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Barriers to therapy adherence in narcolepsy

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ABSTRACT

Background: Treatment adherence (TA) in narcolepsy is a complex phenomenon influenced by various factors beyond patient-related aspects. The management of narcolepsy involves non-pharmacological and symptomatic pharmacological treatment. Factors such as chronic daytime sleepiness, cognitive deficits, psychiatric comorbidities and adverse effects of pharmacological treatment are aspects of narcolepsy that could undermine TA, impacting patients' ability or willingness to consistently follow treatment plans. The aim of this study was to identify the factors influencing TA in narcolepsy and to determine the most significant barriers to adherence.

Methods: An online survey was conducted during the pandemic, assessing demographic and clinical data, medication usage, and adverse effects of treatment. Various questionnaires, such as the Adherence Barriers Questionnaire (ABQ) and Epworth Sleepiness Scale (ESS), were utilized. The ABQ identified patient-specific barriers to medication adherence, while the Patient Health Questionnaire (PHQ-9) assessed depressive symptoms.

Results: We analyzed 243 narcolepsy patients (77 % female, mean age 35.7 ± 12.3 years) with 71 % having narcolepsy type 1 (NT1). The average ESS score was 16.4 (SD ± 3.7). Adherence barriers (AB) were identified in 89 % of patients (216/243) based on ABQ score. The most common barriers reported were "Forgetfulness" (77 %), "Depression" (57 %), and "Side effect-driven medication reduction/stopping behavior" (49 %). Approximately 72 % of patients reported side effects from their narcolepsy medication, leading to discontinuation in 78 % of cases. A moderate correlation was found between the severity of adherence barriers (ABQ score) and levels of depression (PHQ-9 score; rs = 0.412, p = 00.000), as well as ESS score (p = . 048). The results of this study may have been influenced by the pandemic situation.

Conclusion: Adherence barriers are common (89 %) and diverse among people with narcolepsy. Many barriers are related to excessive daytime sleepiness (EDS), cognitive deficits or depressive symptoms, highlighting the importance of recognizing and addressing them for optimal TA. Medication side effects, especially occurring when polypharmacology is utilized, also significantly contribute to adherence challenges. Effective communication regarding therapy adherence and improved detection and management of EDS and depression are crucial for enhancing TA in narcolepsy patients.

1. Background

Narcolepsy is a rare chronic immune-mediated neurological disorder, which has a prevalence of 25–53/100,000 worldwide [1,2]. Narcolepsy is categorized into two types: Narcolepsy type 1 (NT1), distinguished by low cerebrospinal fluid hypocretin-1 levels and the presence of cataplexy, and Narcolepsy type 2 (NT2), characterized by normal hypocretin-1 levels and the absence of cataplexy [3]. Typically emerging in

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childhood or early adolescence [4], this heterogeneous disorder involves excessive daytime sleepiness (EDS), cataplexy (in NT1), sleep paralysis, hypnopompic/hypnogogic hallucinations, fragmented nocturnal sleep, and automatic behavior as its main symptoms [5]. Other commonly reported symptoms include fatigue and cognitive impairment [6].

Pharmacological treatment for narcolepsy focuses on symptom management, often necessitating lifelong medication, with options including fixed regimens and as-needed therapies to address EDS, cataplexy, and disturbed nocturnal sleep [7]. Non-pharmacological strategies such as cognitive and behavioral interventions, scheduled naps, sleep hygiene, balanced diet, and physical activities also benefit patients [8,9]. The use of complementary and alternative medicine (CAM) is reported by some patients, with CAM users tending to show lower adherence to physician-recommended medications [10]. The self-management required for chronic conditions like narcolepsy is complex and is often further complicated by disease symptoms and comorbidities such as depression [11].

The term "adherence" lacks a uniform definition, but the World Health Organization (WHO) defines it as the extent to which a person's behavior aligns with the recommendations from their healthcare providers [12].

The measurement of treatment adherence presents a unique challenge as there is no universally accepted "gold standard" [13,14]. Methods include subjective assessments from healthcare providers and patients (e.g., self-report questionnaires) [15], as well as objective strategies involving electronic measuring devices [16], analysis of prescription/claims data, and biochemical measurements [17].

Adherence to long-term therapies for chronic disorders, such as narcolepsy is usually around 50 % in developed countries, leading to poorer health outcomes for patients and increased healthcare costs [12]. Beyond the economic implications, adherence plays a major role in ensuring patient safety.

Although there are no specific studies on narcolepsy TA in general, a study on adherence to wakefulness-promoting medication in patients with narcolepsy showed that only about 55 % of the patients had good adherence [18]. In similar chronic conditions such as epilepsy, non-adherence (NA) is a prevalent issue, with up to 68 % of patients not following their prescribed antiepileptic drug regimens [19].

Compared to the general population, individuals with narcolepsy experience a significant reduction in health-related quality of life. This includes lower satisfaction with physical well-being [20], energy levels, and social functioning [21], and a higher incidence of comorbid conditions such as obesity, diabetes, and depression [22,23].

Patients are often financially constrained by the disease, as they are more likely to be unemployed and have lower incomes compared to matched control groups [24,25].

While patient characteristics like young and old age, female gender, low socioeconomic status, and low educational attainment are recognized predictors of NA to chronic disease medications [26–29], the adverse effects of the medications themselves present a major obstacle to TA [30,31]. Also, polypharmacy, usually defined as taking at least 5 medications at the same time, can increase the likelihood of more side effects occurring, which in turns can affect TA [32,33]. Additionally, cognitive impairments, such as those seen in patients with Alzheimer's dementia or severe depression, significantly affect therapy adherence [34]. It is hypothesized that narcolepsy patients may exhibit low adherence due to disease symptoms, comorbidities, medication regime changes, and limited access to specialists. However, evidence of the specific causes of NA to therapy in patients with narcolepsy is lacking so far. This study aims to determine general adherence barriers (AB) and identify factors influencing TA in narcolepsy patients in Germany.

2. Methods

This study was a cross-sectional, anonymized online survey of adult patients with narcolepsy (NT1 and NT2) in Germany. Diagnosis information was based on patients self-reporting. The self-reported diagnosis was crosschecked for conflicting information (e.g., self-reported NT1, but the question about cataplexy was answered with "no") during the survey. If the diagnosis crosscheck provided conflicting results, the patient was excluded from analysis.

The online survey (LimeSurvey) was administered between November 2020 and May 2021. The study patients were contacted in two major German narcolepsy out-patient clinics (Witten and Berlin, in total approx. 1000 patients/per year) by narcolepsy self-help groups and the German Narcolepsy Network (www.narkolepsie-netzwerk.de) reaching approx. 2500–5000 individuals with narcolepsy in Germany.

The survey included sociodemographic and disease-related (e.g., symptoms, medication) questions. To capture treatment-related factors, the patient's medication was queried. The presence of side effects was recorded. It was also assessed whether a change was made before the current medication and whether this was due to side effects. The severity of EDS in narcolepsy was assessed by the Epworth Sleepiness Scale (ESS).

The Adherence Barriers Questionnaire © (ABQ) [35] with 16 items was selected to measure patients' adherence barriers (AB) regarding narcolepsy treatment. Each item of the ABQ is formulated as a statement to be assessed on a 4-point Likert scale ("strongly agree", "generally agree", "generally disagree", and "strongly disagree", related to score values from 1 to 4 or rather 4 to 1 depending on the formulation of each item), which deliberately left out a mean response option to force the respondents to decide. Based on the patient's responses, item-specific scores and the total ABQ score, indicating the number and strength of AB present in a patient, were calculated. Additionally, scores in three ABQ subscales were evaluated: Medication-related/healthcare system--related barriers (e.g., poor patient-physician relationship, costs of therapies, waiting period for consultations, with the items 8,11,12,13, 14), unintentional patient-related barriers (factors such as depression, dementia, level of forgetfulness, with the items 1,2,9,10) and intentional patient-related barriers (medication or health beliefs, attitude towards treatment, with the items 3,4,7,15,16). The patient health questionnaire (PHQ-9) was used as a survey instrument of depressiveness. With nine questions and a score range of 0–27 points, a screening statement can be made for mild (10–14 points), moderate (15–19 points), and severe depression (20–27 points). A patient was assigned to a barriers group if the average score per item belonging to this scale was >2, or at least one subscale item had a score of 4.

The survey included open-ended questions on non-pharmacological TA, where non-responses did not result in participant exclusion. The survey assessed participants' self-reported adherence to physicians' treatment recommendations on sleep hygiene, daily routine, physical activity, diet, and driving habits, as well as patients' perceptions of the extent to which they were informed by their physicians about the topics of disease development and progression, treatment options, behavioral interventions, medication use, side effects, and current research. The survey also gathered information on the use of CAM in managing narcolepsy, and assessed the frequency and reasons for any medication changes prior to the current treatment, particularly focusing on alterations due to side effects.

The survey included a total of 242 questions consisting of multiple choice, Yes/No, and Likert scale questions, along with validated questionnaires. A subset of these questions, specifically related to CAM use in narcolepsy, was analyzed in a separate publication [10]. The complete survey is available upon request from the authors.

Descriptive statistics were applied to characterize sociodemographic variables and sleepiness scales. For continuous variables, summary statistics (mean, standard deviation, range) were provided, while frequency statistics were reported for categorical and ordinal variables. Spearman's rank correlation was used to examine the association between severity of treatment barriers, as indicated by the ABQ score, and three other variables: the severity of illness, as measured by the ESS; the number of naps per day; and the most common comorbidity, depression,

as measured by the PHQ-9 score. According to Cohen (1992), r values of 0.10, 0.30, and 0.50 were set to demarcate small, medium, and large effects, respectively. The chi-square test was used to compare characteristics of patients with high and low adherence barriers for categorical variables. For all comparisons, P values < 0.05 were considered as statistically significant. Statistical analyses were performed using SPSS software release 27.0 (IBM Corp. Released 2020. IBM SPSS, Version 26.0. Armonk, NY: IBM Corp). Questionnaires were excluded if they had incomplete sociodemographic data (not 100 %), an unspecified narcolepsy type, or incomplete ABQ data.

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

3. Results

3.1. Sample characteristics

The online survey received responses from 272 patients with narcolepsy. However, 29 questionnaires (11 %) were omitted from the analysis due to incomplete sociodemographic data or failure to fully complete the ABQ.

In the final analysis, 243 patients were included: 173 (71 %) with NT1 and 70 (29 %) with NT2. The average age of the respondent at the time of the survey was 35.7 ± 12.3 years (range: 18–82 years), with more women (n = 186, 77 %) than men having participated (Table 1a). The mean age at diagnosis was reported to be 28.9 ± 10.6 years (range:11–61 years), resulting in a mean duration from disease diagnosis to time of the survey of 6.8 ± 7.9 years (range: 0–49 years). The mean ESS score was 16.4 ± 3.7 (range: 2–23).

The majority of the surveyed patients (n = 189, 78 %) reported living with family, a partner, or others. Employment status varied, with 75 patients (31 %) fully employed and 49 (20 %) partly employed. Unemployment was reported by 73 patients (30 %), while 46 (19 %) were retired at the time of the survey (Table 1). Housing status and level of educational attainment did not differ significantly between patients with low (≤25) versus high (>25) ABQ scores (alone: 22 % vs. 22 %; secondary school completed: 22 % vs. 22 %); however, patients with low ABQ scores were more likely to be employed full-time (48 % vs. 29 %, p = 0.039).

The majority of survey patients (n = 165, 68 %) reported having at least one comorbidity, with depression being the most common (affecting 80 patients, 33 %). The prevalence of depression was significantly higher among patients with a high ABQ score (35 % vs 15 %, p = 0.034). The mean score of the PHQ-9 was 13.6 points (range: 4–27). Of the patients, 1 % (2/243) had minimal, 15 % (37/243) mild, 42 % (103/243) moderate, and 42 % (101/243) severe depressive symptoms.

There were statistically significant differences between NT1 and NT2 in housing, with more NT1 patients living alone (26 % vs. 13 %, p = 00.026). In addition, more NT1 patients reported suffering from diagnosed depression (37 % vs 21 %, p = 00.015) and fragmented sleep (85.5 % vs 69, p = 00.002) (see Suppl. Tabl. 1). Despite the noted differences between NT1 and NT2 patients, these variables did not show a significant correlation with ABQ score (see Suppl. Tables 2 and 3).

When examining the current medication use among narcolepsy patients, two drugs were found to significantly correlate with ABQ score (Table 2). Sodium oxybate (SO, i.e. Xyrem) was taken by 17 % of patients (n = 41) at the time of the survey. Among all patients with a low ABQ score of less than or equal to 25 points, more patients were taking SO than in the group with a higher ABQ score of over 25 points (33 % compared to 15 %, p = 0.015). The same was found for a combination of modafinil + SO (18.5 % vs. 4 %, p = 00.003). Conversely, methylphenidate users (19 % of patients; n = 47) were more likely to have a high ABQ score (21 % vs. 4 %, p = 0.029). It was evaluated for the two common combination therapies, modafinil + SO and pitolisant + modafinil, which are shown in Table 2.

Seventy-five percent of patients (n = 183) had tried at least one other medication prior to their current treatment. Seventy-two percent (n = 175) of patients reported side effects from their current or previous narcolepsy medication. Of those who experienced side effects, 78 % (n = 136/175) discontinued their medication due to their severity. The medications and the number of side effects reported are listed in Table 3.

Table 1
Sociodemographic and clinical data of narcolepsy patients with high and low adherence barriers and total participants.

	Total (n = 243)	≤25 ABQ Points (n = 27)	>25 ABQ Points (n = 216)	p-value
Female gender in % (n)	77 (186)	63 (17)	78 (169)	0.077
Age in years, mean (SD; range)	35.7 (±12.3; 18–82)	39.1 (±14.6; 19–82)	35.24 (±11.9; 18–74)	0.798
Narcolepsy Type 1 in % (n)	71(173)	10(17)	90(156)	0.317
Narcolepsy Type 2 in % (n)	29(70)	14(10)	86(60)	0.317
Age when narcolepsy diagnosis was made, in years, mean (SD)	28.9 (±10.6)	30.0 (±10.5)	28.7 (±10.6)	0.278
Housing				
Alone in % (n)	22 (54)	22 (6)	22 (48)	1.00
Together with family, partner, others in % (n)	78 (189)	78 (21)	78 (168)	1.00
Education				
Currently in training in % (n)	6 (14)	0	6 (14)	0.173
Secondary School in % (n)	22 (53)	22 (6)	22 (47)	0.904
High School in % (n)	13 (32)	22 (6)	12 (26)	0.140
(Technical-) University degree in % (n)	38 (93)	34 (9)	39 (84)	0.576
Apprenticeship/Training in % (n)	21 (51)	22 (6)	21 (45)	0.867
Employment				
Fully employed in % (n)	31 (75)	48 (13)	29 (62)	**0.039**[a]
Partly employed in % (n)	20 (49)	22 (6)	20 (43)	0.777
Retired in % (n)	19 (46)	15 (4)	19 (42)	0.563
Not employed in % (n)	30 (73)	15 (4)	32 (69)	0.067
Comorbidities				
Yes in % (n)	68 (165)	37(10)	72 (155)	**<0.001**[a]
Non in % (n)	32 (78)	63(17)	28 (61)	**<0.001**[a]
Most frequent comorbidity				
Depression in % (n)	33 (80)	15 (4)	35 (76)	**0.034**[a]
Epworth Sleepiness Scale				
Mean, (SD; range)	16.4 (±3.7, 2–23)	16.0 (±4.5, 6–22)	16.5 (±3.6, 2–23)	0.235
≤10 Points	6 (15)	15 (4)	5 (11)	**0. 048**[a]
>10 Points	94 (228)	85 (23)	95 (205)	**0. 048**[a]
Swiss Narcolepsy Scale, mean (SD; range)	−15.4 (±39.6;-110-66)	−10.5 (±44.8;-90-66)	−16.0 (±38.9;-110-66)	0.244
At least one change of medication in % (n)	75 (183)	74 (20)	75 (163)	0.875
Side effects medication in % (n)	72 (175)	63 (17)	73 (158)	0.266
Of those, side effects so severe that medication was discontinued in % (n)	78 (136/175)	76 (13/17)	78 (123/158)	0.897
CAM use in % (n)	32 (79)	22 (6)	34 (73)	0.226
Most frequent narcolepsy symptoms in % (n)				
Excessive daytime sleepiness in % (n)	98 (238)	96 (26)	98 (212)	0.523
Concentration and memory deficits in % (n)	82 (199)	70 (19)	83 (180)	0.099
Fragmented sleep in % (n)	81 (196)	89 (24)	80 (172)	0.251
PHQ-9 in % (n)				
Minimal-mild depressiv symptoms in % (n)	16 (39)	33 (9)	14 (30)	**<0.009**[a]
Moderate to severe symptoms in % (n)	84 (204)	67 (18)	86 (186)	**<0.009**[a]

[a] p-value <0.05; CAM = Complementary and alternative medicine.

Table 2
Current medication treatment data of narcolepsy patients with high and low adherence barriers and total participants.

	Total (n = 243)	≤25 ABQ Points (n = 27)	>25 ABQ Points (n = 216)	p-value
Medication, in % (n)				
non	16 (38)	7 (2)	17 (36)	0.212
yes	84 (205)	93 (25)	83 (180)	0.212
Modafinil	33 (80)	48 (13)	31 (67)	0.074
Sodium Oxybat (i.e. Xyrem)	17 (41)	33 (9)	15 (32)	**0.015**[a]
Modafinil + Sodium Oxybat	6 (14)	18.5 (5)	4 (9)	**0.003**
Solriamfetol (Sunosi®)	13 (32)	19 (5)	13 (27)	0.383
Pitolisant (Wakix ®)	21 (50)	30 (8)	19 (42)	0.217
Pitolisant + Modafinil	5 (13)	11 (3)	5 (10)	0.158
Clomipramine	4 (10)	7 (2)	4 (8)	0.361
Methylphenidate	19 (47)	4 (1)	21 (46)	**0.029**[a]
Dexamphetamine	5 (12)	4 (1)	5 (11)	0.753
Venlafaxine	16 (38)	26 (7)	14 (31)	0.119
Other Antidepressants	14 (35)	7 (2)	15 (33)	0.272
Other	14 (34)	7 (2)	15 (32)	0.296

[a] p-value <0.05.

Modafinil was reported as the single agent with the most frequent side effects (92 %, n = 158), followed by methylphenidate (68 %, n = 110) and pitolisant (Wakix ®) (64 %, n = 195). Combinations of wake-promoting agents were reported with even more side effects, such as pitolisant (Wakix ®) + methlyphednidate (98 %, n = 45), or sodium oxybate (i.e. Xyrem) + pitolisant (Wakix®) (97 %, n = 38). A high number of patients stated that they had already taken a combination of an agent against symptoms of narcolepsy (sodium oxybate (i.e. Xyrem), solriamfetol (Sunosi®, pitolisant (Wakix ®), methylphenidate, dexamphetamine) and cataplexy and/or depression (venlafaxine or other antidepressants). 91 % (n = 45) of the 111 patients reported experiencing side effects from this combination (p = 0.022). Table 4 shows that the majority of patients take one (n = 87) or two (n = 73) medications at the same time. Furthermore, it can be seen that the more medications are combined, the greater the probability of side effects occurring,

Table 3
Medication treatment (current and past: multiple selection therefore possible) of narcolepsy patients and number of side effects occurred under this medication or medication combinations.

	Total (n = 243)	Occurred side effect (n = 175)
Medication, in % (n)		
Modafinil	92 (201)	92 (158)
Sodium Oxybat (SO, i.e. Xyrem)	46 (86)	49 (79)
Solriamfetol (Sunosi®)	25 (45)	26 (42)
Pitolisant (Wakix®)	60 (113)	64 (105)
Methylphenidate	67 (125)	68 (110)
Dexamphetamine	16 (29)	17 (28)
Modafinil + Sodium Oxybat	28 (52)	29 (47)
Pitolisant + Modafinil	33 (62)	35 (58)
SO + Pitolisant	16 (39)	97 (38)
SO + Solriamfetol	(58)	95 (55)
Pitolisant + Solriamfetol	(17)	94 (16)
Pitolisant + Methlyphednidat	(46)	98 (45)
Clomipramine	14 (27)	14 (23)
Venlafaxine	44 (82)	46 (74)
Other Antidepressants	44 (82)	43 (69)
Combination of medication for narcolepsy symptoms incl. sodium oyxybate and an antidepressant agent	45 (111)	91 (101)
Combination of medication for narcolepsy symptoms excl. sodium oyxybate and an antidepressant agent	45 (109)	91(99)
Other	27 (50)	28 (46)

*p-value <0.05.

Table 4
Polypharmacy of current medication.

Number of Medication	Total (n = 243)	Side effect occurred: yes (n = 152)
0	16 (39)	–
1	36 (87)	62 (54)
2	30 (73)	80 (59)
3	13 (32)	87.5 (28)
4	4 (10)	90 (9)
5	1 (2)	100 (2)

A large portion of patients adhered closely to physician's recommendations on various aspects of disease management. The adherence rates for specific aspects were as follows: 69 % (164/239) for sleep hygiene, 74 % (178/240) for maintaining a daily structure, and 47 % (110/236) for regular sports activities. Regarding nutrition, slightly more than half of patients (54 %; 128/238) followed the physician's recommendations as much as possible. The highest adherence was seen with driving recommendations, with 90 % (189/209) following them closely. There was no statistically significant association found between the rates of adherence for any of these recommendations and ABQ score (see Table 6). 85 % of patients reported that it was very important for them to be well-informed about their disease (n = 206/243). Slightly more than half, 53 % (n = 129/243), rated the accessibility (by phone, email, or in person) of their treatment provider as "good", 32 % (n = 78/243) as "adequate" and 15 % as "barely accessible" (n = 36/243). Furthermore, about one-third of patients (n = 164, 32 %) reported using CAM as part of their narcolepsy treatment.

3.2. Adherence barriers

The average ABQ score was 32.6 ± 6.5 points (range: 19–55 points). A substantial majority of respondents, 89 % (n = 216), had scores above 25 points, indicating a high severity of AB and an increased risk for NA. Respondents with an increased NA risk (ABQ >25) were generally younger (mean age of 35.2 years vs. 39.1 years, p = 0.798) and more likely to be female (78 % vs. 63 %, p = 0.077); however, these differences did not reach statistical significance. Notably, patients with ABQ scores above 25 points had a significantly higher rate of depression (35 % versus 15 %, p = 0.034).

In nearly one-third (33 %) of patients (n = 81), more than five different barriers were present (Fig. 1). One percent of narcolepsy patients (n = 3) reported not being affected by any of the ABQ barriers. The most frequently reported barriers were "Forgetfulness" (ABQ item 9; n = 187, 77 %), "Depression" (ABQ item 10; n = 138, 57 %), and "Side effect-driven medication reduction/stopping behavior" (ABQ item 15b; n = 119, 49 %). Among those scoring above 2 on the ABQ item for "Depression", 46 % (64/138) reported concomitant depression within the comorbidity question section of the survey, and 94 % (130/138) were classified as having moderate to severe depression according to PHQ-9 score.

In Table 5, ABQ items are correlated with narcolepsy types. Specifically, item 13, which indicates a need for help in everyday life, was statistically reported more frequently by patients with NT1 compared to those with NT2 (23 % vs. 11 %, p = 0.047).

Generally, a significant proportion of patients are afraid of the side effects of their medications (n = 97, 40 %), and even 30 % of patients (n = 73) are of the opinion that all medications are "poison" and that taking them should be "avoided" (Fig. 1/Tabl. 5).

In more than the half of the patients, unintentional adherence barriers (n = 139, 57 %), and medication/health system-related adherence barriers were present (n = 133, 55 %; Fig. 1). Interestingly, also intentional adherence barriers, which relate to a patient's conscious

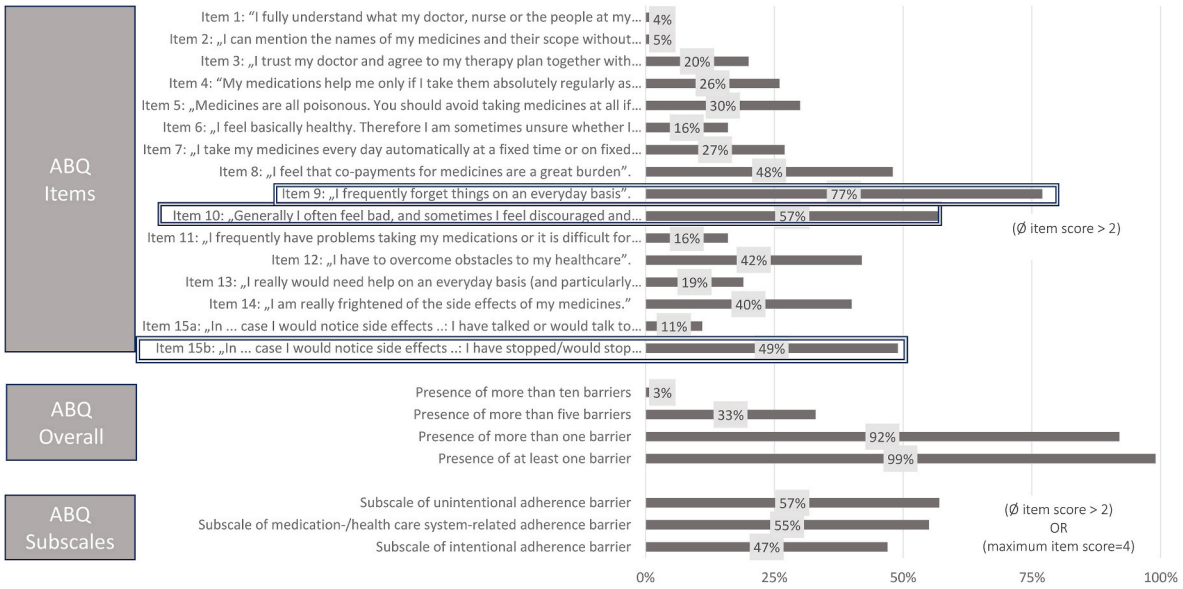

Fig. 1. Proportion of patients affected by adherence barriers asmeasured by the ABQ in percentage (%).
The figure shows the percentage of patients affected by each of the adherence barriers, with patients defined as "affected" if their item score exceeds 2. Also shown is the percentage of patients affected by adherence barriers within each of the three ABQ subscales. The definedbarriers' groups/subscales is shown. A patient was defined to be affected by adherence barriers within a particular subscale if the average score per item belonging to this subscale was greater than 2, or at least one subscale item had a score of 4. Marked the items with highest adherence barrier Item 9, 10, 15b. The top 3 adherence barriers (corresponding to items 9, 10 and 15b) are marked.

decisions/attitudes/beliefs, were present in nearly half of the patients (n = 115, 47 %).

3.3. Correlation between adherence barrier burden and disease severity/ depression scales

The severity of AB (ABQ score) correlated significantly with the severity of depression (PHQ-9), with a moderately strong effect (see Fig. 2; $r_s = 0.412$, $p < 0.001$, $n = 243$). The result was statistically significant according to the Chi-square test, i.e., patients with higher AB also had moderate to severe depressive symptoms more frequently (86 % vs 67 %, p = 00.009). The statistical correlation between ABQ score and the number of naps during the day was not significant ($r_s = 0.121$, p = 00.062, n = 240)(see Fig. 3). No significant correlation was observed between ABQ score and ESS score when assessed using Cohen's test ($r_s = 0.076$, p = 00.235, n = 243). However, when analyzed using the Chi-square test, the ESS score was significantly higher in patients with ABQ scores above 25 points (95 % vs. 85 %; p = 0.048).

4. Discussion

This is the first study to determine general adherence barriers in narcolepsy patients. According to the evaluation of the ABQ score, adherence barriers in patients with narcolepsy are high as hypothesized (89 %). NT1 and NT2 had similar ABQ scores (90 % vs. 86 %), so that no difference can be made between the narcolepsy types with regard to the prediction of NA [18]. More NT1 patients lived alone (26 % vs 13 %, p = 00.026), which indicates greater social isolation, maybe due to symptoms or depression. It is also conceivable that the increase depression and symptom burden leads to living alone. Also, NT1 suffered more often from diagnosed depression (37 % vs 21 %, p = 00.015) and fragmented sleep (85.5 % vs 69, p = 00.002). This can be explained by the symptoms and severity of symptoms of NT1. The ABQ items "Forgetfulness", "Depression", and "Side effect-driven medication reduction/stopping behavior" were mostly common in the analyzed sample. As expected, part of the AB were directly related to the disease itself [6]. NT1 also reported item 13 "daily need for help" statistically more frequently (23 % compared to 11 %, p = 0.047), which can be explained by higher symptom severity and impairment in everyday life in NT1. It is important to mention that an existing AB alone does not make a prediction. It is a sum of different AB that result in a score above 25 points and thus a higher probability of NA. An AB alone is not yet pathological and can apply to many people. That depression may also influence TA was also assumed [34], but the high number of patients in whom depression or depressed mood was among the highest AB is surprising. The difference between diagnosed depression (33 % of all patients) and moderate-severe depression (84 %) recognized by PHQ-9 is very large. The PHQ is a screening tool for depression and does not reflect a diagnosis. It should also be noted that narcolepsy is often initially misdiagnosed as depression or other psychiatric disorders [36]. Also, some of the questions in the PHQ-9 are overlapping with symptoms of narcolepsy, such as: "Trouble falling or staying asleep, or sleeping too much" or "Feeling tired or having little energy". Conversely, it is conceivable that once narcolepsy has been diagnosed, depressive symptoms are more likely to be attributed to narcolepsy and depression is less frequently diagnosed in addition. It can be concluded that physicians should put a focus on the recognition and treatment of comorbid depression. This possible bilateral relationship is also found in other aspects, such as depression and EDS or employment status and depression. However, it should also be borne in mind that the study was conducted during the pandemic and lockdown. It is possible that the PHQ-9 reflects the reduction in the quality of life that some individuals experienced during this time [37,38]. Thus, unintentional adherence barriers were the highest subscale precisely because of these factors; here, too, practitioners need to recognize and address barriers that are unconscious to the patient. Of course, side effects of medications influence TA [30], but according to the results of this study, even more attention should be paid to the uncoordinated and independent discontinuation of patients. This was also reflected in the level of the medication/health system-related subscale, whereby access to specialists (travel distance, waiting time, and accessibility) also had an influence here and therefore improvements in patient care would be desirable. 30 % of the patients do not trust the physician and do not agree to their therapy plan. Also ~50 % of the patients had intentional barriers (conscious attitude against

Table 5
ABQ items with frequencies (Ø item score >2) and NT 1 & NT 2 in % (n).

in % (n)	Total (n = 243)	NT1 (n = 173)	NT2 (n = 70)	p-value
Item 1: "I fully understand what my doctor, nurse or the people at my pharmacy have explained to me so far".	4 (10)	5 (8)	3 (2)	0.530
Item 2: „I can mention the names of my medicines and their scope without hesitation".	5 (11)	4 (7)	6 (4)	0.571
Item 3: „I trust my doctor and agree to my therapy plan together with him/her".	20 (48)	23 (39)	13 (9)	0.086
Item 4: "My medications help me only if I take them absolutely regularly as recommended".	26 (63)	28 (48)	21 (15)	0.309
Item 5: „Medicines are all poisonous. You should avoid taking medicines at all if possible".	30 (72)	32 (55)	24 (17)	0.246
Item 6: „I feel basically healthy. Therefore I am sometimes unsure whether I really have to take my medicines daily".	16 (39)	17 (30)	13 (9)	0.388
Item 7: „I take my medicines every day automatically at a fixed time or on fixed occasions".	27 (66)	30 (52)	20 (14)	0.110
Item 8: „I feel that co-payments for medicines are a great burden".	48 (117)	50 (85)	46 (32)	0.629
Item 9: „I frequently forget things on an everyday basis".	77 (188)	76 (132)	80 (56)	0.533
Item 10: „Generally I often feel bad, and sometimes I feel discouraged and depressed."	57 (138)	60 (103)	50 (35)	0.174
Item 11: „I frequently have problems taking my medications or it is difficult for me to keep me on the accompanying conditions of the medication intake".	16 (39)	17 (29)	14 (10)	0.634
Item 12: „I have to overcome obstacles to my healthcare".	42 (103)	43 (74)	41 (29)	0.848
Item 13: „I really would need help on an everyday basis (and particularly related to my treatment with medicines). But I do not get any help".	19 (47)	23 (39)	11 (8)	0.047[a]
Item 14: „I am really frightened of the side effects of my medicines."	40 (98)	42 (73)	36 (25)	0.351
Item 15a: „In … case I would notice side effects .: I have talked or would talk to my doctor about them as soon as possible".	11 (27)	12 (21)	9 (6)	0.423
Item 15b: „In … case I would notice side effects .: I have stopped/would stop my medications or took/would take less of them".	49 (118)	60 (88)	43 (30)	0.258

[a] p-value <0.05.

therapy adherence); reducing this type of barrier is enormously challenging.

No differences were found between the different levels of AB in terms of age, gender, living situation or level of education. The significant difference in full-time employment can presumably be explained by the fact that patients who can work full-time have lower symptom severity and/or good disease management. In general, patients with a high AB burden had more comorbidities (72 % compared to 37 %). This indicates that comorbidities have a relevant influence on adherence. In particular, the likelihood of comorbid depression was also significantly higher (35 % compared to 15 %). This demonstrates the importance of recognizing and treating depression, as it significantly impairs and worsens adherence to treatment for other conditions [11]. This is also reflected in the correlation between a high ABQ score and depression severity (PHQ-9) ($p < 0.001$). In people with narcolepsy, a close monitoring and early treatment of depression is necessary.

Table 6
Adherence to the recommendation and narcolepsy patients with high and low adherence barriers.

	Total	≤25 ABQ Points	>25 ABQ Points	p-value
The doctor's recommendation regarding				
schedule sleep breaks during the day	N = 239	N = 27	N = 212	
mostly followed in % (n)	69 (164)	67 (18)	69 (164)	0.816
mostly not followed in % (n)	31 (75)	33 (9)	31 (66)	0.816
regular daily structure	N = 240	N = 27	N = 213	
mostly followed in % (n)	74 (178)	85 (23)	73 (155)	0.165
mostly not followed in % (n)	26 (62)	15 (4)	27 (58)	0.165
regular exercise	N = 236	N = 27	N = 209	
mostly followed in % (n)	47 (110)	56 (15)	45.5 (95)	0.322
mostly not followed in % (n)	54 (126)	44(12)	54.5 (114)	0.322
dietary recommendation	N = 238	N = 27	N = 211	
mostly followed in % (n)	54 (128)	59 (16)	53 (112)	0.544
mostly not followed in % (n)	46 (110)	41 (11)	47 (99)	0.544
drive vehicle	N = 209	N = 25	N = 184	
mostly followed in % (n)	90 (189)	96 (24)	90 (165)	0.313
mostly not followed in % (n)	10 (20)	4 (1)	10 (19)	0.313
take medication as prescribed	N = 237	N = 27	N = 210	
mostly followed in % (n)	89.5 (212)	100 (27)	88 (185)	0.058
mostly not followed in % (n)	10.5 (25)	0 (0)	12 (25)	0.058

*p-value <0.05.

In the treatment of narcolepsy, medication changes are often necessary (75 %), but patients with higher AB had side effects more frequently (63 % vs. 73 %). This may indicate the importance of taking patients' side effects seriously and addressing them together, as other studies have shown that medication side effects are associated with lower adherence [30,31]. Since our study reported large differences with regard to side effects, more information should also be provided when prescribing the medication.

Modafinil was the highest reported side effect, with 92 % (n = 158), followed by methylphenidate at 68 % (110). However, this was only reflected in a high AB for methylphenidate ($p = 0.029$). This may be due to the fact that the side effects may be perceived as stronger here. In contrast, sodium oxybate (i.e. Xyrem), which also caused side effects in almost half of the patients (49 %, n = 79), was more frequently associated with a low AB ($p = 0.015$). As known from previous studies, the risk of side effects increases with the higher number of medications. This was also found in our study. A large percentage of patients reported combining either in their current or previous medication for narcolepsy symptoms and an antidepressive agent (45 %) and were particularly likely to have suffered from side effects (91 %). This underlines the importance of avoiding polypharmacy. Due to the special nature of this medication, precise information is usually provided about the dosage and possible side effects. It was assumed that the symptoms of the disease itself, represented barriers to therapy, which could be partially confirmed, forgetfulness as the highest AB. There was a slight effect between the ABQ score and the ESS ($p = 0.048$), which implies that the severity of excessive daytime sleepiness is an AB.

The fact that 85 % of patients stated that it was very important for them to be well informed could show that a large proportion of patients are interested in actively participating in their disease and that this potential should be further exploited.

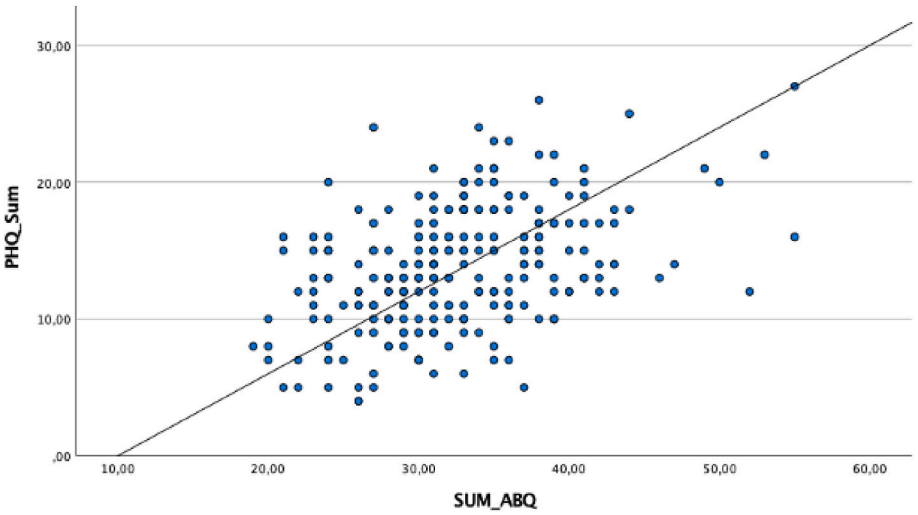

Fig. 2. Scatter plot: correlation between ABQ score and PHQ score
Sum values of ABQ or PHQ: Severity of ABQ scores correlated with the severity of depressiveness (PHQ-9): $r_s = 0.412$, $p < 0.001$, $n = 243$.

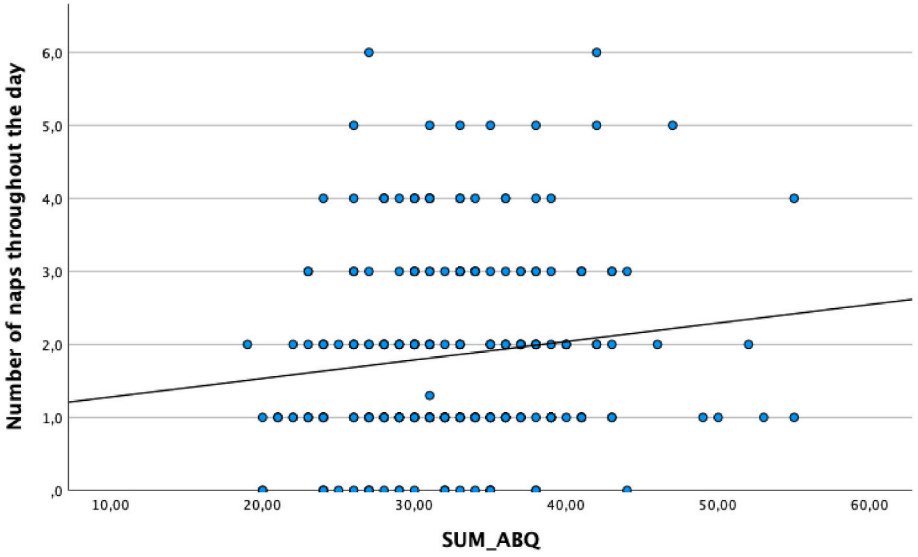

Fig. 3. Scatter plot: correlation between ABQ score and number of naps throughout the day.
Sum values of ABQ and number of naps per day. Outliers (three patients with >10 naps over the day) were excluded. Severity of ABQ scores correlated with numbers of naps per day: $r_s = 0.138$, $p = 00.031$, $n = 240$.

There are several studies that have investigated the effects of the COVID-19 pandemic on narcolepsy patients. The study results differ significantly depending on where the study was conducted. In France, for example, a country comparable to Germany in terms of the social structure and standards of its healthcare system, the lockdown was rated as positive by a large proportion of patients (42.5 % [39,40]). Some of the subjects benefited from an increase of hours in night sleep time and a mean decrease on the Epworth Sleepiness Scale during lockdown. Nevertheless, 13 % stated that they rated the lockdown as negative due to feeling isolated and psychological distress [40]. Other results were found in a study conducted in Brazil. The social structure, with a large disparity between income groups and healthcare, differs significantly from Germany. Here the study showed an increase in narcolepsy symptoms, such as cataplexy, sleep paralysis, hallucinations, nocturnal awakenings, and sleepiness. The medication was changed, with more stimulants and fewer antidepressants being taken [37]. A study conducted in Italy showed that home office patients benefited from better implementation of behavioral measures (increased nighttime sleep duration and daytime naps) and improved their daytime sleepiness [38]. Participation in this study was possible from November 2020 and May 2021, during which time there were several lockdowns and continued restrictions on public and private life. Based on the two studies conducted in Europe, it could be postulated that at least some of the patients in this study also benefited from the regulations during the COVID-19 pandemic. Compliance with behavioral recommendations and daytime sleepiness may even have been positively influenced.

4.1. Limitations

The study had limitations, including limitations about diagnostic certainty in an online format. 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. Participants were not incentivized monetarily, and the survey required a relatively substantial time commitment of around 30–40 min, reducing the

likelihood of unqualified participation. The study coincided with COVID-19 containment measures (e.g., lockdown, home office, quarantine rules), possibly affecting results [37,38]. This might also had an influence in the response rate. Due to the given response rate, a potential selection bias cannot be excluded. Adherence barriers were assessed by patient self-reports, introducing the potential for reporting errors.

Although the ABQ was originally validated for patients with atrial fibrillation, we utilized this tool due to the absence of a validated adherence questionnaire for narcolepsy. We recognize that the disease-specific contexts differ significantly, and some items in the ABQ may not fully capture the nuances of narcolepsy treatment adherence. Future studies should focus on developing and validating a questionnaire tailored specifically to narcolepsy. This has limitations that we recognize, but we still believe that the ABQ can cover general barriers well across indications. For example, topics such as lack of trust in practitioners, attitude towards medication, (administrative/practical) hurdles and discontinuation reaction to side effects can also be applied to narcolepsy patients without restrictions. The online administration of the ABQ may lead to potential misinterpretation of some items, as respondents did not have the opportunity to seek clarification. This limitation highlights the need for future studies to consider more interactive or in-person survey methods to ensure accurate understanding and responses. In narcolepsy management, the practice of individualized medicine often involves patients discontinuing medications due to side effects as part of a personalized treatment approach. This differs from conditions like atrial fibrillation, where adherence to medication is more rigidly enforced. The ABQ responses should be interpreted with this context in mind, recognizing that medication changes due to side effects can reflect a nuanced and patient-centered approach to treatment. In narcolepsy management, the practice of individualized medicine often involves patients discontinuing medications due to side effects as part of a personalized treatment approach. This differs from conditions like atrial fibrillation, where adherence to medication is more rigidly enforced. The ABQ responses should be interpreted with this context in mind, recognizing that medication changes due to side effects can reflect a nuanced and patient-centered approach to treatment.

This study's cross-sectional design limits our ability to establish causal relationships between treatment adherence and factors such as employment status, depression, and hypersomnolence. While we observed significant correlations, it is possible that these factors both influence and are influenced by treatment adherence. For example, poor adherence could exacerbate symptoms of depression and hypersomnolence, which in turn might impact employment status. Conversely, challenges related to employment and mental health could affect a patient's ability to adhere to their treatment regimen. It was shown that many medications mean a higher risk of more side effects, which in turn can increase the AB. Patients often combine wake-promoting agents with antidepressants. It is not shown in this study whether patients took the antidepressants for depressive symptoms or for cataplexy. Future longitudinal studies are necessary to unravel these complex interactions and determine the directionality of these relationships.

Further studies with larger numbers of patients and outside of a pandemic are needed to confirm the results. Additional and more specific instruments, such as the Narcolepsy Severity Scale [41], should also be used to assess symptoms. More data on polypharmacy and AB is also needed. In the future iSPHYNCS study [42], a study that is expected to lead to better and earlier diagnosis, better prognosis and personalized management, the topic of therapy adherence will be included. Since the concept of TA is also based on the factor of the professionals, a study should also be made on the side of the physicians.

5. Conclusion

The barriers to treatment adherence for narcolepsy patients are often high and multifaceted. Most AB are related to the symptoms of the disorder itself, such as forgetfulness, or to frequent co-morbidities such as depressive symptoms, which underscores the importance of recognizing and treating these for the TA. Side effects, in particular when multiple drugs are applied are also an important source of AB. To prevent AB, special attention should be paid to indications for co-morbid depression and solutions for experienced side effects.

CRediT authorship contribution statement

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

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.2024.06.028.

List of abbreviations

AB	Adherence barriers
ABQ	Adherence Barriers Questionnaire
CAM	Complementary and alternative medicine
ESS	Epworth Sleepiness Scale
ICSD	International Classification of Sleep Disorders
NA	Non-Adherence
NT1	Narcolepsy Type 1
NT2	Narcolepsy Type 2
PHQ-9	Patient Health Questionnaire-9
SF36 (VR-36)	Short Form 36 (Veterans Rand-36) health quality questionnaire/
TA	Therapy adherence
WHO	World Health Organization

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