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ORIGINAL ARTICLE

Association of Herbal Cannabis Use With Negative Psychosocial Parameters in Patients With Fibromyalgia

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Objective. **Patients with chronic pain, including fibromyalgia (FM), may seek treatments outside of mainstream medicine. Medicinal cannabinoids are popularly advocated for pain relief but with limited evidence for efficacy in FM. The extent of use of cannabinoids in FM is unknown.**

Methods. **We have documented the self-reported prevalence of cannabinoid use in 457 patients with the diagnosis of FM and referred to a tertiary care pain center. We validated the diagnosis of FM and examined the associations of cannabinoid use in these patients.**

Results. **Cannabinoids were being used by 13% of all patients, of whom 80% used herbal cannabis (marijuana), 24% used prescription cannabinoids, and 3% used both herbal cannabis and prescription cannabinoids. One-third of all men used cannabinoids. Current unstable mental illness (36% versus 23%; $P = 0.002$), opioid drug–seeking behavior (17% versus 4%; $P = 0.002$), and male sex (26% versus 7%; $P = 0.0002$) were all associated with herbal cannabis use. There was a trend for cannabinoid users to be unemployed and receiving disability payments. The diagnosis of FM was validated in 302 patients, with 155 assigned another primary diagnosis. When the FM group was analyzed separately, significant associations were lost, but trends remained.**

Conclusion. **Cannabinoids were used by 13% of patients referred with a diagnosis of FM. The association of herbal cannabis use with negative psychosocial parameters raises questions regarding the motive for this self-medication practice. Although cannabinoids may offer some therapeutic effect, caution regarding any recommendation should be exercised pending clarification of general health and psychosocial problems, especially for those self-medicating.**

INTRODUCTION

Herbal cannabis has been used for the treatment of pain for centuries. However, in more recent times, this use has been mostly outside of mainstream medicine (1). In the past few decades, pharmacologic preparations of cannabinoids have become available and are used for treatment of pain as well as other symptoms, including nausea and spasticity. Fibromyalgia (FM) is a pain syndrome reported to affect between 2% and 3% of the population, is more common in women, and has no ideal treatment (2–4). Given that pharmacologic treatment outcomes for patients with FM are mostly modest, patients may turn to unconventional self-administered modalities (5). Medicinal cannabinoids represent one such treatment that is popularly advocated for the management of pain conditions, with evidence of efficacy mostly for neuropathic pain (6). The

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Significance & Innovations

- Physicians should be alert to the negative psychosocial associations with self-medication with herbal cannabis in patients with fibromyalgia.
- The risks associated with herbal cannabis in combination with other pharmacologic treatments for fibromyalgia are unknown, but may be considerable.
- It is possible that some patients may be dishonestly using the diagnosis of fibromyalgia to justify use of herbal cannabis.

advocacy and popular use of medicinal cannabinoids extend far beyond the evidence-based literature, without formal recommendation for use in many conditions and with limited knowledge of the true risk/benefit ratio of this intervention.

The identification of an extensive endocannabinoid system that is present throughout the human body, with evidence for a role in pain modulation, as well as other effects, has triggered interest in this system and its role in health and disease (1). Cannabinoids exist as natural molecules in the plant *Cannabis sativa*, commonly known as marijuana, or as synthetic compounds that can be legally prescribed in some countries. The presence of cannabinoid receptors in both the peripheral and central nervous systems raises the question of whether exogenous cannabinoids may be analgesic in pain conditions such as FM (7).

Two factors have limited the clinical study of cannabinoids in disease. First, marijuana, the most common form of cannabinoid, is an illegal substance in most countries, and persons using this agent are subject to prosecution. Second, the group of cannabinoids as a whole, whether natural or synthetic, is often associated with a social stigma in view of the legalities concerning the use of marijuana, the most popular illicit substance worldwide.

In a previous study, we have reported the use of opioids in patients carrying a diagnosis of FM and observed that some were using illicitly obtained herbal cannabis for reported symptom relief (8). The prevalence of the use of cannabinoids, either herbal or pharmacologic preparations, in FM patients is unknown and therefore warrants examination. The intent of this study was to record the use of any cannabinoid and the association of cannabinoid use in a population of patients referred to a multidisciplinary pain center with a diagnosis of FM.

MATERIALS AND METHODS

Study design. All patients referred to the Alan Edwards Pain Management Unit from January 2005 to December 2010 with a referring diagnosis of FM were evaluated in a designated FM clinic. This multidisciplinary unit is staffed by health care professionals from the following disciplines: rheumatology, anesthesiology, pain medicine, family medicine, psychology, physiotherapy, and nursing. In January 2011, we conducted a retrospective chart review of all 457 patients seen in the FM clinic, a cohort that has previously been described (8).

Most patients were referred by primary care physicians, with only a minority referred by specialists from other disciplines. Patients retained the diagnosis of FM if they fulfilled the 1990 American College of Rheumatology criteria at the time of intake and constituted the FM group (2). Patients diagnosed with some other primary condition that was either medical or psychological/psychiatric to account for reported symptoms were categorized as non-FM (non-FM group).

Data recorded at the time of the initial evaluation were extracted using a predetermined protocol and included demographic, disease-related, and psychosocial information. Demographic information included age, sex, education level, current employment status, and any current disability payments. Symptom and disease-related information included current pain level as measured by a 10-cm visual analog scale (VAS) and functional status as measured by the Fibromyalgia Impact Questionnaire (FIQ) (9).

All patients were evaluated by a psychologist to examine for a diagnosis of any previous or current psychological/psychiatric condition, with diagnoses made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Mental health status was verified by additional report by a treating mental health care professional, when applicable. Patients presenting with serious uncontrolled mental health problems were classified as having a current unstable mental illness. Patient report of previous suicide attempts, current suicide ideation, or history of current or previous substance abuse (alcohol and/or illicit drug use) was documented. Opioid drug–seeking patients were identified according to the criteria of Portenoy if they demonstrated aberrant drug-related behaviors (10). This is a measure to specifically address opioid drug seeking in the health care setting. Current cannabinoid use, either licit as for prescription cannabinoid or herbal cannabis accessed with Health Canada authorization or illicit as for illegally accessed herbal cannabis, was recorded. If patients affirmed that they were using herbal cannabis, they were asked whether the use was for medicinal or for recreational purpose, and they were asked to estimate the amount that was used on a daily basis. Users of herbal cannabis usually report use in grams or joints, with a single rolled joint reported to be made up of 0.5 gm on average.

Statistical methods. Demographic information, mental health status, and report of substance use were examined according to cannabinoid use or nonuse for the patient cohort. Univariate analysis of variance was used to compare means in normally distributed continuous data, and chi-square tests were used to compare proportions for categorical data. The medians for nonparametric variables were compared using the Kruskal-Wallis one-way analysis of variance. Analyses were conducted for the entire group

Table 1. Demographic and disease information for 457 patients referred with a diagnosis of fibromyalgia, stratified according to cannabinoid use*

	All patients (n = 457)	Cannabinoids (n = 59)	No cannabinoids (n = 398)	Cannabinoids vs. no cannabinoids, *P*
Age, mean ± SD years	47 ± 11	45 ± 10	48 ± 11	NS
Sex				0.0006
Male	40 (9)	13 (33)	27 (67)	
Female	417 (91)	46 (11)	371 (89)	
Education (n = 436)				
Incomplete	50 (11)	9 (15)	41 (10)	NS
High school	132 (29)	16 (27)	116 (29)	NS
College	156 (34)	22 (37)	134 (34)	NS
University	98 (21)	10 (17)	88 (22)	NS
Unemployed	308 (67)	46 (78)	262 (66)	NS
Disability	165 (36)	23 (39)	142 (36)	NS
Diagnosis				
Fibromyalgia	302 (66)	36 (61)	266 (67)	NS
Not fibromyalgia	155 (34)	23 (39)	132 (33)	NS
Unstable mental illness	110 (24)	20 (34)	90 (23)	NS
Opioids	144 (32)	28 (47)	116 (29)	0.007
Drug-seeking behavior	25 (6)	8 (14)	17 (4)	0.009
Previous suicide attempts	28 (6)	5 (8)	23 (6)	NS
Suicide ideation	30 (7)	5 (8)	35 (9)	NS

* Values are the number (percentage) unless otherwise indicated. NS = not significant.

at entry, as well as for the 2 subgroups, specifically, the FM and non-FM groups.

This study was approved as a chart review with extraction of relevant data by the office of the Director of Professional Services of the Montreal General Hospital.

RESULTS

We examined the medical records of 457 patients who were referred with the diagnosis of FM and had been evaluated in the FM clinic during the 5-year study period. Demographic and disease-related information is shown in Table 1. After evaluation by a rheumatologist, 302 (66%) were confirmed as having FM and constituted the FM group, whereas 155 (34%) were assigned some other primary diagnosis (the non-FM group). The FM and non-FM groups did not differ significantly for any parameters, including age (48 versus 46 years), female sex (93% versus 88%), current employment status (32% versus 34%), current disability (37% versus 35%), and any cannabinoid use (12% versus 15%). Of the 155 subjects in the non-FM group, 140 had a diagnosis other than FM to explain the symptom of pain, 51 of whom also had a current serious mental health/psychiatric problem. Diagnoses other than FM were as follows: regional pain syndrome and spinal pain (n = 88), rheumatic disease diagnosis (n = 37), neurologic condition (n = 10), and only a current unstable mental health/psychiatric condition (n = 15). The 155 non-FM patients were managed according to their specific diagnosis and usual clinical practice in our pain center. The FM patients had a mean FIQ score of 65.7 and a mean pain VAS score of 6.4 and were taking, on average, 1.9 prescription medications for the management of their symptoms.

Fifty-nine (13%) of all 457 patients reported using medicinal cannabinoids. When the cohort was examined by sex, cannabinoids were used significantly more commonly in men compared to women (13 [33%] versus 46 [11%]; $P = 0.0006$), with significant values noted for herbal cannabis use (12 [30%] versus 35 [8%]; $P = 0.0002$). There were no other differences between men and women with regard to demographic, disease-related, or psychosocial parameters. Cannabinoid use was by prescription formulation (n = 14), herbal cannabis (marijuana) use (n = 47), and both prescription and herbal cannabis use (n = 2). Of the 14 patients taking a prescription cannabinoid, 13 received nabilone and 1 received dronabinol. All 47 patients using herbal cannabis reported smoking marijuana with consumption of between 0.5 and 6 gm daily, with 34 (72%) reporting use of ~1 gm or less a day. For the total group of cannabinoid users, concomitant opioid use was recorded in 28 patients (47%). Ten (71%) of the 14 patients using a prescription cannabinoid were also using an opioid.

When the cohort was grouped according to cannabinoid use (either by prescription formulation and/or herbal cannabis) or no cannabinoid use, male versus female sex (33% versus 11%; $P = 0.0006$), current opioid use (47% versus 29%; $P = 0.007$), and drug-seeking behavior (14% versus 4%; $P = 0.009$) were all significantly associated with cannabinoid use (Table 1). When the FM group and the non-FM group were analyzed separately, the above associations, with the addition of current unstable mental illness, remained significant for the non-FM group, but not for the FM group (data not shown). For all patients, herbal cannabis use versus nonuse was associated with younger age (44 versus 48 years; $P = 0.02$), male sex (26% versus 7%; $P = 0.0002$), drug-seeking behavior (17% versus 4%; $P = 0.002$), and current unstable mental illness (36% versus 23%; $P = 0.002$), with a trend observed for unemployment, disability, and opioid use (Table 2).

Table 2. Demographic and disease information for 457 patients referred with a diagnosis of fibromyalgia, stratified according to herbal cannabis use*

	Herbal cannabis (n = 47)	No herbal cannabis (n = 410)	Cannabis vs. no cannabis, *P*
Age, mean ± SD years	44 ± 10	48 ± 11	0.0176
Male sex	12 (26)	28 (7)	0.0002
Unemployed	36 (77)	272 (66)	NS
Disability	20 (43)	145 (35)	NS
Current unstable mental illness	17 (36)	93 (23)	0.0021
Opioids	19 (40)	125 (30)	NS
Drug-seeking behavior	8 (17)	17 (4)	0.0019
Diagnosis			
Fibromyalgia	26 (55)	276 (67)	NS
Other primary diagnosis	21 (45)	134 (33)	NS

* Values are the number (percentage) unless otherwise indicated. NS = not significant.

Current unstable mental health illness was present in 110 (24%) of all patients, 17 of whom were using herbal cannabis. Suicide attempts and suicide ideation were reported by 28 (6%) and 40 (9%) of the entire cohort, respectively, with no significant difference between cannabinoid users and nonusers. Twenty-five patients (6%) were classified as opioid drug seeking, 8 (32%) of whom reported current cannabis use. Nineteen (76%) of the opioid drug seekers were diagnosed with an additional current unstable mental illness. Seventeen (68%) of the opioid drug–seeking patients volunteered a history of previous substance abuse, whereas 13 (52%) were using the label of FM without consistent evidence for presence of pain, in order to procure opioid medications.

DISCUSSION

We have recorded patient report of medicinal cannabinoid use in 13% of a large cohort of patients referred to a multidisciplinary pain center and carrying a diagnosis of FM. Herbal cannabis in the form of smoked marijuana was the most common method of delivery, reported by 10% of the total patient population. Herbal cannabis was more commonly used by men as well as younger patients. Opioid drug–seeking behavior and current unstable mental illness were also strongly associated with herbal cannabis use in the entire cohort, although this association disappeared when we restricted analysis to the FM patients only. Following such stratification, numbers are small and associations may appear due to chance. Additionally, this study does not permit any conclusions regarding causality because temporal relationships were not assessed. There was a nonsignificant trend for herbal cannabis users to use opioids concomitantly, to be unemployed, and to be receiving disability payments. The unemployment rate of 77% for herbal cannabis users suggests either the absence of a favorable effect on function or more serious functional impairment among those using cannabis. Although we did not examine the efficacy of cannabinoids on FM symptoms, our findings raise important questions about the rationale for the use of herbal cannabis in this cohort of patients with FM.

The importance of the cannabinoid system in health and disease is increasingly appreciated. The endocannabinoid system constitutes a complex system of receptors and endogenous ligands that are distributed extensively throughout the nervous system as well as non-nervous tissues. Endocannabinoid molecules are categorized as lipid mediators, are produced by breakdown of phospholipids, and follow an alternate pathway to that downstreaming from arachidonic acid to the inflammatory cytokines (11). The cannabinoid system has known modulatory effects on pain, inflammation, immune functions, and even joint damage (12–15). It is therefore reasonable to question whether the effects of cannabinoid agonists, either natural or synthetic, may have relevance to the management of patients with pain conditions such as FM.

The use of cannabinoids in conventional medicine has been limited in view of legalities concerning illicit use of the plant *C sativa*, popularly known as marijuana. Similar to a report from Holland, where most patients obtained cannabis from the illegal circuit, cannabinoid consumption in our study was by herbal smoked marijuana for three-quarters of users, with no patient having authorization from Health Canada for the possession of dried marijuana (16). Therefore, the access to herbal cannabis in this study was by illicit means for all users. More prevalent use of cannabinoids, especially herbal cannabis, by men compared to women and younger patients deserves commentary. Population surveys indicate that men are twice as likely to use illicit drugs, including marijuana, than women, with US estimates of 11.2% versus 6.8% (17). It is also notable that ever use or occasional use of marijuana for adolescents in Canada does not differ by sex, whereas heavy use was more common in men compared to women (14.3% versus 8.7%) (18). Surveys in multiple sclerosis and chronic noncancer pain have reported an association between medical cannabis use and younger age, male sex, and prior nonmedicinal cannabis use (19,20). Therefore, we might speculate that the male patients in our study were more familiar with cannabis and therefore willing to try cannabis as a treatment. Alternately, they may have been using cannabis primarily for recreational reasons, with illness as a justification for this use. In contrast, women may have been more wary of the use of cannabis, either due to limited previous exposure or perhaps not

willing to use cannabis in the setting of a home and possibly in the presence of children.

The use of medicinal marijuana in Canada is regulated by the Marihuana Medical Access Division of Health Canada, with 4,884 persons holding an authorization to possess dried marijuana as of January 2010, and with Health Canada estimates that 10.7% of Canadians had used cannabis in that year (21). Therefore, it can be conservatively estimated that cannabis was legally used for medicinal purposes by 0.14% of the Canadian population. The true numbers of persons self-medicating with cannabis is likely higher than these estimates and supports the finding of 10% use in our study, similar to findings in Canadian patients with multiple sclerosis and chronic noncancer pain (19,20). Our findings are in concordance with those of Bronstein et al, who identified the presence of marijuana in 9% of urine samples when almost 1 million tests were performed in patients with chronic pain (22).

Most information regarding the clinical use of cannabinoids is based on observational studies, with a paucity of clinical trials in rheumatic conditions or FM. Arthritis was reported to be the reason for cannabinoid use by one-quarter to one-third of persons in 2 population surveys of chronic pain reported from Australia and the UK (23,24). Two issues reported in both of these studies are concerning. First, medicinal use of cannabinoids was associated with recreational use in one-third to one-half of users in each study, and second, both studies reported the use of cannabinoids also to self-medicate for depression. Similarly, in the current study, one-third of cannabinoid users were found to have an uncontrolled mental illness, but we did not record whether patients had previously been recreational users of cannabis. The association between recreational and medicinal use of cannabinoids and their use for self-management, particularly for mood disorders, requires further clarification. Although cannabinoids may have anxiolytic properties, continued use in the setting of unstable mental illness is of great concern.

In the absence of an ideal treatment for FM, it is understandable that patients may seek symptom relief by the use of nonprescribed or unconventional therapies. As cannabinoids are popularly reputed to relieve pain, sleeplessness, and stress, all of which are symptoms commonly present in FM, self-medication with cannabinoids may be a treatment option chosen by some patients. Indeed, mainstream medicine recognizes a symptom-based management approach as a logical treatment strategy for persons with FM (4). Even though pain relief remains the focal point of the management of patients with FM, a treatment that is able to address multiple symptoms could be considered ideal (25). In a small study of 9 patients with FM, orally administered Δ^9-tetrahydrocannabinol (Δ^9-THC) reduced electrically induced pain as well as daily reports of pain, but not axon-induced flare, with 5 of the 9 patients withdrawing because of side effects related to the treatment (26). Reports of a formal evaluation of cannabinoids in FM are limited to 2 small randomized controlled studies (27,28). The synthetic cannabinoid nabilone, an agent without the psychoactive effect of Δ^9-THC, was reported to have a significant effect on pain and function as measured by the FIQ in 40 patients with FM (28). In the second study, our group reported that nabilone performed equally to amitriptyline for effect on sleep (27). In an uncontrolled study, pain scores were reduced 2 hours after cannabinoid use in 28 FM patients, but with no impact on function as measured by the Short Form 36 health survey or the FIQ (29). Based on this limited evidence, the role of cannabinoids in FM remains unclear.

We have also once again demonstrated an inaccurate diagnosis of FM for one-third of the referred patients, with serious current mental illness observed in one-third of the non-FM group (30). Persons with uncontrolled mental illness seeking health care may present pain as a more plausible symptom, rather than focusing on the mental health issues. This prevalent inaccuracy in diagnosing FM attests to the continued challenges associated with this condition and the possibility that some persons may misrepresent subjective symptoms to health care professionals in order to access prescription medication. The finding that 6% of patients were drug seekers, with three-quarters diagnosed with unstable mental illness and one-third reporting use of medicinal cannabinoids, is notable. Indeed, the true prevalence of aberrant drug-seeking behavior may have been underestimated, since we conformed to strict criteria in order to categorize patients as such (10). Drug abuse in FM has not previously been recognized, although it is prevalent in patients with chronic pain (22). This raises the serious issue of the potential for the use of a factitious diagnosis of FM in order to procure prescription medication or to condone use of herbal cannabis. Physicians should be vigilant in ensuring that the diagnosis of FM is valid.

Our study raises questions regarding the concomitant use of cannabinoids and opioids. Opioid use in the primary care setting has been associated with substance use disorders and marijuana use (31). Although opioids and cannabinoids may have a synergistic effect when used for pain relief, the combination of 2 agents that both have neurophysiologic effects on mood and cognition requires careful clinical evaluation (32). This is especially true in the context of symptoms of fatigue, mood disorder, and cognitive dysfunction reported in patients with FM. There are increasing reports of opioid use in FM, although this category of drugs has neither been tested in this condition nor are they recommended by any current FM guidelines (8). It is possible that physicians who had prescribed opioids for these patients were unaware of current cannabinoid use. The additive effect of these 2 groups of compounds, although possibly beneficial for pain, may have negative psychosocial effects in the short term, and unknown long-term effects.

Risks associated with medicinal cannabinoid use may be categorized as those due to immediate effects of the agent, either alone or combined with other substances, and the lesser-known long-term effects. Acute side effects are mostly related to the psychoactive properties of cannabinoids such as dizziness, drowsiness, and impact upon cognition, whereas the long-term risks are largely unknown (33). Exacerbation or even precipitation of psychiatric disease has been reported, particularly for recreational use, in young adults. Many unknown factors remain regarding long-term effects of cannabinoids, in-

cluding whether effects of synthetic or natural cannabinoids may be similar, effects on psychological health and other physiological functions in patients with FM, and long-term effects of interactions with other prescription medications (34,35). While the abuse potential for the pharmacologic preparations dronabinol and nabilone is reported to be low, that for therapeutic herbal cannabis requires study (35–37).

A number of limitations to this study must be acknowledged. The sample size of 457 patients with 70% positively diagnosed with FM is relatively small, especially when evaluating a characteristic (i.e., cannabinoid use) that was present in only 13% of subjects. Therefore, our results may not accurately reflect practices in the wider population of individuals with FM. Patients with FM referred to a multidisciplinary pain center clinic may not necessarily be representative of the average patient being managed in primary care or in the community. We acknowledge that our data may have inaccuracies, since information on substance and medication use was based on voluntary patient report only and the true prevalence may be underreported. Urine drug screening, which was not done in our study, would have given a more objective measure of actual use. We are also unable to comment on either the efficacy or safety of use of cannabinoids in patients with FM because this was a cross-sectional study.

We have observed cannabinoid use by 13% of persons referred with a diagnosis of FM, with only one-quarter having acquired cannabinoids legally. The mostly illicit use of herbal cannabis may be driven by factors such as poor effect from current available medications, popular advocacy, or familiarity with marijuana from recreational use. Although we did not evaluate the efficacy of cannabinoids for symptoms of FM, we have particular concerns regarding the high rate of poor mental health in cannabinoid users. We also believe that drug seekers may be using the diagnosis of FM even more frequently than we have documented, with cannabinoid use raising suspicions. Although cannabinoids as pharmacologic preparations may offer some therapeutic effect for patients with FM, the current evidence should prompt physicians to examine for global psychosocial well-being, and not focus only on the single outcome measure of pain (36,38).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Ms Fitzcharles had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ste-Marie, Fitzcharles, Gamsa, Ware, Shir.

Acquisition of data. Ste-Marie, Fitzcharles, Gamsa.

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