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Cannabidiol Use for Fibromyalgia: Prevalence of Use and Perceptions of Effectiveness in a Large Online Survey

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Abstract: **Cannabidiol (CBD) is widely advertised as helpful for chronic pain management but research is limited. Using a cross-sectional, anonymous survey, we examined patterns of naturalistic CBD use among individuals with fibromyalgia (FM) and other chronic pain conditions. Our objective was to better understand rates of CBD use, reasons for use and discontinuation, communication with healthcare professionals about CBD, and perceptions of CBD effectiveness and safety among people with FM. After excluding incomplete surveys, our study population consisted of N = 2,701 participants with fibromyalgia, primarily in the United States. Overall, 38.1% reported never using CBD, 29.4% reported past CBD use, and 32.4% reported current CBD use. Past-year cannabis use was strongly associated with past or current CBD use. Those using CBD typically did so due to inadequate symptom relief, while those not using CBD typically cited safety concerns as their reason for not using CBD. Two-thirds of participants disclosed CBD use to their physician, although only 33% asked for physician advice on using CBD. Participants used CBD for numerous FM-related symptoms (most commonly pain), and generally reported slight to much improvement across symptom domains. Around half of participants reported side effects, which were typically minor. Our findings are limited by selection bias and our cross-sectional design, which prevents causal associations. In conclusion, CBD use is common among individuals with FM and many individuals using CBD report improvements across numerous FM-related symptoms. Our findings highlight the need for additional rigorous studies to better understand CBD's potential for FM management.**

Perspective: ***This article indicates that CBD use is common among people with fibromyalgia, and the results suggest that many derive benefit from using CBD across multiple symptoms domains. Clinicians should discuss CBD use with fibromyalgia patients, and future studies are needed to rigorously assess CBD's therapeutic value for fibromyalgia symptoms.***

Key words: *Fibromyalgia, cannabidiol, chronic pain, symptom relief, prevalence.*

Introduction

Fibromyalgia (FM) is a common chronic pain condition, affecting 2 to 4% of the population.[2,16] FM is characterized by widespread pain and is often accompanied by a cluster of co-occurring symptoms, including sleep problems, depression, cognitive dysfunction (ie,

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fibro-fog), and fatigue.[16] While FM is best managed with a combination of pharmacological and nonpharmacological interventions (eg, exercise, self-management skills, acupuncture),[16] many nonpharmacological interventions remain poorly covered by insurance,[5] leaving people with FM to rely mainly on insurance-covered medications. Unfortunately, pharmacologic interventions for FM (eg, duloxetine, pregabalin, milnacipran – all of which are FDA approved) only work in a subset of individuals, have modest effects sizes, and have adverse effects that can preclude long-term use.[15,29,30] Indeed, an 11-year longitudinal observational registry study showed that while use of these agents increased from 10% to 39% among individuals with FM, pain, fatigue, and disability measures generally did not improve.[55] Similarly, in a consumer report study, none of these approved medications were rated as among the 10 most effective therapies, instead being ranked as among the top 10 most harmful.[28] As such, many individuals with FM experiment with alternative interventions to optimize symptom management. Thirty-one states have legalized cannabis for pain and/or FM,[6] and some individuals with FM have turned to cannabis and compounds derived from cannabis, such as cannabidiol (CBD).

There have been numerous clinical trials of cannabis and Δ-9-tetrahydrocannabinol (THC) in chronic pain conditions, with results suggesting analgesic effects but also a significant side effect profile, including intoxication as well as abuse potential.[46] While CBD is far less studied, it is a popular alternative therapy, and is particularly attractive to consumers as it is both fairly well-tolerated (causing mostly nonserious side effects) and nonintoxicating, with little or no abuse potential.[32,41] After the 2018 Farm Bill removed CBD products derived from hemp (*Cannabis sativa* with <0.3% Δ-9-tetrahydrocannabinol [THC]) from the Controlled Substances Act,[18] CBD products (eg, candies, cosmetics, soft-gels, tinctures) have flooded the marketplace. Some CBD manufacturers tout their products as wonder drugs, useful for numerous conditions such as Alzheimer's disease, epilepsy, anxiety, and cancer.[1] While the preclinical literature suggests that CBD has wide-ranging therapeutic activity (indeed, product claims are often based on preclinical data),[31,32] most of these findings have not been rigorously tested in large clinical trials, with the exception of CBD's anticonvulsant activity in the rare childhood epileptic conditions Dravet and Lennox Gastaut syndromes.[23,47] While some small clinical trials suggest that CBD may be anxiolytic,[20,21,34,36,57] analgesic,[37,56] and useful for sleep,[13] these trials typically involved short dosing regimens (<1 month), nonstandardized products, widely variable doses (eg, topically applied, 100–900 mg orally) and small sample sizes. Despite this relative lack of evidence and uncertainty about effective dosing, CBD products are frequently used by consumers, with one recent large cross-sectional study showing the greatest use being for chronic pain, followed by arthritis/joint pain, anxiety, depression, sleep disorders, and headache.[19]

Given the challenges associated with FM medications and the wide-ranging use of CBD products, we conducted a large online survey to examine CBD product use among individuals with FM. Our goal was to characterize the prevalence of CBD product use among individuals with FM, reasons for using or not using CBD products, and perceptions of effectiveness and safety. Similar to results seen in a large study of individuals with arthritis,[25] we hypothesized that the majority of individuals with FM would use or have used CBD products and that most would report that it was useful for FM symptom management – especially anxiety, pain, and sleep.

Methods

We collaboratively designed the survey, drawing on commonly asked questions about CBD in the FM community (LM) as well as our expertise in cannabinoids (KFB) and chronic pain (DAW).[3,7,8] We recruited participants with FM by sending out an anonymized survey link via the Qualtrics survey platform (Provo, UT) to a listserv with members of the National Fibromyalgia Association (NFA). The NFA also shared the survey link via press releases, Facebook, and other social media platforms in April and May of 2020. To prevent duplicate responses, we used the "Prevent ballot box stuffing" setting in Qualtrics, which blocks people from accessing a survey more than once from the same IP address.

We collected demographic information including sex, age, race/ethnicity, household income, education level, rating of overall health, employment status, and location. We classified participants as living in locations with and without legal cannabis based on local laws. We also asked all participants whether they had used marijuana (defined as containing little or no CBD) in the past year. Participants also selected all of their physician-diagnosed pain conditions (including FM), with an option for free text entry for unlisted conditions. Participants were asked questions about their use of CBD, which was defined as "a component of cannabis that does not get you high" (in contrast to THC, which was defined as "the component of cannabis that does get you high"). Participants were subsequently sub-grouped based on their CBD product use patterns as: never used, past but not current use, and current use. Those with past but not current CBD product use indicated how long they used these products before discontinuing, and those who currently used CBD products were asked how long they had used them.

All study procedures were approved by the Institutional Review Board at the University of Michigan Medical School under protocol HUM00170424. Participants freely consented to participate, were not compensated, and could terminate participation at any time.

Measures

Symptoms of FM and Other Common Chronic Pain Conditions

Participants completed the 2011 FM Survey Criteria, which have been widely used in epidemiological studies[54] and contain measures of symptom severity (eg,

cognitive dysfunction, problems sleeping) and a body map to indicate 0-19 tender points. This measure is scored continuously, with values ranging from 0 to 31 and the cut-off for FM at 13. Participants also completed the Complex Medical Symptom Inventory (CMSI),[49-51,53] which is used to measure functional somatic burden and screen for chronic overlapping pain conditions (COPCs, conditions sharing similar features with fibromyalgia and that are similarly difficult to manage). The CMSI is scored from 0 to 41, with higher scores indicating more symptoms of COPCs.

CBD Use: Rationale for or Against

We asked participants whether they had ever used CBD products to manage pain or other symptoms, and the reasons for this decision. Participants who had discontinued CBD product use were asked why as well as how long they had used CBD products before discontinuing.

Disclosure of CBD Use to Physicians

Participants with past or current use of CBD products were asked whether they had disclosed CBD product use to their physician. Those who had disclosed use were asked to characterize their physician's comfort level with them using CBD on a 5-point Likert scale ranging from very uncomfortable through very comfortable as well as an option of "could not tell." Participants who had used CBD products were also asked whether they had asked their physician for advice on how to use CBD products.

Current CBD Use

Frequency of CBD Use

Participants indicated how frequently they used CBD products, both in days per week and times per day.

Type of CBD Product

Participants indicated the type of CBD product they used most often from list of, "CBD isolate (solely CBD)," "Full spectrum CBD with less than 0.3% THC" and "CBD with more than 0.3% THC."

Perceptions of CBD Effectiveness

Participants selected symptoms for which they used CBD products from a list that included pain, insomnia or sleep problems, anxiety, fatigue, depression, memory or clarity of thought, joint stiffness, muscle spasms, and other. We chose these symptoms as they frequently co-occur with FM and other chronic pain conditions.[44,52] For each symptom selected, participants rated how their symptom had changed since using CBD products using a 7-point Likert scale adopted from the Patient Global Impression of Change, ranging from "very much worse" to "very much improved." Participants rated how their overall health had changed since using CBD using the same 7-point Likert scale.

Safety

We asked participants if they had experienced any side effects from CBD products. We selected our list of possible side effect options from the drug labels of Epidiolex and dronabinol, which are FDA approved CBD and THC, respectively. We included dronabinol side effects because some products have been shown to contain substantial quantities of THC despite being labeled as CBD.[9] Participants who endorsed side effects selected the frequency with which they encountered each side effect.

Statistical Analysis

We first characterized the study population using descriptive statistics. We assessed clinical and demographic differences between complete surveys and those surveys that did not meet inclusion criteria to investigate biases within our included sample. We subgrouped participants by their use of CBD products: never, past, and current. We also examined differences in CBD product use rationale and physician interactions between participants with and without access to legal cannabis. We used Pearson's Chi-square (X^2) test to assess differences in proportions for categorical variables (eg, income level, race/ethnicity) and reported results as frequency (percent, %). We assessed between-group differences in continuous variables (reported as mean $\pm$ standard deviation (SD) if normally distributed, otherwise as median $\pm$ interquartile range (IQR)) using analysis of variance (ANOVA) and conducted post-hoc testing using Tukey's test. To investigate possible explanatory variables for past or current CBD product use compared to no CBD product use, we performed univariate and multivariate multinomial regression analyses with the following indicator variables: age, sex, past-year marijuana use (yes/no), CMSI score, FM-score, and number of diagnosed chronic pain conditions (continuous variables). The "no CBD" group was used as the reference group against which comparisons were made. All analyses were conducted in STATA/SE 14.2 (StataCorp, College Station, TX).

Results

Overall, 3,455 participants started the survey, and 2,762 completed the survey (79.3% completion rate). Only complete surveys were used in subsequent analyses. Of these, 3 (0.1%) did not answer the appropriate questions about CBD product use and 58 (2.1%) did not report having FM. These individuals were not included in the analysis leaving N = 2,701 participants with physician diagnoses of FM in the analytic sample.

Demographics

The survey took ~24 minutes to complete on average, with N = 59 (2.2%) of participants taking >1 hour to

complete the survey. In the final study population, 1,028 (38.1%) had never used CBD products, 795 (29.4%) had used CBD products in the past but did not currently use it, and 878 (32.5%) currently used CBD products. Nearly all (88.7%) of those who had discontinued CBD products did so within 6 months of initiation, and 74.6% of those currently using CBD products had used it for greater than 6 months.

Participants were 94.7% female and mostly white with a mean age of 56.7 ± 12 (Table 1). Study participants lived in all 50 states as well as Canada (4.4%) and other countries outside the US (1.8%). The states most represented in the study population were California (9.4%), Michigan (5.7%), Texas (4.6%), Florida (4.6%), and Pennsylvania (4.5%). Over two-thirds (70.7%) lived in places with access to legal marijuana (medical or adult-use). The distribution of participants in the "never use", "past use" and "current use" groups varied significantly ($P < .003$), driven by a higher percentage of individuals living in locations with legal marijuana in the "current use" group (75.1%). The distribution of past year marijuana use was significantly different between groups ($P < .0001$), with participants who never used CBD products reporting lower marijuana use than those who had used CBD products in the past or who reported currently using CBD products. Most reported past-year marijuana use was for medical purposes. Unsurprisingly, more participants with access to legal marijuana reported past year use than those who without (36.5% vs 25.1%, $P < .0001$).

Medical Conditions, FM Score, CMSI

Participants reported a median of 5.0 ± IQR 4.0 physician diagnosed pain conditions (Table 2). All participants had FM, and the most common comorbid pain conditions were chronic low back pain (49.2%), osteoarthritis (44.8%), irritable bowel syndrome (44.7%), and migraine (41.8%). Participants who used CBD products in the past reported significantly more conditions than those who had never used CBD products (difference = 0.30, 95% confidence interval [CI]: 0.006–0.60, $P = .045$), as did those who currently used CBD products (difference = 0.53, 95% CI: 0.24–0.82, $P < .001$). The average score on the 2011 FM survey criteria was 18.5 ± 5.7, and 84.0% of participants had a score ≥13, indicating a positive diagnosis for FM. [Note: As FM scores do fluctuate over time or after treatments,[43] it is possible that some participants were diagnosed with FM and then had improvements in symptoms that caused them to no longer meet the ≥13 point threshold.] Those in the "past use" group had significantly higher FM scores than those in the "never use" group, (difference = 0.68, 95% CI: 0.05–1.31, $P = .031$), as did those in the "current use" group (difference = 0.65, 95% CI: 0.03–1.26, $P = .036$). Similarly, when compared with the "never use" group, more participants in the "past use" group and "current use" group met diagnostic criteria for FM. The average CMSI score was 20.6 ± 7.8. Those in "past use" group had significantly higher CMSI scores than the "never use" group (difference = 1.10, 95% CI: 0.23 −1.96, $P = .008$), as did the "current use" group (difference = 1.35, 95% CI: 0.51–2.19, $P = <.001$).

Attrition Analyses

Attrition analyses were conducted between those who were not included (n = 754) versus those who did (n = 2,701). There were no demographic differences between those who did and did not complete the survey except with regards to employment status, were fewer in the attrition sample were retired or unemployed. Compared to the overall sample, those in the attrition sample had past year marijuana use patterns more similar to participants currently using CBD products. Those in the attrition sample had significantly lower FM and CMSI scores (2.2 and 1.5 points, respectively, P's ≤ .01), reported on average −0.64 fewer diagnosed chronic pain conditions ($P = .002$). Similarly, there was a significantly different distribution between those in the attrition sample and those in the included sample ($X^2 = 9.5$, $P < .008$), with a higher percentage (13%) of those in the attrition sample reporting "very good" overall health than those in the included sample (8.2%). These differences may be partially due to missing data in the attrition sample, ranging from 23.6% completing the question on chronic pain conditions to 69.0% completing the question on overall health. Further, only n = 129 (17.1%) in the attrition sample reporting having fibromyalgia, compared to 100% of the included sample, which may have affected these results.

Multinomial Regression Modeling: Associations of Variables With Past or Current CBD Product Use

In univariate analyses, CMSI, FM score, number of conditions, and past-year marijuana use were all associated with past or current CBD product use compared to no CBD product use, and age was additionally associated with current CBD product use (Tables 3 and 4, R^2 ranging from 0.0005 to 0.0762). However, in the full model (which included all variables, $R^2 = 0.0795$), only past-year marijuana use was significantly associated with a higher odds of past CBD product use compared to no CBD product use. Similarly, only past-year marijuana use and number of diagnosed pain conditions were significantly associated with higher odds of current CBD product use compared to no CBD product use.

Rationale for not Using, Discontinuing, or Using CBD Products: Overall and by Legal Marijuana Status

The rationale for using or not using CBD products among each subgroup are displayed in Table 5. The most common reasons for not using CBD products typically related to safety concerns, eg, concern about side effects or interactions with medications. The three most common reasons for CBD product use (combined among those with past and current use) were: 1) inadequate

Table 1. Sociodemographic Characteristics for Sample: Overall and by CBD use Participants using CBD Were Slightly Older Than Those who did not.

	Overall (n = 2,701)	*Never (n = 1,028)*	*Past (n = 795)*	*Current (n = 878)*	*X2*	*F*	P
Sex					8.6		.20
Female	95.0%	95.7%	94.5%	95.0%			
Male	4.3%	3.9%	5.2%	4.1%			
Gender nonconforming	0.6%	0.4%	0.4%	0.9%			
Missing	0.1%	0.2%	0.0%	0.0%			
Age						7.0	<.001
Mean (SD)	56.6 (12.0)	57.5 (11.9)	56.9 (11.7)	55.5 (12.2)			
Annual household income (US$)					11.2		.025
Less than $50,000	42.1%	44.3%	42.1%	39.4%			
$50,001-$99,999	31.1%	29.6%	32.3%	31.8%			
$100,000+	19.1%	16.3%	19.5%	22.0%			
Missing	7.7%	9.8%	6.0%	6.8%			
Education					19.2		.004
High school degree, GED, or less	13.4%	16.6%	12.3%	10.7%			
Associates degree or some college	43.7%	43.3%	44.2%	43.6%			
Bachelor's degree (BA, BS, AB, BBA)	23.8%	22.5%	24.5%	24.6%			
Masters, Professional or Doctoral degree	18.4%	16.4%	18.6%	20.6%			
Missing	0.7%	1.2%	0.4%	0.5%			
Past-year marijuana use					430.5		<.001
None	66.8%	88.4%	61.0%	46.7%			
Recreational only	4.4%	4.0%	5.3%	4.2%			
Medical only	19.8%	4.8%	24.7%	33.1%			
Medical and recreational	8.7%	2.7%	8.6%	15.9%			
Missing	0.2%	0.1%	0.5%	0.0%			
Employment status					8.8		.84
Unemployed (looking for work)	2.1%	2.1%	2.1%	2.1%			
Student	0.6%	0.4%	0.9%	0.7%			
Full time (40+ h per wk)	19.4%	20.7%	17.4%	19.7%			
Part time (<40 h per wk)	8.1%	8.4%	8.1%	7.7%			
Unemployed (not looking for work)	4.0%	4.1%	4.2%	3.8%			
Retired	30.8%	31.6%	30.6%	30.0%			
Self-employed	4.7%	4.2%	4.7%	5.2%			
Unable to work	30.1%	28.1%	31.9%	30.8%			
Missing	0.3%	0.4%	0.3%	0.1%			
Relationship status							
Single (never married)	9.0%	9.9%	8.2%	8.7%	9.2		.33
Married	61.2%	60.2%	61.3%	62.4%			
In a domestic partnership	5.3%	4.2%	5.8%	6.3%			
Divorced	17.6%	17.2%	18.5%	17.2%			
Widowed	5.9%	6.8%	5.7%	5.1%			
Missing	0.9%	1.7%	0.6%	0.3%			
Race/Ethnicity (could select ≥1)					18.4		.19
American Indian/Alaska Native	2.2%	1.8%	2.6%	2.3%			
Asian	1.0%	1.3%	0.4%	1.4%			
Black or African American	3.6%	4.5%	3.4%	2.8%			
Hispanic or Latino	4.9%	5.1%	3.9%	5.6%			
Native Hawaiian/Other Pacific Islander	0.4%	0.3%	0.8%	0.3%			
White/Caucasian	89.5%	87.7%	91.4%	89.9%			
Other	2.0%	2.2%	1.9%	1.8%			
Missing	0.4%	0.5%	0.3%	0.5%			
Legal cannabis					6.0		.003
Yes	70.7%	68.1%	69.2%	75.0%			
No	28.5%	31.0%	29.7%	24.4%			
Missing	0.8%	0.9%	1.1%	0.6%			

Fewer participants in the "no use" group had used cannabis (defined as containing little or no CBD) in the past year than those in the "past use" or "current use" groups.

symptom relief (64.3%); 2) personal research leading to use (54.7%); and 3) recommended by a friend (44.8%). Participants most commonly discontinued CBD product use because they felt that it did not work (62.3%).

In terms of rationale for not using CBD products, 35.8% of those in places without legal marijuana were worried about CBD's legality, compared with only 20.7% in places with legal marijuana. Similarly, only

Table 2. Clinical Phenotype for Study Population by CBD use Participants Reported Numerous Comorbid Chronic Pain Conditions With Fibromyalgia and Generally Poor Health.

CBD use	*Overall (n = 2,701)*	*Never (n = 1,028)*	*Past (n = 795)*	*Current (n = 878)*	*F*	X^2	P
# Diagnosed pain conditions					9.5		<.001
Median (IQR)	5 (4) n = 2,701	5 (4) n = 1,028	5 (4) n = 795	5 (4) n = 878			
Overall health						9.7	.28
Excellent	18 (0.7%)	8 (0.8%)	8 (1.0%)	2 (0.2%)			
Very Good	222 (8.2%)	98 (9.5%)	55 (6.9%)	69 (7.9%)			
Good	954 (35.3%)	366 (35.6%)	275 (34.6%)	313 (35.6%)			
Fair	1,093 (40.5%)	404 (39.3%)	330 (41.5%)	359 (40.9%)			
Poor	404 (15.0%)	145 (14.1%)	126 (15.8%)	133 (15.1%)			
Missing	10 (0.4%)	7 (0.7%)	1 (0.1%)	2 (0.2%)			
CMSI					8.1		<.001
Mean (SD)	20.6 (7.8) n = 2,701	19.8 (7.9) n = 1,028	20.9 (8.0) n = 795	21.1 (7.8) n = 878			
FM score					4.3		.014
Mean (SD)	18.5 (5.7) n = 2,694	18.0 (5.7) n = 1,027	18.7 (5.8) n = 795	18.7 (5.7) n = 872			
Fibromyalgia positive per 2011 criteria							
n (%)	2,264 (84.0%)	832 (81.0%)	682 (85.8%)	750 (86.0%)	5.7		.003

Table 3. Associations of Demographic/Clinical Characteristics With Past CBD use Compared to no CBD use all Results Were Produced Using Multinomial Regression Modeling.

Predictor	*Univariate associations β (95% CI)*	P-*value*	*Full model OR (95% CI)*	P-*value*
Age	−0.004–0.004	.27	1.0 (0.99–1.01)	.41
Sex	−0.64–0.16	.24	0.73 (0.48–1.13)	.16
Past-year marijuana use	0.77 (0.65–0.89)	<.001	2.16 (1.91–2.43)	<.001
CMSI	0.02 (0.006–0.03)	.003	1.01 (0.99–1.02)	.38
FM-score	0.02 (0.005–0.04)	.012	1.01 (0.99–1.03)	.54
# pain conditions	0.04 (0.008–0.08)	.015	1.02 (0.98–1.06)	.34

OR = odds ratio; CI = confidence interval.

4.9% of those in places with legal cannabis reported discontinuing CBD products due to concerns over CBD's legality, versus 11.9% in places without legal marijuana. Despite these differences, the main findings were the same: Most participants stopped using CBD products because they did not work or due to expense. Lastly, the main reasons for initiating CBD product use were quite congruent between participants who lived in places with and without legal marijuana: 1) Inadequate relief from current medications (62.7%–64.8%), 2) personal research (54.4%-54.9%), and 3) recommended by a friend (41.9%–52.2%).

Physician Interactions

Only 28.3% of participants initiated past or current CBD product use based on the recommendation of a medical professional or physician. The majority of participants reported telling their physician about using CBD products, with 48.3% reporting that their physician was either a little or very comfortable with CBD product use versus 27.3% who were a little or very uncomfortable with CBD product use. However, only 33.3% asked their physician for advice on how to use CBD products. Seventy-one percent of participants in locations with legal marijuana told their physician about using CBD

Table 4. Associations of Demographic/Clinical Characteristics With Current CBD use Compared to no CBD use all Results Were Produced Using Multinomial Regression Modeling.

Predictor	*Univariate associations β (95% CI)*	P-*value*	*Full model OR (95% CI)*	P-*value*
Age	−0.01 (−0.02 – −0.01)	<.001	1.0 (0.99–1.01)	.43
Sex	0.14 (−0.27–0.55)	.51	0.98 (0.62–1.54)	.92
Past-year marijuana use	1.06 (0.94–1.17)	<.001	2.83 (2.52–3.18)	<.001
CMSI	0.02 (0.01–0.03)	<.001	1.0 (0.99–1.02)	.58
FM-score	0.02 (0.004–0.04)	.014	0.99 (0.97–1.01)	.59
# pain conditions	0.07 (0.04–0.11)	<.001	1.06 (1.02–1.11)	.005

OR = odds ratio; CI = confidence interval.

Table 5. Rationale for not Using, Using, and Discontinuing CBD Rationale for Using or not Using CBD.

Rationale for never using CBD (n = 1,024)	%
My symptoms are well-controlled	4.6%
Not enough research on CBD	26.7%
Worried about side effects	33.2%
Worried about interactions with my other medication	39.5%
My physician is not comfortable with me using CBD	11.4%
Too expensive	33.3%
Worried about CBD's legal status	25.5%
CBD products are not well regulated and can be contaminated	33.2%
Other	25.5%
Concerned what my friends or family would think	7.2%
Worried about being drug tested for my job	11.7%
Past CBD use rationale (n = 795)	
Recommended by a friend	45.2%
Recommended by a physician or medical professional	23.4%
Recommended by personnel at a medical cannabis dispensary	6.6%
Read about it in the news	32.8%
Personal research	45.6%
Not getting adequate relief from other medications	58.0%
Other	4.6%
Rationale for CBD discontinuation (n = 795)	
Expense	46.7%
Did not work	62.3%
Negative side effects	8.6%
Other	13.7%
Family or friends disapproved	1.0%
Concern about legality	7.0%
Drug test concerns	5.5%
Discouraged by medical professional	2.5%
Current CBD use rationale (n = 878)	
Recommended by a friend	43.8%
Recommended by a physician or medical professional	32.3%
Recommended by personnel at a medical cannabis dispensary	9.9%
Read about it in the news	27.8%
Personal research	62.3%
Not getting adequate relief from other medications	69.2%
Other	6.0%

Most reasons for not using CBD were due to concerns about safety (eg, not enough research, worried about drug interactions).

products, compared to 62% of those without. However, perceptions of physician comfort were quite similar between those with and without legal marijuana (47.3% vs 52.9% comfortable, 28.2% vs 25.7% uncomfortable). Participants with and without access to legal marijuana were similarly likely to ask their physician about how to use CBD products (33.5% vs 32.9%).

CBD Use and Perceptions of Effectiveness

The majority (54%) of participants used CBD products every day, compared with 1 to 3 days/week (22%) and 4 to 6 days/week (24%). Most survey participants reported using CBD products once or twice per day (40.4% and 37.6%, respectively) while 21.9% used it 3 or more times per day. With regards to CBD product content, 41.7% of participants used CBD with <0.3% THC, 26.8% used CBD isolate, 20.2% used CBD with >0.3% THC, and 11.1% did not indicate which product they used most often. Participants used CBD products for a wide variety of symptoms (median 3.0 ± IQR 3.0), with the most common being pain, joint stiffness, muscle spasms, and anxiety. On average, changes in most symptoms fell between slightly improved and much improved, as did the average change in overall health (Fig 1). The follow percentages of participants reported "much" or "very much" improvement for the following symptoms: 30.5% for pain, 40.1% for insomnia/sleep problems, 40.0% for anxiety, 20.0% for fatigue, 32.3% for depression, 21.9% for memory/clarity of thought, and 43.2% for other symptoms. Note: we were unable to analyze changes in joint stiffness and muscle spasms.

Perceptions of Safety

Of the n = 878 participants using CBD products, 50.7% reported side effects (Table 6), with a median of 1.0 side effects ± IQR 1.0 per participant (n = 793 side effects total). Most were minor, with sleepiness (51.4%) being most commonly reported. Some participants reported rare, more serious side effects that are typically associated with THC, including paranoia (2.0%), hallucinations (1.3%), and vomiting (0.2%).

Discussion

We examined CBD product use among a large sample of individuals with FM that included representation from all 50 states in the US as well as outside the US. Our results provide a novel snapshot into trends of and reasons for CBD product use for FM. Despite the dearth of rigorous data showing that CBD may be analgesic in humans, nearly a third currently used CBD to manage pain or other symptoms, which is more than double the 14% in the American public currently using CBD products estimated by a 2019 Gallup poll.[10] However, our results are quite consistent with a 2019 survey conducted by the Arthritis Foundation, which found that 29% of respondents (most commonly with osteoarthritis and rheumatoid arthritis) currently used CBD products.[25] This high use prevalence may be due to a greater willingness to try alternative interventions and/or need to address the higher symptom burden of individuals with FM – especially those symptoms that CBD products are purported to be most helpful (ie, pain, anxiety, sleep).[16] Indeed, participants in our study reported numerous physician-diagnosed pain conditions (which was associated with higher odds of CBD product use) and significant clinical burden (measured via the 2011 FM survey criteria and CMSI). Further, their most common reason for CBD product use was inadequate symptom relief from other medications. Thus, our sample may have consisted of individuals who have tried many treatment options with limited success – a common occurrence with FM.[2,16]

Past-year use of marijuana (ie, cannabis with little or no CBD and containing >0.3% THC) for any purpose

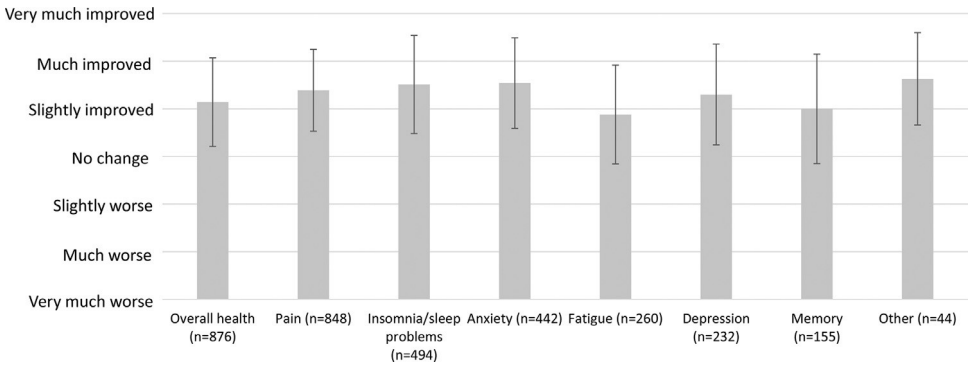

Figure 1. Self-reported effectiveness of CBD for managing FM-related symptoms changes were assessed using the patient global impression of change for each symptom. Error bars are ± standard deviation.

varied widely between subgroups, and was strongly associated with higher odds of past or current CBD product use. Compared to participants living in places without legal marijuana, a greater proportion of participants in places with legal marijuana also currently used CBD products. These findings suggest that individuals who use marijuana are more amenable to CBD products, which may be because they have greater knowledge related to CBD and/or are more comfortable with the legal, regulatory, and medical gray area currently occupied by marijuana and CBD products.[9,18] Indeed, while many participants reported that their physician was comfortable with their use of CBD products, physician recommendations were a small contributor to participants' impetus for initiating CBD product use and the majority of participants did not ask their physician for advice on how to use CBD products. Conversely, discomfort with this uncertainty is reflected by the concerns cited by those who never used CBD products, which mostly related to safety – medication interactions, lack of research, and lack of regulation.

Table 6. Reported Safety Profile of CBD of the n = 878 Participants who Currently Used CBD, n = 445 Reported Side Effects.

Side effect	Count of reported side effects	Percent reporting side effect
Sleepiness	230	51.7%
Insomnia	13	2.9%
Decreased appetite	26	5.8%
Diarrhea	16	3.6%
Lack of energy	38	8.5%
Poor quality sleep	10	2.2%
Dizziness	41	9.2%
Nausea	17	3.8%
Headache	26	5.8%
Sore throat	29	6.5%
Vomiting	1	0.2%
Anxiety	11	2.5%
Dry mouth	160	36.0%
Dry eyes	57	12.8%
Paranoia	9	2.0%
Altered mood	31	7.0%
Panic attack	5	1.1%
Disorientation	10	2.2%
Hallucinations	6	1.3%
Tremor	6	1.3%
Rashes	2	0.4%
Increased heart rate	17	3.8%
Other	32	7.2%

This table displays the percent of participants reporting each side effect.

Most participants who discontinued CBD products stopped within 6 months of initiating use, most commonly because of lack of effect and expense. As the evidence around whether CBD is an effective analgesic remains preliminary, discontinuation may be affected by several factors. As with other therapies for FM, it is possible that CBD only works in a subset of participants.[30] This discontinuation may also be due to inaccurate labeling, as many CBD products are known to have less CBD than the amount claimed on the label.[9,26] It is also possible that the doses seen in positive clinical trials with CBD (eg, 100–900 mg orally for anxiety) may be cost-prohibitive and resulted in ineffective sub-therapeutic dosing, especially given that 30.1% of individuals in the current study were unable to work and 42.1% made < $50,000/year. While there is some observational evidence suggesting that lower doses of CBD (eg, 15–75 mg) may positively affect sleep, anxiety, and pain,[12,45] more rigorous studies are needed to verify these results.

Three-quarters of those currently using CBD products had done so for >6 months. Combined with the modest improvements reported across various symptom domains (eg, pain, mood, and sleep), these results are relatively similar to outcomes from other medications for FM, ie, for some there is no benefit (resulting in discontinuation) while others receive partial rather than complete symptom relief.[15,29] These results are also consistent with those from a large cross-sectional survey of individuals using CBD products, in which most used CBD products for multiple symptoms and reported partial symptom relief.[19] It is possible that part or all of the benefit could be attributable a significant placebo effect associated with expectations enhanced by aggressive CBD product marketing, much of which focuses on pain-related symptoms (eg, anxiety, sleep, pain). In

addition, one-third of participants using CBD products also reported past-year medical cannabis use and 20.2% reported using CBD products with >0.3% THC, so the reported benefits may be due to synergism between CBD, THC, and other cannabis plant components (eg, minor cannabinoids, terpenes) rather than CBD alone.[40] This finding is supported by a recent clinical trial in FM showing that a single inhalation of cannabis with CBD+THC resulted in greater pain relief and experimental pain responses than placebo, while CBD-dominant cannabis did not.[48] However, a growing body of preclinical and clinical research suggests that CBD may have actual therapeutic effects on anxiety,[4,20,21,34,36,57] sleep,[13,14] inflammation,[35,38] and pain,[24,37] due in part to CBDs interactions with the serotonergic system (via $5HT_{1A}$),[22,42] endocannabinoid system (cannabinoid receptor 1 antagonist and allosteric modulator),[33] and the TRPV1 receptor[11,22] – systems that are involved in pain and mood regulation.

Participants who discontinued CBD products typically stopped because it did not work or was too expensive rather than due to negative side effects. Although a very small proportion of participants did report hallucinations, vomiting, panic attacks, and paranoia, the side of effects reported for CBD products were typically minor, which generally aligns with CBD's reported safety profile[32] and also contributes to our understanding of why participants may prefer CBD over THC-containing cannabis or other medications – such as duloxetine, milnacipran, pregabalin - as they can carry more significant side effect burdens.[29] However, CBD is not without risk, and given the its widespread use further studies are needed to understand drug-drug interactions and other CBD-related safety issues. Given the lack of regulation for CBD products,[9] it is possible that the reported serious negative side effects (eg, vomiting, hallucinations) were due to THC or contaminants, such as synthetic cannabinoids or pesticides or other adulterants.[39] As FM is often characterized by generalized sensory hypersensitivity,[16] participants may also have a higher risk of negative side effects from CBD than the general public, although this latter hypothesis remains to be tested.

Limitations

Our study was limited in several ways. First, our cross-sectional design and questions about past behaviors and reasoning make our results subject to recall bias, and prevent us from accurately examining symptom changes over time. Second, given the widespread popularity of CBD, it is possible that reported perceptions of CBD product effectiveness are colored by expectancy biases. Third, because we do not know the number or characteristics of people who did not take the survey versus those who completed it, our findings may be influenced by selection bias. While our attrition analyses suggest that those who did not complete the survey were demographically quite similar to those who did not, those in the attrition sample had significantly less clinical burden. Fourth, while FM affects roughly twice as many women as men,[16] our study population was >90% women. This reflects a potential issue with generalizability, especially since men use cannabis more frequently than women [17,27] and thus might also be more likely to use CBD products. Fifth, we did not examine the effect of dosing (quantity or administration route) and frequency of use on perceived therapeutic effects, so we are unsure how these perceived effects related to quantities of CBD consumed. Given that the current CBD and pain clinical trials literature currently only includes unstandardized transdermal products,[37,56] future studies should better characterize the relative effects of different administration routes and dosing patterns on perceived CBD product benefits. Sixth, our survey was conducted during the first months of lockdown due to the COVID-19 pandemic, which may have influenced use of and perceptions towards CBD given the stress and disruption associated with this dramatic change. Future studies are needed to understand how the pandemic affected CBD product use among people with FM.

Strengths

Our study also had several strengths. Our large study population had a high survey completion rate (~80%) with representation from all 50 states as well as outside the US. To our knowledge, this was one of the first studies to characterize rationale for and patterns of CBD product use among people with FM, which is a common and often debilitating pain condition that is difficult to treat. We characterized our population well through use of validated measures of FM-related symptoms. Further, rather than simply assessing use patterns and self-reported outcomes from people who currently use CBD products, we included those who never used CBD products and those who had discontinued CBD products, providing a better sense of the proportion of individuals who find CBD products to be useful. These data are timely given CBD's growing popularity and that it has been minimally examined as a therapeutic option for FM, demonstrating the need for more rigorous investigations of CBD for FM symptoms.

Conclusions

The majority of participants in our large, online survey reported past or current use of CBD products, citing inadequate symptom relief as their main reason for trying it. The main concern of those who had not tried CBD products was safety. Many participants indicated that CBD products were helpful for a broad array of symptoms associated with FM and chronic pain, including pain, anxiety, and sleep. Our results highlight the importance of continued research – both longitudinal cohorts and clinical trials – to better understand CBD's therapeutic effects in FM and chronic pain, as well as the need for a stronger regulatory apparatus to ensure consumer safety.

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References

1. Administration USFaD. Warning Letters and Test Results for Cannabidiol-Related Products. 2019. Available at: https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products Accessed April 15, 2020

2. Bair MJ, Krebs EE: Fibromyalgia. Ann Intern Med 172: ITC33-ITC48, 2020

3. Bennett RM, Jones J, Turk DC, Russell IJ, Matallana L: An internet survey of 2,596 people with fibromyalgia. BMC Musculoskelet Disord 8:27, 2007

4. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schroder N, Nardi AE, Martin-Santos R, Hallak JE, Zuardi AW, Crippa JA: Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology 36:1219-1226, 2011

5. Boehnke KF: Pain management: Assembling a tool kit, building a life. JAMA 320:2201-2202, 2018

6. Boehnke KF, Gangopadhyay S, Clauw DJ, Haffajee RL: Qualifying conditions of medical cannabis license holders in the United States. Health Aff (Millwood) 38:295-302, 2019

7. Boehnke KF, Scott JR, Litinas E, Sisley S, Clauw DJ, Goesling J, Williams DA: Cannabis use preferences and decision-making among a cross-sectional cohort of medical cannabis patients with chronic pain. J Pain 20:1362-1372, 2019

8. Boehnke KF, Scott JR, Litinas E, Sisley S, Williams DA, Clauw DJ: Pills to pot: Observational analyses of cannabis substitution among medical cannabis users with chronic pain. J Pain 20:830-841, 2019

9. Bonn-Miller MO, Loflin MJE, Thomas BF, Marcu JP, Hyke T, Vandrey R: Labeling accuracy of cannabidiol extracts sold online. JAMA 318:1708-1709, 2017

10. Brenan M. 14% of Americans Say They Use CBD Products. 2019. Available at: https://news.gallup.com/poll/263147/americans-say-cbd-products.aspx Accessed April 21, 2020

11. Campos AC, Moreira FA, Gomes FV, Del Bel EA, Guimaraes FS: Multiple mechanisms involved in the large-spectrum therapeutic potential of cannabidiol in psychiatric disorders. Philos Trans R Soc Lond B Biol Sci 367:3364-3378, 2012

12. Capano A, Weaver R, Burkman E: Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. Postgrad Med 132:56-61, 2019

13. Carlini EA, Cunha JM: Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol 21:417S-427S, 1981

14. Chagas MH, Eckeli AL, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira ET, Camilo MR, Bergamaschi MM, Schenck CH, Hallak JE, Tumas V, Crippa JA: Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: A case series. J Clin Pharm Ther 39:564-566, 2014

15. Clauw DJ: Pain management: Fibromyalgia drugs are 'as good as it gets' in chronic pain. Nat Rev Rheumatol 6:439-440, 2010

16. Clauw DJ: Fibromyalgia: A clinical review. JAMA 311:1547-1555, 2014

17. Compton WM, Han B, Jones CM, Blanco C, Hughes A: Marijuana use and use disorders in adults in the USA, 2002–14: Analysis of annual cross-sectional surveys. The Lancet Psychiatry 3:954-964, 2016

18. Corroon J, MacKay D, Dolphin W. Labeling of cannabidiol products: A public health perspective. Cannabis and Cannabinoid Research. 2020

19. Corroon J, Phillips JA: A cross-sectional study of cannabidiol users. Cannabis Cannabinoid Res 3:152-161, 2018

20. Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simoes MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, Santos Filho A, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JE: Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. J Psychopharmacol 25:121-130, 2011

21. de Faria SM, de Morais Fabricio D, Tumas V, Castro PC, Ponti MA, Hallak JE, Zuardi AW, Crippa JAS, Chagas MHN: Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. J Psychopharmacol 34:189-196, 2020

22. De Gregorio D, McLaughlin RJ, Posa L, Ochoa-Sanchez R, Enns J, Lopez-Canul M, Aboud M, Maione S, Comai S, Gobbi G: Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. Pain 160:136-150, 2019

23. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S: Cannabidiol in Dravet syndrome study G. trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 376:2011-2020, 2017

24. Dixon HX, Benjamin DC, Meng T, Yujiang F: The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. Curr Pharmaceut Biotechnol 20:1-13, 2019

25. Foundation A. Patients Tell Us About CBD Use. 2019. Available at: http://blog.arthritis.org/news/patients-tell-us-cbd-use/ Accessed June 5, 2020

26. Gurley BJ, Murphy TP, Gul W, Walker LA, ElSohly M: Content versus label claims in cannabidiol (CBD)-containing products obtained from commercial outlets in the state of Mississippi. J Diet Suppl, 2020. 1-9

27. Han B, Compton WM, Blanco C, Jones CM: Trends in and correlates of medical marijuana use among adults in the United States. Drug Alcohol Depend 186:120-129, 2018

28. Hauser W, Jung E, Erbsloh-Moller B, Gesmann M, Kuhn-Becker H, Petermann F, Langhorst J, Thoma R, Weiss T,

Supplementary data

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Wolfe F, Winkelmann A: The German fibromyalgia consumer reports - a cross-sectional survey. BMC Musculoskelet Disord 13:74, 2012

29. Hauser W, Petzke F, Sommer C: Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 11:505-521, 2010

30. Hauser W, Walitt B, Fitzcharles MA, Sommer C: Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther 16:201, 2014

31. Hurd YL: Leading the next CBD wave-safety and efficacy. JAMA Psychiatry 77:341-342, 2020

32. Iffland K, Grotenhermen F: An update on safety and side effects of cannabidiol: A review of clinical data and relevant animal studies. Cannabis Cannabinoid Res 2:139-154, 2017

33. Laprairie RB, Bagher AM, Kelly ME, Denovan-Wright EM: Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br J Pharmacol 172:4790-4805, 2015

34. Linares IM, Zuardi AW, Pereira LC, Queiroz RH, Mechoulam R, Guimaraes FS, Crippa JA: Cannabidiol presents an inverted U-shaped dose-response curve in a simulated public speaking test. Braz J Psychiatry 41:9-14, 2019

35. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M: The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. Proc Natl Acad Sci U S A. 97:9561-9566, 2000

36. Masataka N: Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. Front Psychol 10:2466, 2019

37. Nitecka-Buchta A, Nowak-Wachol A, Wachol K, Walczynska-Dragon K, Olczyk P, Batoryna O, Kempa W, Baron S: Myorelaxant effect of transdermal cannabidiol application in patients with TMD: A randomized, double-blind trial. J Clin Med 8, 2019

38. Philpott HT, O'Brien M, McDougall JJ: Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. Pain 158:2442-2451, 2017

39. Poklis JL, Mulder HA, Peace MR: The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids. Forensic Sci Int 294:e25-e27, 2019

40. Russo EB: Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 163:1344-1364, 2011

41. Russo EB: Cannabidiol claims and misconceptions. Trends Pharmacol Sci 38:198-201, 2017

42. Russo EB, Burnett A, Hall B, Parker KK: Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res 30:1037-1043, 2005

43. Schrepf A, Moser S, Harte SE, Basu N, Kaplan C, Kolarik E, Tsodikov A, Brummett CM, Clauw DJ: Top down or bottom up? An observational investigation of improvement in fibromyalgia symptoms following hip and knee replacement. Rheumatology (Oxford) 59:594-602, 2019

44. Schrepf A, Williams DA, Gallop R, Naliboff BD, Basu N, Kaplan C, Harper DE, Landis JR, Clemens JQ, Strachan E, Griffith JW, Afari N, Hassett A, Pontari MA, Clauw DJ, Harte SE, Network MR: Sensory sensitivity and symptom severity represent unique dimensions of chronic pain: a MAPP Research Network study. Pain 159:2002-2011, 2018

45. Shannon S, Lewis N, Lee H, Hughes S: Cannabidiol in anxiety and sleep: A large case series. Perm J 23:18-041, 2019

46. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, Murnion B, Farrell M, Weier M, Degenhardt L: Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: A systematic review and meta-analysis of controlled and observational studies. Pain 159:1932-1954, 2018

47. Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, Lyons PD, Taylor A, Roberts C, Sommerville K, Group GS: Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 391:1085-1096, 2018

48. van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M: An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. Pain 160:860-869, 2019

49. Warren JW, Clauw DJ: Functional somatic syndromes: Sensitivities and specificities of self-reports of physician diagnosis. Psychosom Med 74:891-895, 2012

50. Warren JW, Clauw DJ, Langenberg P: Prognostic factors for recent-onset interstitial cystitis/painful bladder syndrome. BJU Int 111:E92-E97, 2013

51. Warren JW, Howard FM, Cross RK, Good JL, Weissman MM, Wesselmann U, Langenberg P, Greenberg P, Clauw DJ: Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. Urology 73:52-57, 2009

52. Williams DA: Phenotypic features of central sensitization. J Appl Biobehav Res 23:e12135, 2018

53. Williams DA, Schilling S: Advances in the assessment of fibromyalgia. Rheum Dis Clin North Am 35:339-357, 2009

54. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Hauser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB: Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 38:1113-1122, 2011

55. Wolfe F, Walitt BT, Katz RS, Lee YC, Michaud KD, Hauser W: Longitudinal patterns of analgesic and central acting drug use and associated effectiveness in fibromyalgia. Eur J Pain 17:581-586, 2013

56. Xu D, Cullen B, Tang M, Fang Y: The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral neuropathy of the lower extremities. Curr Pharmaceut Biotechnol 21:390-402, 2019

57. Zuardi AW, Rodrigues NP, Silva AL, Bernardo SA, Hallak JEC, Guimaraes FS, Crippa JAS: Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. Front Pharmacol 8:259, 2017