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Association of adherence to therapy and complementary and alternative medicine use with demographic factors and disease phenotype in patients with inflammatory bowel disease

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Abstract

Background and aims: Previous studies have suggested an increasing use of complementary and alternative medicine (CAM) in patients with inflammatory bowel disease (IBD). Furthermore, a significant number of IBD patients fail to comply with treatment. The aim of our study was to evaluate the prevalence of non-adherence and the use of CAM in Hungarian patients with IBD. **Methods:** A total of 655 consecutive IBD patients (CD: 344, age: 38.2 [SD 12.9] years; UC: 311, age: 44.9 [15.3] years) were interviewed during the specialist visit by self-administered questionnaire including demographic and disease-related data as well as items analyzing the extent of non-adherence and CAM use. Patients taking more than 80% of each prescribed medication were classified as adherent.

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Results: The overall rate of self-reported non-adherence (CD: 20.9%, UC: 20.6%) and CAM (CD: 31.7%, UC: 30.9%) use did not differ between Crohn's disease (CD) and ulcerative colitis (UC). The most common causes of non-adherence were: forgetfulness (47.8%), too many/unnecessary pills (39.7%), being afraid of side effects (27.9%) and too frequent dosing. Most common forms of CAM were herbal tea (47.3%), homeopathy (14.6%), special diet (12.2%), and acupuncture (5.8%). In CD, disease duration, date of last follow-up visit, educational level and previous surgeries were predicting factors for non-adherence. Alternative medicine use was associated in both diseases with younger age, higher educational level, and immunosuppressant use. In addition, CAM use in UC was more common in females and in patients with supportive psychiatric/psychological therapy.

Conclusions: Non-adherence and CAM use is common in patients with IBD. Special attention should be paid to explore the identified predictive factors during follow-up visits to improve adherence to therapy and improving patient–doctor relationship.

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1. Introduction

Inflammatory bowel disease (IBD) is a multifactorial entity with both, genetic and environmental factors contributing to disease pathogenesis.¹ Worldwide, the incidence rates for IBD vary from 0.5 to 24.5 per 100,000 person-years,² with the majority of patients being disabled during various parts of their lives. This characteristic may also suggest poor adherence (i.e., a percentage of the prescribed doses is not taken) outside the clinical trial settings.^{3,4}

Treatment of IBD can involve several medications with varying regimens, dietary modifications, and potentially, surgery, depending on symptoms, severity of illness, and response to treatment. Adherence to the pharmacological treatment is a complex process, where the doctor–patient relationship, treatment regimen and other disease-related factors play key roles. The undesirable side effects of some medications (e.g., weight gain, cushingoid appearance, and immune suppression) and the complex treatment regimens for IBD patients (e.g., varying dosing schedules and pill quantities for each medication) are likely to disrupt adherence and the effective management of this condition. These data are consistent with the hypothesis that many patients engage in an implicit cost–benefit analysis in which beliefs about the *necessity* of their medication are weighed against *concerns* about the potential adverse effects of taking it and that these beliefs are related to medication adherence, as in other chronic conditions.⁵

Research on adherence in IBD is limited. Studies in adults have revealed medication non-adherence prevalence rates ranging from 15 to 72%.^{3,4,6–8} For example, a cross-sectional study of US outpatients with quiescent ulcerative colitis (UC) found that only 40% were adherent to maintenance therapy with mesalazine (mesalamine).³ In the UK, approximately 15% of patients fail to even redeem prescriptions at the pharmacy.⁹ Moreover, treatment non-adherence rates may vary considerably between countries. In Europe, a survey of 203 IBD patients revealed self-reported non-adherence rates ranging from 13% in France, to 26% in Italy, 33% in the UK and 46% in Germany. The overall non-adherence rate was 29% across Europe,¹⁰ where non-adherence was defined as taking <80% of the prescribed medication. Similarly high rates of non-adherence were reported from Eastern Europe. Overall,

the intentional non-adherence rate was reported by 38.9% of patients, and 18.6% of the patients discontinued therapy at least once.⁴ In a Canadian study, UC diagnosis was associated with a higher risk for non-adherence (OR: 4.42).¹¹

Suggested predictors of non-adherence include age, since younger patients tend to be less adherent than older patients,^{6,12} gender,^{3,13} full-time employment,¹¹ educational level,^{4,11,14} recent diagnosis,¹² drug type, formulation and dosing regime^{3,12} and in Crohn's disease (CD) complicated disease course.⁸ Moreover, the partnership between patient and treating physicians are of utmost importance in determining medical adherence, where effective patient–physician dialog is central to promoting patient adherence. Both the quality and quantity of the visits are important. Sewitch et al.⁶ found an increased risk of intentional non-adherence to be associated with being treated by the same physician for more than 1 year, not scheduling another appointment, and greater total discordance between the patient and the physician.

Complementary and alternative medicine (CAM) includes a wide range of practices and therapies outside the realms of conventional western medicine.¹⁵ CAM use is also common among patients with IBD. The reported rates of CAM use in IBD have increased from 4–13% observed in the late 1980s¹⁶ to 31–68%^{17,18} almost a decade later. Although these rates may not be directly comparable with each other due to differences in the definition of CAM use, they show a clear trend of increasing CAM use in IBD patients, parallel to the boom observed in the general population. In general population surveys, use of CAM was associated with higher education and income, poorer health status, and a holistic orientation to health.¹⁹ Partly conflictive data are available in IBD. In a Canadian study,²⁰ CAM use was associated with more severe disease activity, use of CAM for other purposes, and a desire for an active role in treatment decisions. CAM use was also associated with younger age in those with Crohn's disease, and less confidence in their IBD physician in those with ulcerative colitis. In contrast, patient's age, gender, disease diagnosis, or duration of disease were not predictive of any type of alternative medicine use in a multicentric study including Canada, Ireland, Sweden and the US.¹⁷ However, no data on the prevalence of and reason for CAM use are available from Eastern Europe.

The aim of our study was to prospectively evaluate the prevalence of and predictors for non-adherence and CAM use in

a large cohort of Hungarian patients with IBD. In addition, we analyzed the association between medical non-adherence/CAM use and demographic data and clinical phenotype.

2. Materials and methods

A total of 655 consecutive IBD patients (CD: 344, males/females: 143/201, age: 38.2 [SD 12.9] years; UC: 311, males/females: 158/153, age: 44.9 [SD 15.3] years) were prospectively interviewed during an outpatient specialist visit using a self-administered questionnaire. Participating centres were all referral gastroenterology units with a special focus on IBD. The diagnosis was based on the Lennard–Jones criteria.²¹ Age, disease duration, last follow-up visit by a gastroenterologist, the presence of familial IBD, location, medical therapy, need for surgery (resections), and smoking habits, and in CD, disease behavior and perianal involvement, were investigated by reviewing the medical charts by the physician and completing a questionnaire. In the UC cohort, there were no post-colectomy patients. The disease phenotype was determined according to the Montreal classification.²²

The questionnaire included 25 detailed questions regarding demographics and disease-related data as well as items analyzing the extent of non-adherence and CAM use. Type (oral vs topical) and frequency of medications prescribed was recorded as well as magnitude of (30%, 30–50%, 50–80% and >80% of prescribed medication taken) and reason for both intentional and non intentional non-adherence to oral or topical medication for the last 12 months. We did not record the adherence data for biological therapy, since at the time of the study, most of the IBD patients received infliximab (adalimumab was used in only two patients), and biological exposure in UC was minor. We also recorded the frequency, type, and reason for CAM use. In addition, frequency and reason for supportive therapy by a psychiatrist or psychologist was recorded. Patients taking more than 80% of each prescribed medicine were classified as adherent. Detailed clinical phenotypes were determined by reviewing the medical charts by the treating physician. The clinical data of the CD and UC patients are presented in Table 1.

The study protocol was approved by the Ethical and Science Committee of the Ministry of Health (ETT TUKEB, ad 260/PI/2009, ad.8-103/2009-1018EKU). Each patient was informed of the nature of the study and signed the informed consent form.

2.1. Statistical analysis

Variables were tested for normality using Shapiro Wilk's *W* test. *T*-test with separate variance estimates, χ^2 -test and χ^2 -test with Yates correction were used to evaluate differences between different subgroups of IBD patients. Binary logistic regression was used to compare the association between clinical, demographic data and non-adherence or CAM use. Each variable with a $p \leq 0.1$ identified in univariate association testing was included in the binary logistic regression models. A p value of <0.05 was considered as significant. Peter Laszlo Lakatos performed the statistical analysis using the SPSS15.0 (SPSS Inc, Chicago, IL) software.

Table 1 Clinical characteristics and demographic data of patients with inflammatory bowel diseases.

	CD (n=344)	UC (n=311)
Male/female	143/201	158/153
Age (years)	38.2±12.9	44.9±15.3
Duration (years)	8.5±7.6	11.0±8.6
Last follow-up visit by specialist (months)	6.5±7.5	8.6±9.6
Place of residence (rural/urban/missing)	83/211/50	92/160/59
Education level (High/medium/low/missing)	37/179/87/41	54/136/72/49
Familial IBD ¹	31 (9.0%)	23 (7.4%)
Location (n) In CD		
L1	69	–
L2	114	
L3	158	
L4 only	3	
Maximum extent (n) in UC		
Proctitis	–	84
Left-sided		123
Extensive		104
Behavior (n)		
B1	158	–
B2	95	
B3	91	
Perianal disease ¹	113 (32.8%)	–
<i>Current medical therapy</i>		
5-ASA use ¹	66 (19.2%)	268 (86.2%)
Topical 5-ASA use ¹	14 (4.1%)	73 (23.4%)
Steroid use ¹	127 (36.9%)	72 (23.1%)
Azathioprine/methotrexate use ¹	197 (57.3%)	85 (27.3%)
Infliximab use ¹	39 (11.1)	1 (0.6%)
Surgery/reoperation in CD ¹	161 (46.8%) / 67 (19.5%)	–
Smoking habits (n)		
No	176	217
Yes	98	33
Former	70	61

Location: L1: terminal ileum, L2: colon, L3: ileocolon, L4: upper gastrointestinal.

Behavior: B1: non-stricturing non-penetrating, B2: stricturing, B3: penetrating.

PSC: primary sclerosing cholangitis.

¹ n (%).

3. Results

3.1. Non-adherence rate and CAM use in patients with inflammatory bowel disease

The overall rate of self-reported non-adherence and CAM use was not different between CD and UC (see Fig. 1). The most common causes of non-adherence were: forgetfulness, too many/unnecessary pills, being afraid of side effects, and too complicated administration schedule (Table 2). Most common forms of CAM were: herbal tea use, homeopathy, and

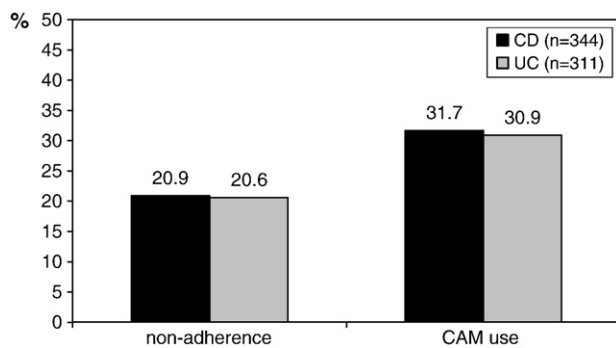


Figure 1 Frequency of self-reported non-adherence and complementary and alternative medicine (cam) use in patients with inflammatory bowel diseases.

special diet or acupuncture (Table 3). In addition, 52 (25.4%) of CAM users reported that they use also other forms of CAM without further explanation. Most common reasons for CAM use reported by the patients were supplementary therapy in addition to prescribed conventional medicines (80.5%, 165/205), having the feeling that medical therapy is not effective enough (17.5%), to treat side effects of the conventional medical therapy (6.8%), and the belief that it is more effective than conventional medical therapy (4.4%).

The overall frequency for seeking supportive therapy from a psychiatrist or psychologist was similar in both diseases (CD: 13.9% [45/323] and UC 13.5% [37/275]). The most common motivation for this was inability to deal with the diagnosis and psychosocial pressure because of the disease in the family or at work.

3.2. Association between non-adherence, CAM use, and disease phenotype or demographic data

In CD, non-adherence was associated with disease duration and in patients with a last follow-up visit beyond one year

Table 2 Reported causes for medical non-adherence ($n=136$) in patients with inflammatory bowel diseases.

	Frequency
Forgetfulness	47.8%
Too many/unnecessary pills	39.7%
Being afraid of side effects	27.9%
Too frequent dosing	13.9%
Too complicated administration schedule	4.4%

Table 3 Common types of complementary and alternative medicine use ($n=205$) in patients with inflammatory bowel diseases.

	Frequency
Herbal tea	47.3%
Homeopathy	14.6%
Special diet	12.2%
Acupuncture	7.8%
Energy transfer	5.8%
Magnetic therapy	1.9%

Table 4 Predictive factors for self-reported non-adherence in patients with Crohn's disease in univariate analysis (χ^2 -test).

Factor	Non-adherent (%)	p value	OR (95% CI)
Duration			
< 10 years	22.4	0.013	–
10–20 years	10.0		
> 20 years	34.5		
Last follow-up visit			
< 12 months	19.0	0.019	2.13 (1.12–4.05)
\geq 12 months	33.3		
Educational level ($n=303$)			
Low	35.1	0.026	–
Medium	22.9		
High	13.8		
Immunosuppressant use			
Yes	17.3	0.068	1.63 (0.96–2.75)
No	25.3		
Previous surgeries			
No	25.4	0.003	
1	22.3		
2 or more	6.0		

($p=0.019$, OR: 2.13, 95% CI: 1.12–4.05, Table 4). In addition, educational level, previous surgeries, and immunosuppressant use were also associated with non-adherence (Table 4), but not with disease location, behavior, smoking status, 5-ASA or steroid use. There was also no difference between patients receiving oral or topical therapy. The number of concomitant medications was also not predictive of medical non-adherence. In a logistic regression analysis, the level of education and previous surgeries were identified as independent factors, with a strong tendency for date of last follow-up visit and immunosuppressant use (Table 5). In contrast, none of the factors analyzed was associated with probability of non-adherence in UC.

In both forms of IBD, alternative medicine use was associated with younger age, higher educational level, and immunosuppressant use (Table 6). In CD, CAM use was also more common in patients receiving 5-ASAs, while in UC, it was

Table 5 Logistic regression: predictive factors for self-reported non-adherence in patients with Crohn's disease.

Factor	Coefficient	p value	OR	95% CI
Disease duration	0.220	0.361	–	–
Date of last follow-up visit	0.638	0.072	1.89	0.96–3.79
Low education level	0.541	0.028	1.72	1.06–2.78
No immunosuppressant use	0.527	0.075	1.69	0.95–3.03
Previous surgery	0.559	0.011	1.75	1.14–2.69

The coefficient is equivalent to the natural log of the OR; p value: level of significance; OR: odds ratio; 95% CI: 95% confidence interval.

Table 6 Predictive factors for complementary and alternative medicine (CAM) use in patients with inflammatory bowel diseases in univariate analysis.

Factor	CAM use (%)	<i>p</i> value	OR (95% CI)
<i>Crohn's disease</i>			
Age			
<40 years	40.4	<0.001	2.63 (1.59–4.39)
>40 years	20.5		
Educational level (<i>n</i> =303)			
Low	21.6	0.018*	–
Medium	31.8		
High	41.4		
5-ASA use			
Yes	46.2	0.008	2.09 (1.20–3.64)
No	29.1		
Immunosuppressant use			
Yes	37.5	0.017	1.78 (1.11–2.88)
No	25.2		
<i>Ulcerative colitis</i>			
Age			
<40 years	44.4	<0.001	2.39 (1.45–3.94)
>40 years	25.0		
Gender			
Females	39.7	0.017	1.82 (1.11–3.00)
Males	26.5		
Place of residence (<i>n</i> =252)			
Urban	35.7%	0.01	2.47 (1.22–4.94)
Rural	21.2%		
Educational level (<i>n</i> =262)			
Low	16.7	0.018*	–
Medium	33.1		
High	38.2		
Psychiatric/psychological supportive care (<i>n</i> =275)			
Yes	59.5	0.001	3.18 (1.56–6.50)
No	31.6		
Immunosuppressant use			
Yes	51.3	<0.001	2.90 (1.67–4.96)
No	24.7		
Steroid use			
Yes	47.1	0.004	2.24 (1.29–3.90)
No	28.4		

p calculated by χ^2 -test or *linear-by-linear association.

more common in females, steroid users, and in patients with additional psychiatric or psychological therapy. In addition, CAM use in UC was associated with the number of concomitant medications, gradually increasing from 25.8% in patients receiving only one medication to 52.4% in patients receiving three or more different medication types ($p=0.004$). No other clinically relevant associations—including drug formulation—were found in either CD or UC. The number of concomitant medications was not predictive for CAM use. In addition, there was no association between non-adherent attitude—magnitude and CAM use (data not shown).

In a multivariate analysis, age (Coefficient: -0.904 , $p=0.002$, OR: 0.41; 95% CI: 0.23–0.72) and 5-ASA use (Coefficient: 0.693, $p=0.042$, OR: 1.99, 95% CI: 1.38–3.89) were identified as independent predictors for CAM use in CD.

Table 7 Logistic regression: predictive factors for complementary and alternative medicine use in patients with ulcerative colitis.

Factor	Coefficient	<i>p</i> value	OR	95% CI
Female gender	0.439	0.169	–	–
Age>40 years	-0.681	0.036	0.51	0.27–0.96
Urban residency	0.668	0.012	2.07	1.14–3.83
Education level	0.319	0.206	–	–
Immunosuppressant use	0.989	0.009	2.69	1.28–5.64
Steroid use	0.549	0.14	–	–
Psychiatric/psychological therapy	1.001	0.023	2.72	1.15–6.45

The coefficient is equivalent to the natural log of the OR; *p* value: level of significance; OR: odds ratio; 95% CI: 95% confidence interval.

However, in UC, age, place of residence, immunosuppressant use, and additional psychiatric/psychological therapy were identified as independent predictors for CAM use in a logistic regression analysis (Table 7).

4. Discussion

This is one of the first studies to investigate the prevalence and predictors of medical non-adherence and CAM use in Eastern Europe. In the present study, the authors found a relatively high prevalence of self-reported non-adherence and CAM use in a large Hungarian IBD cohort followed-up at referral IBD centres. The rate of medical non-adherence reported in the present study (approx. 21%) is within the range reported from European centres (29%),¹⁰ by using similar methodology and definition of non-adherence. A drawback of this method, however, is that it can both under- and overestimate adherence, and its accuracy depends on the patient's cognitive abilities, the honesty of replies, as well as the interviewer's correct interpretation of responses. The patient may forget doses taken or missed. The most common causes of non-adherence, as reported by the patient (e.g., forgetfulness, too many/unnecessary pill, being afraid of side effects) were similar to that reported in previous studies.^{8,11}

By using univariate and multivariate analysis, the date of the last follow-up visit, lower educational level, previous surgeries, and immunosuppressant use were also associated with non-adherence in patients with Crohn's disease. In contrast, a higher education level and full-time employment were also associated with a non-adherent patient behavior in some,⁴ but not all previous studies.⁸ In a recent Italian study,¹² non-adherence was 43% in patients <40 years old compared to 34% in those older than 40 years ($p=0.041$, OR: 1.5, 95% CI: 1.01–2.13). A recent diagnosis and disease duration shorter than 5 years was also associated with significantly worse adherence (24% of the patients) than a longer-standing disease (15% of the patients; $p=0.001$, OR: 2.1, 95% CI: 1.30–3.39) in the same study. In the present study, both short and very long disease duration was associated with higher non-adherence rates. In addition, we failed to identify the previously reported association between gender and medical adherence.^{3,6,23}

An association between medical adherence and complicated disease course in CD was reported by Spanish authors.⁸ Better adherence was significantly associated with a more complicated disease course (steroid dependency, steroid refractoriness, need for infliximab treatment, hospitalization, or surgery) in patients with short disease duration. Similarly, in the present study, a higher number of previous resection surgeries and need for immunosuppressant therapy suggesting a more aggressive disease course was associated with improved self-reported adherence in patients with CD. In both, CD and UC, active disease was associated with higher adherence even if steroids were included in the treatment regimen.⁶ In contrast, other studies reported low adherence rate after long-term remission.^{3,12} Very high non-adherence rates (74.3%) were reported for azathioprine in CD patients who were in a long term (>48 months) clinical remission.²³

In UC, Kane et al.³ reported by means of a univariate analysis, the male gender, not being in a relationship, left-sided disease, and a history of more than four concomitant medications were negatively associated with adherence. Conversely, being married, a recent colonoscopy, and greater extent of disease support adherence. In contrast, in the present study, none of the factors analyzed were associated with probability of non-adherence.

Non-adherence to therapy might also be due to the drug formulation causing discomfort (difficulty in swallowing tablets or using enemas) or side effects (pain or abdominal distension, difficulty in retaining enemas). Most studies are consistent in finding that topical therapy with enemas, suppositories or foams is more likely to be associated with non-adherence than oral therapy. In an Italian study,¹² topical therapy with enemas was associated with significantly more non-adherence (68% of users) than oral therapy (40% of users; $p=0.001$, OR: 0.25, 95% CI: 0.11–0.60). In contrast, in the present study, the use of topical 5-ASA was not associated with lower adherence rates. Of note, however, only 23.4% of the UC patients received this form treatment; most of them as adjunctive therapy with oral 5-ASA.

The association between the type of oral medications and non-adherence is also complex. Reasons for non-adherence with oral therapy include multiple daily doses and a high number of concomitant medications. The undesirable side effects of some medications (e.g., weight gain, cushingoid appearance, and immune suppression) and the complex treatment regimens for IBD patients (e.g., varying dosing schedules and pill quantities for each medication) are likely to disrupt adherence and effective management of this condition. In the study by Kane et al.,³ besides being males, single and having left-sided disease, non-adherent patients were statistically more likely to be simultaneously taking four or more medications (60% vs. 40%). In an Italian study, the need to take medications during work hours ($p=0.001$, OR: 3.5, 95% CI: 2.27–5.26), and multiple daily doses ($p=0.045$, OR: 2.8, 95% CI: 0.99–7.70) were significantly associated with non-adherence in adults.¹² Similarly, adolescents whose regimen involved more than one daily medication administration had more adherence barriers.²⁴ Interestingly, some studies did not report a direct association. For example, in the study by Cervený et al.,⁴ the non-adherence rate at any time point was 40% on aminosaliclates, 29% in patients on systemic steroids, and 31% in patients on immunosuppressants in IBD, supporting the

notion that adherence is influenced by multiple parallel factors, including gender, age, disease phenotype, course, and disease activity. In the present study, we did not find an association between the drug type, dosing regimen, and concomitant number of medications and medical adherence except for the reported better adherence in patients on immunosuppressants. However, the better adherence in those patients might be partly secondary to the more aggressive disease course as highlighted by the higher surgical need in those patients.

Finally, the partnership between patient and treating physicians are of utmost importance in determining medical adherence, where effective patient–physician dialog is central to promoting patient adherence.¹² Sewitch et al.⁶ found an increased risk for intentional non-adherence to be associated with being treated by the same physician for more than 1 year, not scheduling another appointment, and greater total discordance between the patient and the physician. Similarly, a last follow-up visit beyond 1 year was predictive for reduced adherence in the present study.

A limitation of the present study is that the no direct methods for measuring medication adherence were used. However, only a limited number of drugs can be monitored in this manner. In IBD, bioassays measuring 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN) levels have been suggested as potentially useful objective adherence markers for 6-mercaptopurine (6-MP)/azathioprine (AZA).^{25,26} The bioavailability and completeness of absorption of various drugs, as well as the rate of metabolism and excretion, are factors that make it difficult to correlate drug concentrations in blood or urine with adherence. Moreover, the ability of direct methods to identify non-adherence also depends on the accuracy of the test and the degree to which the patient was non-adherent before the urine or blood sample was taken.

The rate of CAM use (approx. 31%) found in the present study is in concordance with international trends reporting increasing number of CAM users in the average population as well as in IBD in the last decade.^{18,20,27} Alternative medicine use was associated in both diseases with younger age, higher educational level, and immunosuppressant use, while in UC it was also associated with gender, number of concomitant medications, and additional psychiatric or psychological therapy. In both diseases, age, while in UC, also place of residence, immunosuppressant use, and additional psychiatric/psychological therapy were identified as independent predictors for CAM use in a multivariate analysis.

In a Canadian study,²⁰ CAM use was associated with more severe disease activity, use of CAM for other purposes, and a desire for an active role in treatment decisions. CAM use was also associated with younger age in those with Crohn's disease, and less confidence in their IBD physician in those with ulcerative colitis. In contrast, patient age, gender, disease diagnosis, or duration of disease was not predictive of any type of alternative medicine use in a multicentre study including Canada, Ireland, Sweden, and the US.¹⁷ Moreover, in a phone survey study,²⁸ CAM use could not be predicted by either greater or less hospitalizations, conventional doctor visits, or GI specific visits. CAM was sought mostly to palliate pain or diarrhea. Of note, however, rates and predictors may not be directly comparable with each other due to differences in the definition of CAM use.

In conclusion, non-adherence and CAM use is common in patients with IBD. Special attention should be paid to explore the identified predictive factors during follow-up visits to improve adherence to therapy, understand motivation for CAM use, and improve patient–doctor relationship.

Conflict of interest

None.

Ethical permission

The study protocol was approved by the Ethical and Science Committee of the Ministry of Health (ETT TUKEB, ad 260/PI/2009, ad.8-103/2009-1018EKU). Each patient was informed of the nature of the study and signed the informed consent form.

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Author contribution to the paper – PLL–study design, data collection, data analysis, supervising the collection and validation of patients and manuscript preparation; GyD, OG, KP, TK, FN, AS, PD, TSz, JB, LB, AK, IR, MP, IA, and JP–data collection and manuscript preparation; LL–study design, supervising the collection and validation of patients data collection and manuscript preparation. All authors have approved the final, submitted draft.

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