ORIGINAL ARTICLE

Utilization and Impact of Complementary and Alternative Medicines in Symptomatic Autoimmune Hepatitis Patients

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Abstract

Background Complementary and alternative medicine (CAM) use has become increasingly common. It is also prevalent in patients with chronic liver disease, but the scope, depth, and safety of use is not well known.

Aims This study aimed to evaluate the prevalence and patterns of CAM use in autoimmune hepatitis (AIH) patients.

Methods Electronic invitation to complete a 22 item CAM-specific questionnaire was posted weekly to well-established AIH Facebook communities (combined membership of 4700 individuals) during a 6-week study period. Age ≥ 18 years and AIH diagnosis made by a treating physician were the eligibility criteria.

Results The prevalence of ever CAM use among participants was 56.4%, and nearly 42% used CAM after AIH diagnosis. Among those reporting CAM use after diagnosis, 53.7% (51/95) indicated CAM was used to mitigate AIH-related phenomenon, most often targeting liver inflammation/fibrosis (67.7%), fatigue (51%), joint pain (47.1%), and sleep issues (45.1%). Most frequent physical CAM strategies were exercise (49.5%) and yoga (34%), whereas most frequent consumable CAM included healthier eating (45.3%), cannabidiol preparations (45.3%), and probiotics (44.3%). Seventy-five percent reported that CAM improved AIH symptoms and no severe adverse events were reported.

Conclusions CAM use in AIH patients is prevalent, yet providers have historically failed to document their patient's CAM strategies. Beyond inherent drug-induced liver injury risk, drug-drug interactions remain a concern and could alter baseline immunosuppression levels in AIH. Despite a majority found CAM approaches that improved targeted symptoms, all were unable to alter the course of chronically prescribed medications by physicians.

Keywords Supplement · Complementary and alternative medicine · CAM · Autoimmune hepatitis · AIH

Introduction

Complementary and alternative medicine (CAM) products and strategies have increased in popularity across North America, Europe, and Australia [1–3]. CAM includes natural health products such as vitamins, homeopathic remedies, exercise, diet, mental health, and herbal medicines. In the United States, CAM use rates among the general population have risen from 32.3% in 2002 to 38% in 2007 [1] and more recent estimates have shown over 50% of patients requiring healthcare have used CAM either in conjunction with or separate from conventional healthcare [4].

CAM use is prevalent in patients with chronic liver disease (CLD) but is not well studied. For instance, CAM use among CLD patients in the United States (U.S.) has been observed in 41% compared to 33% of patients without CLD [1, 5]. Furthermore, CAM use among CLD patients has been reported higher outside the United States, as a Taiwanese study showed 66% of CLD used CAM during the past ten years [6, 7]. Concerningly, underlying chronic liver disease may increase risk of toxicity or adverse side effects of CAM. Altered drug metabolism [8], increased risk of drug-induced liver injury (DILI) [9], and concurrent medications often utilized in CLD patients are possible factors but are challenging to predict given a wide array of available products and often undisclosed CAM use [10].

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Despite the increase in CAM use, most physicians remain poorly educated about the variability and range of products and unaware of their own patient's CAM practices. Physicians do not routinely collect patient CAM history at office visits, and less than 23% disclose their CAM use when interviewed [11]. Inadequate CAM knowledge and physician ignorance of patient use can severely affect patients' health, as some CAM have well documented adverse side effects or interactions with prescription medication [5, 12, 13].

A rare chronic liver disease, autoimmune hepatitis (AIH), has been suggested to have increasing incidence and prevalence in several regions. Multiple therapeutic options are available for liver-specific inflammation observed in patients AIH, yet patients continue to suffer from poorly-controlled extrahepatic symptoms (i.e., fatigue, insomnia, anxiety, depression, and pain) [14]. We previously observed that 25% of AIH patients have used cannabidiol (CBD) to treat these symptoms [4], yet utilization of CAM outside CBD is unknown. We aimed to examine the overall use of CAM strategies among AIH patients using a large, well-established online cohort. We hypothesized that CAM use is prevalent in AIH patients and patterns of use can help identify unmet therapeutic needs in AIH patients and possible drug-drug interactions.

Methods

AIH Patients

A cross-sectional survey study using the Autoimmune Hepatitis Association (AIHA) Facebook communities (www.facebook.com) was conducted over six weeks (Fig. 1). The AIHA communities included a public community page and a member-only group. We previously described this approach for collecting patient-reported disease attributes [12] as well as recruitment to an ongoing AIH biorepository at Indiana University [8]. At the time of the study, the membership of a private AIHA community was over 2800 individuals. No membership numbers are associated with the public AIHA community group, yet the number of registered members to the AIHA was nearly 1900 at the time of the study. A digital invitation to complete a CAM survey was posted in each group weekly over the study duration (June-July 2020). The invitation included a hyperlink directed to an IRB-approved REDCap database for data collection.

CAM Survey Tool

The CAM questionnaire was composed of 22 questions (Supplementary Table 1) and collected participant
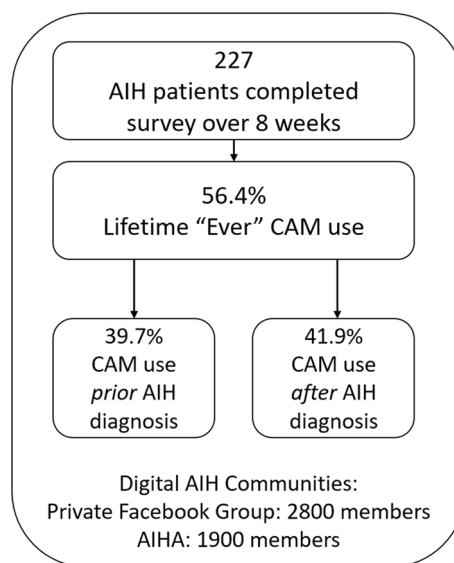

Fig. 1 CAM survey completion among AIH patients in online patient communities

demographics, AIH disease characteristics, CAM history and current use, and CAM-related adverse events. Categorical responses were multiple-choice, but also included few short answer responses (i.e., specific supplement utilized). CAM use was defined as use of at least one natural health product such as vitamins, homeopathic remedies, exercise, diet, mental health, and herbal medicines. Participants were required to be aged ≥ 18 years and previously were diagnosed with AIH by a physician.

Adverse events (AE) were defined by the Food and Drug Administration's (FDA) Code of Federal Regulations (CFR) Title 21 as any unfavorable or unintended symptom temporarily associated with the use of CAM [15]. Severe adverse events (SAE) were defined as an AE that resulted in one of the following: life-threatening, required hospitalization, or resulted in disability.

Statistical Analysis

We employed a logistic regression model (CI 95% and p-value < 0.05) for categorical variables, and the outcome was CAM use. Cofounders were sociodemographic (age, sex, educational level, country, race, and socioeconomic index). Continuous variables were summarized as means, and standard deviations and p values were obtained using the Student's T test. P values for discrete variables were obtained from the Chi-Square test. Adjusted Odd Ratios were obtained for each variable. Survey data were analyzed using SPSS 25 software.

Results

Patient Demographics and AIH History

A total of 227 AIH patients successfully completed the study questionnaire, and 56.4% reported ever using CAM. The majority of participants were female (92.9%) and Caucasian (85.2%). The mean age at survey completion was 50.1 years and the mean duration of AIH was 6.1 years. In the most recent liver biopsy, 23.5% of participants reported no fibrosis, 43.7% had early fibrosis (stage I/II), and 27.8% had advanced fibrosis (stage III/IV). Only 5.0% of participants reported never having a liver biopsy. Most (50.1%) reported current treatment of AIH with a thiopurine (azathioprine, 44.5%; 6-mercaptopurine: 5.7%), yet nearly half of participants also reported treatment with a corticosteroid (prednisone 37%, budesonide 14%). Many participants were employed (45.5%) and had a bachelor's degree (25.9%) with private medical insurance (65.0%) (Table 1).

Demographics of CAM Use

In total, 128 (56.4%) AIH patients reported ever using CAM (Table 1). There was no difference between groups ever/never using CAM according to demographics such as age, race, ethnicity or region. Furthermore, no AIH disease characteristics (duration, fibrosis level, current therapy) or type of insurance held were different across CAM use groups. However, participants that ever-used CAM were more often employed (46.9% vs 43.5%) or retired (20.3% vs 15.2%, p=0.026) as well as more likely to have a Bachelor's (28.9% vs 22.2%) or Graduate degree (28.9% vs 16.2%, p=0.012) compared to participants never using CAM.

Timing and Indication for CAM

Prior to the diagnosis of AIH, 90 (39.6%) participants reported CAM use for a variety of reasons: general health (61.1%), joint support (26.7%), immune support (18.9%), weight loss (17.8%), sedative (14.4%), gastrointestinal symptoms (14.4%), depression/anxiety (12.2%), body building (2.2%), sexual performance (1.1%), and other (7.8%). After the diagnosis of AIH, 95 (41.9%) cases reported CAM used for general health (38.6%), pain relief (25.5%), immune support (25%), depression/anxiety (15.9%), sedative (11.4%), energy booster (11.4%), gastrointestinal symptoms (6.8%), weight loss (4.5%), and other (13.6%). Among those with CAM use after AIH diagnosis, 51 (53.7%) indicated CAM use was directed at treating AIH-related phenomenon: 67.7% for liver-specific concerns (fibrosis/inflammation), 45.1% for sleep issues, 47.1% for joint pain, 51% for fatigue, 13.7% for itch, and 3.9% other (Table 2).

Specific CAM Use Among Participants

CAM use after AIH diagnosis was reported among 95 (41.9%) participants and the most frequent CAM strategies across all categories included exercise (49.5%), healthier eating (45.3%), and cannabidiol (CBD) preparations (45.3%) (Table 3). The most prevalent physical strategies included exercise (49.5%), yoga (34%), massage (26%), and chiropractic therapy (26%). Prevalent dietary modifications included healthier eating (45.3%), low carb diets (18.5%), vegetarian diets (12.3%). Prevalent consumable CAM included CBD preparations (45.3%), probiotics (44.3%), multivitamins (32.9%), melatonin (30.9%), vitamin D (29.8%), and milk thistle (21.6%). Among all CAM users after AIH diagnosis, 79% found at least one CAM strategy improved the targeted symptom or indication.

Among AIH patients using CAM to treat AIH-related phenomenon, liver concerns (fibrosis/inflammation) were the most common. Forty-one participants (41/51, 80.3%) most frequently utilized milk thistle, apple cider vinegar, multivitamins, ginger, turmeric, CBD, and a healthier diet to improve liver concerns. A majority (75%) stated that these CAM strategies relieved associated complaints. Fatigue (40/51, 78%) was treated with B-complex vitamins, meditation, and coffee (89% reported improvement). General pain (36/51, 70.6%) was treated with CBD and massage (85% reported improvement). Sleep disturbances (33/51, 64.7%) were treated with melatonin, yoga, and meditation (95% reported improvement). Finally, itch (10/51, 19.6%) was treated with over-the-counter diphenhydramine (53% reported improvement). No participants reported that CAM was able to reduce or eliminate their current doctor prescribed treatment regimens for any other these concerns.

Adverse Events Related to CAM

Only five participants reported an adverse outcome related to CAM use. Among these, AIH disease duration ranged from four to thirteen years, and current age ranged from 30 to 69 years old. All five participants were female. Stage of fibrosis included no fibrosis at the last biopsy to cirrhosis. Adverse events attributed to CBD preparations were reported by three participants (2.3%): hunger (1), dry mouth (1), red eyes (1), euphoria (1), and itchiness (1). Two participants reported side effects are significant enough to seek their physician's advice, but no emergency room visits, or hospitalizations were reported.

Table 1 Demographics and selected characteristics of AIH participants and CAM use cohorts

	AIH cases (N=227)	Ever used CAM (n=128)	Never used CAM (n=99)	p value*
CAM ever, %	56.40%	100%	0%	
Age of survey completion (years)	50.1 (13.3)	49.9 (13.1)	50.4 (13.5)	0.764
AIH disease duration (years)	6.1 (2.6)	43.2 (15.3)	45.1 (14.7)	0.368
Gender, % female	92.50%	94.50%	89.90%	0.189
Race				
Caucasian	88.60%	89.80%	87.80%	0.42
African-American	2.60%	1.60%	4.00%	
Multiple	1.80%	2.30%	1.00%	
Other	4.80%	7.00%	6.10%	
Ethnicity				
Hispanic	3.50%	3.10%	4%	0.92
Continent				
North America	84.10%	85.20%	82.80%	0.603
Europe	12.30%	12.50%	12.10%	
Australia	3.10%	2.30%	4.00%	
North America				
USA	81.40%	81.30%	81.80%	0.212
Canada	3.10%	3.90%	2.00%	
Gross household income/year				
<$20,000	7.90%	7.00%	9.10%	0.392
$20,001–$50,000	22.90%	21.90%	24.20%	
$50,001–$100,000	35.70%	32.80%	39.40%	
$100,001–$150,000	18.90%	19.50%	18.20%	
>$150,000	13.70%	18.00%	8.10%	
Employment				
Employed	45.40%	46.90%	43.40%	0.026
Retired	18.10%	20.30%	15.20%	
Unemployed	15.40%	13.30%	18.20%	
Part-Time	11.90%	7.00%	18.20%	
Self-Employed	9.30%	12.50%	5.10%	
Level of education				
Some college	29.10%	28.10%	30.30%	0.012
Bachelor''s degree	26%	28.90%	22.20%	
Graduate degree	23.30%	28.90%	16.20%	
GED	11.90%	6.30%	19.30%	
Technical school	6.10%	7.80%	11.10%	
Some high school	0.40%	0.00%	1.00%	
Medical insurance				
Private	64.80%	71.10%	56.60%	0.15
Medicaid	18.90%	15.60%	23.20%	
Medicare	11%	8.60%	14.10%	
Uninsured	5.30%	4.70%	6.10%	
Fibrosis on biopsy				
F0	23.30%	21.10%	26.30%	0.074
F1	16.30%	14.80%	18.20%	
F2	26.20%	32.80%	18.20%	
F3	15.40%	12.50%	19.20%	
F4	12.30%	13.30%	11.10%	
No biopsy completed	4.80%	5.50%	4.00%	

Table 1 (continued)

	AIH cases (N=227)	Ever used CAM (n=128)	Never used CAM (n=99)	p value*
Current immunosuppression				
Prednisone	37.00%	32.80%	42.40%	0.137
Budesonide (Entocort)	14%	14.10%	14.10%	0.986
Azathioprine (Imuran)—thiopurines	44.40%	58.6%	48.5%	0.13
6-Mercaptopurine (6MP)	5.70%	4.7%	7.1%	0.443
Mycophenolate mofetil (CellCept, Myfortic)	15.40%	12.5%	19.2%	0.166
Tacrolimus (Prograf)	3.10%	0.8%	6.1%	0.023
Naltrexone (Narcan)	3.04%	3.1%	0.0%	0.204
No medications	17.60%	23.3%	18.2%	0.106

*p value, comparison of ever used CAM versus never used CAM

Table 2 Demographics and selected characteristics of AIH participants to use CAM prior and after AIH diagnosis

CAM category	CAM study cohort (N=227)	
	CAM use prior AIH diagnosis (N=90)	CAM use after AIH diagnosis (N=95)
		CAM use not targeting AIH symptoms (N=44)
Body building	2 (2.2%)	0
Depression/anxiety	11 (12.2%)	7 (15.9%)
Energy booster	13 (14.4%)	5 (11.4%)
Gastrointestinal symptoms	13 (14.4%)	3 (6.8%)
General health/well being	55 (61.1%)	17 (38.6%%)
Immune support	17 (18.9%)	11 (25%)
Joint support/arthritis	24 (26.7%)	5 (11.4%)
Pain relief	13 (14.4%)	9 (25.5%)
Sedative/sleep aid	26 (28.8%)	5 (11.4%)
Sexual performance	1 (1.1%)	0
Weight loss	16 (17.8%)	2 (4.5%)
Other	7 (7.8%)	6 (13.6%)
		CAM use targeting AIH symptoms (N=51)
Liver concerns (inflammation, fibrosis)		33 (67.7%)
Sleep issues		23 (45.1%)
Joint pain		24 (47.1%)
Fatigue		26 (51%)
Itch		7 (13.7%)
Other		2 (3.9%)

Discussion

CAM use continues to increase in developed countries [1–3]. More recent estimates have shown more than 50% of patients requiring healthcare have used CAM either in conjunction with or separate from conventional healthcare [4]. In this first ever detailed assessment of CAM use in AIH patients, we observed that over half (56%) of all participants reported ever using CAM, and 42% had used CAM after AIH diagnosis. Employed or retired AIH patients with advanced educational degrees were more likely to use CAM compared to those unemployed or part-time workers with a GED or technical training. The most frequent AIH-related phenomenon targeted by consumable and physical CAM was liver fibrosis/inflammation, fatigue, joint pain, and sleep issues. The most common consumable CAM agents included CBD preparations, healthier diets, physical activity, probiotics, multivitamins, melatonin, and milk thistle. The most frequent physical CAM strategies included exercise, yoga, and acupuncture. Among all AIH patients using CAM for any indication after AIH

Table 3 Prevalence of CAM use among AIH participants prior and after diagnosis

	Prior AIH diagnosis ($N=90$) (%)	After AIH diagnosis ($N=95$) (%)
Vitamins and minerals		
CBD oil	12.20	45.30
Probiotics	13.30	44.30
Multivitamins	35.50	32.90
Melatonin	36.60	30.90
Vitamin D	14.40	29.80
Milk thistle	5.50	21.60
Calcium	11.10	12.30
Apple cider vinegar	0	12.30
Vitamin C	12.20	8.20
Ginger	1.10	6.20
B-Complex	5.50	4.40
Dietary modifications		
Healthier eating	51.10	45.30
Low carb diet	4.40	18.50
Vegetarian diet	13.30	12.30
Keto diet	8.90	11.30
Paleo diet	5.50	10.30
Vegan diet	4.40	8.20
Juicing	15.50	8.20
Detoxification	4.40	7.20
Essential oils	23.30	20.60
Physical treatment		
Exercise	82.20	49.50
Massage	53.30	26.00
Yoga	37.80	34.00
Chiropractic	40.00	26.80
Acupuncture	26.70	20.60
Professional physical therapy	36.70	12.40
Tai Chi	8.90	5.10
Mental therapy		
Meditation	28.90	27.80
Counseling	21.10	17.50
Spiritual healing	3.30	7.20
Any CAM improved symptoms		
Yes	70	79
No	30	21

Reporting therapies with prevalence > 5%

diagnosis, 79% reported improved targeted symptoms, but none could reduce the need for physician-prescribed medications. Fortunately, no severe adverse events or hospitalizations were reported, and only 5 participants reported adverse reactions and two emergency room evaluations.

AIH cases in our study reported a generally similar frequency of CAM use compared to other autoinflammatory conditions such as IBD (41%) [16] and systemic lupus erythematosus (50%) [17] and the U.S. population (50%) [18, 19]. However, our results differ from other chronic illnesses; patients with breast cancer reported 96.5% ever using CAM and 86.1% after diagnosis [20]. In a previous study, we observed CBD preparations were used in 25% of AIH patients to improve factors impacting quality of life, often targeting pain and sleep, and fatigue [10]. Here, we found AIH patients with lower household incomes were more likely to use CBD. This was opposite of our observation in the current study, as income did not differ between consumers of all CAM (Table 1). In fact, participants that have utilized CAM were more likely to have received higher education and be currently employed or retired compared to never CAM users. Other studies have suggested higher education and current employment do positively correlate with CAM use but may indicate subgroups with more resources for physical CAM [21, 22]. Often, physical CAM strategies (i.e., yoga, acupuncture, and chiropractor) are costlier and require a trained practitioner. In contrast, consumable CAM (i.e., CBD and vitamins) may have overall lower costs given widespread availability.

Most study participants (75%) reported that CAM strategies relieved targeted complaints. The most frequent CAM strategies that improved symptoms were physical activity (49.5%) (i.e., exercise, yoga), healthier eating (45.3%), and CBD preparations (45.3%). Recent studies have shown that patients with an autoimmune illness may be able to increase physical fitness and quality of life with a structured exercise training regime. A study examining a 12-week resistance training program in multiple sclerosis patients found that exercise improved voluntary isometric contraction and muscle power [23]. Other studies have found correlations between healthy eating and autoimmune disease management. A recent study found that patients following the autoimmune protocol diet for treating inflammatory bowel disease (IBD) in conjunction with IBD medication, resulted in reduced symptoms and in some cases potentiated clinical remission [24].

Our study revealed that CAM use for AIH-related symptoms was most often targeting fatigue, pain, sleep disturbance, and itch, with over 78% of AIH patients observing improvement in these areas with at least one CAM strategy. Recent studies have found similar results of CAM use reducing symptoms of fatigue, pain, and insomnia. CAM use in cancer patients has supported acupuncture, massage, yoga, meditation, and relaxation training to help alleviate fatigue [25]. In this same study, multivitamins were ineffective at reducing cancer-related fatigue [25]. Other studies researching CAM's efficacy in relation to pain and insomnia in patients with chronic illness found that CAM was helpful in reducing pain (i.e., exercise, acupuncture, and chiropractic medicine) and decreasing sleep disturbances (i.e., melatonin, meditation, and yoga) [26, 27]. Even though AIH

patients in our study reported improvement in AIH-related symptoms with CAM use, no patients reported reduction or cessation of chronically prescribed medications. Numerous studies suggest attempts to eliminate chronically prescribed medications in favor of CAM are an ultimate risk to patient outcomes. However, when CAM is used in conjunction with prescription medication regimens, data supports CAM may be able to improve disease outcomes and patient quality of life [23–27].

FDA-approved medications have pharmacokinetic data that can provide theoretical drug-induced liver injury (DILI) risk among patients with cirrhosis or hepatic impairment. Yet, these types of data are largely unavailable for consumed CAM. Beyond this, CAM products are a substantial risk for DILI even among healthy individuals, as nutritional supplements account for 20% of hepatotoxicity cases in the U.S. [18]. Although there is limited data to suggest patients with cirrhosis are at higher risk of DILI, the dose of medication and extent of hepatic metabolism has correlated with DILI [28, 29]. Nearly 28% of study participants in our study reported advanced fibrosis at most recent liver biopsy. Advanced liver fibrosis in AIH cases did not seem to be a deterrent to CAM use as we observed similar proportions of fibrosis levels across ever versus never CAM groups (Table 1). It is challenging to comment on DILI risk among participants in this study, as there was a wide variability of products, preparations, and limited pharmacokinetic data. Further, the bioavailability of a compound is a related risk factor for DILI, yet this aspect is often challenging to predict in patients with cirrhosis [9].

The safety of CAM in AIH may also be challenged by innate liver disease and concurrent medication use. For instance, CBD is a potent inhibitor of CYP3A4 and 2C19 and both corticosteroids (prednisone or budesonide) and calcineurin inhibitors (such as tacrolimus or cyclosporine) undergo metabolism via CYP3A4, thus pose a possible risk to 51% of patients currently taking corticosteroids and 3.1% using tacrolimus in our study. Inhibition of CYP3A4 and 2C19 by CBD may increase drug levels and/or potentiate side effects of these immunosuppressive regimens. Clinicians and AIH patients taking corticosteroids, tacrolimus, or cyclosporine should approach CBD with caution and monitor for adverse effects or toxicity [10].

We were reassured that only 5 participants reported adverse events, of which 2 required a dedicated physician's visit, but no hospitalizations or severe adverse events occurred. Further given this safety profile and a relatively positive response to a variety of CAM strategies (i.e., 79% improvement of symptoms targeted after AIH diagnosis), CAM, in general, is worthy of further dedicated investigational studies of AIH. These findings are pivotal, as health-related quality of life in AIH is significantly reduced [21, 22]. The frequent use of CAM to reduce AIH symptoms highlights critical treatment gaps that are increasingly prevalent in this rare disease.

We readily admit to the limitations of this study, much of which is rooted in the patient-reported aspects of AIH and memory recall bias of historical CAM use. However, AIH patients have exhibited excellent diagnosis agreements compared to their medical records [8]. This limitation also provides strength, as the utilization of anonymity via this survey platform is likely to promote more honest responses to the spectrum of CAM use. Furthermore, the standardization of the definition of the terms "alternative, traditional or complementary medicine" is also a factor that makes comparisons with studies difficult. A limitation of the present study was asking about homeopathy, acupuncture and medicinal plants, and herbal medicines. These terms may vary in meaning, such as "medicinal plants" and "herbal medicines": according to WHO document, published in 2013, have different meanings [30]. The study's strength is it is the first to collect data about the prevalence and safety of CAM use in a representative survey of AIH patients.

In summary, CAM use in AIH patients is associated with socioeconomic status, but not demographic or disease-related factors. AIH patients were often able to find a CAM strategy (CBD, healthy eating, exercise, yoga, meditation, and vitamins) to improve AIH-related symptoms (fatigue, sleep issues, joint pain, fatigue, itch) and overall quality of life. Though a majority saw improvement of symptoms, patients did not reduce or eliminate prescribed medication regimens. Given minimal adverse events were reported and a positive response to a variety of CAM strategies (i.e., 79% improvement of symptoms targeted after AIH diagnosis), CAM seems worthy of further dedicated investigational studies of AIH. Based on these conclusions, a hypothesis for future research would be examining the physiological efficacy of CAM in AIH and domains related to improved quality of life.

Declarations

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