ORIGINAL ARTICLE

Cannabinoid Use in a Tertiary Headache Clinic: A Cross-Sectional Survey

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ABSTRACT: ***Objective:*** This study seeks to determine the prevalence and nature of cannabis use in patients with headache in a tertiary headache clinic and to explore patients' empiric experience in using cannabinoids therapeutically. ***Background:*** Many patients with headache report cannabinoid use as an effective abortive and/or preventive therapy. Mounting evidence implicates cannabinoids in pain mechanisms pertaining to migraine and other headache types. ***Methods:*** A cross-sectional study surveyed 200 patients presenting with any headache disorder to a tertiary headache clinic in Calgary, Alberta. Descriptive analyses were applied to capture information about headache diagnoses and the frequency, doses and methods of cannabinoid delivery employed, as well as patients' perceptions of therapeutic benefit and selected negative side effects. ***Results:*** Active cannabinoid users comprised 34.0% of respondents. Approximately 40% of respondents using cannabinoids engaged in very frequent use (≥300 days/year). Of cannabinoid modalities, liquid concentrates were most popular (39.2%), followed by smoked cannabis (33.3%). Patients endorsed cannabinoid use for both prevention and acute therapy of headaches, often concurrently. Sixty percent of respondents felt cannabinoids reduced headache severity, while 29.2% perceived efficacy in aborting headaches. Nearly 5% of respondents volunteered that they had encountered a serious problem such as an argument, fight, accident, or work issue as a result of their cannabis use. Approximately 35.4% of users had attempted to reduce their use. ***Conclusion:*** This survey shows that over one-third of patients with headache disorders in a tertiary headache clinic use cannabis as a treatment for their headaches. Of these, about 25% and 60% perceive improvements in headache frequency and severity, respectively. The results of this survey will aid neurologists and headache specialists in understanding the landscape of cannabinoid use in a more severely affected population and inform future-controlled studies of cannabinoids in headache patients.

RÉSUMÉ : Utilisation de produits du cannabis au sein d'une clinique tertiaire spécialisée dans les céphalées : une étude transversale. ***Objectif*** **:** Cette étude vise à déterminer la prévalence et la nature de l'utilisation thérapeutique de produits du cannabis chez des patients aux prises avec des céphalées et à explorer leur expérience empirique. ***Contexte*** **:** Nombreux sont les patients aux prises avec des céphalées qui ont signalé une utilisation efficace de produits du cannabis à titre de thérapie abortive et/ou préventive. En effet, des preuves sans cesse plus nombreuses ont montré que les cannabinoïdes ont à voir avec les mécanismes de la douleur liés aux migraines et à d'autres types de céphalées. ***Méthodes*** **:** Notre étude transversale a porté sur 200 patients qui ont fréquenté une clinique tertiaire spécialisée située à Calgary (Alberta) et qui ont consulté pour tout type de trouble céphalalgique. Des analyses descriptives ont été effectuées afin de recueillir des renseignements sur les diagnostics de céphalées et sur leur fréquence, sur les doses et sur les méthodes d'administration des produits du cannabis utilisés ainsi que sur la perception des patients en ce qui regarde les bénéfices thérapeutiques et certains effets secondaires négatifs. ***Résultats*** **:** Les utilisateurs actifs de produits du cannabis ont représenté 34,0 % de nos répondants. Environ 40 % de ces utilisateurs étaient des utilisateurs très fréquents (≥ 300 jours par année). En ce qui regarde les modalités de consommation du cannabis, les concentrés liquides se sont avérés les plus populaires (39,2 %) suivis par le cannabis fumé (33,3 %). Les patients ont soutenu consommer des produits du cannabis pour la prévention de même que pour le traitement aigu des céphalées, le tout souvent en parallèle. Soulignons que 60 % des répondants ont exprimé le sentiment que le cannabis permettait de réduire la gravité de leurs céphalées alors que 29,2 % d'entre eux ont fait état d'une efficacité permettant de les arrêter. Près de 5 % des répondants ont déclaré avoir fait face à un problème grave en raison de leur consommation, par exemple une dispute, une bagarre, un accident ou un problème au travail. Enfin, approximativement 35,4 % des utilisateurs ont affirmé avoir tenté de réduire leur consommation. ***Conclusion*** **:** Cette étude a montré que plus du tiers des patients souffrant de céphalées ayant fréquenté une clinique tertiaire spécialisée utilisaient le cannabis comme modalité thérapeutique. De ce nombre, environ 25 % et 60 % d'entre eux ont perçu des améliorations en ce qui regarde respectivement la fréquence et la gravité de leurs céphalées. Les résultats de cette étude pourront donc aider les neurologues et les spécialistes des céphalées à mieux comprendre l'utilisation des produits du cannabis au sein d'une population plus gravement affectée et à contribuer aux futures études contrôlées portant sur l'utilisation du cannabis chez des patients souffrant de céphalées.

Keywords: Headache, Migraine, Cannabis, Cannabinoids, Marijuana, CBD, Cannabidiol, THC, Δ9-tetrahydrocannabinol

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Introduction and Background

Many patients with headache disorders believe cannabinoids are an effective abortive or preventive therapy and use them to manage headache symptoms. Descriptions of current usage patterns would help physicians to better understand the prevalence and parameters of cannabinoid use for headache. A

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Canadian experience is likely to vary from descriptions elsewhere given unique attitudes and culture as they pertain to cannabis.

Previous Descriptions of Cannabinoid Use in Headache Sufferers

Use of cannabis in the treatment of headache and other cranial pain syndromes dates back to antiquity.[1] A handful of small case series has investigated the use of cannabis in treating various headache types including migraine, tension-type headache, and chronic daily headache. An excellent summary of these studies is provided by Lochte and colleagues in their 2017 review, *The Use of Cannabis for Headache Disorders*.[2] These studies suggest that cannabinoids could have a role in the prevention of headache. In a group of 145 migraine patients monitored over an average period of 3 years, Aviram et al. found that >60% of subjects treated with medical cannabis experienced long-term reduction in migraine frequency, lessened disability, and reduced acute medication use.[3] Gibson et al. examined a group of 589 adult cannabis users, 161 of which experienced migraine. Of these individuals, 76.4 % used cannabis to treat their migraines. Although these individuals tended to report more severe migraines, they reported significantly superior migraine relief from cannabis compared to traditional acute medications, even after controlling for headache severity.[4] Nunberg et al., in 2011, reported on 1655 patients seeking physician recommendation for medical cannabis. Subjects seeking medical cannabis specifically for treatment of "neurological disorders," including migraine and other headaches, comprised 16.6% of respondents.[5] Of these, 40.8% reported improvement of headache symptoms with cannabis use. Currently, randomized double-blind placebo control studies demonstrating efficacy of cannabinoids in migraine treatment are scarce. A search of *ClinicalTrials.org* reveals three current studies assessing cannabinoids in migraine; one recently completed (unpublished) assessing inhaled dronabinol for acute migraine, with another study exploring the efficacy of inhaled cannabis for acute migraine treatment actively recruiting. A study of combination cannabidiol, cannabigerol, and tetrahydrocannabinol in chronic migraine is poised to begin imminently.

The Crossroads of Cannabinoid and Headache Physiology

The past decade has seen significant strides in our understanding of the trigeminovascular complex and its role in the generation of migraine and other headache types. A detailed review of this subject was provided by Ong et al., in 2018.[6] Russo has suggested an endocannabinoid deficiency (congenital or acquired) may underlie migraine, fibromyalgia, and irritable bowel syndrome: disorders that share in common hyperalgesia and central sensitization.[7] This theory posits that a deficient endocannabinoid tone (whether from abnormal production or metabolism of anandamide (AEA) and 2-arachidonoylglycerol, or the relative number and activity of cannabinoid receptors) may result in symptoms, implying that cannabinoid modulation or supplementation may be of therapeutic benefit. This hypothesis is supported by mounting basic science evidence implicating the endocannabinoid system in headache mechanisms: in particular, migraine. While a comprehensive discussion of mounting evidence of endocannabinoid mechanism involvement in migraine and pain is beyond the scope of this paper, Russo's 2016 review provides an excellent orientation.[7] A cursory review is provided here. AEA is a major endogenous cannabinoid acting at multiple levels of the neuraxis. In an intravital microscopy model, it has been shown to inhibit neurogenic dural vasodilation (calcitonin gene-related peptide and nitrous oxide induced) via cannabinoid-1 (CB_1) receptor inhibition of trigeminal neurons.[8] *In vivo*, AEA may also act as a vasodilator of dural blood vessels by activating vanilloid type 1 ($TRPV_1$) receptors. Activation of CB_1 receptors inhibits trigeminocervical complex neurons with A-fiber and C-fiber input after $TRPV_1$ inhibition.[9] Cortical spreading depression, the physiologic phenomenon purported to underlie migraine aura, may be suppressed in a dose-dependent fashion by tetrahydrocannabinoid (THC) and the experimental CB1 agonist, WIN.[10] The endocannabinoid system also contributes to the descending modulation of pain transmission via the ventrolateral periaqueductal gray (vlPAG) and rostral ventromedial medulla.[11] AEA is tonically released in the periaqueductal gray, a region implicated in migraine generation; pharmacologic blockade of local CB1 receptors here results in hyperalgesia and AEA supplementation, analgesia.[12] AEA has demonstrated serotonin receptor activity with significant potentiation and inhibition of 5-HT1A and 5-HT2A receptors, respectively, implicating serotonergic mechanisms already established as targets in the treatment of migraine.[13] Cerebrospinal fluid levels of AEA were found to be significantly lower in chronic migraineurs compared to controls, lending credibility to the idea that when depleted, loss of AEA's inhibitory influence results in activation of the trigeminovascular system, and thus, migraine.[14]

Taken together, these findings suggest a potential for cannabinoids as a therapeutic agent in headache worthy of additional study. Little is currently known about the specifics of cannabinoid use within the headache patient population. This study seeks to determine the prevalence and nature of cannabis use in patients with headache disorders by means of cross-sectional data collection, using a survey and chart review, in a tertiary care headache center in Calgary, Alberta, Canada.

Methods

Research Setting

All patients seen in the Calgary Headache Assessment and Management Program (CHAMP) for initial consultation or in follow-up from May 1 to November 30, 2019 were asked to participate in a standardized written survey lasting 10–15 minutes, conducted in the context of a clinical visit. Inclusion criteria included patients aged ≥18 years, able to give consent, and with a diagnosis of any headache type confirmed by a neurologist with headache expertise.

Ethical Considerations

Approval was obtained through the University of Calgary Conjoint Health Research Ethics Board. All participants signed a written consent form prior to participation. No incentive for participation was offered.

Sample Size

Health Canada has estimated the prevalence of cannabis use in the general population through two surveys: the Canadian Tobacco, Alcohol and Drugs Survey (CTADS) and the Canadian

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Student Tobacco, Alcohol and Drugs Survey (CSTADS). CTADS 2017 indicates that 15% of Canadians aged 15 years and older (or 4.4 million) have used cannabis in the past 12 months (19% among aged 15–19 years; 33% among aged 20–24 years; and 13% among aged 25 years and older). Our aim was to estimate the prevalence cannabis use among headache sufferers; based on an expected prevalence of cannabis use of 15%, a sample size of 200 subjects (rounded up from ∼196) was determined using the following formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

where n = sample size, Z = Z score for a level of confidence (95%), P = expected prevalence or proportion, and d = precision (5%).

Data Collection

Subjects were surveyed about their specific headache diagnoses, as well as monthly headache frequency, age of headache onset, and characteristics of cannabis usage such as frequency, strains used, and preparations/methods of delivery (See Appendix I for a copy of survey). We defined active cannabis use as use within the past year and asked respondents about their monthly frequency of use for all reasons and whether they engaged in daily use. Additional assessments included monthly days of therapeutic use, costs associated with cannabinoid use, age of initiation, and respondents' opinions regarding the efficacy of cannabis in aborting, preventing, as well as in treating common headache-related symptoms, such as nausea, anxiety, and depression. When subjects were unsure of benefit or did not experience specific features, they were instructed to select "Don't know" from the list of available options. The survey further explored selected negative side effects (e.g. memory impairment, attempts to reduce use, and whether respondents had encountered a serious problem such as an argument, fight, accident, or work issue as a result of use).

Recruitment continued until data had been collected on 200 individuals. Subject's charts were reviewed to corroborate age, sex, and formal headache diagnosis by their neurologist. When there was a discrepancy (e.g. migraine vs. tension-type headache, episodic vs. chronic), the headache diagnosis rendered by their neurologist was taken.

Data Analysis

Sample characteristics are reported using means, standard deviations, and frequency distributions. Two-tailed t-tests were used to determine if cannabinoid users and nonusers differed in terms of age, headache onset, and monthly headache days (p-values calculated with standard formulas using an online calculator: https://www.usablestats.com/calcs/2samplet&summary=1). Results were considered statistically significant with a two-sided p-value of less than 0.05. As not all respondents answered every question, the number of respondents (n) is reported wherever applicable. Ten respondents could not provide a specific age of onset, recalling only that headaches began in "childhood" or their "teens." A corrected average was calculated, with respondents assigned an age value based on the midpoints of the age category they indicated (child: 3–12 years, 7.5, teen 13–19 years, 16).

Results

Patient Demographics

Table 1 illustrates respondents' baseline characteristics. Thirty-four percent reported using cannabinoids in the past year ($n = 68/200$). Cannabinoid users and nonusers did not differ significantly in average monthly headache days (18.7 ± 8.7 vs. 19.0 ± 10.0, $p = 0.8168$). However, cannabinoid users were on average likely to be younger (21.2 ± 13.8 vs. 26.8 ± 16.4, $p = 0.0192$) and to have had their headaches begin at a younger age (21.0 ± 13.5 vs. 26.0 ± 16.4, $p = 0.03$). While there is some variability between groups with respect to some of the less common secondary headache types, the groups were comparable in terms of migraine diagnoses. 149 of 200 respondents, or roughly 75%, carried a diagnosis of some form of migraine.

Over a third of respondents using cannabinoids engaged in very frequent use, with more than a quarter using cannabinoids on a daily basis (Table 2). Compared to monthly use for all reasons, headache-specific treatment days occurred at a lower frequency, implying cannabinoid use recreationally or for other indications on other days.

The majority of cannabinoid users do not concurrently use tobacco or partake in additional recreational drug use (Appendix II). About a fifth of cannabinoid users described a history of other recreational drug use; in these instances, opioids, mushrooms, and cocaine were reported most frequently.

Liquid concentrates were the most popular of the cannabinoid modalities reported, with dried and smoked cannabis following closely behind (Table 3). Individual doses varied significantly between individuals when reported. Information on cannabinoid dosing and type/strains was collected, however is not reported here due to incompleteness of the data set. Of 101 modalities and 65 respondents, quantity and dosing information was provided in only 51 instances. In 32 cases, respondents specifically indicated they did not know the dose; in the others, no information was given. Of the dried modalities (34), only 18 respondents could identify which strains they were using.

Cannabinoid Users' Perceptions of Selected Benefits and Negative Effects

Table 4 illustrates respondents' opinions of cannabinoids' effect on various headache features such as frequency, severity, migraine-associated symptoms, and related mood disorders. Table 5 depicts respondents' opinions regarding selected potential negative side effects related to cannabinoid use.

The majority of users obtained cannabinoids from an authorized source online or in-person (62.1%), with over a quarter of respondents engaging multiple sources including dealers, friends, and family (Table 6). Almost a fifth of users did not pay for their cannabinoids, receiving them from friends, family, or acquaintances. Half of cannabinoid users are spending less than $100 every 3 months; however, some spend in excess of $1000 every 3 months.

Discussion

Respondent Demographics

Active cannabinoid users comprised roughly a third of our survey respondents, more than double the Health Canada

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Table 1: Survey respondent demographics

	Nonusers		Cannabinoid users	
n	**%**	***n***	**%**	
n (of 200 subjects)	132	66.0	68	34.0
Female	103	78.0	54	79.4
Male	29	22.0	14	20.6

	Nonusers			Cannabinoid users			
u	***n***	**SD**	***u***	***n***	**SD**	***p*-Value**	
Age (mean)	46.6	132	13.9	41.7	68	11.8	0.016
Average monthly headache days	19.0	131	10.0	18.7	68	8.7	0.8168
Age of headache onset	26.0	132	16.4	21.0	68	13.5	0.03

Headache diagnoses	Nonusers		Cannabinoid users	
	N	**%**	***n***	**%**
Chronic migraine	75	46.3	40	44.9
Episodic migraine	24	14.8	10	11.2
Posttraumatic headache	12	7.4	9	10.1
Medication overuse headache	8	4.9	8	9.0
Tension-type headache	6	3.7	2	2.2
New daily persistent headache	4	2.5	1	1.1
Chronic cluster headache	3	1.9	1	1.1
Idiopathic intracranial hypertension	3	1.9	0	0.0
Occipital neuralgia	2	1.2	0	0.0
Episodic cluster headache	2	1.2	2	2.2
Hemicrania continua	2	1.2	1	1.1
Cervicogenic headache	2	1.2	1	1.1
Headache attributed to intracranial neoplasm	2	1.2	0	0.0
Hemiplegic migraine	0	0.0	2	2.2
Undifferentiated	9	5.6	3	3.4
Other*	8	4.9	9	10.1

u = mean.

*Conglomerate of less-common headache diagnoses for which there was only one respondent.Nonusers: Trigeminal Neuralgia, Spontaneous Intracranial Hypotension, Primary Exertional Headache, Persistent SUNA, Hypnic Headache, Headache Attributed to Raised Intracranial Pressure, Headache attributed to Chiari malformation type I, Atypical Facial Pain.

Users: Trigeminal Neuralgia, Headache Attributed to Raised Intracranial Pressure, Trigeminal Neuropathy, Primary Stabbing Headache, Headache Attributed to Non-Vascular Intracranial Disorder, Headache Attributed to Ischemic Stroke, Headache Attributed to Intracranial Vascular Malformation, Headache Attributed to Genetic Vasculopathy (CADASIL), Headache Attributed to Craniotomy.

estimates of cannabinoid use in the general population (15% by CTADS). This is not unexpected as this survey addresses a chronic pain population. Users and nonusers were comparable in terms of migraine diagnoses. Three-quarters of respondents carried a diagnosis of some form of migraine, reflecting the population of our tertiary headache center. The findings of our study echo similar findings of perceived benefit for acute and preventive use in other cross-sectional studies assessing cannabinoid use in headache sufferers[3,4,5] but is limited in generalisability due to the heterogeneity of headache types represented in our sample. Estimates of main groups of primary headache types from older studies are superficially comparable.[15,16] Differences may reflect use of older diagnostic criteria and variance in local referral patterns. There is some variability between groups with respect to some of the less common secondary headache types, likely due to a small sample size of 200, and the relatively lower frequencies with which these present. Our sample size was determined based on estimates of cannabinoid use in the general public. Although a sample size of 200 may appear small, population prevalence is likely to be lower than

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Table 2: Respondents' frequency of cannabinoid use

Active cannabinoid users	***n*(200)**	**%**
	68	34.0
Frequency of use (per month)	***n*(68)**	**%**
Less than once monthly	10	14.7
Once per month	6	8.8
2–3 times per month	7	10.3
4–8 times per month (about 1–2 times per week)	8	11.8
9–24 times per month (about 3–6 times per week)	10	14.7
25–30 times per month (one or more times per day)	27	39.7
Approximate daily use	***n*(64)**	**%**
	17	26.6
Monthly use specifically for headache treatment	***n*(65)**	**%**
Less than once monthly	27	41.5
Once per month	3	4.6
2–3 times per month	9	13.8
4–8 times per month (about 1–2 times per week)	3	4.6
9–24 times per month (about 3–6 times per week)	13	20.0
25–30 times per month (one or more times per day)	10	15.4

Table 3: Cannabinoid modalities used by respondents

Number of cannabinoid modalities used	***n*(65)**	**%**
One	41	63.1
Two	17	26.2
Three	4	6.2
Four	1	1.5
Five	2	3.1
Cannabinoid modalities used	***n*(101)**	**%**
Liquid concentrate (oil)	40	39.2
Liq conc – CBD	14	13.7
Liq conc – THC	5	4.9
Liq conc – CBD/THC	13	12.7
Liq conc – NOS	8	7.8
Dried	34	33.3
Edibles	9	8.8
Vaping	7	6.9
Vaping – CBD	1	1.0
Vaping – THC	1	1.0
Vaping – CBD/THC	1	1.0
Vaping – NOS	4	3.9
Topical	5	4.9
Topical – CBD	2	2.0
Topical – THC	0	0.0
Topical – CBD/THC	0	0.0
Topical – NOS	3	2.9
Capsules	4	3.9
Caps – CBD	2	2.0
Caps – THC	1	1.0
Caps – CBD/THC	0	0.0
Caps – NOS	1	1.0
Hashish	1	1.0
Solid concentrate NOS	1	1.0

CBD = cannabidiol; NOS = not otherwise specified; THC = tetrahydrocannabinoid.

that in a chronic pain population, resulting in a larger sample size than might be strictly needed to estimate prevalence using this method.

Cannabinoid users and nonusers did not differ significantly in average monthly headache days; perhaps therapeutic benefit may lay in severity reduction and symptom management. Cannabinoid users were on average likely to be younger, possibly reflecting generational differences in attitudes and willingness to try. Interestingly, those using were more likely to have had their headaches begin at a younger age. This may reflect the eventual use of cannabinoids after exhausting traditional options.

Frequency of Cannabinoid Use

More than a quarter of respondents use cannabinoids on a daily basis. Compared to monthly use for all reasons, cannabinoids were used specifically as headache treatment at a lower rate, implying their use recreationally or for other indications such as sleep or other chronic pain conditions on other days. If cannabinoids are to be recommended for management of headache and related symptoms, it will be important to identify modalities that minimize side effects, cost, and frequency of use, while maximizing therapeutic benefit.

Cannabinoid Modalities Used by Respondents

Liquid concentrates were the most popular, with the more traditional dried and smoked cannabis following closely behind. Individual doses varied significantly between individuals when reported. Information on cannabinoid dosing and type/strains was collected, however were not reported here due to incompleteness of the data set as only half of modalities reported included information on quantity or dose. In roughly a third of cases, respondents specifically indicated they did not know the dose; in the others, no information was given. Of the dried modalities, little more than half of respondents identified which strains they were using. One respondent regularly using edibles indicated "many packages" but could not recall precisely. This is potentially worrisome as an oral route entails delayed/variable absorption with more potential for negative side effects if the number of packages is misjudged. Overall, these data indicate that many

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Table 4: Respondents' perceptions of cannabinoids beneficial effects

	Extremely effective		Somewhat effective		Neither effective nor ineffective		Ineffective		Worsens		Don't Know		Respondents
n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	
Severity	9	13.8	30	46.2	6	9.2	13	20.0	1	1.5	6	9.2	65
Frequency	2	3.1	14	21.5	16	24.6	17	26.2	2	3.1	14	21.5	65
Nausea	16	24.6	9	13.8	5	7.7	12	18.5	2	3.1	21	32.3	65
Photophobia	2	3.1	11	16.9	16	24.6	11	16.9	1	1.5	24	36.9	65
Phonophobia	3	4.6	12	18.5	16	24.6	12	18.5	1	1.5	21	32.3	65
Anxiety	16	24.6	24	36.9	4	6.2	5	7.7	5	7.7	11	16.9	65
Stress	17	26.2	29	44.6	3	4.6	5	7.7	1	1.5	10	15.4	65
Depression	5	7.7	24	36.9	11	16.9	4	6.2	2	3.1	19	29.2	65
Aborting headaches	1	1.5	18	27.7	10	15.4	20	30.8	0	0.0	16	24.6	65
Preventing headaches	0	0.0	11	16.9	10	15.4	18	27.7	0	0.0	26	40.0	65

patients are unaware of the exact dosing they are using. It is generally accepted that the toxicity of cannabinoids is very low compared to most other recreational and pharmaceutical drugs, in contrast with established migraine treatments like triptans, antidepressants, and antiepileptics, etc.; a dose lethal to a 70-kg human has been estimated at approximately 4 g,[17] which practically speaking, could not be achieved through smoking, vaporizing or oral consumption of cannabis.[18] As a phytomedicine; cannabis' therapeutic action is derived from multiple individual constituents in addition to the well-known cannabidiol (CBD) and THC (flavonoids, terpenes, and others); this synergistic gestalt has been referred to as the entourage effect[19] and contrasts the reductionist approach of isolating single-therapeutic compounds with activity at a specific target. The endocannabinoid system has been implicated in a number of functions: pain, mood regulation, learning and memory, and appetite among others.[20] Given its dynamic complexity as a buffering system to external stimuli, it stands to reason that individual patient cannabinoid requirements may fluctuate day to day in response to stress and various disease states, rendering universal dosing problematic.

Ideally, patients should be able to access dosing information as for any of their other prescribed medications, to ensure adequate trials of variants with different properties and minimize costs. The lack of public knowledge surrounding cannabinoids and potency likely stems from the history of criminalization and lack proper medical guidance of these patients in decades past. The Canadian healthcare system has made strides in making cannabis products widely available through safe and regulated channels and establishing specialized medical cannabis centers with skilled professionals experienced in the field. Despite this, access to specialized care remains beyond the reach of many, and some patients may remain uncomfortable discussing cannabis use with their physicians because of perceived social and scientific stigmatization.

Perceptions of Cannabinoids' Therapeutic Benefits

Table 4 illustrates respondents' opinions of cannabinoids' effect on various headache features such as frequency, severity, migraine-associated symptoms, and related mood disorders. Sixty percent of respondents felt cannabinoids were somewhat or extremely effective in reducing headache severity, while 29.2% respondents felt cannabinoids were effective or somewhat effective at aborting their headaches. Almost a quarter of respondents endorsed some positive impact on headache frequency, but when phrased in a slightly different way, none felt cannabinoids were extremely effective at preventing headaches. Almost 25% of respondents indicated that cannabinoids were extremely effective at alleviating nausea, in keeping with established uses of these agents (e.g. chemotherapy-induced nausea). Respondents endorsed somewhat less benefit for relief from phono- and photophobia. In contrast, a majority of respondents felt cannabinoids were somewhat or extremely effective at reducing anxiety and stress. Comparatively, when asked about ability to improve features of depression, fewer respondents felt cannabinoids were extremely effective, while the numbers of respondents who felt cannabinoids were somewhat effective for depression and anxiety were comparable. Patients seemingly reported benefit for anxiety and depression more than for headache itself.

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Table 5: Respondents' perceptions of selected negative effects related to cannabinoid use

	Strongly agree		Somewhat agree		Don't know		Strongly disagree		Somewhat disagree		Neither agree nor disagree		
n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%		Respondents
Experiencing long-term memory issues	1	1.5	3	4.6	12	18.5	33	50.8	6	9.2	10	15.4	65
Experiencing short-term memory issues	14	21.5	30	46.2	2	3.1	8	12.3	6	9.2	5	7.7	65

	Yes		No		Don't know		Other		
n	%	*n*	%	*n*	%	*n*	%		Respondents
Cannabis is contributing to my short-term memory issues	4	6.2	49	75.4	9	13.8	1	1.5	63

	Never		Rarely		From time to time		Fairly often		Very often		
n	%	*n*	%	*n*	%	*n*	%	*n*	%		Respondents
Friends and family have prompted to reduce use	58	89.2	3	4.6	4	6.2	0	0.0	0	0.0	65
Previously tried to stop or reduce use	42	64.6	3	4.6	15	23.1	1	1.5	4	6.2	65
Encountered serious problem due to cannabinoid use	61	93.8	2	3.1	1	1.5	0	0.0	0	0.0	65

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Table 6: Source and cost of cannabinoids

Cannabinoid source	***n*(65)**	**%**
From an authorized retailer	34	35.8
Online from a licensed producer	25	26.3
From a family member or friend	7	7.4
From a compassion club, dispensary, or storefront	6	6.3
I grow my own	5	5.3
From a dealer	5	5.3
It was shared around a group of friends	4	4.2
From an acquaintance	3	3.2
Online from another source	2	2.1
Other	1	1.1
Someone grows it for me	0	0.0
Number of sources	***n*(65)**	**%**
1 source	47	72.3
2 sources	13	20.0
3 sources	3	4.6
4 sources	1	1.5
5 sources	0	0.0
6 sources	1	1.5
Money spent on cannabinoids in the past 3 months	***n*(64)**	**%**
$0	12	18.8
$1–10	2	3.1
$11–25	5	7.8
$26–50	7	10.9
$51–100	6	9.4
$101–150	6	9.4
$151–250	10	15.6
$251–500	9	14.1
$501–750	3	4.7
$751–1,000	1	1.6
$1001–1250	1	1.6
>$1250	2	3.1

Table 7: Fischer et al. guidelines/recommendations for lower-risk cannabis use

1	The most effective way to avoid cannabis use – related health risks is abstinence
2	Avoid early age initiation of cannabis use (i.e. definitively before the age of 16 years)
3	Choose low-potency tetrahydrocannabinol (THC) or balanced THC-to-cannabidiol (CBD) ratio cannabis products
4	Abstain from using synthetic cannabinoids
5	Avoid combusted cannabis inhalation and give preference to nonsmoking use methods
6	Avoid deep or other risky inhalation practices
7	Avoid high-frequency (e.g. daily or near-daily) cannabis use
8	Abstain from cannabis-impaired driving
9	Populations at higher risk for cannabis use – related health problems should avoid use altogether
10	Avoid combining previously mentioned risk behaviors (e.g. early initiation and high-frequency use)

Perceptions of Cannabinoids' Negative Side Effects

While over two-thirds of respondents endorsed some degree of short-term memory impairment, only 6.2% believed this was related to their cannabinoid use. Self-endorsed long-term memory difficulties occurred at a much lower frequency of 6.1%. 10.8% of respondents have been encouraged by friends or family to reduce their use and 35.4% have attempted to reduce use at some point. 4.6% of respondents volunteered that they had encountered a serious problem, such as an argument, fight, accident, or work issue as a result of their cannabis use (Table 5). Such problems may arise for a number of reasons, including the societal stigmatization of cannabis use and other psychosocial determinants that contribute to drug use and addictive behavior (employment status, racial discrimination, neighborhood characteristics, etc.).[21] Regardless of the root causes for these altercations, they represent a possible burden to users. While cannabis toxicity is limited as previously discussed, it has been associated with a variety of short- and long-term health effects. It is important to note that causality in many of these instances remains to be demonstrated, and correlation may be explained, at least in part, by myriad genetic and socioeconomic factors intersecting with likelihood of cannabinoid use. Acute use impacts thinking,[22] physical coordination, and may increase the risk of accidents and injuries.[23] Chronic use has been associated with mental health issues, including dependence.[24] Smoking cannabis is associated with poorer outcomes in pregnancy[25] and can increase the risk of lung diseases.[26] In medical cannabis clinics, alternative routes to smoked cannabis (topicals, suppositories, and edibles) are preferred; these may help mitigate respiratory risks. Benefits of cannabinoids in the treatment of headache need to be weighed against social impacts and potential risks linked to regular and sustained use. Policy focused on minimizing these risks is an important step toward optimization; an international working group of mental health experts has published guidelines for lower-risk cannabis use in the *American Journal of Public Health*, with 10 concrete recommendations for lower-risk use (Table 7).[27]

Source and Cost of Cannabinoids

The majority of users obtained cannabinoids from an authorized source online or in-person (62.1%), with over a quarter of respondents engaging multiple sources including dealers, friends, and family. This figure may be confounded by response bias with an understandable hesitancy to admit to alternative suppliers,

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even when confidentiality is guaranteed. This may have a significant impact therapeutically, as quality and content of the cannabinoid cannot be guaranteed from unofficial sources, and interactions (compounding of negative side effects or potentiation of therapeutic benefits) may occur when multiple modalities are combined.

Fifty percent of cannabinoid users are spending less than $100 every 3 months. However, some users spend in excess of $1000 every 3 months. This could pose significant financial strain on individuals whose headache disability has already impacted income potential. This cost would likely be in addition to other established migraine treatments such as oral preventives, botulinum toxin injections, and the newer CGRP monoclonal antibodies, which may not be fully insured. Further quantitative analysis and randomized clinical trials are required to determine if any therapeutic benefit warrants this additional cost compared to established treatments.

Limitations of the Study

As with any survey-based study, response and recall bias are inherent. Despite guarantees of anonymity, potential respondents may not feel comfortable discussing cannabinoid or recreational drug use in a clinical setting, especially if cannabinoids were sourced illegally. This may have resulted in underestimation of cannabinoid use prevalence. This survey was paper-based; respondents sometimes deviated from questions by writing free text. Efforts to correct and accommodate for this are outlined in methods. In the future, electronic-based surveys with fixed responses could minimize this issue.

Our survey, after collecting initial demography, stated the following:

"If you do not use cannabis or related products, please stop here. The rest of the survey explores use of such things and will not be relevant to you."

As a result of this wording, all respondents endorsing cannabinoid use would be active users, potentially enriching the sample with individuals who continue to derive benefit from cannabinoid use and excluding those who had stopped using for whatever reason. As a result, this survey may have underestimated cannabinoid use in the headache clinic and overestimated therapeutic benefits.

Not all respondents answered all questions; subjects were free to skip those they did not feel comfortable answering. However, most respondents answered most questions. One exception to this was dosing data, which respondents could or would not quantify in almost half of cases. This may be related to the stigma of cannabinoid use, but also because many respondents are uncertain how to quantify what they are using. The wide variety of cannabis agents used, and the lack of participant awareness of individual strains rendered strain-based analysis impossible. Due to size limitations, we were unable to examine the entire gamut of cannabinoid-related side effects (e.g. nausea, sedation, etc.). Participants were offered a free text option to communicate issues (Appendix III). Comorbidities were not described, which if analyzed, might better contextualize subjects' perceptions of cannabinoid efficacy. Most respondents were taking additional preventive agents, confounding the effect of their cannabinoids. These were not described, and there was no assessment of other interventions related to headache. Given the composite nature of all headache conditions included, this study cannot detect nuances in cannabis' ability to alleviate specific headache types and symptoms. Set in a tertiary headache center seeing more severely affected patients, the study may be limited in its generalizability to less affected individuals. The goal of this study was to better understand cannabinoid usage patterns in our headache clinic, in preparation for controlled trials of cannabinoids (e.g. CBD), in a clearly defined subset of headache patients (e.g. chronic migraineurs).

Study Strengths

Published data on cannabinoid use including estimates of use by modality and perceived therapeutic benefit in a chronic migraine setting remain sparse. This survey is the first of its kind in Canada to describe in some detail headache patient demographics, cannabis sources, and usage patterns and assess the subjective effects of cannabis. It took a patient-centric approach that allowed respondents to communicate their perceptions of how cannabinoid use has impacted their condition. A reasonable sample size helped capture an accurate representation of our patient population. Although this study cannot be generalized to all headache patients, it provides a realistic representation of a headache clinic, where knowledge of cannabinoid use is likely to be of value.

Conclusion

In this survey, cannabinoid users comprised roughly a third of respondents. A majority of these participants felt cannabinoids reduced headache severity to some extent, and about 30% felt cannabinoids had some headache-abortive efficacy. Almost a quarter of respondents endorsed some positive impact on headache frequency. The findings of this survey document patient's perceived benefit of cannabinoids in the management of headache. With the recent legalization of cannabis for recreational use in Canada, headache sufferers will increasingly turn to cannabis as a treatment approach when confronted with barriers to accessing headache specialty care and the myriad side effects encountered with typical headache treatments. Benefits of cannabinoids in the treatment of headache need to be weighed against social impacts and potential health effects associated with long-term use. More studies are required to determine the optimal dose, route, frequency, and congener profile for use in specific headache conditions as they intersect with other illnesses. Future policy development requires additional focus on mitigating the potential risks associated with use. The monetary costs of cannabinoids may represent a significant financial burden for some users when considered alongside conventional treatments, and efforts should be made to ensure the commodification of cannabis does not leave this therapeutic tool beyond the reach of those who need it most. The results of this exploratory survey will aid neurologists and headache specialists in understanding the current trends in use of cannabis products in more severely affected headache patients and inform treatment parameters when designing controlled studies of cannabis in this setting.

Disclosures

Drs. Melinyshyn and Amoozegar have no relevant disclosures.

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Statement of Authorship

AM was involved in study design, REB submission, data collection and analysis, and article writing and revision.

FA was involved in study design, REB submission, and article revision.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.215.

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