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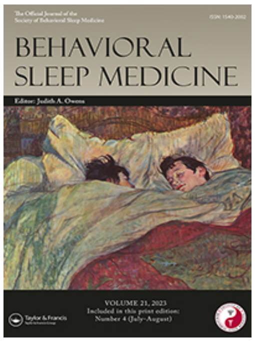

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The Burden of Narcolepsy in Adults: A Population Sampling Study Using Personal Media

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ABSTRACT

Objective: To obtain insight in the spectrum of narcolepsy symptoms and associated burden in a large cohort of patients.

Methods: We used the Narcolepsy Monitor, a mobile app, to easily rate the presence and burden of 20 narcolepsy symptoms. Baseline measures were obtained and analyzed from 746 users aged between 18 and 75 years with a reported diagnosis of narcolepsy.

Results: Median age was 33.0 years (IQR 25.0–43.0), median Ullanlinna Narcolepsy Scale 19 (IQR 14.0–26.0), 78% reported using narcolepsy pharmacotherapy. Excessive daytime sleepiness (97.2%) and lack of energy were most often present (95.0%) and most often caused a high burden (79.7% and 76.1% respectively). Cognitive symptoms (concentration 93.0%, memory 91.4%) and psychiatric symptoms (mood 76.8%, anxiety/panic 76.4%) were relatively often reported to be present and burdensome. Conversely, sleep paralysis and cataplexy were least often reported as highly bothersome. Females experienced a higher burden for anxiety/panic, memory, and lack of energy.

Conclusions: This study supports the notion of an elaborate narcolepsy symptom spectrum. Each symptom's contribution to the experienced burden varied, but lesser-known symptoms did significantly add to this as well. This emphasizes the need to not only focus treatment on the classical core symptoms of narcolepsy.

Introduction

Narcolepsy is a debilitating sleep disorder with a profound effect on quality of life (Tadrous et al., 2021). The core features of narcolepsy are historically described as a "pentad", consisting of excessive daytime sleepiness (EDS), cataplexy, sleep-related hallucinations, sleep paralysis, and fragmented nocturnal sleep (Kornum et al., 2017). However, only few patients present with the full pentad. On the other hand, there are several other symptoms which can be burdensome, for example weight gain and psychiatric symptoms such as depression and anxiety (Barateau et al., 2020; Dauvilliers et al., 2022; Morse & Sanjeev, 2018; Ruoff et al., 2017). Moreover, even when combining pharmacological and non-pharmacological approaches, optimal control of the various symptoms is often not reached and patients are hindered by residual complaints (Maski et al., 2017).

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Most studies on the symptom spectrum of narcolepsy made use of questionnaires. To avoid posing additional burden on this vulnerable population, and to potentially include larger numbers of subjects, some studies used medical insurance claim bases as an alternative (Chen et al., 2020; Parmar et al., 2019; Ruoff et al., 2017; Yeh et al., 2020). Both data collection methods have important limitations. For example, using insurance databases, there is a risk of exclusion of certain parts of the population and coding errors are not unlikely. Questionnaires, on the other hand, typically concentrate on a narrow scope of symptoms and are most apt for measuring the frequency of a symptom rather than the imposed burden. However, narcolepsy symptoms typically vary from day to day and even throughout the day, creating different levels of impact depending on the circumstances. Therefore, questionnaires may fail to capture the full range of functional consequences and may not provide an adequate indication for the strain that narcolepsy can cause. Health-related Quality of Life (HrQoL) scales have been used to fill this gap and showed that narcolepsy may have a deleterious implication on psychosocial functioning, education, recreation, driving, sexual life, and personality (Raggi et al., 2019). Nevertheless, there remains a lack of disease-specific measures that map the broad spectrum of narcolepsy symptoms, the experienced burden posed by each symptom and the consequences on everyday functioning.

Advances in smartphone technology, including the rise of medical health care apps, have yielded important new opportunities to monitor disease symptoms. Such digital applications can be distributed on a large-scale basis through app stores and have the potential to gather large amounts of data to enhance our understanding of different aspects of a disease. For example, they may enable the collection of longitudinal data with a relatively high sampling rate, to further our understanding of the development and stability of narcolepsy symptoms (Almeneessier et al., 2019; Büchele et al., 2018). Based on these premises, we developed the Narcolepsy Monitor, a mobile application for personal use designed for long-term assessment of the experienced burden of a broad spectrum of narcolepsy symptoms (Quaedackers et al., 2020). Based on previous research emphasizing the need for simplicity in digital health tools, we focused on keeping the app as straightforward and intuitive in every aspect of the design. Compared to existing disease-specific measures for narcolepsy (Dauvilliers et al., 2017; Kallweit et al., 2017) the scope of the Narcolepsy Monitor reaches beyond the narcoleptic pentad to include a range of associated symptoms, such as cognitive and psychiatric symptoms. In addition, the Narcolepsy Monitor does not focus on measuring the frequency of a symptom but enables users to assess each individual symptom based on the level of experienced burden.

In this paper, we present the Narcolepsy Monitor as a tool and show its potential to assess a wide range of narcolepsy symptoms. Based on a large population sampling study, we expand the narcolepsy phenotype both in terms of the presence of symptoms and the experienced burden.

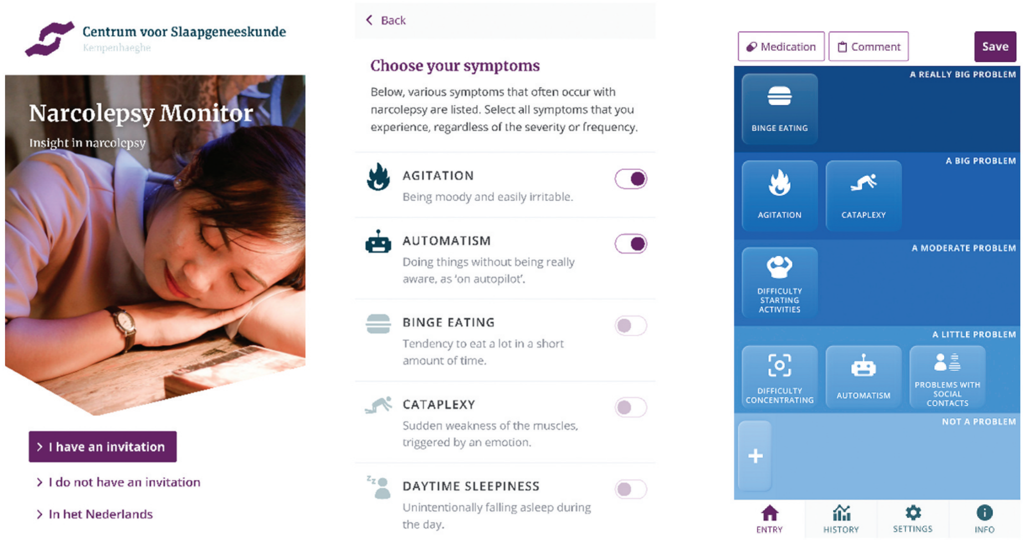
Methods

The study was approved by the Medical Ethics Committee of the Maxima Medical Center in Veldhoven, the Netherlands (file number N19.057).

Measures

Narcolepsy monitor

The Narcolepsy Monitor was designed to monitor the experienced burden of a wide range of narcolepsy symptoms over longer periods of time. Its latest version was released in the Google Play and the App Store in July 2019 (Figure 1a). In the app, a list of 20 symptoms and consequences is presented, which was created based on both expert opinion and feedback from patients (Figure 1b) (Quaedackers et al., 2020). It includes the narcoleptic pentad but is supplemented by symptoms that are often reported by patients but have received less attention in the past. In addition, not only symptoms but also consequences of narcolepsy in daily life are assessed, such as problems at work or school and difficulties with relationships or other social contacts.



Choose your symptoms

Below, various symptoms that often occur with narcolepsy are listed. Select all symptoms that you experience, regardless of the severity or frequency.

AGITATION ●
Being moody and easily irritable.

AUTOMATISM ●
Doing things without being really aware, as 'on autopilot'.

BINGE EATING ○
Tendency to eat a lot in a short amount of time.

CATAPLEXY ○
Sudden weakness of the muscles, triggered by an emotion.

DAYTIME SLEEPINESS ○
Unintentionally falling asleep during the day.

Figure 1. Final design of the Narcolepsy Monitor. Left: the start screen at initial onboarding. In prospective studies, using an invitation code enables the identification of study subjects. In the present study, we used the app in a population-sampling mode, for which subjects started using the app without a personal invitation but consented the use of their anonymous data. Middle: the initial symptom selection screen, so that symptoms that are not experienced by a patient are not shown (this selection can be updated at any time). Right: the primary interaction screen, in which patients list the narcolepsy symptom according to the subjectively experienced burden. The state of the rating can be updated at any given moment if symptom burden changes.

The core interaction concept of the Narcolepsy Monitor comprises a screen showing all present symptoms in a single overview, with the possibility to rate each symptom/consequence (Figure 1c). Importantly, a symptom/consequence is not rated based on its frequency of occurrence, but on the burden it poses to the individual. Symptoms/consequences are represented as icons that can be dragged and dropped to zones representing different levels of experienced burden and can be changed if the degree of burden changes. The experienced burden is scaled into the following categories: "not a problem", "a little problem", "a moderate problem", "a big problem", and "a really big problem" (see Figure 1 right for an example).

Ullanlinna narcolepsy scale

As the collected data in this study are anonymous, we included the Ullanlinna Narcolepsy Scale (UNS, with permission of the authors), to be filled in during the first onboarding process (Hublin et al., 1994). This was done to assess the likelihood of a correct narcolepsy diagnosis and to enable future data analysis against this previously validated tool. The UNS was originally designed to identify symptoms typical for narcolepsy (EDS and cataplexy) and to distinguish them from symptoms of other conditions that mimic narcolepsy. It is one of the most widely used screening questionnaires for narcolepsy (Kallweit et al., 2017). The score of the UNS can range from 0 to 44 with a higher score reflecting a higher frequency of EDS and cataplexy (Hublin et al., 1994). Although a cutoff point of 9 or higher showed a high sensitivity, we preferred a score of 13 or above which has a good sensitivity without a marked loss in specificity (Sarkanen et al., 2019). In our opinion, the risk of unintended exclusion of genuine narcolepsy patients with possibly milder symptoms, was secondary to the unintended inclusion of false positives.

Study procedure

Using social media and contacts at (inter)national patient organizations, an international campaign was started to inform patients with narcolepsy about the availability of the Narcolepsy Monitor. The app can be downloaded without charge from Google Play or the App Store. During the onboarding phase, users are prompted with several questions regarding their narcolepsy symptoms (including the UNS). Also, they are asked if they have been formally diagnosed with narcolepsy by a specialist. Finally, users are asked if they agree to share their anonymous data for scientific research.

Data handling

Personal data available in the Narcolepsy Monitor database is limited to sex, age, education level and work situation. It also contains information on the narcolepsy phenotype, including the symptom rankings. Data cannot be traced back to an individual. The permanent storage of data takes place on secured servers within the Center for Sleep Medicine Center Kempenhaeghe (Heeze, the Netherlands) with temporary storage on internet servers kept as short as possible.

Study participants

Study participants included for the present analysis were selected from the Narcolepsy Monitor users who gave their consent during the onboarding phase to make their anonymous data available for scientific research. To be included, participants had to have used the app at least one time. Moreover, only users who reported a formal diagnosis of narcolepsy made by a physician were used for analysis. Participants, younger than 18 and older than 75 years, were excluded from analysis. In the present study, only data from each first (baseline) entry was used.

Data analysis

Initial data processing was done with a custom-made visualization tool. This tool was implemented using the R programming language and a tailored interactive dashboard. Key features include the design of different plots, including flexible histograms, providing appropriate scaling options, ordering plots to identify groups and trends, and concurrent views to facilitate comparison between dichotomized groups.

Data analysis was performed with the IBM Statistical Package for Social Sciences (SPSS), version 27. The experienced burden was dichotomized, with scoring levels “a big problem” and “a really big problem” considered as a subjectively high burden and scores “not a problem”, “a little problem”, and “a moderate problem” considered as causing a subjectively low experienced burden. Most data were not normally distributed, and median and IQR were used to describe the study population. Chi-square tests were applied for comparison based on sex, and medication regarding the presence and perceived burden of symptoms. To decrease the risk of a type I error, a Bonferroni correction for multiple comparisons was applied, resulting in a significance level of $p < .00125$ for both symptom presence and experienced burden regarding sex differences. In a secondary explorative analysis, we examined the influence of medication use on their respective target symptoms (stimulants on EDS, antidepressants on cataplexy, and sodium oxybate on cataplexy, EDS, and nighttime awakenings). For the effects of medication, a significance level of $p < .01$ was applied.

Results

Participant characteristics

We analyzed data from participants who downloaded the Narcolepsy Monitor between July 2019 and June 2020. This amounted to 1119 downloads resulting in at least a one-time use of the app. After

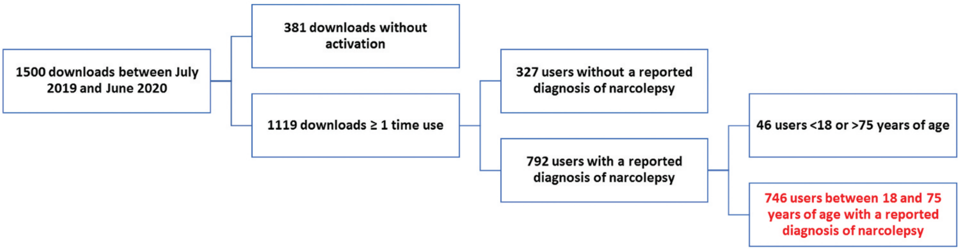


Figure 2. Flow chart of inclusion for the current analysis.

Table 1. Characteristics of participants (see text for selection details).

	Total users	Participants age 18–75 yrs., with reported narcolepsy diagnosis		
		Total	*Female*	*Male*
N	1119	746 (100%)	615 (82.4%)	131 (17.6%)
Age (median, IQR)	31.0 (23.0–41.0)	33.00 (25.0–43.0)	32.0 (25.0–42.0)	35.0 (26.0–46.0)
Ullanlinna score (median, IQR)	19.0 (13.0–25.0)	19.0 (14.0–26.0)	19.0 (13.0–25.0)	21.0 (16.0–26.0)
UNS ≥13%, n)	77.9% (872)	79.5% (593)	78.0% (780)	86.3% (113)
Reported narcolepsy diagnosis (%, n)	70.8% (792)	100% (n = 746)	100% (n = 615)	100% (n = 131)
Medication (%, n)*				
- *No medication reported*	38.0% (425)	22% (164)	23.9% (147)	13.0% (17)
- *Stimulants*	54.9% (614)	71.7% (535)	70.1% (431)	79.4% (104)
- *Antidepressant*	13.2% (148)	15.4% (115)	14.6% (90)	19.1% (25)
- *Sodium Oxybate*	9.8% (110)	13.1% (98)	12.0% (74)	18.3% (24)
- *Other (Benzodiazepine, Baclofen, Melatonin, Gabapentin)*	1.8% (20)	1.7% (13)	1.6% (10)	2.3% (3)
Highest completed education (%, n)				
- *Less than high school*	7.7% (86)	2.7% (20)	2.9% (18)	1.5% (2)
- *High school degree*	28.7% (321)	28.0% (209)	28.8% (177)	24.4% (32)
- *Vocational training*	10.9% (122)	12.1% (90)	10.7% (66)	18.3% (24)
- *College degree*	19.1% (214)	20.5% (153)	21.3% (131)	16.8% (22)
- *Bachelor's degree*	19.6% (219)	21.4% (160)	21.3% (131)	22.1% (29)
- *Master's degree or higher*	14.0% (157)	15.3% (114)	15.0% (92)	16.8% (22)
Occupation/education (%, n)				
- *Work: day shift only*	44.5% (498)	48.5% (362)	48.6% (299)	48.1 (63)
- *Work: shift work*	10.7% (120)	12.3% (92)	11.7% (72)	15.3% (20)
- *Education*	21.8% (244)	15.4% (115)	15.9% (98)	13.0% (17)
- *None*	23.0% (257)	23.7% (177)	23.7% (146)	23.7% (31)

*Participants can enter more than one medication category.

applying the inclusion and exclusion criteria described in the methods, a total of 746 participants remained eligible to be included for analysis (Figure 2).

Participant characteristics are summarized in Table 1. Subjects had a median age of 33.0 years (IQR 25.0–43.0) and a median UNS score of 19.0 (IQR 14.0–26.0). Participants were predominantly female (82%). Almost 80% reported using medication, with stimulants stated to be the most widely used. Almost 60% of the participants had a college degree or higher, while almost a quarter were not enrolled in a work position or education. Although most of the sample was female, the male and female groups were similar in terms of medication use, education level, and occupation status.

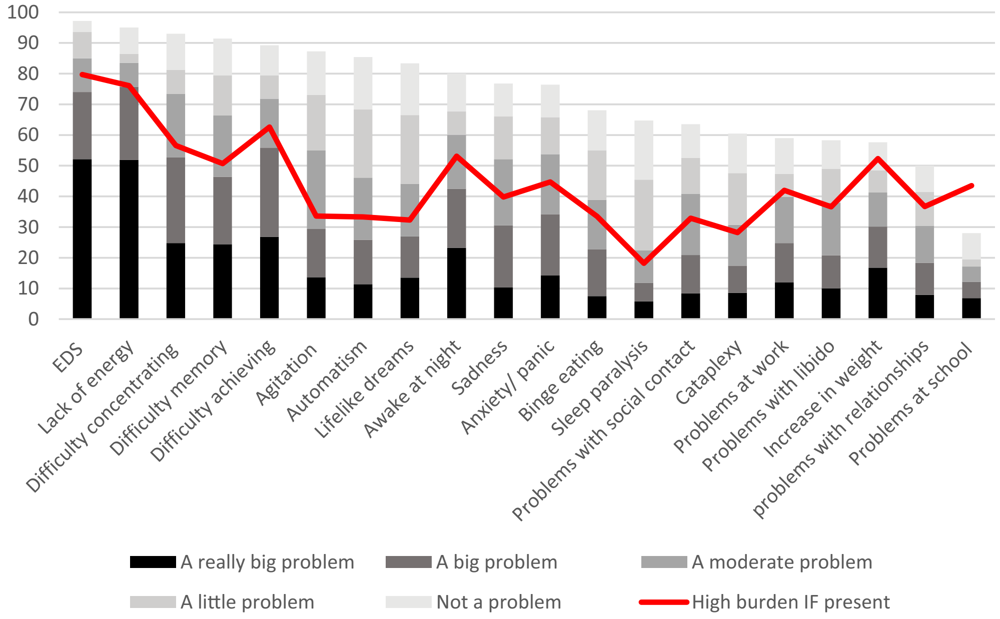


Figure 3. Reported symptom presence and experienced high burden in patients with narcolepsy. Participants were between 18 and 75 years of age and reported to be formally diagnosed with narcolepsy. Bar charts illustrate the presence of narcolepsy symptoms. Red lines depict the percentage of a highly experienced burden (in those subjects who reported that symptom as being present).

Presence of symptoms

Overall, all 20 symptoms and consequences that can be rated in the Narcolepsy Monitor were frequently reported by participants. Nineteen out of the 20 symptoms (except for "problems at school") were experienced by at least 50% of the participants. An obvious majority of the participants reported the presence of EDS, one of the core symptoms of narcolepsy. Interestingly, however, cataplexy only had the 15th position in the presence ranking, despite being regarded as one of the most defining symptoms of narcolepsy. Note that the other symptoms (lifelike dreams, awake at night, and sleep paralysis) of the classic pentad of narcolepsy scored relatively low in their presence. On the other hand, symptoms that are not part of the diagnostic criteria for narcolepsy, such as cognitive and psychiatric symptoms, were strikingly often reported. Problems with concentration or memory were listed by respectively 93.0% and 91.4% of all participants. Over three-quarters of the participants indicated to experience feelings of sadness, about the same as for feelings of anxiety/panic. The influence of narcolepsy on the subjects' daily lives was expressed as problems with social contact, problems at work, problems with relationships, and problems at school. Although these consequences were comparatively low in the ranking of presence, all these consequences (except for "problems at school" since this did not apply to the majority of participants) were still experienced by over half of the study population (see Figure 3).

Experienced symptom burden

In addition to whether a participant experiences a symptom, the degree of burden a symptom poses is rated in the Narcolepsy Monitor. Not only were EDS and lack of energy the most often reported symptoms, they also caused the highest burden, with 79.7% and 76.1% of the patients reporting the symptom as being "a big problem" or "a really big problem". Difficulty with concentration and difficulty with memory caused a high experienced burden in, respectively, 56.5% and 50.7% of cases. Notably, less frequently reported symptoms such as awake at night

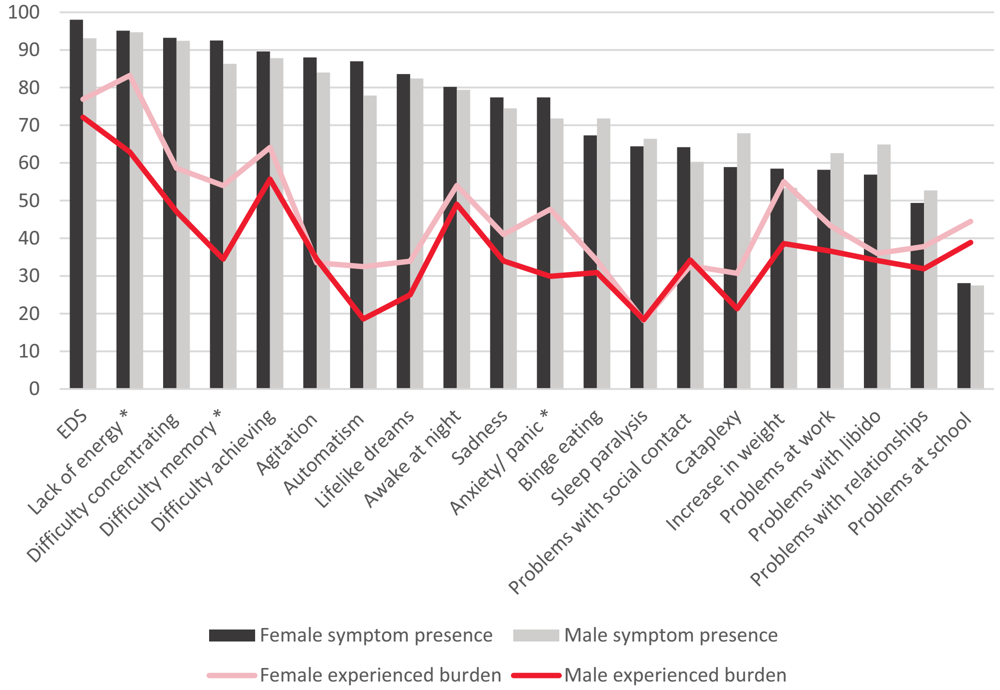


Figure 4. Reported symptom presence and experienced high burden in patients with narcolepsy for males and females. Participants are between 18 and 75 years of age and reported to be formally diagnosed with narcolepsy. Bar charts illustrate the presence of symptoms expressed in percentages. Red lines depict the percentage of a highly experienced burden (in those subjects who reported that symptom as being present). * Experienced burden differs significantly between sexes.

and increase in body weight – if present – caused a high burden in, respectively, 53.1% and 52.3% of subjects. On the other hand, sleep paralysis was only causing a high burden in 18.2% of the cases, followed by cataplexy with 28.2% claiming that cataplexy was highly bothersome (see Figure 3).

Sex differences

An overview of sex differences in symptom presence and high experienced burden is shown in Figure 4. Although EDS, difficulties with memory, and automatisms were slightly more frequently reported by females compared to males (EDS $X^2 = 9.552$, $p = .002$; difficulties with memory $X^2 = 5.397$, $p = .025$; automatism $X^2 = 7.214$, $p = .007$), there were no differences after correction for multiple comparisons. However, female participants did report a significant higher experienced burden for anxiety/panic ($X^2 = 10.175$, $p = .001$), difficulty with memory ($X^2 = 14.256$, $p < .001$), and lack of energy ($X^2 = 26.165$, $p < .001$).

Influencing factors

In the analysis with respect to medication use, we limited ourselves to the influence of the medication on their respective target narcolepsy symptom. Twenty-two percent of the participants did not register any medication use. Participants reporting using antidepressants reported more often the presence of cataplexy compared to participants reporting no medication use ($X^2 = 9.011$; $p = .003$). Participants reporting using sodium oxybate experienced less often a high burden of EDS ($X^2 = 24.090$; $p < .001$) (see Table 2).

Table 2. Presence and burden of symptoms in patients with and without medication.

	Symptom recorded as present				Symptom burden rated as "high"*			
	No medication	*Medication*	X^2	*p*	*No medication*	*Medication*	X^2	*p*
EDS*Stimulants (%, n)	95.3% (201)	97.9% (524)	3.982	0.046	79.6% (160)	98.0% (96)	1.837	0.175
EDS*SO (%, n)	97.1% (629)	98.0% (96)	0.247	0.619	79.2% (498)	56.3% (54)	24.090	<0.001
Cataplexy*AD (%, n)	58.2% (367)	73.0% (84)	9.011	0.003	28.1% (103)	32.1% (27)	0.554	0.457
Cataplexy*SO (%, n)	59.0% (382)	70.4% (69)	4.674	0.031	30.9% (118)	17.4% (12)	5.191	0.021
Awake at night*SO (%, n)	79.5% (515)	83.7% (82)	0.939	0.333	53.4% (275)	51.2% (42)	0.135	0.713

*Symptom burden is considered as "high" in case a symptom is rated as "a big problem" or "a really big problem".

Discussion

Capturing the symptom burden is critical for understanding and supporting patients living with narcolepsy. Our study adds to mounting evidence for a broad spectrum of symptoms in narcolepsy. Symptoms that historically are less likely to be associated with narcolepsy, such as cognitive and psychiatric problems, were shown to be highly present. The data also provide insight into how much of a burden these symptoms may cause. Some symptoms, although relatively less often present, lead to a high burden. While understanding these symptoms and their effects on daily life can be challenging, new technologies, such as smartphone apps, may provide a solution. The Narcolepsy Monitor was developed with the aim of mapping not only the presence but also the subjective burden associated with a wide range of narcolepsy symptoms. Unlike more traditional ways of collecting clinical data, this technological innovation capitalizes on the familiarity of phone users with app stores and their reliability as a channel for distributing software and keeping it updated. Using the Narcolepsy Monitor in this study resulted in the collection of a large number of narcolepsy patients providing self-reported data, in a relatively short amount of time.

Results indicate that EDS was the most frequently reported symptom, and that sleepiness was also perceived as the most bothersome. However, lack of energy (typically explained as fatigue) and cognitive problems (concentration and memory) occurred very frequently as well and contributed substantially to the experienced burden of narcolepsy. In the case of cognitive problems, it remains unclear whether it comprises a separate entity or is rather a "secondary manifestation" of EDS (Bassetti et al., 2021; Maski et al., 2017). Several studies show that subjectively reported cognitive complaints do not correlate with objective test results but do correlate with EDS and depressive symptoms (Zamarian et al., 2015). Psychiatric symptoms (anxiety/panic and sadness) were present in more than three-quarters of the participants.

Cataplexy, besides EDS the other core feature of narcolepsy, was relatively infrequently reported and was perceived as the second least bothersome symptom, after sleep paralysis. It is important to realize, however, that almost 80% of the participants indicate using medication for narcolepsy. The reported presence and perceived burden should therefore largely be regarded as residual symptoms. It may be that cataplexy responds relatively favorably to medication, resulting in the limited reporting of presence and the relatively low perceived burden of cataplexy. However, if this reasoning is applied to EDS, it shows that the effects of medication on EDS are less prominent, still resulting in the highest score in terms of presence and experienced burden. This suggests that either the available medications are less effective for EDS or that EDS is fundamentally more taxing and has a greater effect on well-being (Lammers, 2018; Thorpy, 2020). Yet, the results from our study do not provide any evidence that cataplexy is not frequent or not burdensome if patients are untreated. Results do show that both participants with and without medication, experience a high presence and a high burden of a large variety of symptoms. So even when participants are already being treated with medication, symptoms remain present and could pose an important limitation on wellbeing.

In line with previous research applying health-related applications, the use of the Narcolepsy Monitor was higher in females compared with that of males (Fu et al., 2019; Huberty et al., 2019; Kim et al., 2015). However, males and females did not differ with respect to other characteristics, such as age and the Ullanlinna score. Also, no sex-related differences were found in the presence of symptoms. Yet, females reported experiencing a higher burden in the areas of memory, lack of energy, and panic/anxiety. The reason for this is unknown as of yet. Previously, no sex differences were found in a study that used the Fatigue Severity Scale to measure fatigue in narcolepsy (Droogleever Fortuyn et al., 2012). A possible explanation is that this latter instrument places more emphasis on the limiting consequences of the symptom, whereas the Narcolepsy Monitor measures the perceived burden.

For long, little attention has been paid to the non-pharmacological treatment of narcolepsy, yet, recent European guidelines describe the behavioral treatment as an important keystone in managing narcolepsy (Bassetti et al., 2021; Morgenthaler et al., 2007). As with pharmacological treatment, most attention in behavioral treatment is focused on combating EDS. Although this attention is certainly justified, the other associated symptoms, such as lack of energy, subjective cognitive complaints, and psychiatric symptoms, remain underexposed. Our results imply that treatment requires an orchestrated cooperation among different specialists, with both medical and behavioral expertise involved.

Our study illustrates how technical innovations, including tools running on personal media such as smartphones in combination with app-store-based distribution, can contribute to unraveling the clinical picture of narcolepsy. This new way of measuring enables the collection of large amounts of data in a minimally invasive way. However, the nature of data collection – using the app on an anonymous basis – does not allow verifying the self-reported narcolepsy diagnosis, nor do we possess any formal medical information on the timing and certainty of a diagnosis. However, UNS scores in our cohort were strongly indicative of narcolepsy and virtually in line with previous UNS research in a formally diagnosed narcolepsy population (Sarkanen et al., 2019). Also, medication use in our study population was high, as to be expected in narcolepsy and participants answered confirmative to the question if they were ever formally diagnosed with narcolepsy. Nevertheless, bias could arise from the lack of insights into the motivation of people to download and use the Narcolepsy Monitor. Another source of bias may result from the higher willingness of young people with a higher education, higher socioeconomic status, and more focus on a healthy lifestyle to use mHealth apps (Carroll et al., 2017). Although our sample was relatively young (median of 33), our data regarding education level are comparable to the education levels in the U.S (U.S. Census Bureau, 2021). Given the explorative nature of this study, no firm conclusions can be drawn yet regarding causality or mechanisms of differences. For example, the reason for the experienced burden regarding memory problems in females remains unknown. In addition, the cross-sectional data from this study does not shed light on the development of symptoms. It is known that the narcoleptic phenotype can change with disease duration, especially in the early years after onset, often during childhood. A children's version of the Narcolepsy Monitor is currently being developed that will allow for the collection of data in the pediatric narcolepsy population. In the future, longitudinal datasets obtained with the Narcolepsy Monitor will become available, which will likely provide more insights in the dynamics of symptoms over time.

Conclusion

This study in a large cohort of narcolepsy patients bolsters the growing evidence that narcolepsy encompasses more than the narcoleptic pentad of symptoms. Even though the majority of the participants indicated the use of narcolepsy medication, the reported symptom presence, and moreover the associated experienced burden remained very high. Psychiatric and cognitive symptoms appeared to be highly prevalent. The contribution of each symptom to the experienced burden varied, but lesser-known narcolepsy symptoms did add to the load patients with narcolepsy have to bear. Given the current lack of well-validated clinical tools that can capture the presence of the broader symptom spectrum and the resulting burden, the Narcolepsy Monitor could play a crucial role in future research, and possible daily clinical care as well.

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References

Almeneessier, A. S., Alballa, N. S., Alsalman, B. H., Aleissi, S., Olaish, A. H., & BaHammam, A. S. (2019). A 10-year longitudinal observational study of cataplexy in a cohort of narcolepsy type 1 patients. *Nature and Science of Sleep*, *11*, 231–239. https://doi.org/10.2147/NSS.S229105

Barateau, L., Lopez, R., Chenini, S., Pesenti, C., Rassu, A. L., Jaussent, I., & Dauvilliers, Y. (2020). Depression and suicidal thoughts in untreated and treated narcolepsy: Systematic analysis. *Neurology*, *95*(20), e2755–2768. https://doi.org/10.1212/WNL.0000000000010737

Bassetti, C. L. A., Kallweit, U., Vignatelli, L., Plazzi, G., Lecendreux, M., Baldin, E., Dolenc-Groselj, L., Jennum, P., Khatami, R., Manconi, M., Mayor, G., Partinen, M., Pollmächer, T., Reading, P., Santamaria, J., Sonka, K., Dauvilliers, Y., & Lammers, G. J. (2021). European guideline and expert statements on the management of narcolepsy in adults and children. *European Journal of Neurology*, *28*(9), 2815–2830. https://doi.org/10.1111/ene.14888

Büchele, F., Baumann, C. R., Poryazova, R., Werth, E., & Valko, P. O. (2018). Remitting narcolepsy? Longitudinal observations in a hypocretin-deficient cohort. *Sleep*, *41*(9). https://doi.org/10.1093/sleep/zsy118

Bureau, U. S. C. (2021). *Current population survey's annual social and economic supplement.*

Carroll, J. K., Moorhead, A., Bond, R., LeBlanc, W. G., Petrella, R. J., & Fiscella, K. (2017). Who uses mobile phone health apps and does use matter? A secondary data analytics approach. *Journal of Medical Internet Research*, *19*(4), e125. https://doi.org/10.2196/jmir.5604

Chen, T. -Y., Huang, C. -H., Chung, C. -H., Mao, W. -C., Yeh, C. -B., Yang, C. C. H., Kuo, T. B. J., Yang, S. -S., Chien, W. -C., & Tzeng, N. -S. (2020). Sex and age differences in the association between anxiety disorders and narcolepsy: A nationwide population-based case control study. *Journal of Affective Disorders*, *264*, 130–137. https://doi.org/10.1016/j.jad.2019.12.010

Dauvilliers, Y., Barateau, L., Middleton, B., van der Veen, D. R., & Skene, D. J. (2022). Metabolomics signature of patients with narcolepsy. *Neurology*, *98*(5), e493–505. https://doi.org/10.1212/WNL.0000000000013128

Dauvilliers, Y., Beziat, S., Pesenti, C., Lopez, R., Barateau, L., Carlander, B., Luca, G., Tafti, M., Morin, C. M., Billiard, M., & Jaussent, I. (2017). Measurement of narcolepsy symptoms: The narcolepsy severity scale. *Neurology*, *88*(14), 1358–1365. https://doi.org/10.1212/WNL.0000000000003787

Droogleever Fortuyn, H. A., Fronczek, R., Smitshoek, M., Overeem, S., Lappenschaar, M., Kalkman, J., Renier, W., Buitelaar, J., Lammers, G. J., & Bleijenberg, G. (2012). Severe fatigue in narcolepsy with cataplexy. *Journal of Sleep Research*, *21*(2), 163–169. Epub 2011 Aug 16. https://doi.org/10.1111/j.1365-2869.2011.00943.x

Fu, H. N., Adam, T. J., Konstan, J. A., Wolfson, J. A., Clancy, T. R., & Wyman, J. F. (2019). InfluencE of patient characteristics and psychological needs on diabetes mobile app usability in adults with type 1 or type 2 diabetes: Crossover randomized trial. *JMIR Diabetes*, *4*(2), e11462. https://doi.org/10.2196/11462

Huberty, J., Vranceanu, A. M., Carney, C., Breus, M., Gordon, M., & Puzia, M. E. (2019). Characteristics and usage patterns among 12,151 paid subscribers of the calm meditation app: Cross-sectional survey. *JMIR mHealth Uhealth*, *7*(11), e15648. https://doi.org/10.2196/15648

Hublin, C., Kaprio, J., Partinen, M., Koskenvuo, M., & Heikkilä, K. (1994). The Ullanlinna narcolepsy scale: Validation of a measure of symptoms in the narcoleptic syndrome. *Journal of Sleep Research*, *3*(1), 52–59. https://doi.org/10.1111/j.1365-2869.1994.tb00104.x

Kallweit, U., Schmidt, M., & Bassetti, C. L. (2017). Patient-reported measures of narcolepsy: The need for better assessment. *Journal of Clinical Sleep Medicine*, *13*(5), 737–744. https://doi.org/10.5664/jcsm.6596

Kim, Y., Briley, D. A., & Ocepek, M. G. (2015). Differential innovation of smartphone and application use by sociodemographics and personality. *Computers in Human Behavior*, *44*, 141–147. https://doi.org/10.1016/j.chb.2014.11.059

Kornum, B. R., Knudsen, S., Ollila, H. M., Pizza, F., Jennum, P. J., Dauvilliers, Y., & Overeem, S. (2017). Narcolepsy. *Nature Reviews Disease Primers*, *3*(1), 16100. https://doi.org/10.1038/nrdp.2016.100

Lammers, G. J. (2018). Drugs used in narcolepsy and other Hypersomnias. *Sleep Medicine Clinics*, *13*(2), 183–189. https://doi.org/10.1016/j.jsmc.2018.02.009

Maski, K., Steinhart, E., Williams, D., Scammell, T., Flygare, J., McCleary, K., & Gow, M. (2017). Listening to tHe patient voice in narcolepsy: Diagnostic delay, disease burden, and treatment efficacy. *Journal of Clinical Sleep Medicine*, *13*(3), 419–425. https://doi.org/10.5664/jcsm.6494

Morgenthaler, T. I., Kapur, V. K., Brown, T., Swick, T. J., Alessi, C., Aurora, R. N., Boehlecke, B., Chesson, A. L., Friedman, L., Maganti, R., Owens, J., Pancer, J., & Zak, R. (2007). Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep*, *30*(12), 1705–1711. https://doi.org/10.1093/sleep/30.12.1705

Morse, A. M., & Sanjeev, K. (2018). Narcolepsy and psychiatric disorders: Comorbidities or shared Pathophysiology? *Medical Sciences*, *6*(1), 16. https://doi.org/10.3390/medsci6010016

Parmar, A., Yeh, E. A., Korczak, D. J., Weiss, S. K., Lu, Z., Zweerink, A., Toulany, A., Murray, B. J., & Narang, I. (2019). Depressive symptoms, sleep patterns, and physical activity in adolescents with narcolepsy. *Sleep*, *42*(8). https://doi.org/10.1093/sleep/zsz111

Quaedackers, L., De Wit, J., Pillen, S., Van Gilst, M., Batalas, N., Lammers, G. J., Markopoulos, P., & Overeem, S. (2020). A mobile app for longterm monitoring of narcolepsy symptoms: Design, development, and evaluation. *JMIR mHealth and uHealth*, *8*(1), e14939. https://doi.org/10.2196/14939

Raggi, A., Plazzi, G., & Ferri, R. (2019). Health-related quality of life in patients with narcolepsy: A review of the literature. *Journal of Nervous & Mental Disease*, *207*(2), 84–99. https://doi.org/10.1097/NMD.0000000000000918

Ruoff, C. M., Reaven, N. L., Funk, S. E., McGaughey, K. J., Ohayon, M. M., Guilleminault, C., & Black, J. (2017). High rates of psychiatric comorbidity in narcolepsy: Findings from the Burden of Narcolepsy Disease (BOND) study of 9,312 patients in the United States. *The Journal of Clinical Psychiatry*, *78*(2), 171–176. https://doi.org/10.4088/JCP.15m10262

Sarkanen, T., Alakuijala, A., & Partinen, M. (2019). Ullanlinna narcolepsy scale in diagnosis of narcolepsy. *Sleep*, *42*(3). https://doi.org/10.1093/sleep/zsy238

Tadrous, R., O'Rourke, D., Mockler, D., & Broderick, J. (2021). Health-related quality of life in narcolepsy: A systematic review and meta-analysis. *Journal of Sleep Research*, *30*(6), e13383. https://doi.org/10.1111/jsr.13383

Thorpy, M. J. (2020). RecentLy approved and upcoming treatments for narcolepsy. *CNS Drugs*, *34*(1), 9–27. https://doi.org/10.1007/s40263-019-00689-1

Yeh, J. -Y., Shyu, Y. -C., Lee, S. -Y., Yuan, S. -S., Yang, C. -J., Yang, K. -C., Lee, T. -L., Sun, C. -C., & Wang, L. J. (2020). Comorbidity of narcolepsy and psychotic disorders: A nationwide population-based study in Taiwan. *Frontiers in Psychiatry*, *11*, 205. https://doi.org/10.3389/fpsyt.2020.00205

Zamarian, L., Hogl, B., Delazer, M., Hingerl, K., Gabelia, D., Mitterling, T., Brandauer, E., & Frauscher, B. (2015). Subjective deficits of attention, cognition and depression in patients with narcolepsy. *Sleep Medicine*, *16*(1), 45–51. https://doi.org/10.1016/j.sleep.2014.07.025