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## **Resilience and its correlates in patients with narcolepsy type 1**

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### **Author contributions**

Concept and design (FI, CF, MM, FP, GP, LV, CZ); data collection (AD, AR, FP, GP); data analysis (FI, MM, LV, CZ); data interpretation (all authors); drafting of the manuscript (AD, FI, MM, CF, GV, CZ); critical revision of the manuscript for important intellectual content (all authors). All authors have seen and approved the manuscript.

## **Disclosure statement**

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## **Abstract**

**Study Objectives.** This study aimed to explore resilience and its possible association with sociodemographic and clinical features in patients with narcolepsy type 1 (NT1).

**Methods.** Cross-sectional study involving patients with NT1 and age/sex-matched controls (comparison group). Sociodemographic and clinical data were collected through semi-structured interviews and validated questionnaires, including Epworth Sleepiness Scale (ESS), STAI-State anxiety, Beck Depression Inventory (BDI), SF-36, and Resilience Scale (RS). Different statistical approaches were used to investigate the relationship between resilience and NT1, and associations with sociodemographic and clinical features.

**Results.** The participants were 137 patients (mean age, 38.0 years; 52.6% female) and 149 controls (39.6 years; 55.7% female). Compared to controls, patients had a significantly lower (122.6 vs. 135.5) mean RS score and a twofold risk of having low/mild-range resilience (adjusted OR=1.99, 95% CI 1.13-3.52). Patients with high resilience had similar sociodemographic and narcolepsy characteristics of patients with low resilience, but they reported anxiety and depressive symptomatology less frequently (4.2% vs. 55.8% and 58.3%, respectively), and their SF-36 scores were comparable to those of the comparison group. In patients, RS score was strongly associated with STAI-State anxiety and BDI ( $\rho=-0.57$  and  $-0.56$ , respectively), and weakly with ESS ( $\rho=-0.20$ ) scores.

**Conclusions.** The results of this study suggest that resilience may play a key role in patients' adaptation to NT1. Furthermore, this study supports interventions aimed at increasing patients' resilience, and provides a base for further studies, preferably longitudinal and including objective measures, directed toward understanding the relationship between resilience, depression and QoL in patients with narcolepsy.

**Keywords:** narcolepsy, cataplexy, sleepiness, anxiety, depression, quality of life, adaptation, resilience.

## **BRIEF SUMMARY**

**Current Knowledge/Study Rationale.** Narcolepsy type 1 is a central disorder of hypersomnolence that may strongly affect patients' quality of life despite effective symptomatic treatment. It has been hypothesized that psychological factors could play a key role in patients' adaptation to the disorder, but research on this subject is scarce.

**Study Impact.** The results of this study support the hypothesis that resilience may play a key role in patients' adaptation to the disease, supporting early interventions aiming to foster resilience in patients with narcolepsy type 1. The results may stimulate future research, preferably with a longitudinal design and including objective measures, aimed at clarifying the relationship between resilience, depression, and quality of life in patients with narcolepsy and other chronic disorders.

## INTRODUCTION

Narcolepsy is a rare central disorder of hypersomnolence that is currently divided into two categories, narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2), both of which are associated with excessive daytime sleepiness (EDS), sleep paralysis, hypnagogic hallucinations and disrupted nocturnal sleep.<sup>1</sup> Cataplexy (i.e., a sudden loss of muscular tone in response to strong emotions) is pathognomonic for NT1, that is associated with low cerebrospinal orexin A levels. Orexins are neuropeptides involved in the regulation of a wide range of complex behaviors, including sleep/wakefulness, emotion, and feeding and metabolism.<sup>2</sup>

Narcolepsy onset typically occurs during childhood or young adulthood, but the disease is largely under- or mis-diagnosed and may remain undiagnosed for several years, exacerbating the disease burden.<sup>3-7</sup> Endocrine and metabolic comorbidity, especially precocious puberty and obesity, are frequent in NT1.<sup>7-9</sup>

Narcolepsy is associated with a higher risk of developing anxiety and depression or depressive symptoms.<sup>10,11</sup> Due to the role of the orexinergic system in stress response,<sup>12-14</sup> and the anxiolytic and antidepressant activity of orexins demonstrated in murine models,<sup>15,16</sup> it was suggested that the high psychiatric comorbidity in patients with NT1 could be due to the orexin deficiency. However, the similar prevalence of depressive symptoms found in patients with NT1 and NT2 indicates that this orexin deficiency alone cannot be the cause.<sup>11</sup>

On the other hand, the high frequency of psychiatric disturbances might reflect the psychosocial burden of narcolepsy.<sup>10,17</sup> The disease is indeed associated with a remarkable quality of life (QoL), social, and work impairment,<sup>3,18-21</sup> and with social stigma.<sup>22-24</sup>

NT1 treatment is still symptomatic, and the most widely-used drugs are stimulants, wake-promoting agents, sodium oxybate, and anticataplexy drugs, often in association. Pharmacologic treatment, together with planned daytime naps, is effective in improving

symptoms, but evidence of an effect on QoL is scarce,<sup>25</sup> and considerable inter-individual variation is reported.<sup>20,26,27</sup> Indeed, some studies indicated that EDS and cataplexy are not the only factors that contribute to a reduced QoL in patients with NT1,<sup>28,29</sup> suggesting the existence of personal factors that influence the patient's adaptation to the disorder that might buffer the adverse effects related to this condition.<sup>3,20,29-31</sup> Since NT1 affects the mental wellbeing more than the physical wellbeing,<sup>21</sup> the role of psychological factors such as resilience is worth exploring, with the goal of identifying potential modifiable targets for intervention in order to improve disease adaptation. Resilience refers to the ability of individuals to effectively adapt to acute stress, adversity, or trauma, without losing their psychological wellbeing and physiological equilibrium.<sup>32</sup> While the involvement of the orexinergic system in stress resilience is being increasingly explored,<sup>13-15,33,34</sup> studies investigating resilience in patients with NT1 are scarce. The objective of our study was to fill the knowledge gap by: 1) describing the resilience profile of patients with NT1 in contrast with people without narcolepsy, and 2) assessing correlations between resilience and sociodemographic variables, NT1 symptoms, anxiety, depression, and QoL in patients with NT1.

## **METHODS**

### *Study design*

Cross-sectional study with a comparison group.

### *Setting and participants*

The "Psychosocial impact of narcolepsy" study involved patients with a definite diagnosis of NT1 according to the International Classification of Sleep Disorders,<sup>1</sup> and people without sleep

complaints (comparison group or controls). To be eligible, participants had to be adults who were able to understand the study purposes and read written Italian.

Patients were recruited from the Narcolepsy Center of Bologna. The center is located in the Emilia Romagna Region but takes patients that, for the most part (71%), come from other Italian regions.<sup>35</sup> Controls were recruited from among people (specifically: parents, children, partners, or friends) from all over the country accompanying patients with narcolepsy or other neurological disorders (e.g., headache, neuromuscular disorders) at the tertiary neurological outpatient clinic of the IRCCS Institute of Neurological Sciences of Bologna (ISNB). The study was performed between February 2017 and July 2019.

#### *Protocol Approval and Informed Consent*

The study was approved by the local ethical Committee (Comitato Etico Interaziendale Bologna-Imola, protocol number: 16181). All participants provided written informed consent; confidentiality was guaranteed.

#### *Data collection*

All participants underwent a semi-structured interview to investigate: a) socio-demographic features (including gender, age, education, sentimental status, and working status); b) age at onset of symptoms and age at diagnosis (only patients); and c) height and weight (in order to calculate body mass index-BMI).<sup>3</sup>

#### *Questionnaires*

Patients were asked to fill in a self-administrated questionnaire regarding NT1 symptoms (i.e., cataplexy, disrupted nocturnal sleep, hypnagogic hallucinations, and sleep paralysis) while both patients and controls were asked to fill in the following validated questionnaires:



- the Epworth Sleepiness Scale (ESS) for the assessment of sleepiness (a score  $\geq 11$  indicates EDS);
- the SF-36 Health Survey questionnaire to assess the health-related QoL. The SF-36 consists of 36 questions that can be divided into 8 scales. Each of the 8 summed scores is linearly transformed on a scale from 0 (negative health) to 100 (positive health) to provide a score for each subscale, and two summary measures can thus be calculated: a physical (Physical Component Summary, PCS) and a mental component (Mental Component Summary, MCS);
- the State-Trait Anxiety Inventory (STAI) State-Anxiety scale to assess the respondents' feelings of anxiety "at this point in time"; the total score ranges from 20 to 80 (scores of  $< 40$  indicated no anxiety, 40-50 mild anxiety, 51-60 moderate anxiety, and  $> 61$  severe anxiety);
- the Beck Depression Inventory (BDI) to assess depressive symptoms (total score  $> 13$  suggests presence of clinically relevant depressive symptomatology);
- the 24-item Italian version of the Resilience Scale (RS) for the assessment of the degree of individual resilience,<sup>36</sup> considered as a positive personality characteristic that enhances individual adaptation<sup>37</sup> (total scores of 147 or above indicate high resilience, scores from 121 to 146 mid-range resilience, and scores lower than 121 low resilience).<sup>36</sup>

### *Statistical analysis*

Descriptive statistics were presented as absolute (N) and relative frequencies (%) for categorical variables and as means with standard deviation (SD) for continuous variables. Normality distributions were checked using the Shapiro-Wilk test.

Differences between patients and controls in terms of sociodemographic and clinical characteristics were evaluated with a t-test or Mann-Whitney U test for continuous variables and with a chi-square test for categorical variables.

A multivariable logistic regression model was performed to evaluate the association between level of resilience (low/mid-range vs. high, dependent variable) and group (patients vs. controls), sex and age (independent variables). The result was presented as Odds Ratio (OR) and 95% Confidence Interval (95% CI).

Finally, a one-way Anova or Kruskal Wallis test were performed to assess differences in sociodemographic and clinical characteristics of patients with NT1 according to their level of resilience (low, mid-range and high categories), while Spearman's rho correlation was used to evaluate the correlation between continuous scale of resilience (RS) and EDS (ESS), anxiety and depressive symptomatology (STAI State-Anxiety and BDI), and QoL (PCS and MCS).

A p-value of  $\leq 0.05$  was considered significant. Statistical analysis was performed with Stata SE 14.2.

## **RESULTS**

One hundred and thirty-seven patients with NT1 who completed the RS were matched for age and sex with 149 controls. Sociodemographic and clinical characteristics of patients and controls are reported in Table 1, while Table 2 summarizes the characteristics of patients related to narcolepsy (age at onset, age at diagnosis, symptoms, etc.).

### *Sociodemographic characteristics (Table 1)*

There were no significant differences in age or sex between the group of patients with NT1 and the comparison group: the mean age was 38.0 and 39.6, respectively, and 52.6% and 55.7% of participants were female, respectively. Education level, sentimental status, and work activity all significantly differed, with patients more frequently having a low level of education (25.6%

of patients had completed at most elementary or middle schools vs. 13.4% of controls) and less frequently having a partner (50.4% vs. 80.5%) or a work/study activity (73.7% vs. 84.6%).

#### *Clinical characteristics (Table 1)*

According to BMI, patients were significantly less frequently of normal weight (32.9% vs. 66.9%) and more frequently obese than controls (23.4% vs. 10.8%). Patients showed higher levels of EDS (mean ESS 12.3 vs. 5.5, and ESS score  $\geq 11$  in 60.7% of patients vs. 7.3% of controls) and anxiety (mean STAI-State anxiety of 39.5 vs. 35.6), and reported experiencing no anxiety less frequently (13.9% vs. 28.4%) and severe anxiety more frequently (32.1% vs. 16.9%) than controls. The patient group also presented depressive symptomatology more frequently in terms of both mean BDI (11.4 vs. 6.1) and rate of patients with a BDI score  $> 13$  (32.9% vs. 12.4%), and lower SF-36 PCS (48.7 vs. 53.4) and MCS (40.7 vs. 47.4) mean scores.

#### *Resilience*

As for resilience, the mean RS score was significantly lower in patients with NT1 than in controls (122.6 vs. 135.5), and patients had a low level of resilience more often (38.0% vs. 18.8%) and a high level of resilience less frequently (17.5% vs. 30.2%) compared with controls (Table 1). There were no significant associations between levels of resilience and sociodemographic characteristics, except age, that was positively associated with resilience (data not shown). Therefore, only sex and age were included in the multivariable analysis. This model (Table 3) showed that patients with NT1 (vs. comparison group) had a twofold risk of having low or mild-range resilience (vs. high category) with an adjusted OR = 1.99, 95% CI 1.13-3.52. An inverse correlation trend was found between age and resilience (adjusted OR = 0.98, 95% CI 0.96-1.00,  $p=0.057$ ); no association was found between sex and resilience ( $p=0.621$ ).

### *Factors associated with resilience and resilience levels in patients with NT1*

In patients with NT1, there were no significant associations between levels of resilience and age at onset, age at diagnosis, or diagnostic delay (data not shown).

The comparisons between patients according to their level of resilience (Table 4) showed that patients with low, mid-range, and high resilience did not significantly differ with regard to sociodemographics, BMI, or NT1 symptoms. However, there was a trend ( $p=0.059$ ) concerning the mean ESS score, that was 13.1 in patients with low resilience, 12.1 in those with mid-range resilience, and 10.0 in patients with high resilience.

On the other hand, from the group of patients with low resilience to that with high resilience there was a significant decrease in the rate of patients with severe anxiety (from 55.8% to 4.2%) and  $BDI > 13$  (from 58.3% to 4.2%), mean STAI-State anxiety and BDI scores decreased from 46.3 to 30.1 and from 18.3 to 4.1, respectively, while PCS and MCS increased (from 46.3 to 53.5 and from 34.1 to 48.5, respectively), with patients with high resilience showing scores that were comparable to those of the controls.

With regard to pharmacological treatment, there were no significant differences, even when comparing patients in terms of their use of different antidepressant drugs (data not shown).

Table 5 shows Spearman's correlations, always significant, between RS score and ESS, STAI-State anxiety, BDI, PCS, and MCS scores in patients with NT1: PCS and MCS increased according with RS ( $\rho=0.31$  and  $\rho=0.44$  respectively), while increasing resilience was associated with the reduction of the ESS ( $\rho=-0.21$ ), STAI-State anxiety ( $\rho=-0.57$ ), and BDI ( $\rho=-0.56$ ) scores.

## **DISCUSSION**

This study explored resilience and its possible association with symptoms, anxiety, depression, and QoL in patients with NT1 through comparison with a sex- and age-matched control group.

We found that, compared to controls, patients with NT1 had a significantly lower resilience and a twofold risk of having low/mild-range resilience, while there was a trend suggesting that age was a protective factor: as age increased the resilience score decreased. Patients with high resilience had similar sociodemographic and narcolepsy characteristics of those with low resilience, but they reported anxiety and depressive symptomatology almost never, and their quality of life was comparable to that of controls. In patients, resilience was strongly associated with anxious and depressive symptomatology, and only weakly with sleepiness.

In this study, we used the RS, which is considered one of the best tools for investigating resilience in both adults and adolescents.<sup>36</sup> Several studies using the RS have reported that patients suffering from chronic diseases had a low or mid-range resilience level.<sup>38</sup> However, most studies did not have a comparison group and those with a comparison group did not find significant differences.<sup>39,40</sup> Focusing on neurological disorders, the mean RS score was found to be in the mid-range ( $136.8 \pm 17.3$ ) in patients with epilepsy,<sup>41</sup> and low in patients with multiple sclerosis ( $113.4 \pm 21.4$ ) and neuromyelitis optica spectrum disorder ( $117.0 \pm 29.0$ ).<sup>42</sup> However, the only study investigating resilience in older patients with multiple sclerosis compared with healthy older adults did not find significant differences with regard to the RS score (148.4 vs. 148.3).<sup>43</sup> Therefore, an association between neurologic disorders and lower RS scores cannot be affirmed, due to the scarcity of studies comparing patients with people without neurologic disorders.

On the other hand, pre-clinical findings suggest that orexins are involved in stress resilience.<sup>15,16,33</sup> It is therefore possible that the lack of orexin predisposes patients with NT1

to a lower resilience, but the finding that 30% of patients had a high level of resilience indicates that other factors are involved.

Studies investigating resilience in neurologic disorders generally did not find associations between resilience and disease severity.<sup>43</sup> In our study, only a trend for reduced ESS scores in patients with higher resilience and a weak correlation between ESS and RS were observed.

These results could suggest a relationship between sleepiness and resilience, especially when considering that patients with high resilience had a mean ESS score in the normal range.

Further studies are needed to better address this issue, also in light of the positive correlation between resilience and sleep quality found in studies involving healthy subjects.<sup>44,45</sup>

On the other hand, in our study, both anxious and depressive symptomatology were strongly correlated with resilience, and among patients with high resilience fewer than 5% had psychological problems. Interestingly, the high-resilience group of patients had similar sociodemographic and NT1 characteristics of patients with lower resilience, but their QoL was comparable with that of people without narcolepsy. The finding that patients with high resilience have an unimpaired QoL suggests that, as we hypothesized, resilience may play a key role in patients' adaptation to NT1, consistently with what happens in several neurodegenerative diseases.<sup>46</sup> From this perspective, the positive trend showing a protective role of age towards low resilience could contribute to explain the positive association between age and QoL in patients with narcolepsy found by several studies.<sup>21</sup> On the other hand, since almost all the patients with high resilience also reported a lack of depressive symptomatology, it is possible that our results reflect the complex relationship between resilience, depression and QoL. Finally, due to the cross-sectional nature of our study it is not possible to exclude the possibility that lower resilience scores are consequent to the development of anxiety or depression.

In any case, the results of our study may have several implications. First, our findings support pilot trials to test interventions that foster resilience in patients with NT1 in order to help them to better adapt to the disorder. It is commonly recognized that psychological interventions have positive effects on individual resilience,<sup>38,47</sup> and interventions promoting resilience in other neurological conditions have been successfully tested.<sup>48-50</sup> Since psychological resilience can aid in the successful adjustment to illness, targeting resilience early on may help patients deal with all the different facets of the disease and live a better life.<sup>46</sup> Secondly, these results suggest that the measures of resilience like the RS could help to identify patients with low and mid-range resilience who, in light of the strong association between resilience and anxiety and depressive symptoms, should be routinely screened and monitored for anxiety and depression. Finally, the empirical evidence provided by our study may stimulate new hypotheses regarding the role of orexin in terms of both resilience and depression.

A limitation of this study may be the small number of patients enrolled. Nevertheless, NT1 is a rare condition, and our study was one of the few involving a population of patients with a diagnosis of NT1 according to the more recent internationally accepted criteria. Another critical point could be represented by the strategy used to recruit participants included in the comparison group. On one hand, the recruitment of family members and people within the support network who are close to patients with neurologic disorders may explain the high levels of anxiety and depressive symptoms found in the control group. On the other hand, since a genetic predisposition to narcolepsy<sup>2,17</sup> may be shared within family cohorts, the presence of relatives in the comparison group may have made some differences between patients and controls smaller or undetectable. Unfortunately, we did not record information regarding the existence of family relations between patients and controls. Therefore, we could not calculate the rate of relatives of patients with NT1 in the comparison group. However,

sociodemographic and clinical features differed between patients and controls in a manner that was consistent with previous studies and the mean RS score of the comparison group mirrored that of the Italian general population, suggesting that the recruitment strategy had little or no influence on the main study results.

Finally, longitudinal studies are required to clarify the relationship between resilience, depression, and QoL in patients with narcolepsy; future investigations should consider collecting more objective (i.e., biological) measures from blood or cardiovascular metrics that could support the subjective inventory correlations, since studies on resilience and depression have demonstrated that there are many potential neural and non-neural factors involved in both humans and animal models.<sup>51,52</sup>

The strengths of this study include the comprehensive description of participants, including both clinical and sociodemographic features, and the use of several validated scales to explore different domains. Furthermore, our study examines a psychological phenomenon that has not yet been explored in narcolepsy, laying the groundwork for future research into modifiable factors associated with disease adaptation.

## **CONCLUSIONS**

The results of this study support the hypothesis that narcolepsy symptoms are not the only determinants of the QoL impairment experienced by people with NT1 and that resilience may have a key role in patients' adaptation to the disease. In line with patients' request for a more holistic approach to their care,<sup>53</sup> the study supports the testing of early interventions in order to increase patients' resilience and help them to better adapt to the disorder. Our results also encourage further studies, preferably with a longitudinal design and including objective measures, aimed at clarifying the relationship between resilience, depression, and quality of life in patients with narcolepsy and other chronic disorders.



## **ABBREVIATIONS**

BDI: Beck Depression Inventory

BMI: Body Mass Index

CI: Confidence Interval

ESS: Epworth Sleepiness Scale

MCS: Mental Component Score.

NT1: Narcolepsy Type 1

QoL: Quality of Life

OR: Odds Ratio

PCS: Physical Component Score

RS: Resilience Scale

SF-36: Short Form 36

STAI: State-Trait Anxiety Inventory

## REFERENCES

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Mahoney CE, Cogswell A, Koralnik IJ, Scammell TE. The neurobiological basis of narcolepsy. *Nat Rev Neurosci*. 2019;20(2):83-93.
3. Ingravallo F, Gnucchi V, Pizza F, et al. The burden of narcolepsy with cataplexy: how disease history and clinical features influence socio-economic outcomes. *Sleep Med*. 2012;13(10):1293-1300.
4. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. 2014;15(5):502-507.
5. Maski K, Steinhart E, Williams D, et al. Listening to the Patient Voice in Narcolepsy: Diagnostic Delay, Disease Burden, and Treatment Efficacy. *J Clin Sleep Med*. 2017;13(3):419-425.
6. Plazzi G, Clawges HM, Owens JA. Clinical Characteristics and Burden of Illness in Pediatric Patients with Narcolepsy. *Pediatr Neurol*. 2018;85:21-32.
7. Vignatelli L, Antelmi E, Ceretelli I, et al. Red Flags for early referral of people with symptoms suggestive of narcolepsy: a report from a national multidisciplinary panel. *Neurol Sci*. 2019;40(3):447-456.
8. Poli F, Pizza F, Mignot E, et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep*. 2013;36(2):175-181.
9. Mohammadi S, Moosaie F, Saghazadeh A, Mahmoudi M, Rezaei N. Metabolic profile in patients with narcolepsy: a systematic review and meta-analysis. *Sleep Med*. 2021;81:268-284.
10. BaHammam AS, Alnakshabandi K, Pandi-Perumal SR. Neuropsychiatric Correlates of Narcolepsy. *Curr Psychiatry Rep*. 2020;22(8):36.

11. Li X, Sanford LD, Zong Q, et al. Prevalence of Depression or Depressive Symptoms in Patients with Narcolepsy: a Systematic Review and Meta-Analysis. *Neuropsychol Rev.* 2021;31(1):89-102.
12. Li SB, Jones JR, de Lecea L. Hypocretins, Neural Systems, Physiology, and Psychiatric Disorders. *Curr Psychiatry Rep.* 2016;18(1):7.
13. Grafe LA, Bhatnagar S. Orexins and stress. *Front Neuroendocrinol.* 2018;51:132-145.
14. Yaeger JDW, Krupp KT, Jacobs BM, et al. Orexin 1 Receptor Antagonism in the Basolateral Amygdala Shifts the Balance From Pro- to Antistress Signaling and Behavior. *Biol Psychiatry.* 2022;91(9):841-852.
15. Staton CD, Yaeger JDW, Khalid D, et al. Orexin 2 receptor stimulation enhances resilience, while orexin 2 inhibition promotes susceptibility, to social stress, anxiety and depression. *Neuropharmacology.* 2018;143:79-94.
16. Summers CH, Yaeger JDW, Staton CD, Arendt DH, Summers TR. Orexin/hypocretin receptor modulation of anxiolytic and antidepressive responses during social stress and decision-making: Potential for therapy. *Brain Res.* 2020;1731:146085.
17. Bassetti CLA, Adamantidis A, Burdakov D, et al. Narcolepsy - clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nat Rev Neurol.* 2019;15(9):519-539.
18. Black J, Reaven NL, Funk SE, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. *Sleep Med.* 2014;15(5):522-529.
19. Rocca FL, Finotti E, Pizza F, et al. Psychosocial Profile and Quality of Life in Children With Type 1 Narcolepsy: A Case-Control Study. *Sleep.* 2016 Jul 1;39(7):1389-98.
20. White M, Charbotel B, Fort E, et al. Academic and professional paths of narcoleptic patients: the Narcowork study. *Sleep Med.* 2020;65:96-104.
21. Tadrous R, O'Rourke D, Mockler D, Broderick J. Health-related quality of life in narcolepsy: A systematic review and meta-analysis. *J Sleep Res.* 2021;30(6):e13383.

22. Kapella MC, Berger BE, Vern BA, Vispute S, Prasad B, Carley DW. Health-related stigma as a determinant of functioning in young adults with narcolepsy. *PLoS One*. 2015;10(4):e0122478.
23. Barbero L, Govi A, Pizza F, Plazzi G, Ingravallo F. Parental Fitness Questioned on the Grounds of Narcolepsy: Presentation of Two Cases. *J Clin Sleep Med*. 2017;13(8):1017-1018.
24. Varallo G, Pingani L, Musetti A, et al. Portrayals of narcolepsy from 1980 to 2020: a descriptive analysis of stigmatizing content in newspaper articles. *J Clin Sleep Med*. 2022.
25. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine systematic review, meta-analysis, and GRADE assessment. *J Clin Sleep Med*. 2021;17(9):1895-1945.
26. Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline and expert statements on the management of narcolepsy in adults and children. *J Sleep Res*. 2021;30(6):e13387.
27. Franceschini C, Pizza F, Cavalli F, Plazzi G. A practical guide to the pharmacological and behavioral therapy of Narcolepsy. *Neurotherapeutics*. 2021;18(1):6-19.
28. Daniels E, King MA, Smith IE, Shneerson JM. Health-related quality of life in narcolepsy. *J Sleep Res*. 2001;10(1):75-81.
29. Vignatelli L, D'Alessandro R, Mosconi P, et al. Health-related quality of life in Italian patients with narcolepsy: the SF-36 health survey. *Sleep Med*. 2004;5(5):467-475.
30. Bruck D, Costa A. The natural history of health and symptoms in narcolepsy: a to-year longitudinal study. *Aust J Prim Health*. 2003; 9.1: 59-67.
31. Vignatelli L, Plazzi G, Peschechera F, Delaj L, D'Alessandro R. A 5-year prospective cohort study on health-related quality of life in patients with narcolepsy. *Sleep Med*. 2011;12(1):19-23.

32. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry*. 2004;161(2):195-216.
33. Grafe LA, Eacret D, Dobkin J, Bhatnagar S. Reduced Orexin System Function Contributes to Resilience to Repeated Social Stress. *eNeuro*. 2018;5(2):ENEURO.0273-17.2018.
34. Ji MJ, Zhang XY, Chen Z, Wang JJ, Zhu JN. Orexin prevents depressive-like behavior by promoting stress resilience. *Mol Psychiatry*. 2019;24(2):282-293.
35. Ingravallo F, Vignatelli L, Pagotto U, et al. Protocols of a diagnostic study and a randomized controlled non-inferiority trial comparing televisits vs standard in-person outpatient visits for narcolepsy diagnosis and care: TElemedicine for NARcolepsy (TENAR). *BMC Neurol*. 2020 May 11;20(1):176.
36. Girtler N, Casari EF, Brugnolo A, et al. Italian validation of the Wagnild and Young Resilience Scale: a perspective to rheumatic diseases. *Clin Exp Rheumatol*. 2010;28(5):669-678.
37. Wagnild GM, Young HM. Development and psychometric evaluation of the Resilience Scale. *J Nurs Meas*. 1993;1(2):165-178.
38. Kim GM, Lim JY, Kim EJ, Park SM. Resilience of patients with chronic diseases: A systematic review. *Health Soc Care Community*. 2019;27(4):797-807.
39. Moreira JM, Bouissou Morais Soares CM, Teixeira AL, Simões E Silva AC, Kummer AM. Anxiety, depression, resilience and quality of life in children and adolescents with pre-dialysis chronic kidney disease. *Pediatr Nephrol*. 2015;30(12):2153-2162.
40. Priori R, Giardina F, Izzo R, et al. Resilience in women with primary Sjögren's syndrome. *Rheumatol Int*. 2021;41(11):1987-1994.

41. Tedrus GMAS, Limongi JM Junior, Zuntini JVR. Resilience, quality of life, and clinical aspects of patients with epilepsy. *Epilepsy Behav.* 2020;103(Pt A):106398.
42. Nakazawa K, Noda T, Ichikura K, et al. Resilience and depression/anxiety symptoms in multiple sclerosis and neuromyelitis optica spectrum disorder. *Mult Scler Relat Disord.* 2018;25:309-315.
43. Sadeghi-Bahmani D, Kidwell A, Bollaert R, Motl RW. Resilience among older adults with multiple sclerosis: Pattern and correlates. *Mult Scler Relat Disord.* 2022;57:103360.
44. Jeon HJ, Bang YR, Park HY, Kim SA, Yoon IY. Differential effects of circadian typology on sleep-related symptoms, physical fatigue and psychological well-being in relation to resilience. *Chronobiol Int.* 2017;34(6):677-686.
45. Hao X, Li M, Li J, Lv M, Qin Y, Li K. Sleep quality in relation to social support and resilience among rural empty-nest older adults in China. *Sleep Med.* 2021;82:193-199.
46. Ovaska-Stafford N, Maltby J, Dale M. Literature Review: Psychological Resilience Factors in People with Neurodegenerative Diseases. *Arch Clin Neuropsychol.* 2021;36(2):283-306.
47. Joyce S, Shand F, Tighe J, Laurent SJ, Bryant RA, Harvey SB. Road to resilience: a systematic review and meta-analysis of resilience training programmes and interventions. *BMJ Open.* 2018;8(6):e017858.
48. Wagner JL, Smith G, Ferguson P, van Bakergem K, Hrisiko S. Feasibility of a pediatric cognitive-behavioral self-management intervention: Coping Openly and Personally with Epilepsy (COPE). *Seizure.* 2011;20(6):462-467.
49. Alschuler KN, Arewasikporn A, Nelson IK, Molton IR, Ehde DM. Promoting resilience in individuals aging with multiple sclerosis: Results from a pilot randomized controlled trial. *Rehabil Psychol.* 2018;63(3):338-348.

50. Pakenham KI, Mawdsley M, Brown FL, Burton NW. Pilot evaluation of a resilience training program for people with multiple sclerosis. *Rehabil Psychol*. 2018;63(1): 29–42.
51. Han MH, Nestler EJ. Neural Substrates of Depression and Resilience. *Neurotherapeutics*. 2017;14(3):677-686.
52. Dudek KA, Dion-Albert L, Kaufmann FN, Tuck E, Lebel M, Menard C. Neurobiology of resilience in depression: immune and vascular insights from human and animal studies. *Eur J Neurosci*. 2021;53(1):183-221.
53. Xiao L, Chen A, Parmar A, Frankel L, Toulany A, Murray BJ, Narang I. Narcolepsy Treatment: Voices of Adolescents. *Behav Sleep Med*. 2022;20(2):260-268.

**Table 1. Sociodemographic and clinical characteristics: comparisons between patients and controls.**

		<b>Patients with NT1 N= 137</b>	<b>Controls N= 149</b>	<i>p</i>
<b>Female N (%)</b>		72 (52.6)	83 (55.7)	0.593
<b>Age (years) Mean (SD)</b>		38.0 (15.6)	39.6 (14.0)	0.159
<b>Education N (%)</b>	Elementary/middle	35 (25.6)	20 (13.4)	<0.001
	High school	80 (58.4)	75 (50.3)	
	More than high school	22 (16.0)	54 (36.3)	
<b>Had a partner N (%)</b>	Yes	62 (50.4)	120 (80.5)	< 0.001
<b>Student or employed N (%)</b>	Yes	101 (73.7)	126 (84.6)	0.024
<b>BMI class N (%)</b>	Normal	45 (32.9)	99 (66.9)	< 0.001
	Overweight	40 (29.2)	33 (22.3)	
	Obesity	32 (23.4)	16 (10.8)	
<b>ESS Mean (SD)</b>		12.3 (4.9)	5.5 (3.4)	<0.001
<b>ESS<math>\geq</math>11 N (%)</b>		74 (60.7)	10 (7.3)	<0.001
<b>STAI-State anxiety Mean (SD)</b>		39.5 (11.4)	35.6 (10.6)	0.002
<b>STAI-State anxiety</b>	No anxiety	19 (13.9)	42 (28.4)	0.001
	Mild	58 (42.3)	53 (35.8)	
	Moderate	16 (11.7)	28 (18.9)	
	Severe	44 (32.1)	25 (16.9)	
<b>BDI Mean (SD)</b>		11.4 (10.3)	6.1 (6.7)	<0.001
<b>BDI&gt;13 N (%)</b>		45 (32.9)	18 (12.4)	<0.001
<b>Quality of life Mean (SD)</b>	SF-36 PCS	48.7 (9.0)	53.4 (7.3)	<0.001
	SF-36 MCS	40.7 (12.0)	47.4 (9.2)	<0.001
<b>Resilience Mean (SD)</b>		122.6 (25.7)	135.5 (17.6)	<0.001
<b>Resilience level N (%)</b>	Low	52 (38.0)	28 (18.8)	<0.001
	Mid-range	61 (44.5)	76 (51.0)	
	High	24 (17.5)	45 (30.2)	

NT1: Narcolepsy Type 1; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale, SF-36: Short Form 36; PCS: Physical Component Score; MCS: Mental Component Score; BDI: Beck Depression Inventory.

**Table 2. Patients' narcolepsy-related characteristics**

(N=137).

<b>Age at onset Mean (SD)</b>	20.1 (12.5)
<b>Age at diagnosis Mean (SD)</b>	28.3 (13.5)
<b>Symptoms/last month N (%)</b>	
Cataplexy	87 (63.5)
Disrupted nocturnal sleep	86 (62.8)
Hypnagogic hallucinations	51 (37.2)
Sleep paralysis	44 (32.1)
<b>Pharmacological treatment N (%)</b>	
Stimulants	76 (55.5)
Sodium oxybate	86 (62.8)
Anticatataplexy	32 (23.4)
Other	6 (4.4)
None	12 (8.8)

\*The anticatataplectic drug was venlafaxine in 25/32 cases and clomipramine or duloxetine chlorhydrate in the remaining 7/32 cases.



**Table 3. Multivariable logistic model with resilience (low/mid-range vs. high) as dependent variable.**

<b>Independent variables</b>	<b>OR</b>	<b>95% CI</b>	<b>p</b>
Narcolepsy Type 1			
No	reference	-	0.017
Yes	1.99	1.13-3.52	
Sex			0.621
Female	reference	-	
Male	1.15	0.65-2.00	
Age	0.98	0.96-1.00	0.057

OR: Odds Ratio; 95% CI: 95% Confidence Interval

**Table 4. Sociodemographic and clinical characteristics of patients with NT1 according to their resilience level.**

	<b>Low resilience N= 52</b>	<b>Mid range resilience N=61</b>	<b>High resilience N=24</b>	<b>p</b>
<b>Female N (%)</b>	28 (53.8)	31 (50.8)	13 (54.2)	0.935
<b>Age Mean (SD)</b>	37.0 (15.8)	38.6 (16.2)	38.6 (13.9)	0.764
<b>Education N (%)</b>				0.104
Elementary/middle	11 (21.1)	13 (21.3)	5 (20.8)	
High school	37 (71.1)	29 (47.5)	14 (58.3)	
More than high school	4 (7.7)	19 (31.1)	5 (20.8)	
<b>Had a partner N (%)</b>	20 (46.5)	27 (47.4)	15 (65.2)	0.228
<b>Student or employed N (%)</b>	33 (63.4)	49 (80.3)	19 (79.2)	0.102
<b>BMI class N (%)</b>				0.702
Normal	17 (39.5)	22 (41.5)	6 (28.6)	
Overweight	14 (32.6)	16 (30.2)	10 (47.6)	
Obese	12 (27.9)	15 (28.3)	5 (23.8)	
<b>ESS Mean (SD)</b>	13.1 (5.5)	12.1 (3.9)	10.0 (5.7)	0.059
<b>ESS<math>\geq</math>11 N (%)</b>	34 (65.4)	36 (59.0)	11 (45.8)	0.273
<b>Symptoms/last month N (%)</b>				
Cataplexy	34 (65.4)	40 (65.5)	13 (54.2)	0.578
Disrupted nocturnal sleep	36 (70.6)	36 (61.0)	14 (58.3)	0.467
Hypnagogic hallucinations	21 (41.2)	22 (37.3)	8 (33.3)	0.798
Sleep paralysis	17 (34.0)	20 (35.1.0)	7 (29.2)	0.873
<b>STAI-State anxiety Mean (SD)</b>	46.3 (11.3)	37.4 (9.5)	30.1 (6.8)	<0.001
<b>STAI-State anxiety</b>				<0.001
No anxiety	1 (1.9)	9 (14.8)	9 (37.5)	
Mild	14 (26.9)	31 (50.8)	13 (54.2)	
Moderate	8 (15.4)	7 (11.5)	1 (4.2)	
Severe	29 (55.8)	14 (22.9)	1 (4.2)	
<b>BDI Mean (SD)</b>	18.3 (11.5)	8.8 (7.1)	4.1 (4.6)	<0.001
<b>BDI&gt;13 N (%)</b>	28 (58.3)	16 (26.2)	1 (4.2)	<0.001
<b>Quality of life Mean (SD)</b>				
PCS	46.3 (10.2)	48.9 (8.3)	53.5 (5.5)	0.038
MCS	34.1 (11.7)	43.1 (10.6)	48.5 (8.2)	<0.001
<b>Pharmacological treatment for narcolepsy N (%)</b>				
Stimulants	25 (48.1)	36 (59.0)	15 (62.5)	0.379
Sodium oxybate	32 (61.5)	40 (65.6)	14 (58.3)	0.802
Anticataplexy	16 (30.8)	11 (18.0)	5 (20.8)	0.266
Other	4 (7.7)	1 (1.6)	1 (4.2)	0.292
None	6 (11.5)	3 (4.9)	3 (12.5)	0.359

NT1: Narcolepsy Type 1; BMI: Body Mass Index; ESS: Epworth Sleepiness Scale; SF-36: Short Form 36; PCS: Physical Component Score; MCS: Mental Component Score; STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory.

**Table 5. Spearman correlations between resilience and sleepiness, anxiety, depressive symptoms, and quality of life in patients with NT1.**

<b>Continuous variable</b>	<b><i>Rho</i></b>	<b><i>p</i></b>
<b>ESS</b>	-0.20	<0.015
<b>STAI-State anxiety</b>	-0.57	<0.001
<b>BDI</b>	-0.56	<0.001
<b>SF-36 PCS</b>	0.31	<0.001
<b>SF-36 MCS</b>	0.44	<0.001

NT1: Narcolepsy Type 1; ESS: Epworth Sleepiness Scale, STAI: State-Trait Anxiety Inventory; BDI: Beck Depression Inventory; SF-36: Short Form 36; PCS: Physical Component Score; MCS: Mental Component Score.