



Cannabidiol (CBD) Consumption and Perceived Impact on Extrahepatic Symptoms in Patients with Autoimmune Hepatitis

Karan Mathur¹ · Vahin Vuppalachchi¹ · Kayla Gelow¹ · Raj Vuppalachchi¹ · Craig Lammert¹

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Abstract

Background and Aims Utilization and safety of cannabidiol (CBD) in patients with autoimmune hepatitis (AIH) are currently unknown. We aimed to identify the frequency of CBD use, impact on symptoms, and safety profile.

Methods An invitation to complete a CBD-specific questionnaire was posted every other day to well-established autoimmune hepatitis Facebook communities (combined membership of 2600 individuals) during a 10-day study period. Age ≥ 18 years and an AIH diagnosis by a physician were the eligibility criteria for participation in the survey.

Results In total, 371 AIH patients (median age 49 years, 32% reported advanced fibrosis) completed the questionnaire. Respondents were 91% women, 89% Caucasian, and 89% from North America. Ninety-three (25%) respondents were ever CBD users, with 55 of them (15% of the survey responders) identified as current users. Among ever users, 45.7% reported their treating doctors were aware of their CBD use. The most common reason cited for CBD use was pain (68%), poor sleep (62%), and fatigue (38%). Most respondents using CBD for these symptoms reported a significant improvement in pain (82%), sleep (87%), and fatigue (61%). In ever CBD users, 17.3% were able to stop a prescription medication because of CBD use: pain medication (47%), immunosuppression (24%), and sleep aids (12%). Side effects attributed to CBD use were reported in 3% of CBD users, yet there were no reported emergency department visits or hospitalizations.

Conclusion CBD use was not uncommon in patients with AIH, and its use was associated with reports of improvement in extrahepatic symptoms.

Keywords AIH · CBD · Fatigue · Pain

Introduction

Autoimmune hepatitis (AIH) is a chronic liver disorder in which clinical presentation can vary widely from non-specific extrahepatic symptoms to fulminant hepatic failure [1]. Immunosuppressive therapy is the mainstay of treatment for AIH [2] and has been associated with improvement in symptoms, liver biochemistries, and histologic inflammation [3]. Unfortunately, impairment of emotional and mental health is prevalent in AIH and can diminish the health-related quality

of life in these patients [4, 5]. The etiology of this phenomenon remains unclear, yet may be linked to common AIH symptoms such as pain, fatigue, and sleep disturbances [6, 7].

Complementary and alternative medical strategies have become a popular approach for patients with chronic diseases [8] and often are utilized to target pain, anxiety, and depression [9]. Cannabidiol (CBD), one of the more than 110 different cannabinoids that have been isolated by researchers from Cannabis Sativa plant, is more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the “high”) that comes from tetrahydrocannabinol (THC), the psychoactive cannabinoid. CBD has received lot of recent attention after Food & Drug Administration’s (FDA) approval of purified CBD, Epidiolex, as treatment for two rare forms of epilepsy [10]. Utilization of CBD outside this indication for a variety of symptoms such as pain, glaucoma, anxiety has had mixed reviews and is not recognized by the FDA as an ailment

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✉ Craig Lammert
clammert@iu.edu

¹ Division of Gastroenterology and Hepatology, Department of Medicine, Indiana University School of Medicine, 702 Rotary Circle, Suite 225, Indianapolis, IN 46202, USA

that CBD can treat [11, 12]. Furthermore, there is a shift in legal status after the 2018 Farm Bill allowing for expanded cultivation of industrial hemp and permission for the transfer of hemp-derived products across state lines for commercial or other purposes. Removal of hemp-derived products from Schedule 1 status has led to an explosion of CBD-related products to be available legally in some states. However, adding CBD, regardless of its extraction source, to food, beverages, and dietary supplements, is currently not permitted by the FDA.

Research in a rare disease is challenging due to limited access to patients. However, patients with rare disease are increasingly colocated virtually online through social media outlets such as Facebook, Instagram or through traditional Web sites that promote peer-to-peer connections (www.patientslikeme.com) or nonprofit organizations dedicated to their disease [13]. Our group in the past has successfully leveraged social media to conduct research in online cohorts of autoimmune hepatitis by deploying surveys that even included confirmation of diagnosis by procuring medical records and biosamples [14, 15]. In the current study, we aimed to identify the frequency of CBD use in AIH patients and assess the impact on symptoms and safety profile using two large AIH-specific social media groups.

Methods

We conducted a cross-sectional survey study using AIH social media communities on Facebook (www.facebook.com): Autoimmune Hepatitis Research Network and Autoimmune Hepatitis Association. We have previously described this approach for collecting patient-reported disease attributes [16] as well as recruitment to an ongoing AIH biorepository at Indiana University [15]. At the time of the survey, the combined membership of these online communities was over 2600. An online invitation to participate in a research study collecting information on CBD use was posted on these groups every other day for 10 days (October 2018). The survey included a link directed to an IRB-approved Redcap database for data collection.

Survey Tool

The questionnaire was composed of 33 questions (Supplementary Table 1) assessing participant demographics, AIH disease characteristics, history of and current CBD use, and adverse effects. Participants were required to be aged ≥ 18 years and have previously received a diagnosis of AIH from a medical doctor.

Statistical Analysis

Survey data were analyzed using SPSS 25 software. Continuous variables were summarized as median and the 25th and 75th percentiles, and *p* values were obtained with the Wilcoxon rank-sum test.

Results

A total of 371 participants with AIH completed the questionnaire during the study period. The group was predominantly female (91.4%) and Caucasian (88.9%) and had a median age of 49 years at survey completion (Table 1). The median age of AIH diagnosis was 42 years. Of the 319 patients who reported having liver biopsy completed, 34.5% had early fibrosis, 32.1% had advanced fibrosis, and 34% did not know the stage of fibrosis reported on most recent biopsy.

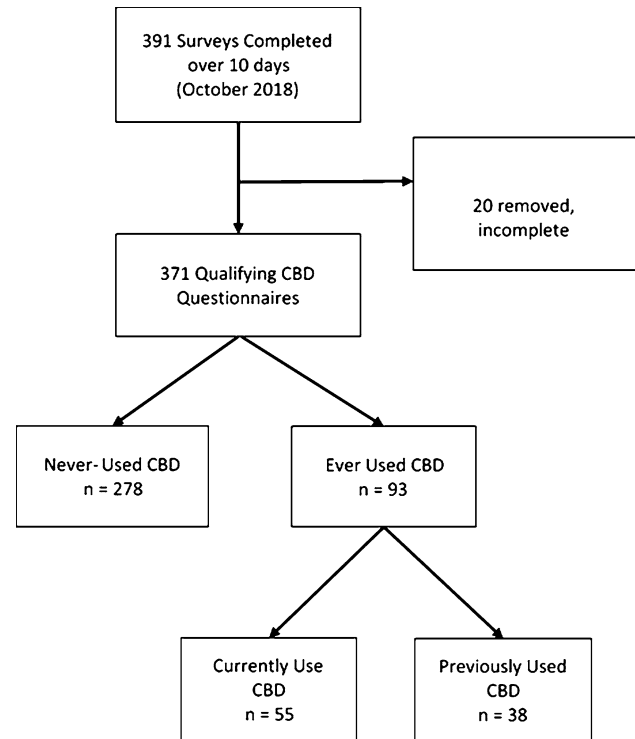
Immunosuppressant Therapy for AIH

At the time of the survey, 88.1% of patients were on immunosuppressive medications: 35.2% on prednisone, 12.4% on budesonide, 52.3% on azathioprine (AZA), 6.5% on 6-mercaptopurine (6-MP), 13.2% on mycophenolate mofetil (MMF), 4.6% on tacrolimus, 0.8% on sirolimus, 1.1% on cyclosporine (CSA), and 12.4% on ursodeoxycholic acid (UDCA). In total, 198 participants (53.4%) were on at least on one immunosuppressant, and 129 (34.8%) were on more than one. There were 118 participants (31.8%) on two immunosuppressants, 10 (2.7%) on three, and 1 (0.3%) on four. Among participants taking more than two immunosuppressants, 99 (76.7%) were taking a combination of steroid and a thiopurine (AZA or 6-MP), 25 (19.3%) a combination of steroid and MMF. Only 12 patients were taking more than one immunosuppressant beyond steroids: 4 (33.3%) on tacrolimus and MMF, 4 (33.3%) on tacrolimus and AZA, 1 (8.3%) tacrolimus and AZA and sirolimus, 2 (16.7%) CSA and AZA, and 1 (8.3%) CSA and MMF.

There were 44 participants (11.9%) not on immunosuppression at the time of the survey, of these, and 35 (79.5%) had been treated previously with immunosuppression. Among all participants, former immunosuppression regimens had included prednisone (224, 60.4%), budesonide (56, 15.1%), AZA (117, 31.5%), 6-MP 14 (3.8%), MMF 32 (8.6%), tacrolimus 10 (2.7%), sirolimus 2 (0.5%), and CSA 9 (2.4%).

Table 1 Demographics and selected characteristics of AIH patients who participated in the current survey

	AIH participants (n = 371)
Age at survey completion (years)	49 (38, 59)
Age at AIH diagnosis (years)	42 (30, 52.25)
Race	
Caucasian	88.9%
Hispanic	3.2%
Black	2.2%
Multiple	2.4%
Other	2.4%
Gender, % female	91.4%
Continent	
North America	81.4%
Europe	14.3%
Australia	2.2%
Asia	0.5%
South America	0.8%
North America	
USA	76.8%
Canada	4.6%
Gross household income/year	
< \$20,000	9.4%
\$20,001–\$50,000	27.0%
\$50,001–\$100,000	32.6%
\$100,001–\$150,000	18.6%
> \$150,000	11.4%
Level of education	
GED	13.7%
Bachelor's degree	24.5%
Graduate degree	19.0%
Some college	32.1%
Technical school	8.1%
Some high school	1.6%
Fibrosis on biopsy	
F1	18.9%
F2	15.8%
F3	19.7%
F4	12.8%
Don't know	28.6%
No biopsy completed	3.5%
Current medication	
Prednisone	35.3%
Budesonide	12.4%
6-Mercaptopurine	6.5%
Azathioprine	52.3%
Mycophenolate mofetil	13.2%
Tacrolimus	4.6%
Cyclosporine	1.1%
Sirolimus	0.8%
Ursodeoxycholic acid	12.4%
None	11.9%

**Fig. 1** Survey completion and CBD use among AIH patients

CBD Therapy

In total, 93 (25.1%) patients reported they had ever used CBD for the treatment of AIH or its perceived symptoms (Fig. 1). Ever CBD users were similar to never CBD users; however, ever users tended to be female ($p < 0.09$) and have lower household incomes ($p < 0.07$) (Table 2). Ever CBD users were also more likely not to be taking any other therapy for the treatment of AIH (12.9% vs. 6%, $p = 0.035$). In total, 278 (74.9%) participants reported they never used CBD because of high cost (18.3%) or they never heard of it (17.6%), but also worried about positive drug screening (10.4%), local laws (9.7%), side effects (4.7%), effectiveness (3.2%), and moral or religious issues (3.2%). Knowledge about CBD use was attributed to information from social media (78.5%), family/friends (69.9%), other patients (24.7%), doctors (20.4%), and other media (19.4%).

Among ever CBD users, 55 (59%) were current users for the treatment of AIH and 38 (41%) were prior users. Among ever users, 45.7% reported their treating doctors were aware of their CBD use at the time of use. The most frequent AIH symptoms treated by participants with CBD were poor sleep (66.7%), pain (66.7%), fatigue (44.1%), “liver inflammation” (29%), and itch (10.8%). Survey participants reported CBD used resulted in significant improvement in sleep (54/59, 93%), pain (55/63, 87.3%), fatigue (25/38, 65.8%), “liver

Table 2 Demographics and selected characteristics of AIH patients according to CBD ever versus never use

	CBD ever	CBD never	<i>p</i>
Age at survey completion, median (Q1, Q3)	47 (37.5, 58)	50 (38, 60)	0.21
Age at AIH diagnosis, median (Q1, Q3)	42 (30, 50)	42 (30, 53)	0.78
Race			
Caucasian	87.10%	89.90%	0.66
Hispanic	2.20%	3.60%	
Black	2.20%	2.20%	
Gender			
Female	95.70%	90%	0.09
Male	4.30%	10%	
Continent			
North America	81%	83.50%	0.45
Europe	18.30%	13.10%	
Australia	1.10%	2.60%	
South America	0.00%	1.10%	
North America			
USA	77.40%	76.60%	0.76
Canada	3.20%	5%	
Gross household income/year			
< \$20,000	9.70%	9.90%	0.07
\$20,001–\$50,000	36.50%	24.50%	
\$50,001–\$100,000	36.50%	32.10%	
\$100,001–\$150,000	3.33%	21.50%	
> \$150,000	8.60%	12.40%	
Level of education			
GED	11.80%	14.40%	0.31
Bachelor’s degree	21.50%	25.50%	
Graduate degree	14%	21.20%	
Some college	40.10%	29.60%	
Technical school	9.70%	7.70%	
Some high school	2.20%	1.50%	
Fibrosis on biopsy			
F1	18.30%	19.40%	0.38
F2	19.40%	14.70%	
F3	24.70%	18%	
F4	11.80%	13.20%	
Current medical treatment for AIH			
Prednisone	39.80%	33.80%	0.3
Budesonide	12.90%	12.20%	0.87
6-Mercaptopurine	7.50%	6.10%	0.63
Azathioprine	41.90%	55.80%	0.02
Mycophenolate mofetil	14.00%	12.90%	0.8
Tacrolimus	4%	5.40%	0.67
None	12.90%	6.10%	0.035

inflammation” (27/32, 84.4%), and itch (7/8, 87.5%). Seventeen (18.3%) ever CBD users reported they were able to stop or reduce a prescription medication because of CBD use. Drug classes reduced or stopped included pain (11/17; 5 narcotics, 4 NSAIDs, two other), immunosuppressants (4/17; 3 steroids, 1 AZA), anxiolytics (3/17; 2 lorazepam,

one diazepam), antidepressants (1/17; sertraline), and sedatives (1/17; zolpidem).

CBD was administered most frequently via sublingual drops (55.9%), oral capsule (32.3%), inhalation (28%), and topically (12.9%). Only a minority of participants reported characteristics of CBD dose (29%). Among

reported dosing information, the median dose was 20 mg (5 mg, 200 mg), the median daily frequency was 1 (1, 2), and total daily dose was 25.5 mg (4.8 mg, 87.5 mg). The median duration of CBD use among current CBD users was 3.5 months (1, 6) and was significantly more than prior CBD users (1 month (1, 3), $p = 0.007$). The most common cause for stopping CBD was cost (50%), worry about positive drug test (10.5%), side effects (10.5%), ineffective (7.9%), the doctor advised against CBD (7.9%), and change in the law (7.1%). There was no difference in the various demographics and medication usage between ever CBD users in either of the histology groups (Table 3).

Serious side effects attributed to CBD therapy were reported by three participants (3.2%) and included: hunger (1), dry mouth (1), red eyes (1), euphoria (1), and itchiness (1). Two participants reported side effects were significant enough to seek their doctor's advice, but there were no emergency room visits or hospitalizations reported.

Discussion

CBD has been used to treat various symptoms in the gastroenterology field with variable outcomes [17–20], yet its use among patients with chronic liver disease remains unknown [21]. In the current study, we observed that 25% of study participants reported ever CBD use directed at the most frequent AIH-related extrahepatic symptoms: pain, sleep, and fatigue. Females and those with lower household incomes were more likely to have used CBD, yet many patients reported their treating doctor was unaware of their use. A majority of ever CBD users saw significant improvement in targeted symptoms with CBD use and very few experienced severe side effects.

The FDA, when supported by rigorous scientific research, has endorsed medical use of marijuana-derived products as drugs for the treatment of disease. Extrapolating the approval of a purified CBD derived from marijuana for a seizure disorder to hemp-derived use of CBD to treat a variety of symptoms can be serious, unproven, risky, and dangerous. Furthermore, in the Epidiolex-treated patients in

Table 3 Demographics and selected characteristics of AIH patients stratified by fibrosis according to CBD ever versus never use

	Advanced fibrosis ($n = 119$)			Non-advanced ($n = 126$)		
	CBD ever $n = 34$	CBD never $n = 85$	p	CBD ever $n = 34$	CBD never $n = 92$	p
Age at survey completion (years)	47 (33, 59)	47 (35, 59)	0.48	50.5 (37, 59)	49.5 (37, 59)	0.99
Age at AIH diagnosis (years)	35.5 (25, 54)	43 (25, 54)	0.49	45 (32, 50)	42.5 (31, 52)	0.83
Race, % Caucasian	79.40%	87.10%	0.34	100%	92.40%	0.44
Gender, % female	97.10%	91.70%	0.44	94.10%	88%	0.26
Continent, % North American	79.40%	80%	0.8	82.40%	75%	0.35
Current medication						
Prednisone	41.20%	37.60%	0.84	38%	34.70%	0.83
Budesonide	8.80%	3.50%	0.35	23.50%	16.30%	0.44
6-MP	5.90%	8.80%	0.69	11.80%	2.20%	0.73
Azathioprine	41.20%	56.50%	0.1	44.10%	54.30%	0.32
Mycophenolate mofetil	17.60%	12.90%	0.57	5.90%	18.50%	0.09
Tacrolimus	8.80%	5.90%	0.69	5.90%	4.30%	0.01
Cyclosporine	2.90%	0.00%	0.29	0.00%	2.20%	0.39
Sirolimus	2.90%	0.00%	0.29	0.00%	2.20%	0.39
Ursodeoxycholic acid	26.50%	14.10%	0.12	20.60%	9.80%	0.13
None	10.60%	11.80%	1	20.60%	7.60%	0.05
Symptoms treated with CBD						
Poor sleep	67.60%	–	–	55.90%	–	0.45
Pain	64.70%	–	–	67.40%	–	1
Fatigue	35.30%	–	–	38.20%	–	1
Inflammation	38.10%	–	–	20.60%	–	0.18
Itch	11.80%	–	–	8.80%	–	1
Serious side effects	2.90%	–	–	2.90%	–	1
ER visits	0.00%	–	–	0.00%	–	1
Hospitalizations	0.00%	–	–	0.00%	–	1

the clinical trials, sleepiness, sedation, and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise and weakness, insomnia, sleep disorder, and poor quality sleep; and infections were reported. Therefore, the CBD use among the patients with AIH as evidenced by the survey respondents is concerning. The usage varied equally among the age groups and liver fibrosis staging suggesting no rationale or vulnerability of specific demographics or disease phenotype from illegal marketing. Depending on the percentage of THC in a product and frequency of use, a positive urine drug screen for cannabinoids is possible. This observation could pose a significant hindrance for patients undergoing liver transplant evaluation for end-stage liver disease associated with AIH.

CBD, a potent inhibitor of CYP3A4 and CYP2C19, can target a variety of channels and receptors including human TRP and voltage-gated channels, serotonin receptors 5-HT1A and 5-HT2A, and G-coupled protein and adenosine receptors [22]. Data on drug interactions in human subjects taking CBD are scarce; however, we hypothesize that there is risk of altered pharmacokinetics in CBD or concurrently administered drugs undergoing metabolism via these CYP systems. The steroid drug class and calcineurin inhibitors [30], metabolized via CYP3A4, are of significant concern given 177 patients (47.7%) of study respondents reported current use of either prednisone or budesonide and 21 patients (5.7%) reported use of either tacrolimus or cyclosporine. The relative infrequency that patients did not report CBD use to their treating doctors (45.7%) and product variability across manufacturers [23, 24], dose [21], and route [25] of administration could further expand this risk.

No published data encapsulate CBD use across populations, yet the frequency of CBD use reported in our study is similar to that observed among adults with liver disease in the USA using other complementary and alternative medicines [26]. Health-related quality of life in AIH is significantly reduced [27, 28]; thus, the use of CBD by patients to mitigate symptoms attributed to AIH outside the liver is not surprising. A majority of patients reported significant improvement in AIH-related indications for use (pain, poor sleep, fatigue, and itch) which included very few serious side effects. Other data about the improvement in these symptoms and safety profiles within other CBD-treated populations are unavailable, but our observations are congruent with a meta-analysis that assessed all cannabinoids for medical use [20].

We readily admit the possible limitation of patient-reported disease and CBD use data in this study. Historically, we have shown that AIH patients participating in similar research approaches exhibit excellent diagnosis agreement when compared to their medical records [15] as well as similar demographics and disease attributes [16]. However, we also believe there are tremendous benefits to

treating physicians and patients allowed by rapid recruitment and dissemination of research regarding emerging and popular healthcare trends [29]. Furthermore, the anonymity offered through social media may allow for unbiased answers for a sensitive topic such as CBD use. CBD has been recently showing up in everything from beauty creams and bath bombs to vape pens, seltzer, and snacks; thus, our survey may underestimate total CBD use among patients. Furthermore, attribution of all reported extrahepatic symptom improvement to CBD use in our study is inappropriate, as we did not collect other interventions or exposures (marijuana, other over the counter supplements, meditation, etc.) that may have been completed concurrently with CBD.

In summary, CBD use in our online cohort was common and associated with a significant improvement in AIH-related symptoms and side effects of immunosuppressant medications. The overall positive therapeutic benefits from this study as well as the observation of few serious side effects would be supportive of future trials (possibly with cannabinoids) aimed at improving health-related quality of life in AIH patients. Strict regulation of product formulation and dose and well as further examination of CBD pharmacokinetics would help alleviate safety concerns in patients taking a wide variety of pharmaceuticals.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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