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Complementary and alternative medicine use in narcolepsy<sup>☆,☆☆</sup>Benedicte Marie Finger<sup>a, \*</sup>, Annika Triller<sup>a</sup>, Ashley M. Bourke<sup>b</sup>, Gert Jan Lammers<sup>c</sup>, Christian Veauthier<sup>d</sup>, Merve Yildizli<sup>a</sup>, Ulf Kallweit<sup>a, e, \*\*</sup><sup>a</sup> Center for Narcolepsy and Clin. Sleep and Neuroimmunology, Institute of Immunology, University Witten/Herdecke, Witten, DE, USA<sup>b</sup> Department of Synaptic Plasticity, Max Planck Institute for Brain Research, Frankfurt, Germany<sup>c</sup> Leiden University, Department of Neurology, Medical Centre, Leiden, the Netherlands<sup>d</sup> Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Interdisciplinary Center of Sleep Medicine, Charitéplatz 1, 10117, Berlin, Germany<sup>e</sup> Center for Biomedical Education and Research (ZBAF), University Witten/Herdecke, Witten, Germany

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## ABSTRACT

**Background:** Management of narcolepsy includes behavior strategies and symptomatic pharmacological treatment. In the general population, complementary and alternative medicine (CAM) use is common in Europe (30%), also in chronic neurological disorders (10–20%). The aim of our study was to evaluate frequency and characteristics of CAM use in German narcolepsy patients.

**Methods:** Demographic, disease-related data frequency and impact of CAM use were assessed in an online survey. Commonly used CAM treatments were predetermined in a questionnaire based on the National Center for Complementary and Alternative Medicine and included the domains: (1) alternative medical systems; (2) biologically based therapies; (3) energy therapies; (4) mind-body interventions, and (5) manipulative and body-based therapies.

**Results:** We analyzed data from 254 questionnaires. Fifteen percent of participants were at the time of survey administration using CAM for narcolepsy, and an additional 18% of participants reported past use. Among the 33% of CAM users, vitamins/trace elements (54%), homeopathy (48%) and meditation (39%) were used most frequently. 54% of the users described CAM as helpful. CAM users more frequently described having side effects from their previous medication ( $p = 0.001$ ), and stated more frequently not to comply with pharmacological treatment than non-CAM users (21% vs. 8%;  $p = 0.024$ ).

**Discussion:** The use of CAM in narcolepsy patients is common. Our results indicate that many patients still feel the need to improve their symptoms, sleepiness and psychological well-being in particular. Frequent medication change, the experience of adverse events and low adherence to physician-recommended medication appears more frequent in CAM users. The impact of CAM however seems to be limited.

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## 1. Background

Narcolepsy is a chronic immune-mediated neurological disorder and is currently classified into narcolepsy type 1 (NT1) or narcolepsy type 2 (NT2), based on the presence (NT1) or absence (NT2) of cataplexy or orexin deficiency [1]. Worldwide, narcolepsy has a

prevalence of 25–53/100,000 [2,3]. Initial symptoms usually occur during adolescence [4]. Chronic excessive daytime sleepiness (EDS), cataplexy (in NT1), sleep paralysis, hypnopompic and/or hypnagogic hallucinations, automatic behavior, cognitive disturbances, fatigue and disturbed night sleep are main symptoms [5]. Diagnostics include a detailed (family) history, questionnaires (e.g. the Epworth Sleepiness Scale (ESS)) [6,7], sleep examinations (polysomnography [PSG] and the Multiple Sleep Latency Test (MSLT)), and optionally also CSF orexin measurement [8,9].

Treatment includes non-pharmacological strategies and drug therapy. Non-pharmacological therapy includes behavioral management recommendations, such as scheduled napping [10]. Currently available drug therapy is purely symptomatic and mainly addresses the key symptoms of excessive daytime sleepiness (EDS)

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and cataplexy [11].

In Germany, 40–62% of the general population indicated general acceptance and use of complementary and alternative medicine (CAM) [12,13]. In regards to disease-specific symptom management, CAM usage rates are lower. For example, 25% of epilepsy patients reported using CAM at least once since disease onset [14]. Within the last year, 10% of patients with epilepsy reported using CAM; 19% for those with migraine [15]. General predictors of CAM use in this context are female sex as well as middle-age and higher socioeconomic status [16,17]. The most commonly used CAMs in the general population are acupuncture, vitamins/trace elements, medicinal herbs, and homeopathy, but the numbers vary widely depending on the study design [17]. Non-adherence and attitudes toward conventional medication can also influence CAM use [18]. The costs for CAM usually have to be paid by the patient herself, and thus, less-resourced individuals are generally less able to pay out-of-pocket for desired treatment [19].

In Germany, CAMs can be offered by a physician with additional training in natural medicine (“Naturheilkunde”), or by a “healing practitioner” (“Heilpraktiker”), a non-physician naturopathic profession recognized by German law since the 1930s. Reimbursement however is limited, too. Also, homeopathy is frequently used in Germany [20].

There are no data available on the use of CAM in narcolepsy. Recent European narcolepsy guidelines indicate that patients request more and better non-pharmacological treatment options [11].

The aim of the study was to assess the frequency of CAM use among narcolepsy patients in Germany and to analyze clinical characteristics of patients using CAM, and also the effects of its use.

## 2. Methods

**Participants:** Adult patients with narcolepsy (NT1 and NT2) were included. Diagnosis information was based upon participants self-reporting. Self-reported diagnosis was crosschecked for conflicting information (e.g. self-reported NT1, but questionnaires on cataplexy answered with “no”) during the survey. If conflicting, data were excluded from analysis.

**Survey:** For assessment an online survey (LimeSurvey) was used, and was administered between November 2020 and May 2021. The study participants were contacted in two major German narcolepsy out-patient clinics (Witten and Berlin, in total approx. 800 patients), by narcolepsy self-help groups, and the German Narcolepsy Network ([www.narkolepsie-netzwerk.de](http://www.narkolepsie-netzwerk.de)). Reaching approx. 1000–4000 individuals with narcolepsy in Germany.

The survey included sociodemographic and disease-related (e.g. symptoms, medication) questions, as well as questions about the frequency and impact of CAM use in narcolepsy management. There are different systems for categorizing CAM treatments in medical research [21]. We classified CAM treatments according to the five domains described by the National Center for Complementary and Alternative Medicine (NCCAM): (1) alternative medical systems; (2) biologically based therapies; (3) energy therapies; (4) mind-body interventions, and (5) manipulative and body-based therapies [22]. The severity of EDS in narcolepsy was assessed by the Epworth Sleepiness Scale (ESS). Additional narcolepsy symptoms were assessed using the Swiss Narcolepsy Scale (SNS) [23]. Participants were asked also about their use of conventional medications. To assess potential causes of non-adherence in patients, we included excerpts from the Adherence Barriers Questionnaire © (ABQ) [24]. The survey included a total of 69 questions consisting of multiple choice, Yes/No, and Likert scale questions, some of which will be analyzed in a second paper on treatment adherence in narcolepsy. For the narcolepsy questions, there were

either yes/no questions (type), date (year) information (onset of illness), or multiple response sets (extended symptom check list). The survey can be requested from the authors.

**Statistics:** Descriptive statistics were applied to characterize sociodemographic variables and sleepiness scales. Data were reported as mean  $\pm$  standard deviation or percentage for continuous variables, and frequency for categorical ones (including ordinal variables). The chi-square test was used to compare characteristics of CAM users vs. non-CAM users for categorical variables. The significance level after Bonferroni correction was set to 0.0066. Statistical analyses were performed using SPSS software release 26.0 (IBM Corp. Released 2020. IBM SPSS, Version 26.0. Armonk, NY: IBM Corp). We excluded questionnaires with incomplete sociodemographic, CAM data and unknown narcolepsy type. All descriptive data had to be filled in as well as data on CAM use, otherwise survey data were also excluded from analysis.

**Ethics:** The study was registered and approved by the ethical committee of the Witten/Herdecke University (No.07/2020).

## 3. Results

272 narcolepsy patients answered the online survey. Of them, 254 were included into analysis ( $n = 181$  (71%) NT1;  $n = 73$  NT2 patients). Eighteen questionnaires were excluded mainly due to incomplete descriptive data or no answers about CAM.

The average age of the participants was 35.8 years ( $SD \pm 12.2$ ; range 18–82), with more women than men having participated ( $n = 195$  (77%) women). The mean age at diagnosis was 28 years for women ( $SD \pm 12.0$ ) and 32 years for men ( $SD \pm 9.9$ ). The average ESS score was 16.4 ( $SD \pm 3.8$ ). The mean duration from disease onset was 29 years (range 11–61 years).

Data on demography, level of education, housing, employment status and comorbidities are shown in Table 1.

Thirty-three percent ( $n = 84$ ) of the patients reported present (15%) or past (18%) CAM use in treating symptoms of narcolepsy with no significant difference between NT1 and NT2 patients ( $n = 62$  (34%) vs.  $n = 22$  (30%);  $p = 0.528$ ).

About half (54%) of the patients who ever used CAM ( $n = 40/74$ ) described it as “helpful” for narcolepsy, with majority in NT1 (64%; NT2: 27%;  $p = 0.006$ ). The frequency of usage of different CAMs are shown in Fig. 1.

Mind-body interventions generally were more often used by women (76% vs. 24% by men). Women used more yoga (42% vs. 5% of men), meditation (45% vs. 4% of men) and art/music therapies (26% vs. 0% of men).

For other CAMs, we detected no differences in gender or in age.

Seventy-five percent of CAM users utilized CAM once a week or more, and 23% only once a month or more. Of patients who currently did not take any conventional pharmacological treatment (15%;  $n = 38$ ), 23% reported current CAM use. Use of both conventional medicine and CAM at the same time was described by 27% of patients (69/254).

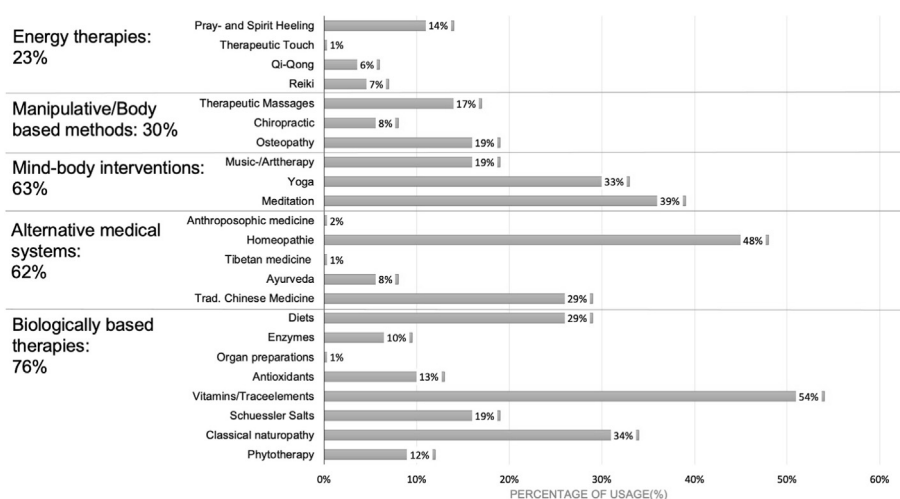
CAM users were more likely to have as comorbidity an autoimmune disease (excluding disorders with hypothyroidism or hyperthyroidism) than non-CAM users. (32% CAM users vs. 13% non-CAM users).

### 3.1. Comparison of users and non-users of CAM

Of the 84 patients who reported past or present CAM use, 73% reported having automatic behavior ( $n = 61$  vs.  $n = 97$  (57%) non-CAM users), 68% hypnagogic/hypnopompic hallucinations ( $n = 57$  vs.  $n = 91$  (53%) non-CAM users), and 70% nightmares ( $n = 59$  vs.  $n = 97$  (57%) non-CAM users). For additional comparison data please see the supplemental figure (S1). Regarding CAM use and

**Table 1**  
Sociodemographic and clinical data of narcolepsy patients.

	ALL (n = 254)	Non-CAM user (n = 170)	CAM user (n = 84)
Female gender in % (n)	77 (195)	78 (133)	74 (62)
Age in years, mean (SD; range)	35.8 (12.2; 18–81)	34.6 (12; 18–65)	38.11 (12.37; 18–82)
Duration from narcolepsy onset, in years, mean (SD)	29.0 (10.5)	28.9 (10.8)	29.1 (9.99)
<b>Housing</b>			
Alone in % (n)	23 (58)	26 (44)	17 (14)
Together with family, partner, others in % (n)	77 (196)	74 (136)	83 (70)
<b>Education completed</b>			
No in % (n)	23 (58)	27 (45)	16 (13)
Yes in % (n)	77 (196)	73 (125)	84 (71)
Secondary School in % (n)	22 (57)	26 (44)	16 (13)
High School in % (n)	13 (32)	15 (25)	8 (7)
(Technical-) University degree in % (n)	39 (98)	32 (55)	51 (43)
Apprenticeship/Training in % (n)	21 (53)	21 (35)	21 (18)
Currently in training in % (n)	5 (14)	6 (11)	4 (3)
<b>Employment</b>			
Fully employed in % (n)	31 (78)	35 (60)	21 (18)
Partly employed in % (n)	20 (50)	20 (34)	19 (16)
Retired in % (n)	19 (49)	12 (21)	33 (28)
Not employed in % (n)	30 (77)	32 (55)	26 (22)
<b>Comorbidities</b>			
Yes in % (n)	68 (173)	66 (112)	73 (61)
Non in % (n)	32 (81)	34 (58)	27 (23)
<b>Most frequent comorbidities</b>			
Depression in % (n)	33 (84)	31 (52)	38 (32)
Other autoimmune disease in % (n)	18 (47)	12 (20)	32 (27)
<b>Epworth Sleepiness Scale</b>			
>10 Points	94 (238)	93 (158)	95 (80)
>16 Points	65 (165)	64 (108)	68 (57)



**Fig. 1.** Usage of different CAMs and CAM subgroups in percentage (%).

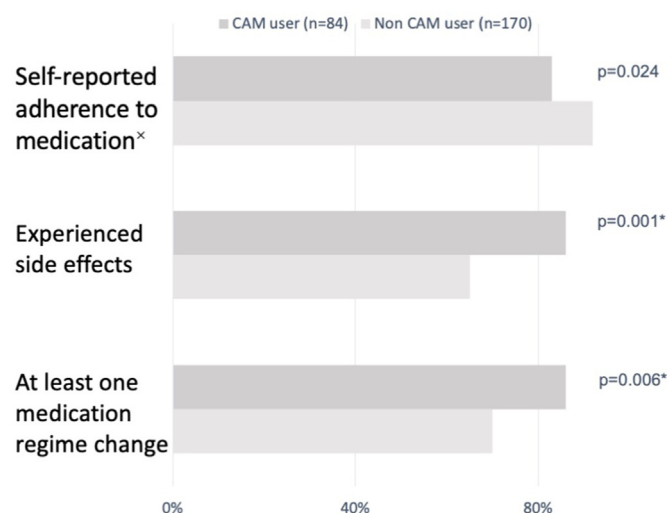
CAMs are divided into five domains, according to the National Center for Complementary and Alternative Medicine (2005). There are different numbers of subgroups for the individual domains. A subgroup was only counted if at least one CAM item was selected at this group (% of n = 84 CAM Users).

other symptoms, no significant differences in gender or in age were found. CAM use was more frequent in participants 1. With a higher educational level ((technical) college 44% vs. apprenticeship 33%), 2. being retired (pensioner 57% vs. working full time 23%), and 3. Having low or no working-time (part-time, retired, unemployed 43% vs. fulltime working 23%).

At least one conventional medication regime change was experienced by 75% (n = 191) of all respondents. Notably, CAM users were significantly more likely to have used at least one other conventional medication prior to their current medication (86% vs. 70%;  $p = 0.006$ ) and significantly more likely to have experienced side effects in contrast to non-CAM users (86% vs. 66%;  $p = 0.001$ ).

See also Fig. 2. Those who previously used dexamphetamines in particular were more likely to use CAM (17% vs. 7%).

We asked whether patients adhere to the recommendations of the treating physicians by using questions from the ABQ, see above. CAM users more frequently stated not to comply with pharmacological treatment than non-CAM users (21% vs. 8%;  $p = 0.024$ ). There were no significant differences among CAM users and non-CAM users in adherence to non-pharmacological treatment/behavioral recommendations such as scheduled napping, regular physical exercise, and maintaining a regular daily rhythm. Additionally, there were no significant differences with regard to the disease duration, presence of sleepiness or the ESS score.



**Fig. 2. CAM and medication: comparisons between CAM-/and Non-CAM users in percentage (%).**

Comparisons between users who had at least one change in their conventional medication ( $p = 0.006$ ), who experienced side effects from their conventional medication ( $p = 0.001$ ), and users who self-reported not being adherent to the prescribed conventional medication ( $p = 0.024$ ). \* = significant, <sup>x</sup> = CAM user ( $n = 76$ ) Non CAM user ( $n = 161$ ).

### 3.2. Attitude towards health issues

We analyzed a subset (three questions) of the ABQ, regarding non-adherence barriers and attitudes toward medications. Eighty percent ( $n = 64$ ) of CAM users stated that they trusted their doctor and mutually agreed on the treatment plan. There was no difference between them and non-CAM users (80% vs. 81%). Costs were stated as a large burden of CAM use, stated forty-five percent (36/80) of CAM users. CAM users ( $n = 80$ ) more often reported having to overcome obstacles to receive healthcare, e. g. doctor/pharmacy is far away (47% vs. 36%;  $p = 0.006$ ) compared to non-CAM users. Among CAM users, fear of side effects of their medications was higher (47%) than among non-CAM users (36%), with no statistical significance.

## 4. Discussion

This is the first study assessing CAM use in narcolepsy patients. Among the general population in Germany, there is a general belief that all CAMs are safe compounds and are usually not causing side effects [25]. Awareness of lack of scientific evidence on the efficacy of CAMs seems to be limited however. Biologically based therapies are the most frequently used CAM subgroup (76%), vitamins and trace elements in particular. This may reflect the desire to increase energy and improve sleepiness and fatigue. The second most frequently used CAM subgroup was mind-body interventions (63%). These were three times more frequently used by women, which is comparable to other Western countries where yoga is used twice as often by women as by men [26]. In this group, meditation (39%) and yoga (33%) were most commonly used, indicating a possible desire for spiritual and psychological contentment and well-being. The predictor female sex in CAM use could be found only in the mind-body interventions subgroup, but not as a general predictor. Homeopathy as an alternative medical system is often represented in German speaking countries (up to 35% in the general population) [17,27]. The data from our study also reflect this among narcolepsy patients (48% of CAM users).

The predictors sex and age, which can be assumed for CAM use

in the German general population, could not be confirmed for German narcolepsy patients. However, the predictor of high socioeconomic status can be assumed, as people with university degrees use more often CAM. CAM use in narcolepsy patients is similar to the general population in Germany, as 15% currently use CAM, this is comparable to other chronic diseases like asthma (15%) or migraine (19%) [15].

In addition to EDS and cataplexy, other symptoms such as automatic behaviors may be more severe in NT1 compared to NT2 [15]. Frequent CAM use in NT1 indicates a particular need for symptom improvement in this group of patients. Further, narcolepsy patients suffering from automatic behaviors, hypnagogic/hypnopompic hallucinations, and nightmares more frequently used CAM. This suggests that these symptoms in particular may not be sufficiently addressed with the available medication and/or are not being sufficiently addressed by physicians. Patients might feel an improvement of EDS or cataplexy, but not of other symptoms, in particular symptoms that could be felt being more “spiritual” or frightening.

The hypothesis that patients who experience lack of efficacy, indicated by frequent regime changes and/or side effects from previous medications have higher rates of CAM use was confirmed. Dissatisfaction with medication probably increases the willingness to use CAM, even though CAM usually has to be paid out-of-pocket and is not reimbursed.

More than half of patients (55%) who have ever used CAM reported high barriers to health care, in contrast to only 37% of patients who have never used CAM. This suggests that poor access to health care may increase the likelihood of narcolepsy patients to use CAM.

### 4.1. Limitations

An online study has limitations. Due to the format of an online study, diagnostic certainty cannot be fully ensured. However, the invitation by centers and patient self-help groups and the typical symptom constellation of the answers strongly suggest an appropriate diagnosis of narcolepsy. In case of contradictions in the data, these cases were excluded. Given that participation in the study did not involve monetary compensation and required a relatively high (30–40 min) time commitment, there was no incentive to participate in the study without a diagnosis. Since the survey period coincided with coronavirus disease (COVID-19) containment interventions (e.g. lockdown, home office, quarantine rules), it cannot be ruled out that this had an impact on the results of the study [28,29].

Larger studies need to confirm the results. Future studies should discuss the motivations of CAM users and for which symptoms patients use CAM. Also, over what period of time CAM was used and which therapies were used and which ones were beneficial or not.

## 5. Conclusion

The use of CAM in narcolepsy patients is common and comparable to the use in other chronic neurological disorders in Germany. The impact however seems to be limited. Data indicate that current treatment options do not sufficiently improve symptoms (EDS in particular), and/or that the regularly used drugs often cause adverse effects. The relatively high use of mind-body interventions points to the need to improve psychological well-being. Patients with higher levels of education, and therefore presumably higher income, patients with lower adherence to conventional medicine, and those with more spare time are more likely to use CAM.



## Potential CIO

G.J.Lammers has received grant for investigator initiated study from Jazz Pharmaceuticals, Bioprojet, UCB Pharma, Consulting fees & Chair Satellite Symposium from Jazz Pharmaceuticals, Advisory board from Jazz Pharmaceuticals and Bioprojet.

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U.Kallweit has received honoraria from AOP, Bioprojet, Harmony Biosciences, Jazz, Takeda and UCB.

B.M.F., A.T., A.M.B., and M.Y. report no conflicts of interest.

## Current knowledge/study rationale

There is are high use and acceptance rates for complementary and alternative medicine in Germany and other Western countries. This study was carried out to determine the extent of CAM use in narcolepsy patients, and to assess whether a certain narcolepsy type or patient profile correlates with higher rates of CAM use and whether CAM use is considered a helpful strategy in the management of narcolepsy symptoms.

## Impact of the study

This is the first study on CAM use in narcolepsy. Our results reveal current or past CAM use in a considerable fraction of narcolepsy patients, particularly in those who experience adverse events from conventional medication, with low adherence to therapy, and who suffer from particular symptoms. These findings are useful for treating physicians and allows assumptions to be made about the demands on conventional medicine.

## CRediT authorship contribution statement

**Benedicte Marie Finger:** Conceptualization, Methodology, Software, Investigation, Writing – original draft, preparation. **Annika Triller:** Investigation, Writing – original draft, preparation. **Ashley M. Bourke:** Visualization, Writing – review & editing. **Gert Jan Lammers:** Conceptualization, Writing – review & editing. **Christian Veauthier:** Writing – review & editing. **Merve Yildizli:** Investigation, Methodology, Software, Writing – review & editing. **Ulf Kallweit:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare no potential conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2023.01.013>.

## List of abbreviations

ABQ	Adherence Barriers Questionnaire
CAM	Complementary and alternative medicine
ESS	Epworth Sleepiness Scale

ICSD	International Classification of Sleep Disorders
MSLT	Multiple Sleep Latency Test
NA	Non-Adherence
NT1	Narcolepsy Type 1
NT2	Narcolepsy Type 2
PHQ-9	Patient Health Questionnaire-9
PSG	Polysomnography
SF36 (VR-36)	Short Form 36 (Veterans Rand-36) health quality questionnaire
SNS	Swiss Narcolepsy Scale
SOREM	Sleep onset REM
REM	Rapid eye movement

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