RESEARCH ARTICLE

Measurement of Narcolepsy Symptoms in School-Aged Children and Adolescents

The Pediatric Narcolepsy Severity Scale

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Abstract

Objective

We validated the Narcolepsy Severity Scale (NSS) in adults with narcolepsy type 1 (NT1) to quantify the severity, frequency, and consequences of the 5 key narcolepsy symptoms over the last month, and we now developed the Pediatric NSS (NSS-P); thus, the aims of this study were to assess NSS-P psychometric properties, validity, and reliability, and to evaluate its responsiveness to treatment in a well-characterized sample of children and adolescents with NT1.

Methods

The NSS was reformulated for children, and the item about driving was removed. The total score of the 14-item NSS-P ranges from 0 to 54, and higher scores reflect more severe disease. Children and adolescents (n = 209, 6–17 years of age) with NT1 diagnosed in 2 Reference Centers for Narcolepsy in France were consecutively asked to fill in the NSS-P. The scale was fully and correctly completed by 160 (10–18 years of age, 68 untreated). Moreover, 65 participants completed it twice (33 before/during treatment, and 32 under the same treatment). The NSS-P psychometric properties, score changes before/during treatment, and convergent validity with other clinical parameters were assessed.

Results

The NSS-P showed adequate psychometric properties with significant item–total score correlations. Factor analysis indicated a 4-factor solution with good reliability. The NSS-P score was lower in treated than untreated patients with a mean difference of 3.71 ± 1.45, with a minimum clinically important difference between untreated and treated patients in the longitudinal sample estimated at 4 points. Four severity levels were defined (mild, moderate, severe, very severe) with between-group differences related to treatment. The NSS-P total score was associated with self-reported sleepiness, insomnia, and depressive symptoms. Its temporal stability was satisfactory.

Discussion

We validated a brief instrument to assess NT1 symptom frequency, severity, and consequences in ≥10-year-old children and adolescents with 4 clinically relevant severity score ranges. This scale constitutes a relevant tool to improve and provide guidance for NT1 management in pediatric populations. The ease of administration, its good psychometric properties, and its sensitivity to detect symptom changes after treatment ensure future use of the NSS-P in clinical and research settings.

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Glossary

BMI = body mass index; **CDI** = Children's Depression Inventory; **DNS** = disrupted nighttime sleep; **EDS** = excessive daytime sleepiness; **ESS** = Epworth Sleepiness Scale; **ESS-CHAD** = ESS for Children and Adolescents; **ISI** = Insomnia Severity Index; **MCID** = minimum clinically important difference; **MSLT** = Multiple Sleep Latency Test; **NSS** = Narcolepsy Severity Scale; **NSS-P** = Pediatric NSS; **NT1** = narcolepsy type 1; **PDSS** = Pediatric Daytime Sleepiness Scale.

Narcolepsy type 1 (NT1) is a lifelong and disabling neurologic disorder with onset commonly occurring in childhood or adolescence.[1] The cause of this orphan disease (NT1 prevalence 5 per 10,000) is the irreversible destruction of hypothalamic orexin/hypocretin neurons probably through an immune-mediated process.[2] NT1 diagnosis is delayed by 10 years on average, likely due to poor symptom recognition and attribution.[3] The primary symptom is excessive daytime sleepiness (EDS), accompanied in most patients by cataplexy (i.e., a sudden loss of muscle tone typically triggered by positive emotions). Other common symptoms include hypnagogic and hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep (DNS).[4,5] However, pediatric narcolepsy presents a distinct phenotype. Children with sleepiness may show higher levels of hyperactivity, impulsivity, and attention deficit than adult patients,[6] and cataplexy may include subtle facial expressions described as cataplectic facies or choreic-like movements, which are rarely observed in adults.[7] Sleep-related hallucinations, sleep paralysis, and DNS seem less frequent in children than in adults with narcolepsy.[8-10]

Narcolepsy management remains only symptomatic in the absence of curative treatments. It relies on the use of psychostimulants for treating EDS; antidepressants for cataplexy, hallucinations, and sleep paralysis; and sodium oxybate for all symptoms, including DNS.[11] Most of the drugs approved for adults are also widely used in children, although few are approved for this population.[12] Psychometric instruments to assess and monitor NT1 symptom severity in pediatric patients (i.e., <18 years of age) are rare. Several daytime sleepiness scales are used,[13-15] as well as a daily diary or questionnaires to capture cataplexy frequency and intensity[13,16,17]; however, a comprehensive tool that quantifies all NT1 symptoms is lacking for children with narcolepsy.

We recently developed the 15-item self-report Narcolepsy Severity Scale (NSS) and validated it in French in adults with NT1 to quantify the severity, frequency, and consequences of the 5 key narcolepsy symptoms over the last month.[18] NSS has 7 items on EDS, including 1 item on driving, 3 items on cataplexy, 2 items on hallucinations and sleep paralysis, and 1 item on DNS.[18] Using this questionnaire, we found that after EDS and cataplexy, DNS was the third most prevalent symptom (95.5% of patients with 3 symptoms), followed by hallucinations and sleep paralysis.[19] In untreated patients, the number of symptoms was associated with shorter diagnosis delay, younger age at onset, and higher Epworth Sleepiness Scale (ESS) and Beck Depression Inventory-II scores. NSS total score correlated with EDS (assessed with the self-reported ESS score and objective measurements), depressive symptoms, and health-related quality of life. Its score decreases after pharmacologic management without a ceiling effect.[19] This scale has good psychometric properties and is considered a reliable and valid clinical tool for symptom quantification[18] with 4 clinically relevant severity score ranges (mild, moderate, severe, and very severe), with between-group differences related to treatment.[19]

We now developed the Pediatric NSS (NSS-P), a self-report questionnaire designed to measure the frequency, severity, and consequences of the 5 key NT1 symptoms in children and adolescents. The aims of this study were (1) to assess NSS-P psychometric properties, validity, and reliability and (2) to evaluate its responsiveness to treatment in a well-characterized sample of children and adolescents with NT1 from 2 Reference Centers for Narcolepsy in France.

Methods

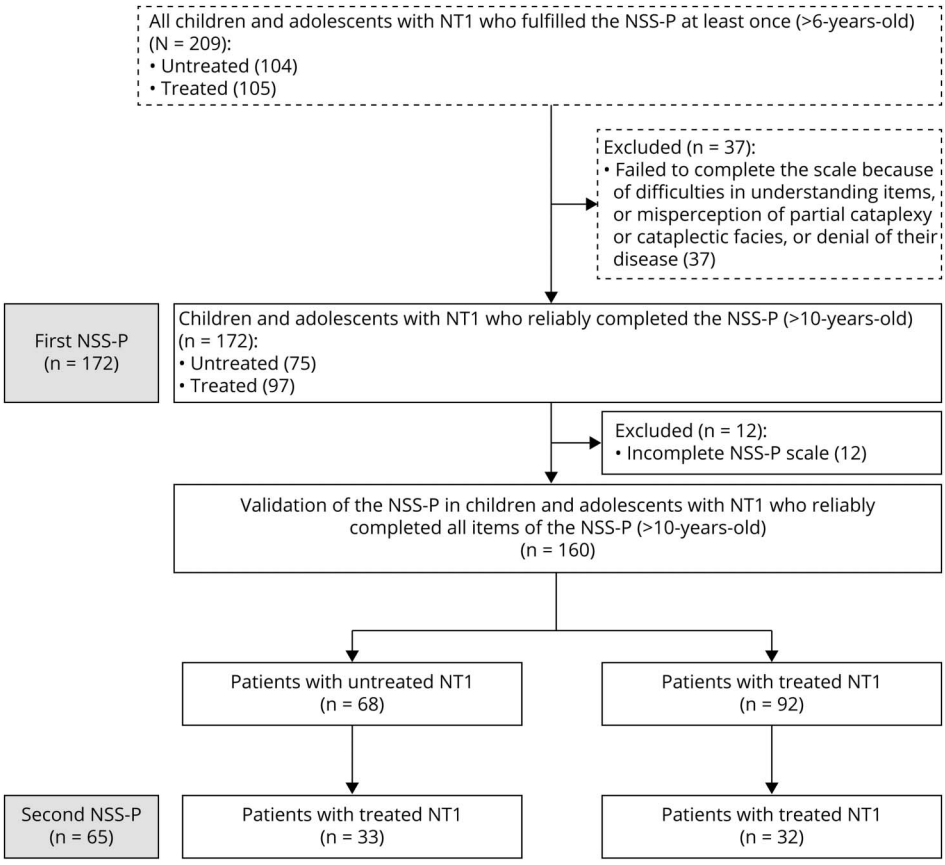
The NSS-P

The NSS-P was adapted from the NSS.[18] Questions were reformulated for ≥6-year-old children and adolescents with adapted wording, and the item about driving (No. 7) was removed. The same item numbering was kept, from 1 to 15 (but without item 7), to ensure a construction similar to that of the adult NSS. The 6 items on symptom frequency are rated with a 6-point Likert scale (0–5), and the 8 items on symptom consequences on daily life are rated with a 4-point Likert scale (0–3). The presence of a narcolepsy symptom is defined by a score ≥1 for at least 1 of the items related to that symptom. The NSS-P total score ranges from 0 to 54, with higher scores reflecting more severe symptoms. Four NSS-P severity levels were defined by dividing the total score in 4 equal ranks, as done with the NSS (mild 0–14, moderate 15–28, severe 29–42, and very severe 43–54).

Study Population

Two hundred nine consecutive 6- to 17-year-old patients with NT1 (41.15% girls, mean age 13.27 ± 2.61 years, 50.24% under pharmacologic treatment) were asked to complete the NSS-P. The physician first ensured that the child/adolescent properly understood the narcolepsy symptoms to recognize and quantify them correctly. Patients were recruited in 2 National Reference Centers for Orphan Hypersomnolence Disorders in France: Robert-Debré Pediatric Hospital in Paris (n = 124) and Gui de Chauliac Hospital in Montpellier (n = 85). NT1 diagnosis was based on the third International Classification of Sleep Disorders criteria[20]: presence of EDS for at least 3 months, mean

Figure Flowchart of the Study Population



NSS-P = pediatric Narcolepsy Severity Scale; NT1 = narcolepsy type 1.

sleep latency ≤8 minutes on the Multiple Sleep Latency Test (MSLT) with at least 2 sleep-onset REM periods, and typical cataplexy or low CSF levels of orexin A (<110 pg/mL).

Moreover, 65 children and adolescents completed the scale on a second occasion during the follow-up: 33 patients untreated the first time and under medication the second time (median between-test interval 176.00 days [range 12.00–2,178 days]) and 32 patients taking the same treatment in both occasions (median interval 183.50 days [range 13.00–1,106.00]) (figure).

Clinical, Electrophysiologic, and Biological Data

All patients underwent the same standardized medical evaluation. Age; sex; body mass index (BMI) categorized as normal weight, overweight (+1 SD for sex and age), or obese (+2 SD); age at disease onset; diagnosis delay; frequency of cataplexy, hypnagogic, and hypnopompic hallucinations; sleep paralysis; and drug status (drug naive, i.e., never exposed to narcolepsy treatment; or withdrawal) were recorded. For patients under medication, drugs and dosages were recorded and classified as psychostimulants (modafinil, methylphenidate, pitolisant), sodium oxybate, and antidepressants.

Self-reported EDS was clinically evaluated with the Pediatric Daytime Sleepiness Scale (PDSS; abnormal score >16) in <12-year-old children[14] and with the ESS for Children and Adolescents (ESS-CHAD; abnormal score >10)[13] in ≥12-year-old patients. Fatigue was evaluated with the Chalder Fatigue Scale[21] (abnormal score >10); depressive symptoms were evaluated with the Children's Depression Inventory (CDI; abnormal score ≥16)[22]; and insomnia symptoms were assessed with the Insomnia Severity Index (ISI; abnormal score >14).[23]

Polysomnographic parameters (total sleep time, sleep efficiency, and nocturnal sleep latency) were collected at NSS-P completion in 99 drug-free patients, and they were evaluated twice (i.e., untreated and treated condition) in 30 patients. For the untreated groups, the mean sleep latency and the number of sleep-onset REM periods were recorded on the MSLT. CSF orexin-A levels were determined in duplicate in 65 patients with the I^{125}-radioimmunoassay kit from Phoenix Pharmaceuticals Inc (Burlingame, CA), according to the manufacturer's recommendations. All values were back-referenced to the Stanford reference samples (HHMI Stanford University Center for Narcolepsy, Palo Alto, CA), with low CSF orexin-A levels (<110 pg/mL) in all.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the local ethics committees (Comité de Protection des Personnes, France: "Constitution of a cohort and of a clinical, neurophysiologic and biological

bank of rare hypersomnolence disorders," NARCOBANK PHRC AOM07-138). Consent to participate was provided by all patients and their parents.

Statistical Analysis

Demographic and clinical characteristics were described with means and SD for continuous variables and percentages or frequencies for categorical variables. The independent Student *t* test was used to compare continuous variables, and the χ^2 or Fisher exact test was used to compare categorical variables. Logistic regression models were used to adjust for study center. Associations between continuous variables were assessed with the Pearson correlation coefficient. The dependent *t* test was used to compare differences between continuous variables at 2 different time points or 2 different conditions, and the McNemar test was used for paired categorical data. To analyze the NSS-P factor structure, a principal component factor analysis was performed using the sample of patients who fully completed the NSS-P at the first visit using a Varimax rotation. The number of factors was determined on the basis of the obtained factor loadings and eigenvalues. Sampling adequacy was measured with the Kaiser-Meyer-Olkin index. The internal consistency (reliability) of the scores for the different items was estimated with the Cronbach coefficient α. Receiver operating characteristic curves were drawn with the NSS-P total scores to identify the best cutoff to discriminate treated and drug-free patients. The best cutoff was defined as the point with the highest Youden Index score [(specificity + sensibility) − 1]. To achieve the scoring sums, all items were dichotomized and were compared to self-reported EDS. The different items were introduced into a single logistic regression model. All β coefficients were standardized, and the lowest one had a value of 1. From this model, a weighted item total score was assigned to each item with the respective β coefficients. The weighted total score was obtained by summing the standardized β coefficients. We also calculated the minimum clinically important difference (MCID) of NSS-P scores between untreated and treated patients in the longitudinal sample on the basis of 2 distribution-based methods: Cohen effect size (0.5 × SD delta) and empirical rule effect size (0.08 × 6 × SD delta), with delta being the NSS-P total score change between untreated and treated conditions. Statistical significance was set at $p < 0.05$. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC) and Stata version 15 (StataCorp, College Station, TX).

Data Availability

Raw data are available on request to the corresponding authors by any qualified investigator.

Results

Two hundred nine consecutive children and adolescents completed the NSS-P. A careful qualitative verification of all questionnaires and related clinical data collected by sleep physicians (L.B., M.L., Y.D.) revealed that the responses of 37 children (32.43% girls, mean age 10.46 ± 2.82 years, 28 <10 years, 35.14% treated) were unreliable. Specifically, major inconsistencies were found between the clinical judgement and the child's responses to NSS-P items due to difficulties in understanding some items despite the explanations provided, lack of recognition of some symptoms such as sleepiness or cataplectic facies, and a real denial of the disease in some children. Of note, children <10 years of age (n = 28, 36% girls, 43% treated) had significant difficulties in quantifying their symptoms without their parents' help, and thus, the scale was filled in with uncertainty. Finally, 172 questionnaires correctly completed by ≥10-year-old children and adolescents with NT1 (97 from Paris and 75 from Montpellier) were retained for the analysis.

Feasibility and Quality of Items

Among the 172 patients with NT1 who completed the NSS-P, age and sex distributions were comparable between centers, but more patients were under treatment in 1 center (table 1 gives the sample characteristics). No ceiling effect was found except for item 1 of the NSS-P, for which 60% of patients had the maximum score (78.38% of drug-free and 45.83% of treated patients). A floor effect was found for items 11 through 14, with the minimum score in 60.00%, 75.29%, 66.47%, and 76.05% of patients, respectively. Missing data were observed for 12 (6.97%) patients (66.67% girls, 13.75 ± 2.09 years of age, 5 [41.67%] treated). Correlation coefficients between items were mostly <0.70, except between items 13 and 14 ($r = 0.83$), confirming their nonredundancy. The validation analyses were performed in the sample of 160 patients without NSS-P missing data that included 68 untreated and 92 treated patients (figure).

Construct Validity of the NSS-P

Internal Consistency

Reliability tests showed a Cronbach α value of 0.81 for the entire sample (N = 160 patients), 0.74 for untreated patients (n = 68), and 0.84 for treated patients (n = 92), indicating a good internal consistency. The correlation of each NSS-P item with the total score was satisfactory (range 0.50–0.69, except for items 2, 5, and 15 with correlations of 0.47, 0.26, and 0.34 respectively).

Factor Analysis

Sampling adequacy was confirmed by a Kaiser-Meyer-Olkin index of 0.74. The eigenvalue-1 criterion retained 4 components that explained 61.95% of the total variance (table 2). The 4 factors included 4 questions on sleep paralysis and hallucinations (factor I: items 11–14), 5 questions on daytime sleepiness (factor II: items 1–4, 6), 3 questions on cataplexy (factor III: items 8–10), and 2 questions on the refreshing effect of a sleep attack and on nighttime sleep (factor IV: items 5 and 15). Communalities, referring to the percentage of variance for each item, were all >0.40 (range 0.42–0.76). The item loading values, representing how strongly each item was associated with the underlying component, were globally high, ranging from 0.47 to 0.87 (table 2).

Table 1 Characteristics of Untreated and Treated ≥10-Year-Old Children and Adolescents With NT1 in the Independent Sample of 172 Patients and in the Dependent Sample of 33 Patients

	Independent sample					Dependent sample				
	Untreated patients (n = 75)		Treated patients (n = 97)			Untreated patients (n = 33)		Treated patients (n = 33)		
Variables	No.	%	No.	%	*p* Value	No.	%	No.	%	*p* Value
Sociodemographic characteristics										
Center										
Montpellier	54	72.00	21	21.65	<0.0001	31	93.94	—	—	
Paris	21	28.00	76	78.35		2	6.06	—	—	
Sex										
Male	39	52.00	59	60.82	0.25	19	57.58	—	—	
Female	36	48.00	38	39.18		14	42.42	—	—	
Age, y[a]	75; 13.91 (1.87)		97; 14.05 (2.09)		0.63	33; 13.94 (1.87)		33; 14.73 (1.74)		<0.0001
Age, y (tertiles)										
<14	34	45.33	39	40.21	0.75	14	42.42	10	30.30	0.05
14–16	22	29.33	29	29.90		11	33.33	9	27.27	
≥16	19	25.33	29	29.90		8	24.24	14	42.42	
Clinical and biological characteristics										
BMI category										
Normal weight	40	57.14	48	52.75	0.32	20	60.61	22	68.75	0.26
Overweight	19	27.14	20	21.98		9	27.27	5	15.63	
Obesity	11	15.71	23	25.27		4	12.12	5	15.63	
Age at disease onset, y[a]	71; 10.28 (3.07)		88; 9.43 (2.94)		0.08	33; 10.62 (2.61)				
Disease duration, y[a]	71; 3.62 (3.05)		88; 4.60 (2.49)		0.03[c]	33; 3.32 (2.12)		33; 4.11 (2.20)		<0.0001
Diagnosis delay, y [a]	54; 2.44 (2.33)		22; 1.68 (2.08)		0.20	31; 2.52 (2.16)		—		
Cataplexy, yes	73	100.00	65	80.25	NA	33	100.00	—	—	
Sleep paralysis, yes	25	33.33	24	29.27	0.58	13	39.39	—	—	
Hallucinations, yes	36	48.65	29	35.37	0.09	17	51.52	—	—	

Continued

Table 1 Characteristics of Untreated and Treated ≥10-Year-Old Children and Adolescents With NT1 in the Independent Sample of 172 Patients and in the Dependent Sample of 33 Patients *(continued)*

	Independent sample					Dependent sample				
	Untreated patients (n = 75)		Treated patients (n = 97)			Untreated patients (n = 33)		Treated patients (n = 33)		
Variables	**No.**	**%**	**No.**	**%**	***p* Value**	**No.**	**%**	**No.**	**%**	***p* Value**
CSF orexin-A levels, pg/mL[a]	49; 18.87 (17.67)		16; 21.44 (17.25)		0.61	28; 20.09 (20.84)		—		
Subjective rating scales										
Self-reported EDS,[d] **yes**	73; 47	64.38	88; 30	34.09	0.0002[c]	32; 18	56.58	27; 16	59.26	0.76
Chalder Fatigue Scale total score										
≤10	40	70.18	24	70.59	0.97	19	65.52	8	88.89	0.08
>10	17	29.82	10	29.41		10	34.48	1	11.11	
ISI total score										
≤14	34	56.67	33	71.74	0.11	16	55.17	18	75.00	0.03
>14	26	43.33	13	28.26		13	44.83	6	25.00	
CDI total score										
<16	33	55.93	28	65.12	0.35	15	51.72	17	80.95	0.03
≥16	26	44.07	15	34.88		14	48.28	4	19.05	
Neurophysiologic data										
Sleep efficiency, %[a]	62; 85.03 (10.15)		37; 79.72 (14.22)		0.04	30; 85.69 (8.03)		30; 86.24 (7.77)		0.11
Total sleep time, min[a]	62; 440.33 (60.78)		37; 453.96 (96.57)		0.38	30; 441.93 (57.27)		30; 454.67 (46.14)		0.11
Night sleep latency, min[a]	62; 6.33 (8.70)		37; 16.68 (12.14)		0.0003	30; 4.38 (4.02)		30; 5.75 (9.69)		0.69
MSLT sleep latency, min[a,b]	62; 3.46 (3.17)		—		—	30; 3.59 (3.37)		—		—
No. of SOREMPs on MSLT, ≥2[b]	58 95.08		—	—	30	100.0		—	—	

Abbreviations: BMI = body mass index; CDI = Children's Depression Inventory; EDS = excessive daytime sleepiness; ISI = Insomnia Severity Index; MSLT = Multiple Sleep Latency Test; NA = not applicable; NT1 = narcolepsy type 1; SOREMP = sleep onset REM period.
[a] Continuous variables are expressed as number; mean (±SD).
[b] In untreated patients.
[c] *p* Value still significant (<0.05) after adjustment for study center.
[d] Self-reported EDS is defined as Pediatric Daytime Sleepiness Scale total score >16 or Epworth Sleepiness Scale for Children and Adolescents total score >10.

Table 2 Factor Structure of the NSS-P Based on the Independent Sample of ≥10-Year-Old Children and Adolescents With NT1

	Study population: 160 patients					
	KMO item by item		Factors			
Items		Communalities	I	II	III	IV
1	0.72	0.58		0.47		
2	0.84	0.53		0.68		
3	0.79	0.69		0.78		
4	0.80	0.65		0.69		
5	0.57	0.50				0.69
6	0.89	0.47		0.51		
8	0.81	0.68			0.78	
9	0.65	0.76			0.87	
10	0.78	0.61			0.52	
11	0.70	0.64	0.74			
12	0.70	0.68	0.80			
13	0.69	0.72	0.83			
14	0.67	0.73	0.83			
15	0.71	0.42				0.59
Cronbach α	0.81					
KMO measure of sampling adequacy	0.74					
Percentage of explained cumulative variance	61.95					

Abbreviations: KMO = Kaiser-Meyer-Olkin; NSSP = Pediatric Narcolepsy Severity Scale; NT1 = narcolepsy type 1.

Temporal Stability

Thirty-two treated patients completed the NSS-P a second time while taking the same drug(s) (29 took psychostimulant, 5 took sodium oxybate, and 7 took antidepressants, alone or in combination). Neither the NSS-P total scores nor the scores of the 4 distinct components differed between evaluations (table 3).

Convergent Validity

The NSS-P convergent validity was good concerning associations with other self-reported assessment of sleepiness, fatigue, and insomnia. Higher NSS-P scores were associated with self-reported EDS in both untreated and treated patients (table 4). The NSS-P total score also was correlated with the Chalder Fatigue Scale, CDI, and ISI scores in both untreated and treated patients (r = 0.46–0.62). Moreover, the ISI total score correlated with item 15 of the NSS-P on DNS (r = 0.47, p = 0.0003 for untreated, and r = 0.69, p <0.0001 for treated patients). No association was found between mean sleep latency on the MSLT and NSS-P total score.

Responsiveness to Medication and Discriminant Validity

Among the 92 treated patients, 91 took at least 1 psychostimulant drug and 26 took an anticataleptic drug (19 took antidepressant and 11 took sodium oxybate, alone or in combination). The NSS-P total score was lower in treated than in untreated patients (n = 68), with a mean difference of 3.71 ± 1.45. The total NSS-P score varied from 12 to 49 in untreated patients and from 1 to 45 in treated patients, showing no ceiling effect. The scores of the factor II items were lower in treated than untreated patients (table 3), as well as the scores of factor III items in patients taking than in those not taking an anticataplectic drug (9.23 ± 2.57 vs 6.17 ± 4.10, p = 0.002). All results remained significant after adjustment for study center. The cutoff value to discriminate between untreated and treated patients was 24 of 54, according to the Youden Index maximum value (sensitivity 64.71%, 95% confidence interval 53.35–76.06; specificity 64.13%, 95% confidence interval 54.33–73.93).

In the dependent group of 33 untreated patients evaluated first in the drug-free and then the treated condition, the NSS-P total score was lower during treatment (30 took at least 1 stimulant, 5 took sodium oxybate, and 5 took an antidepressant), with a mean difference of 3.12 ± 7.52. The scores of the factor I, II, and IV items were lower in the treated condition (table 3). The estimated MCID of the NSS-P score between untreated and treated patients in the longitudinal sample was 3.76 with the Cohen effect size and 3.60 with the empirical rule effect size.

Number of Symptoms and Severity Score Ranges

In the group of 68 untreated patients, 13.24% reported 2 symptoms, 44.12% reported 3 symptoms, 20.59% reported 4 symptoms, and 22.06% reported 5 symptoms. After EDS and cataplexy, the third symptom was often DNS (in 77.94% of patients), followed by hallucinations (in 41.18%) and sleep paralysis (in 32.35%). In the group of 92 treated patients, 20.65% reported 1 or 2 symptoms, 38.04% reported 3 symptoms, 25.00% reported 4 symptoms, and 16.30% reported all 5 symptoms. DNS was reported by 70.65%, hallucinations by 40.22%, and sleep paralysis by 36.96% of treated patients. The mean number of narcolepsy symptoms did not differ between untreated and treated patients; however, items related to EDS (i.e., factor II: items 1–4 and 6) were less severe in treated than untreated patients (table 5). NSS-P total score was divided in 4 equal ranks to define different severity levels: 0 to 14 (mild; 13%), 15 to 28 (moderate; 54%), 29 to 42 (severe; 29%), and 43 to 54 (very severe; 4%). The percentage of patients in the severe/very severe groups was higher in the untreated than treated group (41% and 26%, respectively, p = 0.02). The probability of having self-reported EDS increased with the NSS-P score in both groups (table 6).

When patients were divided in 2 groups in function of the presence or not of self-reported EDS, the NSS-P total score and total weighted score were significantly associated with

Table 3 NSS-P Total Scores and Factors in the Different Groups, and Temporal Stability

	Independent sample				Dependent sample			Dependent sample		
	Untreated patients (n = 68)	Treated patients (n = 92)			Untreated patients (n = 33)	Treated patients (n = 33)		Treated patients (n = 32)	Treated patients (n = 32)	
Variables	Mean (SD)	Mean (SD)	*p* Value	*p* Value[a]	Mean (SD)	Mean (SD)	*p* Value	Mean (SD)	Mean (SD)	*p* Value
NSS-P total score	27.03 (8.23)	23.32 (10.13)	0.02	0.03	25.52 (8.81)	22.39 (8.82)	0.03	21.06 (8.89)	20.38 (7.13)	0.64
Factor I	3.13 (3.96)	3.22 (4.20)	0.90	0.22	2.88 (3.67)	2.76 (3.45)	<0.0001	1.94 (3.34)	2.22 (3.59)	0.45
Factor II	13.09 (3.19)	10.67 (4.20)	0.0002	0.003	12.42 (3.25)	10.45 (3.68)	0.008	9.75 (4.46)	8.91 (3.81)	0.38
Factor III	8.15 (3.69)	7.03 (3.97)	0.07	0.46	7.70 (4.10)	6.70 (3.67)	0.06	6.84 (3.51)	6.9 (72.85)	0.79
Factor IV	2.66 (1.27)	2.39 (1.34)	0.20	0.24	2.52 (1.25)	2.48 (1.37)	0.004	2.53 (1.14)	2.28 (1.05)	0.20

Abbreviation: NSS-P = Pediatric Narcolepsy Severity Scale.
[a] Adjustment for study center.

EDS in unadjusted models and after adjustment for sex, age, and treatment intake ($p < 0.0001$ for all comparisons, data not shown). Therefore, NSS-P item weighting was not needed to highlight between-group differences.

Table 4 Association of the NSS-P Total Score With the Scores of Self-Reported Rating Scales in the Independent Sample (n = 160) of ≥10-Year-Old Children and Adolescents With NT1

	Untreated patients (n = 68)		Treated patients (n = 92)	
	NSS-P total score		NSS-P total score	
Measurements	n; Mean (SD)	*p* Value	n; Mean (SD)	*p* Value
Self-reported EDS[a]				
No	25; 23.72 (7.51)	0.02	55; 20.15 (8.98)	0.0001
Yes	41; 28.93 (8.28)		29; 30.03 (9.72)	
Chalder Fatigue Scale total score				
≤10	37; 24.65 (6.93)	0.001	22; 22.64 (9.78)	0.009
>10	15; 34.40 (6.56)		8; 35.88 (8.74)	
ISI total score				
≤14	33; 24.30 (7.53)	0.002	30; 22.67 (9.69)	0.009
>14	21; 32.33 (6.63)		11; 32.64 (7.62)	
CDI total score				
<16	31; 25.29 (7.27)	0.03	26; 20.54 (7.80)	0.0008
≥16	23; 30.00 (7.22)		12; 35.83 (7.73)	

Abbreviations: CDI = Children's Depression Inventory; EDS = excessive daytime sleepiness; ISI = Insomnia Severity Index; NSS-P = Pediatric Narcolepsy Severity Scale; NT1 = narcolepsy type 1.
[a] Self-reported EDS is defined as Pediatric Daytime Sleepiness Scale total score >16 or Epworth Sleepiness Scale for Children and Adolescents total score >10.

Finally, NSS-P total scores, different factors, and number of symptoms were not significantly different in the 2 study centers, patients with short (≤1 year) and long disease duration, and age groups (population divided according to the mean age [10–14 vs 15–17 years of age] or in tertiles) for the 160 patients stratified as untreated and treated. In addition, no NSS-P score difference was observed between untreated patients who were in withdrawal or were drug-naive at NSS-P completion. In the whole sample, NSS-P total scores did not correlate with age at disease onset, diagnosis delay, BMI, mean sleep latency on the MSLT, and CSF orexin-A levels (taken as continuous variables or as undetectable vs detectable).

Discussion

We provide validation of the NSS-P, a brief self-report questionnaire to quantify the main narcolepsy symptoms, their consequences, and their changes after treatment. The NSS-P was adapted from the adult NSS,[18] with a reformulation of some items and the question about driving removed. The psychometric properties of NSS-P and its internal consistency, content validity, reproducibility, and responsiveness to pharmacologic treatment were satisfactory. The NSS-P assesses the 5 key symptoms of narcolepsy (EDS, cataplexy, hallucinations, sleep paralysis, and DNS), with a good balance between items on these key symptoms. Our findings show that this questionnaire is a reliable tool to assess NT1 symptom severity and symptom consequences and to detect clinically significant changes under medication in ≥10-year-old children.

The NSS-P shows good psychometric properties with good item–total score correlations and an adequate internal consistency. The correlations of items 2, 5, and 15 were weaker, but they address 3 key components of the disease: falling asleep suddenly, the refreshing character of daytime sleep episodes, and DNS. The factor analysis indicated a 4-factor solution with good reliability compared with the 3-factor

Table 5 Number of Narcolepsy Symptoms Based on the NSS-P Item Scores and Total Score in the Independent and Dependent Samples of ≥10-Year-Old Children and Adolescents With NT1

	Independent sample					Dependent sample				
	Untreated patients (n = 68)		Treated patients (n = 92)			Untreated patients (n = 33)		Treated patients (n = 33)		
Variables	No.	%	No.	%	*p* Value	No.	%	No.	%	*p* Value
No. of symptoms										
1–2	9	13.24	19	20.65	0.46	7	21.21	9	27.27	0.09
3	30	44.12	35	38.04		13	39.39	12	36.36	
4	14	20.59	23	25.00		6	18.18	6	18.18	
5	15	22.06	15	16.30		7	21.21	6	18.18	
No. of symptoms[a]	3.51 (0.98)		3.36 (1.01)		0.33	3.39 (1.06)		3.27 (1.07)		0.40
Irresistible need to sleep during the day (item 1)										
<1 episode per day	13	19.12	50	54.35	<0.0001	6	18.18	19	57.58	0.0008
>1 episode per day	55	80.88	42	45.65		27	81.82	14	42.42	
Worried about falling asleep during the day (item 2)										
Not worried at all/not very worried	35	51.47	62	67.39	0.04	24	72.73	24	72.73	0.99
Worried/very worried	33	48.53	30	32.61		9	27.27	9	27.27	
Disruption of activities caused by these daytime sleep attacks (item 3)										
Not important at all/moderately important	17	25.00	47	51.09	0.001	8	24.24	18	54.55	0.01
Important/very important	51	75.00	45	48.91		25	75.76	18	45.45	
Disruption of social and family life by these daytime sleep attacks (item 4)										
Not important at all/moderately important	34	50.00	54	58.70	0.28	18	54.55	22	66.67	0.29
Important/very important	34	50.00	38	41.30		15	45.45	11	33.33	
Feeling after 1 such daytime sleep attacks (item 5)										
Very refreshed/refreshed	36	52.94	65	70.65	0.02	15	45.45	18	54.55	0.41
Tired/very tired	32	47.06	27	29.35		18	54.55	15	45.45	
Time passed before the next episode of daytime sleep attack (item 6)										
>3 h	28	41.18	58	63.04	0.007	16	48.48	18	54.55	0.62
<3 h	40	58.82	34	36.96		17	51.52	15	45.45	
Frequencies of generalized cataplexy episodes (item 8)										
<1/wk	21	30.88	35	38.04	0.35	12	36.36	15	45.45	0.26
>1/mo	47	69.12	57	61.96		21	63.64	18	54.55	
Frequencies of partial cataplexy episodes (item 9)										
<1/wk	23	33.82	38	41.30	0.34	12	36.36	16	48.48	0.29
>1/wk	45	66.18	54	58.70		21	63.64	17	51.52	
Impact of cataplexy episodes on work, social, or family life (item 10)										
Not at all/not very much	40	58.82	63	68.48	0.21	20	60.61	23	69.70	0.37
Much/very much	28	41.18	29	31.52		13	39.39	10	30.30	

Continued

Table 5 Number of Narcolepsy Symptoms Based on the NSS-P Item Scores and Total Score in the Independent and Dependent Samples of ≥10-Year-Old Children and Adolescents With NT1 *(continued)*

	Independent sample					Dependent sample				
	Untreated patients (n = 68)		Treated patients (n = 92)			Untreated patients (n = 33)		Treated patients (n = 33)		
Variables	No.	%	No.	%	*p* Value	No.	%	No.	%	*p* Value
Frequencies of hallucinations (item 11)										
<1/wk	55	80.88	77	83.70	0.64	29	87.88	28	84.85	0.56
>1/wk	13	19.12	15	16.30		4	12.12	5	15.15	
Hallucinations bothering (item 12)										
Not bothered at all/not very bothered	58	85.29	82	89.13	0.47	28	84.85	30	90.91	0.41
Bothered/very bothered	10	14.71	10	10.87		5	15.15	3	9.09	
Frequencies of sleep paralysis (item 13)										
<1/wk	60	88.24	82	89.13	0.86	30	90.91	32	96.97	0.32
>1/wk	8	11.76	10	10.87		3	9.09	1	3.03	
Sleep paralysis bothering (item 14)										
Not bothered at all/not very bothered	55	80.88	77	83.70	0.64	26	78.79	30	90.91	0.21
Bothered/very bothered	13	19.12	15	16.30		7	21.21	3	9.09	
Disturbance in nighttime sleep (item 15)										
Not at all/not too much	40	58.82	57	61.96	0.69	22	66.67	22	66.67	0.99
Much/very much	28	41.18	35	38.04		11	33.33	11	33.33	

Abbreviations: NSS-P = Pediatric Narcolepsy Severity Scale; NT1 = narcolepsy type 1.
[a] Continuous variable expressed as means (±SD).

solution in adult NSS.[18] Factor IV in NSS-P combines 2 questions about the refreshing effect of sleep and DNS, 2 items included in factor II in the NSS. The NSS-P total score is reproducible, without significant changes in the test-retest evaluation in patients receiving stable treatment. The scale convergent validity was confirmed by significant associations with other self-reported assessments of sleepiness, fatigue, insomnia, and depressive symptoms. Some of these scales (ISI and Chalder Fatigue Scale) are not validated in pediatric patients, although they are used in many studies.[8,24] Conversely, self-reported EDS was investigated with dedicated pediatric scales (ESS-CHAD for adolescents and PDSS for the youngest). In the first randomized controlled trial on the efficacy of sodium oxybate in children with NT1, the primary endpoint was the frequency of cataplexy recorded by electronic diaries, and the secondary endpoint was the ESS-CHAD score. The drug showed effectiveness on both measures.[12] This example highlights the lack of and need for a validated comprehensive tool to measure all NT1 symptoms in children.

Narcolepsy symptoms are often typical and easy to recognize by a sleep expert, but symptom intensity and frequency can be very heterogeneous among patients. This is particularly true in pediatric narcolepsy, for which the phenotype may differ from that observed in adults and may vary over time. The number of symptoms per patient in our study was smaller compared to what was observed in adults[19]: 57.4% of untreated children and adolescents had 2 or 3 symptoms (vs 20.3% of adults), 20.6% had 4 symptoms (vs 26.6% of adults), and only 22.1% had 5 symptoms (vs 53.1% of adults). DNS was the third most frequent symptom in children and adolescents (77.9%), as reported in adults evaluated with the NSS (86.2%), followed by hallucinations (41.2% vs 80% in adults) and sleep paralysis (32.3% vs 58.7% in adults).[19] These results are in agreement with the literature showing that the number and severity of narcolepsy symptoms are lower in children than adults with this disease.[9,24-26] Moreover, the proportions of patients with DNS, hallucination, or sleep paralysis in our cohort were not different between treated and untreated patients in both independent and dependent samples. Children could have difficulties in distinguishing hallucinations, sometimes associated with sleep paralysis, from dreaming or could be afraid to report them.[9] Our results are consistent because the evaluation was quantitative and structured and was performed in a large sample of patients.

The responsiveness of the NSS-P to pharmacologic treatment was satisfactory and sensitive enough to detect changes in symptoms after treatment. We report changes of NSS-P total

Table 6 Probability of Having Self-Reported EDS According to the NSS-P Total Score Severity Range in the Independent Sample of 160 ≥10-Year-Old Children and Adolescents With NT1

	Whole sample				Untreated patients				Treated patients			
NSS-P total score	No.	%	Self-reported EDS, yes, n[a]	Risk % (95% CI)	No.	%	Self-reported EDS, yes, n[a]	Risk % (95% CI)	No.	%	Self-reported EDS, yes, n[a]	Risk % (95% CI)
0–14	20	13	3	15.00 (3.21–37.89)	5	8	2	40.00 (5.27–85.34)	15	18	1	6.67 (0.17–31.95)
15–28	81	54	33	40.74 (29.95–52.23)	34	51	20	58.82 (40.70–75.35)	47	56	13	27.66 (15.62–42.64)
29–42	44	29	30	68.18 (52.42–81.39)	26	39	18	69.23 (48.21–85.67)	18	21	12	66.67 (40.99–86.66)
43–54	5	4	4	80.00 (28.36–99.49)	1	2	1	NA	4	5	3	75.00 (19.41–0.99.37)

Abbreviations: CI = confidence interval, EDS = excessive daytime sleepiness, NSS-P = Pediatric Narcolepsy Severity Scale; NT1 = narcolepsy type 1.
[a] Self-reported EDS is defined as Pediatric Daytime Sleepiness Scale total score >16 or Epworth Sleepiness Scale for Children and Adolescents total score >10.

score in the dependent sample before and after medication and in the independent sample (drug-free and treated patients); however, the magnitude of changes was smaller in children (≥10 years old) than in adult patients with NT1 (difference of 4 vs 8 units).[18] On the basis of 2 distribution-based methods, we suggest using an MCID of 4 points in children/adolescents with NT1. Although MCID determination remains controversial with no consensus on the methodology, this estimate represents the smallest change considered beneficial and remains useful for interpreting NSS-P score differences and for determining sample sizes in future clinical trials. The optimal cutoff to discriminate between treated and untreated children/adolescents was 24, like that for adults. However, this cutoff showed a much better specificity in adults (81% vs 64% in children). This can be explained by lower total scores in untreated children than adults with NT1, due to the lower number of items (14 in the NSS-P vs 15 in the NSS) and of symptoms, particularly of symptoms that are less perceived and considered to be less troublesome in children (e.g., cataplectic facies). Similarly, after patients were classified into 4 severity levels, 41% of untreated and 26% of treated children/adolescents were in the severe/very severe groups compared with 68% and 35% of untreated and treated adult patients.[18] Finally, as for the NSS, NSS-P item weighting was not necessary.[18] The NSS-P convergent validity was good concerning associations with other self-reported assessment of sleepiness, fatigue, insomnia, and depressive symptoms. No associations were found between NSS-P total score and age, diagnosis delay, BMI, drug-naive vs withdrawal condition, and mean sleep latency on the MSLT. However, the goal of the self-reported quantification in NSS-P is to cover all disease-related disabilities, not to focus on a single symptom, especially EDS when assessed by neurophysiologic testing (i.e., MSLT) in a laboratory on a given day. As in adults evaluated with NSS, there was no correlation between NSS-P and CSF orexin-A levels in the present study. However, these CSF levels were determined in only a subgroup of 65 patients; all patients were orexin deficient, and thus, we cannot exclude a floor effect due to the low orexin level.

This study has strengths. It assessed the NSS-P psychometric properties in a large sample of drug-free and treated school-aged French-speaking children and adolescents with NT1 and included subgroups with 2 assessments. Patients were well characterized and followed up at 2 French National Reference Centers for Narcolepsy. This bicentric evaluation and the absence of center effect on the NSS-P scores in untreated and treated patients suggest its possible clinical and research use in other centers. Regular monitoring with the NSS-P during follow-up could help to assess treatment efficacy and to guide treatment changes (e.g., dose adjustment or drug switching). The NSS-P can be completed in 5 minutes, allowing ≥10-year-old children and adolescents to play a more active role in the management of their chronic disorder by self-identifying and self-quantifying the main symptoms and complaints and thus understanding the treatment decisions and goals. This is not a diagnostic tool and should be used only to monitor and improve clinical management and to quantify symptoms in future clinical trials. To the best of our knowledge, this questionnaire is the first patient-reported evaluation of the frequency, severity, and consequences of the main NT1 symptoms in a pediatric population. As with the NSS questionnaire, the original NSS-P questionnaire was validated in French and translated into English with the help of the MAPI Research Institute, which hosts and distributes the scale and provides a central clearinghouse for all current and future copyrighted translations that may be used after appropriate permissions or licensure. The NSS was recently validated in other languages.[27,28] It was translated/adapted to Chinese and validated in a Chinese population of adults and >8-year-old children with NT1.[28] Although the authors did not report any NSS score difference between adults and children, the pediatric population was not evaluated independently, the scale wording was not adapted for children, and the item about driving was not removed.[28]

The major limitation of this scale relates to its unreliability in children <10 years of age, due to problems in correctly recognizing and quantifying their symptoms and understanding the items. Accordingly, <10-year-old patients were excluded from the analysis, and consequently, the NSS-P has been validated only in ≥10-year-old children. This

scale could still be used in younger children, depending on their maturity and their parents' help. On the other hand, a parent-rated questionnaire could be developed to enable the evaluation of <10-year-old children. Other symptoms that may occur in NT1 (e.g., fatigue, attention disorders, brain fog, automatic behaviors) and comorbid conditions (e.g., weight gain, depressive symptoms, or parasomnias) are not evaluated by the NSS-P. Additional research is needed to develop new patient-reported outcome measures that could capture these aspects in children. Another limitation is the presence of some missing data in the self-reported rating scales, in disease duration, and in the neurophysiologic assessments. Moreover, the patient global impression and clinical global impression ratings were not included. Subgroups of patients taking the same drug were too small to be individualized and to study the effect of the different drugs and dosages on NSS-P scores.

We validated a brief instrument to assess NT1 symptom frequency, severity, and consequences in ≥10-year-old children and adolescents, with 4 clinically relevant severity score ranges. This scale constitutes a relevant tool to improve and provide guidance for NT1 management in pediatric populations. Its ease of administration, good psychometric properties, and sensitivity to detect symptom changes after treatment ensure the future use of the NSS-P in clinical and research settings.

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