed that current cannabis use (odds ratio or OR = 5.99 CI = 3.45, 10.43, $p < 0.0001$), current opioid use (OR = 3.98, CI = 2.26, 7.01, $p < 0.0001$), migraine frequency (OR = 1.06, CI =1.01, 1.10), and age (OR = 1.02, CI = 1.00, 1.05, $p = 0.026$) significantly predicted the presence of MOH in chronic migraine patients, with decreasing order. Goodness-of-fit statistics showed that the predictive capacity of the model was fit and appropriate (Cox & Snell R square 0.19, Nagelkerke R square 0.25, Hosmer and Lemeshow test $p = 0.86$). Correlogram demonstrated significant associations between cannabis use, opioid use, and MOH (Figure 3). Mild correlation between current cannabis use and current benzodiazepine use was found. No association was found between current cannabis use and current butalbital use. AHC revealed two major natural clusters. Compared to Cluster II, Cluster I patients were younger with less migraine frequency and featured higher MOH burden, current cannabis users, current opioid users (Figure 4).

Discussion

We found that the presence of cannabis use significantly increased the odds of medication overuse headache in patients with chronic migraine. This finding brings up two important questions: 1) Does cannabis use in migraine patients lead to the development of MOH? 2) Can cannabis be used to treat MOH?

The mechanism behind the development and maintenance of MOH is not well understood[28]. Effective migraine therapies that can help reduce the risk of MOH and to treat existing MOH is much needed. A study in rodent model of migraine showed that administration of THC reduces migraine-like pain[29]. Pini et al. conducted the first and only randomized active-controlled crossover study that evaluated the use of cannabinoids for treatment of medication overuse headache[30]. They found that synthetic cannabinoid nabilone (a CB1 receptor agonist) was more effective than ibuprofen at reducing pain intensity and daily analgesic intake in individuals with medication overuse headache[30]. Using cannabis for the acute treatment of headache brings up the concern of whether cannabis can lead to the development of MOH just as other migraine abortive therapies have the potential of doing so. In a recent study that evaluated cannabinoid receptor agonists in a preclinical model of medication overuse headache, the authors explored whether the exposure of rats to cannabinoids would result in latent trigeminal sensitization and vulnerability to typical migraine triggers[31]. They found that cannabinoid receptor agonists (including delta-9-THC) does produce a state of latent sensitization characterized by increased sensitivity

to stress, which is a presumed migraine trigger[31]. Based on these results and our findings, we speculate that cannabis consumption leads to increased sensitization that can exacerbate the progression of medication overuse headache.

Our results did not show opioid-sparing effects of cannabis use in chronic migraine patients with or without MOH. In contrast, we found increased association between current cannabis use and current opioid use. However, longitudinal studies will be the appropriate design to examine this relationship so as to explore cause and effect. There is conflicting evidence in opioid-sparing effects of cannabis in the general population. Some cross-sectional studies demonstrate the protective effect of cannabis use from developing opioid dependence[32] and speculate that cannabis may potentiate opioid efficacy leading to reduced opioid dosage[33]. A study in migraine patients has found that 43% patients substituted their opiates/opioids to cannabis[34]. Other prospective studies indicate that cannabis increases the risk of opioid dependence or opioid use disorder[18,35]. Our study showed mild association between current cannabis use and current benzodiazepine use. Another retrospective study has reported increased benzodiazepine discontinuation among mixed cohort of patients with pain and non-pain conditions[36]. In our study, no association was found between current cannabis use and current butalbital use. Our results are the first to explore relationships and MOH risk among these four dependence-causing drugs commonly used by migraine patients i.e. cannabis-opioid, cannabis-

benzodiazepine, and cannabis-butalbital association. Of these four drugs, cannabis and opioid use significantly contributed to MOH prevalence in chronic migraine patients while adjusting for the other variables. It may be noteworthy to consider that cannabis using CM patients are at increased risk of opioid use, and the consumption of both cannabis and opioid increases the prevalence for MOH.

Many migraine patients are already self-medicating with cannabis[34]. In a 2018 electronic survey study on patterns of medicinal cannabis use, 88% of headache sufferers were using cannabis to treat probable migraine[34]. A dose-finding clinical study involving 48 CM patients found that an oral dose of 200 mg THC-CBD in 200 ml 50% fat emulsion led to a 55% reduction in acute pain severity[37]. This study was followed by a 3-month pilot clinical trial involving 79 CM patients where a daily prophylactic dose of 200 mg THC-CBD in 200 ml 50% fat emulsion showed 40.4% reduction in migraine frequency compared to 40.1% with daily 25mg amitriptyline[37]. Given the vast heterogeneity of unregulated cannabis products, the unproven safety and efficacy of cannabis for the treatment of migraine, and our study raising concerns that cannabis may increase the risk of medication overuse use, clinicians should be cautious about recommending cannabis to their patients for the treatment of migraine. Our data-driven clustering analysis classified the patients into natural subgroups; younger patients (Cluster I) featured higher MOH burden as well as increased cannabis and opioid use compared to older patients (Cluster II). This result can be clinically meaningful as it suggests that clinicians should be vigilant to avoid the

risk of MOH development when prescribing cannabis products to younger migraine patients.

That migraine-related patient characteristics were comparable between cases and referents in our study was a strength for our study. In addition, the regression model's satisfactory goodness-of-fit, optimum sample size, and adjustment for potential confounders (age, sex, migraine frequency, chronic migraine duration) are strengths of this study. With the rise of legal consumption of cannabis products, it is important to fully understand risk of MOH in cannabis using migraine patients.

Limitation of this study include the fact that our hospital-based study from a tertiary headache clinic may not be representative of the general chronic migraine population in the community. However, the demographic involving mostly of female middle-aged patients may offer some degree of representativeness to target population of chronic migraine[38]. By virtue of being a retrospective design, our study was limited to challenges which are inherent to retrospective chart studies, e.g. lack of data to determine temporal association between cannabis use and MOH development or dose response between cannabis use and risk of MOH. Additional possible sources of confounders such as psychological comorbidities, alcohol use and cigarette smoking were not consistently available and hence not studied. Likewise, causative analysis cannot be confirmed based on our results. For example, in the absence of psychological

profiling, the association results from our study might be partly due to dependency-prone personality rather than the biological effects of cannabis or opioids.

Conclusion

Medication overuse headache is significant issue especially among patients with chronic migraine. Our study showed that cannabis use significantly increases the odds of MOH in CM patients.

Appendix 1—Authors

Name	Location	Roles	Contributions
Niushen Zhang	Palo Alto, California, USA	Author	Project concept or design; acquisition of data; interpretation of data; drafting/revising the manuscript for content
Yohannes Woldeamanuel	Palo Alto, California, USA	Author	Project concept or design; acquisition of data; statistical analysis and interpretation of data; drafting/revising the manuscript for content

References:

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38:1–211.
2. Diener H-C, Holle D, Solbach K, Gaul C. Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol. 2016;12:575–583.
3. Zwart J-A, Dyb G, Hagen K, Svebak S, Stovner LJ, Holmen J. Analgesic overuse among subjects with headache, neck, and low-back pain. Neurology. 2004;62:1540–1544.
4. Shand B, Goicochea MT, Valenzuela R, et al. Clinical and Demographical Characteristics of Patients with Medication Overuse Headache in Argentina and Chile: Analysis of the Latin American Section of COMOESTAS Project. J Headache Pain. 2015;16:83.
5. Carlsen LN, Munksgaard SB, Nielsen M, et al. Comparison of 3 Treatment Strategies for Medication Overuse Headache: A Randomized Clinical Trial. JAMA Neurol. Epub 2020 May 26.
6. Evers S, Jensen R, European Federation of Neurological Societies. Treatment of medication overuse headache--guideline of the EFNS headache panel. Eur J Neurol. 2011;18:1115–1121.
7. World Drug Report 2020 (United Nations publication, Sales No. E.20.XI.6).
8. Woodhams SG, Chapman V, Finn DP, Hohmann AG, Neugebauer V. The cannabinoid system and pain. Neuropharmacology. 2017;124:105–120.
9. Rani Sagar D, Burston JJ, Woodhams SG, Chapman V. Dynamic changes to the endocannabinoid system in models of chronic pain. Philos Trans R Soc Lond B Biol Sci. 2012;367:3300–3311.
10. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. Epub 2005.:299–325.
11. Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Pain Physician. 2017;20:E755–E796.
12. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J oral facial pain headache. 2015;29:7–14.
13. Johal H, Devji T, Chang Y, Simone J, Vannabouathong C, Bhandari M. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13:1179544120906461.
14. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study. Lancet Public Heal. 2018;3:e341–e350.
15. Piper BJ, DeKeuster RM, Beals ML, et al. Substitution of medical cannabis for pharmaceutical agents for pain, anxiety, and sleep. J Psychopharmacol. 2017;31:569–575.
16. Nielsen S, Sabioni P, Trigo JM, et al. Opioid-Sparing Effect of

Cannabinoids: A Systematic Review and Meta-Analysis. Neuropsychopharmacology. 2017;42:1752–1765.
17. Olfson M, Wall MM, Liu S-M, Blanco C. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. Am J Psychiatry. 2018;175:47–53.
18. Lynskey MT. Escalation of Drug Use in Early-Onset Cannabis Users vs Co-twin Controls. JAMA. 2003;289:427.
19. Blanco C, Hasin DS, Wall MM, et al. Cannabis Use and Risk of Psychiatric Disorders. JAMA Psychiatry. 2016;73:388.
20. Rhyne DN, Anderson SL, Gedde M, Borgelt LM. Effects of Medical Marijuana on Migraine Headache Frequency in an Adult Population. Pharmacotherapy. 2016;36:505–510.
21. Chan TLH, Zhang N. Chronic Cannabis Use and Treatment Failure of Onabotulinum Toxin A for Chronic Migraine. Can J Neurol Sci. 2019;46:785–786.
22. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–577.
23. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods. 2007;39:175–191.
24. Faul F, Erdfelder E, Buchner A, Lang A-G. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav Res Methods. 2009;41:1149–1160.
25. Cox DR, Snell EJ. Analysis of Binary Data. Second Edition. Chapman & Hall. Epub 1989.
26. Nagelkerke NJD. A note on a general definition of the coefficient of determination. Biometrika. 1991;78:691–692.
27. Hosmer DW, Lemesbow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat - Theory Methods. 1980;9:1043–1069.
28. Krymchantowski A V, Jevoux CC, Krymchantowski AG, Vivas RS, Silva-Néto R. Medication overuse headache: an overview of clinical aspects, mechanisms, and treatments. Expert Rev Neurother. 2020;20:591–600.
29. Kandasamy R, Dawson CT, Craft RM, Morgan MM. Anti-migraine effect of ∆9-tetrahydrocannabinol in the female rat. Eur J Pharmacol. 2018;818:271–277.
30. Pini LA, Guerzoni S, Cainazzo MM, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012;13:677–684.
31. Kopruszinski CM, Navratilova E, Vagnerova B, et al. Cannabinoids induce latent sensitization in a preclinical model of medication overuse headache. Cephalalgia. 2020;40:68–78.
32. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016;17:739–744.
33. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid–

Opioid Interaction in Chronic Pain. Clin Pharmacol Ther. 2011;90:844–851.
34. Baron EP, Lucas P, Eades J, Hogue O. Patterns of medicinal cannabis use, strain analysis, and substitution effect among patients with migraine, headache, arthritis, and chronic pain in a medicinal cannabis cohort. J Headache Pain. 2018;19:37.
35. Olfson M, Wall MM, Liu S-M, Blanco C. Cannabis Use and Risk of Prescription Opioid Use Disorder in the United States. Am J Psychiatry. 2018;175:47–53.
36. Purcell C, Davis A, Moolman N, Taylor SM. Reduction of Benzodiazepine Use in Patients Prescribed Medical Cannabis. Cannabis Cannabinoid Res. 2019;4:214–218.
37. Nicolodi M, Sandoval V, Terrine A. Therapeutic use of cannabinoids - Dose Finding, Effects, and Pilot Data of Effects in Chronic Migraine and Cluster Headache. Abstract presentation at 3rd Congress of the European Academy of Neurology (EAN), Amsterdam, 6/24/17. Eur J Neurol. 2017;24:123–444.
38. Adams AM, Serrano D, Buse DC, et al. The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia. 2015;35:563–578.

Table 1. Patient Characteristics.

	Cases (CM patients with MOH) n = 212	Referents (CM patients without MOH) n = 156	Statistical Difference
Age, years: median (IQR)	43 (33, 54)	40 (31, 49)	NS
Female to Male ratio	5	5	NS
Monthly migraine frequency in last 3 months: median (IQR)	30 (25, 30)	30 (18, 30)	NS
Duration of current CM, years: median (IQR)	5 (2, 12)	4 (2, 10)	NS
Currently using cannabis: number (%)	122 (58%)	28 (18%)	$p = 0.00001$; chi-squared test
Duration of current cannabis use, months: mean (SD)	19 (39)	5 (31)	$p = 0.0004$; *t*-test
MOH medications	See Results Section	N/A	N/A
Duration of current MOH, months: median (IQR)	24 (12, 60)	N/A	N/A
Types of cannabis products used			
Inhaled	47 (22.2%)	7 (4.5%)	$p < 0.00001$; chi-squared test

Ingested	25 (11.8%)	6 (3.8%)	p = 0.011; chi-squared test
Topical	15 (7.1%)	6 (3.8%)	p = 0.275; chi-squared test
Inhaled + Ingested	4 (1.8%)	2 (1.3%)	p = 0.971; chi-squared test
Ingested + Topical	7 (3.3%)	0 (0%)	NA
Inhaled + Ingested + Topical	3 (1.4%)	0 (0%)	NA

Abbreviations: IQR = interquartile range, CM = chronic migraine, SD = standard deviation, N/A = not available.

Table 2. Logistic Regression Results on Prediction of MOH in Chronic Migraine Patients. Significant MOH predictors (age, migraine frequency, opioid use, cannabis use) are shown in bold font. Sex was coded as “1” for female, and “0” for male. Use of benzodiazepine, butalbital, opioid, cannabis was similarly coded as “1” for current users and “0” for non-users. Abbreviation: CM = chronic migraine; B = regression coefficient; OR = odds ratio; CI = confidence interval.

	B	OR (95 CI)	*p*-value
Age (years)	0.024	1.02 (1.00, 1.05)	**0.026**
Sex (female = 1; male = 0)	0.514	1.67 (0.84, 3.32)	0.141
Migraine Monthly Frequency (days)	0.055	1.06 (1.01, 1.10)	**0.009**
Duration of CM (years)	- 0.008	0.99 (0.97, 1.02)	0.557
Benzodiazepine Use (yes = 1; no = 0)	0.16	1.17 (0.47, 2.89)	0.728
Butalbital Use (yes = 1; no = 0)	0.39	1.47 (0.56, 3.88)	0.432
Opioid Use (yes = 1; no = 0)	1.38	3.98 (2.26, 7.01)	**0.000002**
Cannabis Use (yes = 1; no = 0)	1.79	5.99 (3.45, 10.43)	**0.0000001**

Figure Legends

Figure 1. Cannabis usage types among cases and referents.
Cases (blue bar) featured significantly higher usage of inhaled and ingested cannabis types compared to referents (orange bar). *** = p-value less than 0.0001, * = p=value less than 0.05. Abbreviations: CM = chronic migraine, MOH = medication overuse headache.

Figure 2. Predictors of Medication Overuse Headache (MOH) in Chronic Migraine (CM).
Cannabis use, opioid use, migraine frequency, and age significantly predicted the presence of MOH in chronic migraine patients with decreasing order. Cannabis use featured the highest risk with odds ratio of 5.99 (3.45, 10.43). Red diamond squares represent the odds ratio for each variable. Blue horizontal line represents confidence interval. Odds ratio of 1 is depicted by vertical broken line to indicate predictors to its right feature 'MOH' prediction while to the left exhibit 'no MOH' prediction. Abbreviations: MOH = medication overuse headache; CM = chronic migraine.

Figure 3. Correlogram of Variables.
Correlogram displayed that higher associations were found between cannabis use, MOH, and opioid use.

Figure 4. Heatmap displaying agglomerative hierarchical clustering.
Two major natural clusters were identified. Cluster I (top dendrogram, first left branch) exhibited higher MOH burden, higher cannabis use, higher opioid use, younger age and fewer migraine frequency than cluster II (top dendrogram, first right branch).

Figures

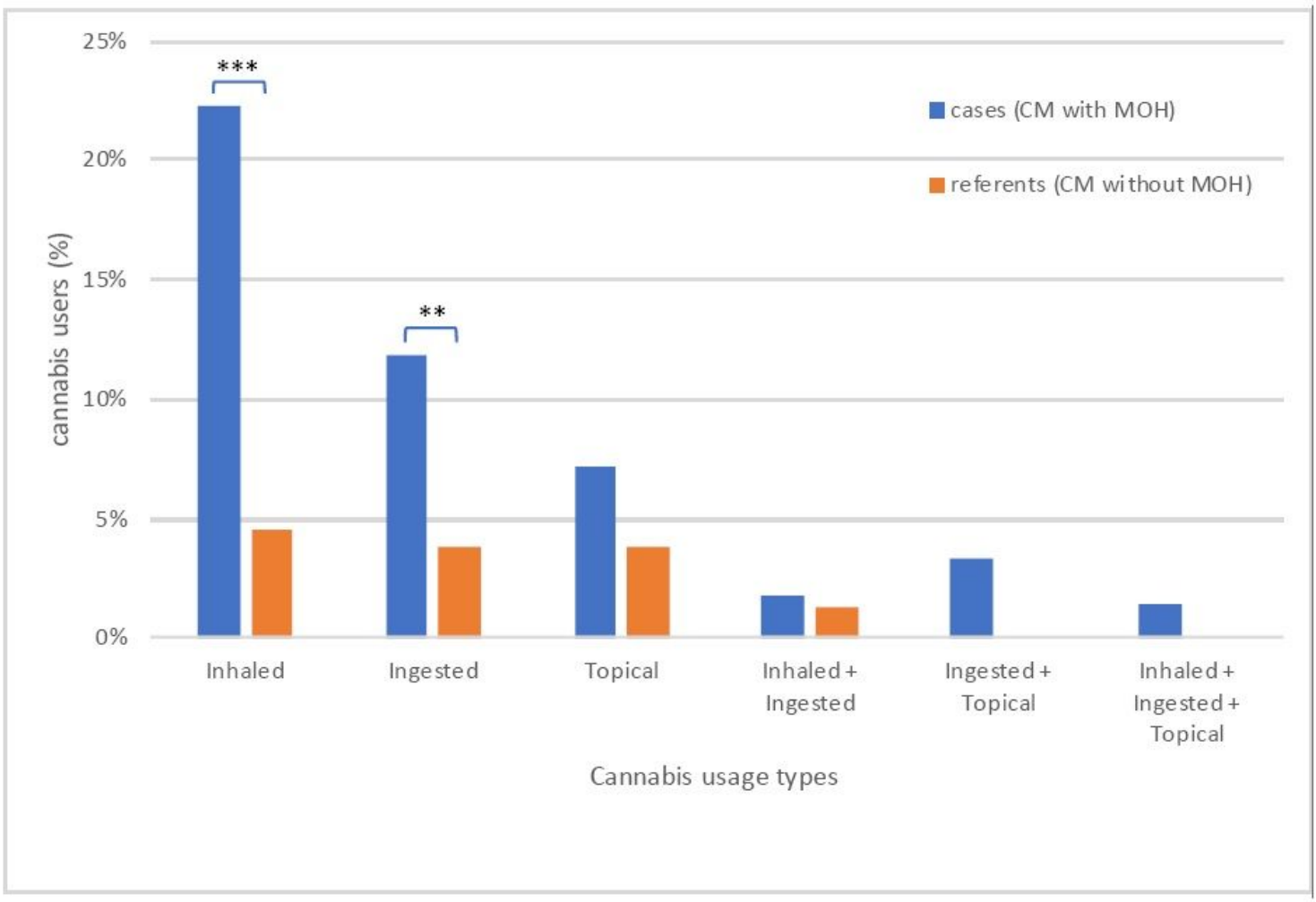

Figure 1

Cannabis usage types among cases and referents. Cases (blue bar) featured significantly higher usage of inhaled and ingested cannabis types compared to referents (orange bar). *** = p-value less than 0.0001, * = p=value less than 0.05. Abbreviations: CM = chronic migraine, MOH = medication overuse headache.

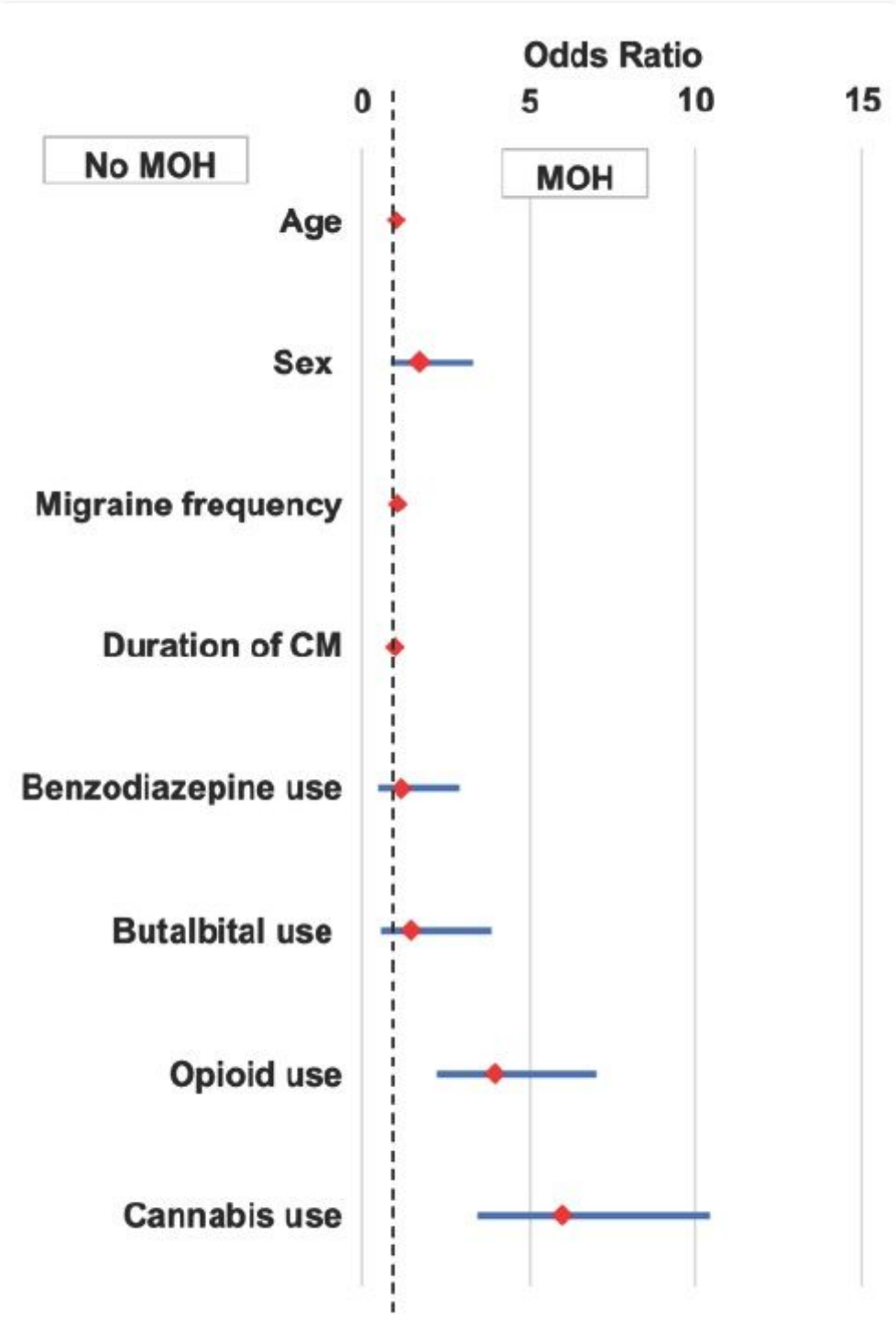

Figure 2

Predictors of Medication Overuse Headache (MOH) in Chronic Migraine (CM). Cannabis use, opioid use, migraine frequency, and age significantly predicted the presence of MOH in chronic migraine patients with decreasing order. Cannabis use featured the highest risk with odds ratio of 5.99 (3.45, 10.43). Red diamond squares represent the odds ratio for each variable. Blue horizontal line represents confidence interval. Odds ratio of 1 is depicted by vertical broken line to indicate predictors to its right feature 'MOH'

prediction while to the left exhibit ‘no MOH’ prediction. Abbreviations: MOH = medication overuse headache; CM = chronic migraine.

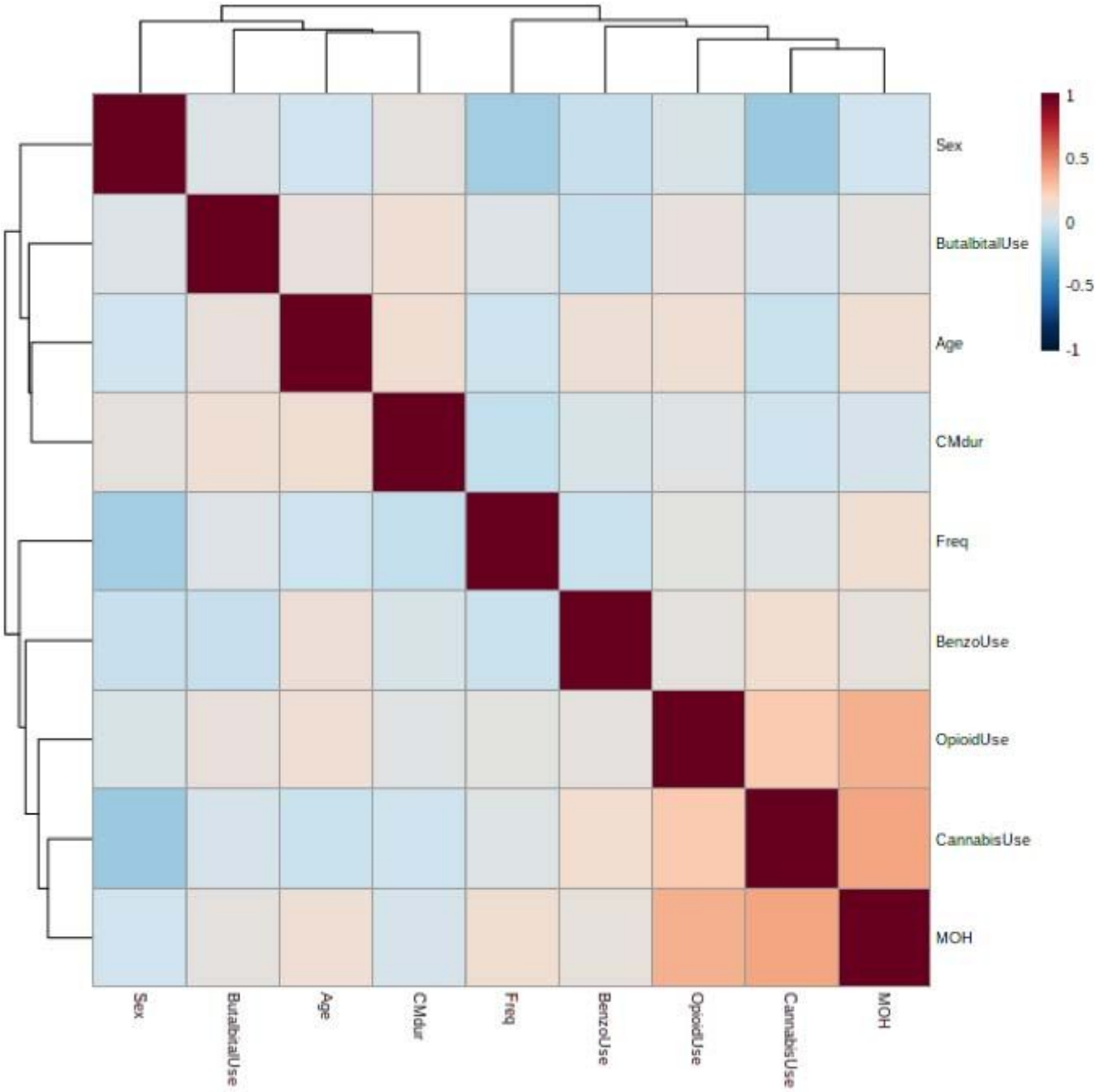

Figure 3

Correlogram of Variables. Correlogram displayed that higher associations were found between cannabis use, MOH, and opioid use.

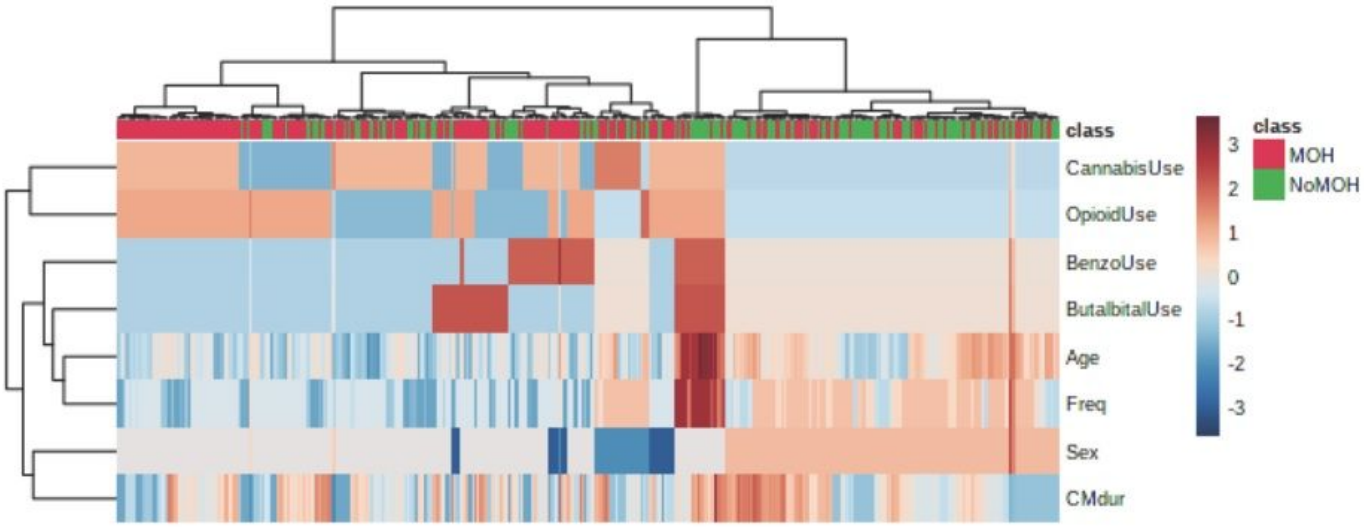

Figure 4

Heatmap displaying agglomerative hierarchical clustering. Two major natural clusters were identified. Cluster I (top dendrogram, first left branch) exhibited higher MOH burden, higher cannabis use, higher opioid use, younger age and fewer migraine frequency than cluster II (top dendrogram, first right branch).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTablee1.docx
- SupplementaryTable.docx