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Complementary and alternative medicine use in children with cystic fibrosis

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ABSTRACT

Purpose: To estimate the overall prevalence of complementary and alternative medicine use among children with cystic fibrosis, determine specific modalities used, predictors of use and subjective helpfulness or harm from individual modalities.
Results: Of 53 children attending the cystic fibrosis clinic in London, Ontario (100% recruitment), 79% had used complementary and alternative medicine. The most commonly used modalities were air purifiers, humidifiers, probiotics, and omega-3 fatty acids. Family complementary and alternative medicine use was the only independent predictor of overall use. The majority of patients perceived benefit from specific modalities for cystic fibrosis symptoms.
Conclusions: Given the high frequency and number of modalities used and lack of patient and disease characteristics predicting use, we recommend that health care providers should routinely ask about complementary and alternative medicine among all pediatric cystic fibrosis patients and assist patients in understanding the potential benefits and risks to make informed decisions about its use.

1. Introduction

Complementary and alternative medicine (CAM) is defined by the National Centre for Complementary and Alternative Medicine as "health care approaches developed outside of mainstream Western, or conventional medicine for specific conditions or overall well-being" [1]. Many people use CAM for the treatment and prevention of illness. In 2007, 38% of American adults and 12% of children had used some type of CAM in the previous year [2] and spent $33.9 billion on various CAM modalities [3].

The prevalence of CAM use is reported to be higher among children with chronic illnesses [4–8]. In adults (ages 16–44 years) with cystic fibrosis (CF) in Australia, 70% report ever using CAM and 45% report currently using CAM for their condition [9]. The limited number of studies of CAM use in children with CF show prevalence rates of 45%–75% [6,10,11]. A variety of different CAM modalities are reported in these studies ranging from prayer and religious methods, to homeopathy, physical therapies such as massage and chiropractic, and nutritional therapies [6,10,11].

For most CAM modalities, efficacy data in individuals with CF is limited or contradictory [12–14]. A few studies with small sample sizes show some reduction in disease burden with acupuncture, beta-carotene, zinc and probiotics [12,15–17]. A newer CAM modality in North American markets, namely salt therapy, or halotherapy, involves breathing in salt particles, either from rooms built with salt or salt emitted from salt lamps. In one small study, the use of salt therapy was associated with modest improvements in lung function in individuals with CF [18].

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While the current literature reports a high prevalence of CAM use in children with CF, previous studies have not rigorously examined potential correlations between patient specific characteristics (e.g. age, income) or disease severity and the likelihood of CAM use [6]. There is also a paucity of studies that examine the perceived benefit or harm of specific CAM therapies according to patients or caregivers [11]. Such studies could allow identification of specific attributes of children with CF that predict a higher prevalence of all CAM or specific types of CAM use, and which specific CAM therapies are felt to be helpful or harmful. This would provide conventional health care providers valuable information on which patients may be CAM users and the subjective helpfulness of CAM modalities, an area where evidence is lacking. It would also aid families in making informed decisions about CAM use, as well as direct future efficacy studies.

In this study, our objective is to identify the prevalence of CAM use among children with CF treated at a Canadian centre, and to further characterize the most frequently used CAM modalities. We are particularly interested in the use of salt therapy, based on anecdotal reports of its use within the local CF population. We additionally aim to determine the perceived benefit or negative effects of specific CAM therapies used in this population, the frequency of communication between families and healthcare teams about CAM use, as well as any relationship between caregiver demographics, disease severity or other patient factors and CAM use. We hypothesize that rates of CAM use would be higher within more affluent families, and in patients whose family members also use CAM. We further hypothesize that older children with more severe CF disease would be more likely to use CAM as an adjuvant treatment for progressive symptoms.

2. Materials and methods

2.1. Patient recruitment

We developed, pilot tested, then administered a questionnaire about current (within the last 6 months) and ever- CAM use to parents or primary caregivers of children aged 1–18 years who attended the multi-disciplinary CF clinic at the tertiary care Children's Hospital, London Health Sciences Centre in London, Ontario, Canada. All patients who had been diagnosed with CF for more than one year were eligible for inclusion in the study. For ethical reasons, patients who had been diagnosed with CF for less than one year were excluded from the study to allow time to adjust to conventional CF treatments before introducing information about CAM methods through this questionnaire. All eligible participant families received a letter of information describing the purpose and content of the study during their routine CF clinic visit. Those who agreed to participate signed a written informed consent form prior to questionnaire completion. There was no stipend for questionnaire completion.

2.2. Questionnaire development and validation

We developed the study questionnaire after performing an extensive literature review to identify previously published questionnaires with some evidence of validity. We incorporated content and design elements from these questionnaires as a framework for our study questionnaire [19]. We then assessed the study questionnaire for face and content validity with a group of 7 pediatricians and CF allied health professionals, including pharmacists, nurses, physiotherapists, dieticians and social workers. After making minor content revisions, we pilot tested the questionnaire with 10 families of children with CF and made further revisions to improve formatting, clarify instructions and emphasize sections of the questionnaire that had been overlooked by some participants.

When administering the questionnaire, study investigators used a script that defined CAM as “any treatment used specifically for CF excluding what was prescribed by their physicians and CF team”. We included sixty-two specific examples of CAM in the questionnaire, as identified through review of the published literature of CAM use in adults with CF and children with other chronic diseases such as asthma and juvenile arthritis. Caregivers indicated whether the CAM method was used currently (within the past 6 months), in the past (more than 6 months ago), whether it was helpful for breathing symptoms, other symptoms, or not helpful (see eFig. 1 in the Supplement). We included the following categories of CAM in the questionnaire: natural health products (herbal remedies, homeopathy), nutrition (vitamins, minerals, special diets), spiritual/mental treatments (biofeedback, relaxation), physical treatments (acupuncture, massage, chiropractic), and other (biofield, salt therapy, humidifiers). The questionnaire allowed participants to provide free text descriptions of additional CAM treatments that may have been used by the child, though not specifically listed in the questionnaire.

We collected information regarding parent/caregiver demographics such as age, sex, education, family income, and ethnic background, along with patient demographics such as age and sex. The questionnaire further explored the reasons for CAM use, potential negative side effects, whether caregivers spoke to their child's healthcare team about CAM use, prevalence of CAM use among other family members, the amount of money spent on CAM per month, and consultation of alternative health care practitioners (i.e. outside their CF or conventional medical care team) regarding CAM use.

We assessed ethnicity of the children participating in the study to look for associations between ethnicity and CAM use. Research investigators defined the options for ethnic background, which included an “Other” option for the caregiver or child to provide free text. Participants classified the ethnic background of the child. Research investigators did not judge the ethnic background of any participant.

2.3. Additional data collection

Through review of clinical notes and other patient records, we collected information regarding markers of disease severity and CF characteristics, such as body mass index (BMI), pulmonary function (forced expiratory volume in once second-FEV_1), emergency room visits and hospitalizations for pulmonary exacerbations in the preceding year, current use of inhaled antibiotics, dornase alpha or hypertonic saline, colonization of respiratory secretions with *Pseudomonas aeruginosa*, *Aspergillus species,* Methicillin-resistant *Staphylococcus aureus* (MRSA), or *Burkholderia cepacia,* CF genotype, and pancreatic sufficiency.

Data was collected from June 2013 to October 2015.

2.4. Analysis

We used descriptive statistics to identify the prevalence of CAM use and the most frequently used methods of CAM, Fisher exact tests and chi square tests to identify differences in categorical baseline demographics and disease indices between those children who did or did not use CAM, Wilcoxon rank sum tests for continuous variables and the Mantel-Haenszel chi square test to identify significant differences in gross annual family income levels between CAM users and non-users. For all comparisons, we considered a p value of less than 0.05 as statistically significant. The software used for the analysis was SAS 9.3.

We performed univariable logistic regression to identify

variables that were significantly ($p < 0.05$) associated with CAM use. Of note, we dichotomized CF genotype to severe (little to no CFTR function) versus non-severe (reduced CFTR function) mutations for this analysis. We then built a multivariable logistic regression model in a stepwise fashion using these significant variables to determine independent predictors of CAM use. We checked model fit using the Hosmer Lemeshow test and c-statistic and chose models with the best model fit characteristics.

We performed exploratory subgroup analyses by dividing CAM into four modalities, namely nutritional treatments, physical therapies, natural therapies and spiritual/mental therapies. We performed additional univariable and multivariable logistic regression to see if there was a relationship between predictors (listed above) and the use of specific types of CAM.

2.5. Ethics approval

This study was approved by the research ethics board at the University of Western, London, Ontario, Canada.

3. Results

Of the fifty-three children with CF who were eligible for this study, all 53 families agreed to participate and completed the study questionnaire, representing 100% study recruitment and response rate. Of these, 79% had ever used at least one method of CAM and 62% are currently using CAM (within the last 6 months). We found that only 40% of participants have spoken to their health care team about their CAM use. The most commonly stated reason for lack of communication by patients/families to their health care team about CAM use is that they have never been specifically asked. We found that 53% of parents or caregivers use CAM. Twenty-one percent of participants consulted a professional outside the healthcare team regarding their CAM use.

Table 1 compares baseline demographic information and indices of CF disease among CAM users and non-users. The genotype distribution of study participants is 62% delta F508 homozygotes, 28% delta F508 heterozygotes and 10% with other mutations.

Table 2 outlines the frequency of use of each CAM method and identifies the most frequently used forms of CAM. See eFig. 2 in the Supplement for a graph displaying the total number of different CAM modalities used by participants. Approximately 21% of participants use no CAM modalities, 15% use one CAM modality, 42% use two to five modalities and 25% use greater than five modalities. Excluding three of the most commonly used methods of CAM (air purifiers, humidifiers and multivitamins), 77% of participants still use some other form of CAM. There were no reported negative side effects from CAM therapies. The amount of money spent on CAM by families in one month is distributed as shown in eFig. 3 in the Supplement.

As shown in Table 3, only family CAM use and income between $20,000 and $50,000 Canadian dollars are significantly associated with patient ever CAM use in univariable logistic regression. After adjustment for age and sex, as shown in Table 4, family CAM use is the only independent predictor of ever CAM use (odds ratio (OR) = 6.61, 95% confidence interval (CI):1.19, 36.6, $p = 0.031$). Unadjusted predictors of current CAM use include family CAM use, lower FEV_1 and use of hypertonic saline inhalations. However, after adjustment for age and sex, family CAM use is again the only independent predictor of current CAM use (OR = 3.93, 95% CI: 1.14, 13.56, $p = 0.031$).

We also evaluated predictors of use of specific categories of CAM (i.e. natural health products, nutritional treatments, physical therapies, spiritual/mental therapies). As per univariable regression

Table 1
Comparison of baseline characteristics between CAM users and non-users.

Outcome		'Ever' CAM use			'Current' CAM use[b]		
		CAM Users (N = 42)[a]	CAM Non-Users (N = 11)[a]	P-Value	CAM Users (N = 33)[a]	CAM Non-Users (N = 20)[a]	P-Value
Categorical variables							
Female sex		57 (24)	27 (3)	0.10	58 (19)	40 (8)	0.21
Family CAM use		62 (26)	18 (2)	0.02[c]	67 (22)	30 (6)	0.01[c]
Parental university education		74 (28)	89 (8)	0.66	79 (23)	72 (13)	0.73
Income <$20,000		13 (5)	0 (0)	0.57	14 (4)	6 (1)	0.64
Income $20,000-$50,000		21 (8)	63 (5)	0.03[c]	21 (6)	41 (7)	0.18
Income >$50,000		63 (24)	38 (3)	0.25	63 (19)	47 (8)	0.22
Ethnicity	Caucasian	93 (39)	100 (11)	>0.99	97 (32)	90 (18)	0.55
	First Nations	13 (5)	0 (0)	0.57	10 (3)	12 (2)	>0.99
Pancreatic insufficiency		88 (37)	100 (11)	0.57	85 (28)	100 (20)	0.14
Pseudomonas aeruginosa positive[d]		33 (14)	46 (5)	0.50	27 (9)	50 (10)	0.09
Pseudomonas aeruginosa, Methicillin-resistant *Staphylococcus aureus* or *Burkholderia cepacia* positive[d]		26 (11)	36 (4)	0.57	21 (7)	40 (8)	0.19
Inhaled treatments (i.e. dornase alpha, hypertonic saline, inhaled tobramycin)		69 (29)	46 (5)	0.17	70 (23)	55 (11)	0.28
Hypertonic saline		36 (15)	9 (1)	0.14	46 (15)	5 (1)	0.002[c]
Severe genotype[e]		76 (32)	91 (10)	0.30 (23)	70	95 (19)	0.05
Hospitalizations[f]		26 (11)	27 (3)	>0.99	27 (9)	25 (5)	>0.99
Continuous variables							
Age of child (years)		9 (4.8)	10 (5.4)	0.79	9 (4.5)	11 (5.3)	0.21
BMI		17 (2.8)	18 (2.9)	0.93	17 (2.2)	18 (3.4)	0.17
FEV_1% predicted		85 (21.9)	77 (19.6)	0.18	89 (19.3)	73 (21.4)	0.01[c]

CAM = complementary and alternative medicine.
BMI = body mass index.
FEV1 = forced expiratory volume in 1 second.
[a] Values are represented as % with total 'N' in parentheses for categorical variables, and as mean with standard deviation in parentheses for continuous variables.
[b] 'Current' CAM Use refers to CAM use within the past 6 months.
[c] Significant $p < 0.05$.
[d] Within the past 6 months.
[e] Genotype with little to no CFTR function on either inherited allele.
[f] Any hospitalization for pulmonary exacerbation within the past 12 months.

Table 2
The frequency of CAM methods used.

Category of CAM	Type of CAM	'Ever' CAM users (%) (n = 42)	'Current' CAM users (%)[b] (n = 33)
Natural health products	Aloe Vera	13	0
	[a]Garlic	9	2
	Homeopathy	6	2
	Sage	4	0
	Chamomile	4	0
	Lemongrass	4	0
	Echinacea	2	0
	Ginger	2	0
Nutritional treatments	[a]Probiotics	25	13
	[a]Omega 3 fatty acids	23	17
	[a]Vitamin D	21	21
	[a]Honey	19	8
	[a]Vitamin C	19	13
	[a]Multivitamins	13	9
	[a]Vitamin E	13	11
	[a]Vitamin A	11	11
	[a]B Vitamins	11	9
	Protein powder	4	2
Nutritional treatments	Zinc	4	2
	Special diets	4	4
	Flaxseed	2	0
	Selenium	2	0
	Magnesium	2	2
Spiritual/mental treatments	Yoga	15	6
	Relaxation techniques	6	6
	Biofeedback	2	2
Physical treatments	Massage	8	4
	Chiropractic	6	4
	Reflexology	2	0
Other CAM treatments	Air purifier	38	28
	Humidifier	28	8
	Salt lamps	4	4
	Biofield therapies	2	2
	Salt rooms	2	0

CAM = complementary and alternative medicine.
[a] These nutritional supplements were used in addition to each participant's usual diet and dietary supplements prescribed by the CF team.
[b] 'Current' CAM Use refers to number of participants using CAM modalities within the past 6 months.

analysis (see eTable 1 in the Supplement), we found family CAM use, age and female sex to be predictors of use of natural health products. The use of inhaled treatments (dornase alpha, hypertonic saline, inhaled tobramycin) and having a severe genotype was associated with less natural health products use. However, in the multivariable regression analysis, our data shows that only family CAM use, and female sex are independently associated with increased use of natural health products while only hypertonic saline use is associated with less use of natural health products (see eTable 2 in the Supplement). We found family CAM use (OR = 4.50, 95% CI: 1.40, 14.5, p = 0.012) to be the only significant predictor for use of nutritional treatments and no factors to be significantly associated with specific use of physical or spiritual/mental CAM treatments.

Overall, families report CAM to be helpful for breathing and/or other CF symptoms in approximately 91% of recorded responses for individual CAM modalities. The perceived benefit of various categories of CAM modalities, as well as specific CAM modalities, are shown in Fig. 1. There were no perceived harms from any CAM modality.

4. Discussion

This study demonstrates a high prevalence (77%–79%) of CAM use among children with CF treated at the Children's Hospital in London Ontario, Canada, as in accordance with the current literature in other chronic disease populations.

Excluding humidifiers and air purifiers, natural health products and nutrition supplements were the most common types of CAM methods used. However, many patients also used physical treatments (massage and chiropractic therapy) and spiritual/mental treatments (yoga, relaxation techniques). We did not find a high prevalence of use of any particular CAM treatment that had not already undergone efficacy studies.

We did not find that income was a barrier to CAM use in this study. Although we did find an association between 'ever CAM use' and gross annual income between $20,000–$50,000, this relationship did not persist in multivariable models that also adjusted for age, sex and family CAM use, a finding that is consistent with previous studies in other chronic disease populations [20].

Children whose other family members used CAM were 6.6 times more likely to use CAM themselves, mirroring the finding of a previous study of CAM use in Canadian children with mixed respiratory diseases [6]. In fact, this was the only significant independent predictor of overall CAM use in the present study, and suggests that family values and views on healthcare may be the biggest driving factors for a child to use CAM. However, the overall prevalence of CAM use was still higher among children with CF compared to their parents/primary caregivers (79% vs. 53%, $p < 0.05$). This could imply that CAM is being used as treatment for symptoms of CF, and is consistent with trends in the literature showing that children with chronic illnesses are more likely to use CAM [8,21–23].

In adjusted analysis, our study did not find an independent association between markers of CF disease severity or phenotype, and overall CAM use. Interestingly, we found that children who were using inhaled treatments were significantly less likely to use a specific type of CAM, namely natural health products. Children who use inhaled therapies are often also taking multiple prescribed medications to treat more advanced CF disease. This may be a reason for disengaging from use of these natural health products. This is supported by our finding in unadjusted analysis that children with a severe genotype, another marker of more severe CF disease, were also less likely to use natural CAM products. Female sex and family CAM use were found to be independently associated with the use of natural health products. The reason for a sex predilection for natural health product use is not clear, but may indicate some gender influence on CAM use that has not been identified previously.

Of the small number of participants who tried salt therapy in our study, all reported that it was helpful for breathing symptoms. While there is some limited evidence for the health benefits of salt therapy [19], sitting in salt rooms for extended periods of time along with other respiratory patients can also promote the spread of infection, which would be harmful for children with CF. This is a method of CAM that physicians and health care teams involved in the treatment of children with CF should be aware of in order to inform families about the possible risks of salt therapy as well as clarify certain efficacy claims. For example, some salt therapy companies use the evidence for the efficacy of nebulized hypertonic saline in CF as support for the value of salt therapy, even though the two are not equivalent [24].

As seen in studies of non-CF children [25,26], only 40% of patients and caregivers in this study had spoken to their health care teams about their CAM use. The most commonly stated reason for this lack of discussion was that the conversation had not been initiated by the health care team. A nonjudgmental attitude towards CAM use by health care providers has been viewed as the most important factor for parents to initiate discussion about their alternative health care practices [26]. However, our study suggests that patients and caregivers would be most willing to discuss their use of CAM when the conversation is initiated by the physician in a

Table 3
Univariable logistic regression analysis for CAM use.

Outcome	'Ever' CAM use				'Current' CAM use[b]			
Variable[a]	Odds Ratio	95% Confidence intervals		P-value	Odds Ratio	95% Confidence intervals		P-value
		Lower	Upper			Lower	Upper	
Pseudomonas aeruginosa positive[d]	0.60	0.16	2.31	0.46	0.38	0.12	1.20	0.10
Pseudomonas aeruginosa, Methicillin-resistant *Staphylococcus aureus* or *Burkholderia cepacia* positive[d]	0.66	0.16	2.72	0.57	0.44	0.13	1.50	0.19
Family CAM Use	7.31	1.40	38.2	0.02[c]	4.67	1.41	15.5	0.01[c]
Parental university education	0.35	0.04	3.16	0.35	1.47	0.38	5.79	0.58
Income $20,000-$50,000	0.16	0.03	0.82	0.03[c]	0.37	0.10	1.39	0.14
Income >$50,000	2.86	0.59	13.8	0.19	2.14	0.63	7.25	0.22
Female sex	3.56	0.83	15.3	0.09	2.04	0.66	6.30	0.22
Inhaled treatments[e]	2.68	0.69	10.4	0.15	1.88	0.60	5.96	0.28
Hypertonic saline	5.56	0.65	47.7	0.12	15.8	1.89	132	0.01[c]
Severe genotype[f]	0.32	0.04	2.82	0.30	0.12	0.01	1.03	0.05
Hospitalizations[g]	0.95	0.21	4.22	0.94	1.13	0.32	4.00	0.86
BMI	1.02	0.80	1.29	0.87	1.21	0.97	1.51	0.10
FEV_1 (% predicted)	0.98	0.95	1.02	0.37	0.96	0.93	0.10	0.03[c]
Age (years)	1.02	0.89	1.18	0.74	1.08	0.96	1.22	0.19

CAM = complementary and alternative medicine.
BMI = body mass index.
FEV_1 = forced expiratory volume in 1 second.
[a] Regression estimates for the following variables are not shown because of non-convergence due to small cell sizes: pancreatic insufficiency, income <$20,000, ethnicity.
[b] 'Current' CAM Use refers to CAM use within the past 6 months.
[c] Significant $p < 0.05$.
[d] Within the past 6 months.
[e] Inhaled treatments include: hypertonic saline, nebulized tobramycin, dornase alpha.
[f] Genotype with little to no CFTR function on either inherited allele.
[g] Any hospitalization for pulmonary exacerbation within the past 12 months.

nonjudgmental manner. Discussing CAM with patients and families gives physicians the opportunity to educate patients about CAM modalities, which can help patients make informed decisions about any treatments they are using, as well as minimize the potential for harm.

Participants did not report perceived harm from any CAM modality used in our study and only a small proportion of participants reported CAM modalities as not helpful. On the contrary, there were a number of CAM modalities that participants perceived as helpful for breathing and other CF symptoms, suggesting these patients are likely to continue to use CAM, despite a lack of proven efficacy. A significant proportion of CAM users in our study were in fact using multiple different modalities and products. Despite the lack of perceived harm from CAM, the potential for harmful interactions when using multiple CAM modalities is a cause for vigilance given many CF patients concurrently take multiple prescribed pharmaceutical agents [27]. Discussing CAM with families allows for an opportunity to identify potential toxic combinations of CAM and conventional medication use. This discussion also promotes trust building in the patient-physician relationship and allows physicians to better understand the values and goals of their patients, which ultimately optimizes patient care.

In a previous study by Tanase and Zanni (2008) investigating CAM use in children with CF, 6% discontinued their conventional CF treatment to use CAM exclusively [13], while a similar study in children with asthma showed that CAM use did not affect adherence to conventional asthma treatments [28]. None of the children using CAM in the present study indicated discontinuation of their conventional CF treatments, suggesting these CAM treatments are truly used as complementary or "adjuvant" therapies and not as alternative therapies.

Given a 100% survey response rate, we can be confident that the findings of this study truly represent practices within our pediatric CF clinic population. However, these study results may not be generalizable to other CF clinics both because of the relatively small sample size that limited the power of our analysis, and more importantly, because CAM use is likely influenced not only by family values as seen in this study, but also by cultural variation of the CF population in different geographic regions as well as local availability and marketing of various CAM therapies.

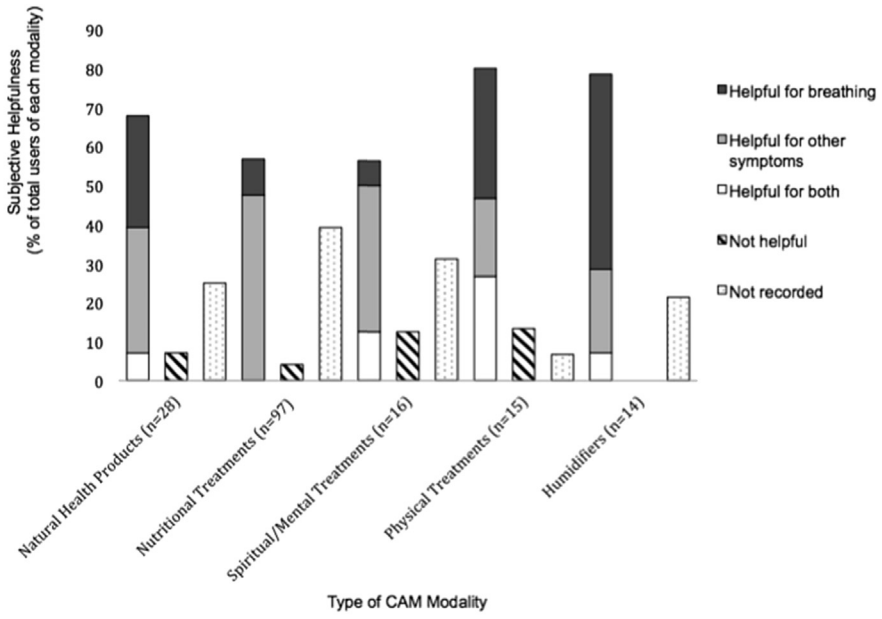
5. Conclusions

Our study illustrates a high prevalence of overall CAM use in children with CF that is associated with CAM use among other family members and not predicted by ethnicity, family income, or

Table 4
Multivariable regression analysis table for CAM use.

Outcome	'Ever' CAM use				'Current' CAM use[a]			
Variable	Odds Ratio	95% Confidence intervals		P-value	Odds ratio	95% Confidence intervals		P-value
		Lower	Upper			Lower	Upper	
Family CAM use	6.61	1.19	36.6	0.03[a]	3.93	1.14	13.56	0.03[b]
Female sex	2.78	0.60	13.0	0.19	1.60	0.48	5.39	0.44
Age	0.98	0.84	1.15	0.79	1.05	0.92	1.19	0.46

CAM = complementary and alternative medicine.
[a] 'Current' CAM Use refers to CAM use within the past 6 months.
[b] Significant $p < 0.05$.



CAM = complementary and alternative medicine

Fig. 1. Perceived benefit of CAM modalities.

markers of disease severity. Although evidence for the efficacy of CAM is limited, this study found that most patients perceive benefit from CAM therapies. This perception of health improvement may be one element of a complex emotional and cognitive process driving the ongoing high prevalence of CAM use, albeit without discontinuation of conventional CF therapies. Given that less than half of CF patients discuss CAM use with their health care team and the lack of patient and disease characteristics predicting CAM use, we recommend that conventional health care providers routinely ask about CAM use among all their CF patients as an opportunity to foster a stronger therapeutic alliance and provide education to patients to help them make informed decisions about CAM use.

Author contributions

Drs. D. Radhakrishnan and Giangioppo had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

A. Radhakrishnan and D. Radhakrishnan conducted and are responsible for the data analysis.

Conception and design of the study: Giangioppo, D. Radhakrishnan.

Acquisition, analysis, interpretation of data: All authors.

Drafting of article: Giangioppo, Kalaci, A. Radhakrishnan, D. Radhakrishnan.

Critical revision of manuscript for important intellectual content: All authors.

Statistical analysis: A. Radhakrishnan, D. Radhakrishnan.

Obtained funding: D. Radhakrishnan.

Administrative, technical, material support: Giangioppo, Kalaci, A. Radhakrishnan, Fleischer, Itterman, D. Radhakrishnan.

Study supervision: D. Radhakrishnan.

Final approval of the version to be submitted: All authors.

Conflicts of interest

None.

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Role of funder/sponsor

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Group information

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Previous presentation

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Additional contributions

We thank the children and caregivers who participated in this study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ctcp.2016.08.006.

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