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Original Article

Rating of daytime and nighttime symptoms in RLS: validation of the RLS-6 scale of restless legs syndrome/Willis–Ekbom disease

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ABSTRACT

Background: The International Restless Legs Scale (IRLS) is the most widely used of the scales rating the severity of restless legs syndrome/Willis–Ekbom disease (RLS/WED). It has been well validated and is the primary end point for most of the therapeutic and nontherapeutic studies of RLS/WED. It has excellent psychometric properties, although it does not capture the severity of RLS under a wide variety of circumstances and times of day. Moreover, the IRLS has a large placebo effect.
Methods: The Restless Legs Syndrome-6 Scale (RLS-6), however, takes another potentially valuable approach. Six items are rated on a 0–10 scale from no symptoms at 0 to very severe at 10. In addition to questions on satisfaction with sleep and sleepiness, the scale rates the severity of RLS for the past week under four separate circumstances: while falling asleep, during the night, during the day while sitting or lying, and during the day when moving around. The purpose of the current study is to report the validation of the RLS-6 under baseline and therapeutic conditions.
Results: The RLS-6 seems to be an acceptable, reliable, precise, valid, and responsive instrument for the assessment of RLS severity in a specific and pragmatic manner.
Conclusions: At present, we view the RLS-6 not as a replacement for the IRLS but as a supplement, as each scale provides information not captured by the other.

1. Introduction

For the evaluation of restless legs syndrome/Willis–Ekbom disease (RLS/WED) severity, three scales have been developed and used in clinical and trial practice: the International Restless Legs Scale (IRLS), the Johns Hopkins Restless Legs Severity Scale (JHRLSS), and the Restless Legs Syndrome-6 Scale (RLS-6). The validations of the IRLS and the JHRLSS have been published [1–6], but the validation of the third, the RLS-6, has only been previously published in abstract form [7].

The IRLS is the most widely used of the three scales, has been translated in to multiple languages, and is the major end point for the rating of RLS/WED severity in most academic and pharmaceutical company studies of RLS/WED. It captures a general impression of overall severity, the severity of arm and leg discomfort, the severity of the need to move, the relief obtained by activity, the number of hours a day and the number of days per week with symptoms, the severity of sleep disturbance and tiredness/sleepiness, as well as the impact of RLS symptoms on mood and quality of life. However, as opposed to the RLS-6, the IRLS does not capture the severity of symptoms during the night or while falling asleep versus the day while at rest or, alternatively, when moving around. As opposed to the JHRLSS, the IRLS also does not determine the severity of RLS as determined by the time of day of usual onset of symptoms [6]. Thus, all three of these scales provide useful, important but different measures of RLS severity. In addition, the RLS-6 has been used

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in multiple clinical trials as an accessory secondary end point together with the IRLS, which has been generally used as the primary end point. Moreover, the IRLS has a large placebo effect [8].

The aim of this study was to validate the RLS-6 according to the classical test theory. The RLS-6 is currently the only scale that has been used to specifically rate the severity of daytime versus nighttime symptoms in RLS; as such, it has been used in many studies and clinical trials, especially those that focus on the daytime symptoms of RLS, independent of the sleep disturbances [9–14].

2. Methods

2.1. Patients

The sample considered for the present study was selected from four multicenter, double-blind, randomized active or placebo-controlled clinical trials [9–14].

The inclusion criteria for these studies were as follows: male and female patients aged 18–75 years (cabergoline (CBG) trials: CALDIR, CABAS-0067-031: CT.gov Identifier: NCT00625547; CATOR, CABAS-0067-033: CT.gov Identifier: NCT00627003) or 18–80 years (lisuride trials: TULIR 02/01, EudraCT Number: 2004-001589-42; TULIR 03/01, EudraCT Number: 2005–003549-16), with all four clinical manifestations of RLS according to the IRLSSG criteria [15]. The severity of symptoms had to be at least moderate according to the IRLS total score at baseline (≥10 for CBG trials; ≥ 15 for lisuride trials), and a "severity at night" score of ≥4 (CBG trials) in the RLS-6 rating scale. Patients were either de novo or unsatisfied with previous RLS therapy.

The patients included in the responsiveness analyses ($n = 261$) comprised 69.73% of women aged (mean ± standard deviation (SD)) 60.94 ± 10.34 years. The age at RLS onset was 46.63 ± 16.45 years and the RLS duration 14.31 ± 13.97 years. The patients were receiving treatment for RLS for 3.25 ± 2.87 years. The IRLS total score was 28.64 ± 5.94 (range: 15–38), and the Epworth Sleepiness Scale (ESS) score was 8.06 ± 5.23 (0–21). Most of these patients had markedly severe RLS (39.85%), followed by moderate or severe disorder (each level 27.60%), as per the Clinical Global Impression of Severity (CGIS).

The exclusion criteria were as follows: 1) Patients with secondary RLS, iron deficiency, or other clinically relevant concomitant diseases, relevant findings in ancillary tests, and skin disorders on the application area (lisuride patch trials) [11,12], although uremic RLS patients were allowed in the TULIR03 study (lisuride); 2) patients with established or suspected hypersensitivity to the tested drug or with nonresponse intolerability to previous CBG or L-dopa therapy [9,10]; 3) concomitant use of drugs with a probable influence on RLS or sleep structure, which had to be discontinued at the start of the washout period 1 week before baseline; and 4) patients previously treated with CBG [9] or the drug had to discontinued two months before screening [10]. Women of childbearing potential had to use a reliable method of contraception. Patients were recruited in the outpatient unit of neurological hospitals or in private neurological sleep laboratories.

2.2. Ethical issues

All four studies were approved by the corresponding ethics committees and patients signed the informed consent forms before inclusion in the study.

2.3. Assessments

In addition to the RLS-6 [7], the following assessments were applied: IRLS, version for clinical trials [16]; ESS [17]; and CGIS [18].

The RLS-6 is composed of six items scoring on a 0–10 scale from no symptom at 0 to very severe at 10. In addition to questions on satisfaction with sleep and sleepiness, the scales rate the severity of RLS for the past week under four separate circumstances, while falling asleep, during the night, during the day while sitting or lying, and during the day when moving around (Table 1). Thus, the severity of RLS under different circumstances and times of day would potentially be captured better with the RLS-6 than with previous RLS severity instruments. The RLS-6 scale was not designed to calculate a total score, but it assesses some specific domains: (1) Sleep quality (items 1 and 6); (2) RLS at Nighttime (items 2 and 3); (3) Daytime RLS manifestations during relaxation (item 4); and (4) RLS during activity (which mainly refers to RLS mimics) (item 5), which is actually a control question to differentiate RLS from other disorders.

The IRLS consists of 10 questions rated from 0 to 4. In addition to the total score, two sub-scores can be obtained: severity and life impact. The scale is applied during a face-to-face interview with the patient where any clarifications regarding the questions can be made to the patient. It is the most extensively used of the RLS severity scales in research studies of all types. It has excellent clinimetric

Table 1
RLS-6 rating scales.

Please, evaluate the following questions for the last 7 days or nights respectively:										
How satisfied are you with your sleep during the last 7 nights?										
completely satisfied										completely dissatisfied
0	1	2	3	4	5	6	7	8	9	10
How severe were your RLS symptoms during the last 7 nights or days respectively in the following situations?										
At falling asleep										
none	very mild									very severe
0	1	2	3	4	5	6	7	8	9	10
During the night										
none	very mild									very severe
0	1	2	3	4	5	6	7	8	9	10
During the day when you were at rest (sitting, lying)										
none	very mild									very severe
0	1	2	3	4	5	6	7	8	9	10
During the day when you were not at rest but engaged in activities (walking, activities in your job, homework, leisure activities)										
none	very mild									very severe
0	1	2	3	4	5	6	7	8	9	10
How tired or sleepy were you during the day (between getting up in the morning and bedtime in the evening) within the last 7 days?										
not at all	very mild									very severe
0	1	2	3	4	5	6	7	8	9	10

The RLS-6 is the result of a joint work undertaken by EURLSSG members. The EURLSSG owns intellectual property over the RLS-6 including but not limited to all and any translations and other derivatives (e.g. electronic versions). The EURLSSG has assigned Mapi Research Trust for the management of the instrument licenses and permission to use. Please consult the Mapi Research Trust website: http://www.proqolid.org.

properties and is used as the benchmark outcome measure for treatment trials in RLS.

The ESS is an eight-item scale to assess excessive daytime somnolence and has been frequently used in Parkinson's disease. The CGIS provides a score from 0 (not assessed) to 7 (among the most extremely ill patients).

2.4. Data analysis

A database for the present study was created from the previously mentioned studies [9–14] and submitted to the National Center of Epidemiology (ISCIII, Madrid, Spain). Descriptive statistics (central tendency and dispersion, and proportions) were applied to the variables in the study to characterize the sample.

The main variables in the study were not normally distributed (graph plot or the Kolmogorov–Smirnov test); therefore, nonparametric statistics were used. The following clinimetric attributes were determined and tested against the corresponding standard values:

Acceptability: This included attributes such as percentage of missing data (standard <10%) [19], mean and median closeness (arbitrary limit for the difference: 10% of the maximum theoretical score) [20,21], range of scores (standard: the complete theoretical range of scores) [22], skewness (between –1 and +1) [22], and the floor-and-ceiling effect (<15%) [23].

Dimensionality: This was explored by factor analysis and principal component analysis. The number of factors was chosen according to the Kaiser criterion (eigenvalue > 1) and scree plot inspection. The Bartlett sphericity index for suitability of the analysis ($p < 0.05$) and the Kaiser–Meyer–Olkin measure for sampling adequacy (>0.60) were considered [24].

Internal consistency: Cronbach's alpha index, as a reliability index (standard, >0.70) [25], and item homogeneity index (standard >0.40) [26] were determined, excluding item 5.

As all patients in the several studies providing the sample received treatment after the baseline assessment, it was not possible to find a stable group according to IRLS scores. Therefore, test–retest was not explored.

Hypotheses testing: A close association ($r \geq 0.60$) was expected between the RLS-6 and IRLS corresponding scores, whereas moderate ($r = 0.40$–0.59) or low correlations ($r \leq 0.39$) were hypothesized between other components of both scales. A moderate association was foreseen between RLS-6 domains and CGIS. Moderate to low correlations were expected with other variables in the study. The limits for internal validity were deemed satisfactory if the inter-domain correlation was between 0.30 and 0.70 [19]. The known-group validity was determined for gender and categories of age, severity of RLS based on the IRLS scores, CGIS, and duration of the RLS. A significant increase of the RLS-6 scores was expected with increasing IRLS score-based and CGIS grades, whereas the relationship with the other variables would be weak or nonsignificant. For the continuous variables, grouping was performed according to the median and interquartile range. Comparisons were analyzed with the Mann–Whitney and Kruskal–Wallis tests, and the Bonferroni correction for multiple comparisons was applied.

Responsiveness: This was defined as the ability of the RLS-6 to detect a change; for comparison, the IRLS was also analyzed. For these analyses, we chose a group of patients receiving placebo ($n = 82$) and a group receiving lisuride ($n = 179$) from two clinical trials with lisuride. They were selected because of their homogeneous follow-up period (90 ± 7 days). The remaining patients in the trials on which this study is based varied widely in their follow-up periods and were therefore not appropriate for this kind of analysis. At baseline, there was no statistical difference between the placebo and lisuride arms for age, gender, age at onset, and RLS duration. A significant intra-group improvement was observed at follow-up (90 ± 7 days) in both groups, although it was higher for the treated arm (except for the item 5). Relative change [27], effect size, standardized response mean, coefficient of responsiveness ($[\text{Mean}(\text{test}_1 - \text{test}_2)_{\text{treatment}} - \text{Mean}(\text{test}_1 - \text{test}_2)_{\text{control}}]/\text{SDtest}_{1\ \text{pooled}}$), and correlation of change between RLS-6 and IRLS were calculated [28,29].

Table 2
Descriptive data of the sample and scales.

	Mean	SD	Min.	Max.
Body mass index	26.53	4.10	16.90	44.98
RLS duration	13.36	13.19	0	59.70
Duration of treatment (a)	2.69	2.95	0	21.93
Age at onset (b)	45.37	16.19	3.63	78.68
IRLS Total score	27.49	6.31	10	40
IRLS Sub-score severity	19.46	3.88	6	24
IRLS Sub-score impact	6.37	3.04	0	12
Clinical Global Impression	4.83	0.94	1	7
Epworth Sleepiness Scale	7.85	4.95	0	22

$N = 892$, except (a) $n = 704$ and (b) $n = 891$.
SD: standard deviation. Min.: Minimum. Max.: Maximum.
IRLS: International Restless Legs Scale.

3. Results

A total of 892 patients, with 71.5% females and of age (mean ± SD) 58.73 ± 11.47 years were included in the study. The descriptive data of the sample are shown in Table 2. There were no missing data. The central tendency and dispersion data of the RLS-6 are displayed in Table 3, together with the parameters of acceptability. The following observations are worth noting: all RLS-6 items and scores

Table 3
Acceptability parameters of the RLS-6.

RLS-6 items	Mean (SD)	Median	Minim	Maxim.	Skewness	Floor effect	Ceiling effect
1. Satisfied with sleep	7.17 (2.42)	8	0	10	–0.63	1.01	23.52
2. RLS symptoms at falling asleep	6.09 (3.00)	7	0	10	–0.39	5.04	17.47
3. RLS symptoms during the night	6.74 (2.60)	7	0	10	–0.58	1.57	18.25
4. RLS symptoms during the day at rest	4.91 (2.62)	5	0	10	–0.08	6.38	3.92
5. 4. RLS symptoms during activities in the day	1.59 (2.06)	1	0	10	1.45	45.35	0.34
6. Tired or sleepy during the day	5.09 (2.78)	5	0	10	0.10	3.58	8.96
RLS-6 domains							
1. Sleep quality (items 1 + 6)	12.26 (4.35)	12	0	20	–0.05	0.11	7.17
2. RLS Nighttime (items 2 + 3)	12.83 (4.79)	13	1	20	–0.19	0.11	11.87
3. Daytime RLS (item 4)	4.91 (2.62)	5	0	10	–0.08	6.38	3.92
4. RLS Mimics (item 5)	1.59 (2.06)	1	0	10	1.45	45.35	0.34

$N = 892$.
RLS-6: Restless Legs Scale – six items.
SD: Standard deviation. Minim.: Minimum. Maxim.: Maximum.

Table 4
Convergent validity between RLS-6 and IRLS items and total score.

IRLS	RLS-6					
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6
IRLS 1	0.61	0.51	0.62	0.45	0.22	0.36
IRLS 2	0.48	0.40	0.48	0.32	0.08[a]	0.27
IRLS 3	0.11[b]	0.08[a]	0.13	0.11	0.42	0.11
IRLS 4	0.69	0.50	0.66	0.30	0.15	0.35
IRLS 5	0.40	0.36	0.37	0.30	0.20	0.76
IRLS 6	0.61	0.49	0.61	0.41	0.22	0.33
IRLS 7	0.37	0.35	0.35	0.31	0.16	0.16
IRLS 8	0.51	0.45	0.54	0.43	0.34	0.30
IRLS 9	0.42	0.37	0.40	0.39	0.31	0.51
IRLS 10	0.40	0.35	0.37	0.34	0.26	0.50
IRLS Total score	0.67	0.57	0.66	0.49	0.35	0.59

$N = 892$.
RLS-6: Restless Legs Scale – six items.
IRLS: International Restless Legs Scale.
(a) $p < 0.05$; (b) $p < 0.01$; the rest, $p < 0.001$.

covered the possible range of scoring (0–10 for individual items as well as 1–20 for domains 1 and 2); the mean–median difference was lower than one point (≤10%) for all RLS-6 values; only one value (item 5) was marginally out of the acceptable range (–1 to +1) for skewness; and a mild ceiling effect was noted in items 1, 2, and 3, and a moderate floor effect in item 5, but items 4 and 6 and the total score of domains 1 (Sleep quality) and 2 (RLS at nighttime) were free of both effects (Table 3).

The factor analysis (item 5 excluded) showed only one factor explaining 55% of the variance (eigenvalue: 2.77; loadings: 0.64–0.83 in orthogonal rotations; Bartlett test, $p < 0.001$; Kaiser–Meyer–Olkin test, 0.77). In terms of the internal consistency (item 5 excluded), Cronbach's alpha was 0.79; the item-total correlation ranged from 0.47 (item 6) to 0.68 (item 1); and the inter-item correlation ranged from 0.36 (item 3 to item 6) to 0.75 (item 1 to item 3), with an item homogeneity index of 0.46.

The correlation coefficients of the RLS-6 items ranged from 0.08 to 0.76 (mean: 0.40) with the IRLS items and from 0.35 to 0.67 with the IRLS total score (Table 4). The correlations between RLS-6 and IRLS sub-scores of severity and impact were high to moderate (Table 5). Overall, the correlation coefficients from domains 3 (Daytime RLS manifestations) and 4 (Possible RLS mimics) indicated moderate or weak associations; the association between RLS-6 domains and CGIS was moderate or weak; and a negligible association was noted between the RLS-6 and ESS (Table 5). The latter two findings were similar to the correlations ESS–IRLS ($r_S = 0.06$; $p = 0.08$) and ESS–CGIS ($r_S = 0.03$; $p = 0.31$). Finally, the RLS-6 scores showed negligible correlation with age, body mass index, and RLS duration (all, $r_S \leq 0.16$), and a weak relationship with the duration of treatment for RLS ($N = 702$; RLS-6 domains 1–3, $r_S = 0.19$–0.23; $p < 0.0001$).

Table 5
Convergent validity of the RLS-6 domains.

	RLS-6 domains			
	1. Sleep quality	2. RLS Nighttime	3. Daytime RLS	4. RLS Mimics
IRLS – Total score	0.74	0.68	0.49	0.35
IRLS – Subscale severity	0.62	0.70	0.46	0.25
IRLS – Subscale impact	0.70	0.49	0.41	0.31
Clinical Global Impression of severity	0.51	0.50	0.33	0.11
Epworth Sleepiness Scale	0.10	–0.08	–0.02	0.10

$N = 892$.
IRLS: International Restless Legs Scale.

The inter-domain correlations (internal validity) between domains 1 and 3 ranged from 0.44 to 0.67. Domain 4 (Possible RLS mimics) showed a coefficient of 0.46 with domain 3 (Daytime RLS manifestations during relaxation), and a correlation lower than 0.30 with the other two. In terms of the known-group validity, the RLS-6 scores did not differ significantly by gender, age, or RLS duration categories as a whole, and they were significantly correlated with the RLS severity determined by the IRLS and CGIS categories (Table 6).

The relative change, effect size, and standardized response mean for each arm of the clinical trial and scale are shown in Table 7. These parameters were sensitive to both the placebo and lisuride effect, although all of them were higher in the active treatment group. The RLS-6 domain 4 (Possible RLS mimics) showed the lowest effect size and standardized response mean of all RLS-6 dimensions, and the differences between the placebo and treated arms were minimal (in the centesimal order). The coefficient of responsiveness between arms was 0.01–0.49 for the RLS-6 components and 0.83 for the IRLS (Table 7).

In the placebo arm, the correlation between the change in the RLS-6 subscales and that in the IRLS total score was 0.67 for RLS-6 domain 1 (Sleep quality), 0.70 for domain 2 (RLS at nighttime), 0.62 for domain 3 (Daytime RLS), and 0.20 for domain 4 (RLS mimics). In the lisuride arm, the values were 0.72, 0.82, 0.70, and 0.33, respectively.

4. Discussion

The analysis of the clinimetric properties of RLS-6 was carried out on data of a wide and representative sample of patients from four clinical trials including broad ranges of age, age at onset, duration of disease, and severity of the RLS manifestations. This study was preceded by analyses of some clinimetric properties of RLS-6 in 299 patients from an interim analysis of the two clinical trials with CBG contributing to the data set of the present study [7,9,10], For most of the results, the values were close to those of the present study.

In the early evaluation study of RLS-6 by Professor Ralf Kohnen, item 5 was analyzed jointly with item 4 [7]. However, there are several arguments for analyzing item 5 separately from the other items in the current analysis. First, conceptually, item 5 was included in the scale to discriminate RLS from non-RLS symptoms rather than assessing the severity of RLS. True RLS would not be expected to be more severe during activities such as walking. Second, this item was combined with item 4 in the early evaluation study by Prof Kohnen to evaluate symptoms during the daytime, which was initially correct. However, at present, we consider it more pragmatic to separate these two items, reserving item 4 for evaluating genuine RLS symptoms during the daytime. Third, the findings of the validation analysis favor the decision of leaving item 5 apart. It was the only item with out-of-the-limit skewness and moderate floor effect. After excluding item 5, the scale is unidimensional, evaluating (only) RLS severity. The convergent validity of this item/dimension with the IRLS was, overall, the lowest, and it also showed the lowest responsiveness (ES and SRM) to effective treatment. Therefore, the research team decided to consider item 5 separately from item 4 in this first formal and wide validation study.

There were no missing data, which can be attributed to their origin (monitored clinical trials). According to the IRLS and CGIS, most of the patients showed moderate or high severity of their symptoms with an IRLS score of 27.48 ± 6.34, which was reflected by the total score of the RLS-6 items that reached their potential maximum score. The RLS-6 domains showed negligible skewness and floor-and-ceiling effects [22,23]. They also cover their complete theoretical range of scores (Table 3), in spite of the restriction imposed by the inclusion criteria of the original studies (IRLS total score ≥ 10 for CBG trials and ≥15 for lisuride trials). The apparent discrepancy between

Table 6
Discriminative validity of the RLS-6.

Categories	n	Sleep quality	RLS at nighttime	Daytime RLS	Possible mimics
Gender					
Males	254	11.98 ± 4.34	12.46 ± 4.77	4.63 ± 2.60	1.56 ± 1.97
Females	638	12.37 ± 4.35	12.98 ± 4.80	5.02 ± 2.62	1.60 ± 2.09
p^a	–	0.34	0.15	0.06	0.76
Age categories*					
<52	228	12.82 ± 4.37	12.92 ± 4.65	5.05 ± 2.60	1.79 ± 2.22
52–61	222	12.61 ± 4.49	13.07 ± 4.90	4.93 ± 2.73	1.82 ± 2.13
62–66	223	11.90 ± 4.37	12.63 ± 4.77	4.75 ± 2.65	1.22 ± 1.73
≥67	219	11.70 ± 4.01	12.0 ± 4.87	4.88 ± 2.51	1.52 ± 2.08
p^b	–	0.02	0.73	0.69	0.015
RLS duration (years)*					
<3.3	222	11.82 ± 4.34	12.04 ± 4.66	4.78 ± 2.38	1.80 ± 2.12
3.30–8.86	223	12.37 ± 4.48	13.07 ± 4.70	5.06 ± 2.64	1.76 ± 2.05
8.87–19.77	223	12.22 ± 4.34	12.64 ± 4.79	4.78 ± 2.64	1.37 ± 1.90
≥ 19.78	224	12.63 ± 4.23	13.56 ± 4.91	5.00 ± 2.81	1.41 ± 2.13
p^b	–	0.33	0.006	0.49	0.01
IRLS score					
0–10	3	4.33 ± 4.51	6.00 ± 4.24	1.67 ± 0.58	1.00 ± 0.00
11–20	133	7.56 ± 2.94	7.89 ± 3.27	3.06 ± 2.15	0.70 ± 1.22
21–30	435	11.17 ± 3.28	11.78 ± 4.10	4.44 ± 2.36	1.25 ± 1.69
31–40	321	15.75 ± 3.29	16.36 ± 3.46	6.33 ± 2.41	2.41 ± 2.47
p	–	0.0001	0.0001	0.0001	0.0001
Clinical global					
Impression	3	12.67 ± 3.51	9.33 ± 0.58	2.00 ± 3.46	0.00 ± 0.00
1	7	11.43 ± 4.86	11.43 ± 3.74	4.14 ± 2.67	0.43 ± 0.53
2	43	8.47 ± 4.57	8.86 ± 4.49	3.53 ± 2.59	1.53 ± 2.29
3	267	10.03 ± 3.54	10.39 ± 4.39	4.12 ± 2.34	1.37 ± 1.71
4	351	12.3 ± 3.9	12.9 ± 4.11	4.83 ± 2.50	1.42 ± 1.91
5	208	15.43 ± 3.50	16.30 ± 3.88	6.21 ± 2.56	2.11 ± 2.44
6	13	18.15 ± 1.99	19.08 ± 1.50	7.85 ± 1.82	3.23 ± 3.49
7	0	–	–	–	–
p^b	–	0.0001	0.0001	0.0001	0.007

* Categories according to interquartile range. SD: Standard deviation.
(a) Mann–Whitney test; (b) Kruskal–Wallis test. Bonferroni correction: significant if $p < 0.0025$.
RLS-6: Restless Legs Scale – six items.
IRLS: International Restless Legs Scale.
RLS: Restless Legs Syndrome.

the scales must be related to their different structure and content and to the consideration of scores from RLS-6 domains (parts) versus the IRLS total score (all).

Domain 4 (Possible RLS mimics; item 5 of RLS-6) performed differently, with mild skewness and a moderate floor effect, which must be attributed to its particular nature. The RLS-6 acceptability, therefore, was considered satisfactory.

Interestingly, the exploratory factor analysis showed that RLS-6 was a unidimensional scale, with all items loading highly on the same factor. Thus, the five items of the RLS-6 focused on evaluating the aspects of RLS severity are grouped around a unique construct, the RLS. In the preliminary study, a two-factor solution was found, although RLS-6 item 5 (RLS during activity) was included as it may have been essential for the appearance of the separate "day-time" factor identified [7]. The factor analysis results of the present study are in line with the reliability indices tested, showing overall satisfactory values of internal consistency, which surpass the threshold values for Cronbach's alpha and the homogeneity index [25,26]. The value of the latter (0.37) was coincident with the preliminary validation study [7]. To summarize, both the structure and internal consistency of the RLS-6 were suitable.

RLS-6 item 1 (satisfaction with sleep) and 3 (severity of RLS symptoms during night) were closely associated with IRLS items 1 (discomfort in legs or arms), 4 (sleep disturbances due to RLS), and 6 (self-perceived RLS severity). However, item 6 of the RLS-6 was also highly correlated with the IRLS item 5 (both assessing tiredness and sleepiness during the day) (Table 4). Most of the correlations between items from both scales were moderate in magnitude, but the total scores (including IRLS severity and impact sub-scores) showed a strong or moderate correlation between scales, except for RLS-6 domain 4 (Possible RLS mimics), which was weakly correlated with the IRLS (Table 5). These results are close to those found

Table 7
Responsiveness of the RLS-6.

	Placebo (n = 82)			Lisuride (n = 179)			Coefficient of responsiveness
RLS-6	RC (%)	Effect size	SRM	RC (%)	Effect size	SRM	
Sleep quality	–21.8	0.61	0.52	–37.6	1.13	0.80	0.49
Nighttime RLS	–30.7	0.75	0.69	–47.6	1.36	0.92	0.48
Daytime RLS	–28.7	0.54	0.47	–46.2	1.01	0.73	0.38
Possible mimics	–40.3	0.30	0.31	–44.2	0.34	0.35	0.01
IRLS	–25.3	1.10	0.73	–41.0	2.09	1.10	0.83

RLS-6: Restless Legs Scale – six items.
IRLS: International Restless Legs Scale, total score.
RC: Relative change. SRM: standardized response mean.

in the early validation study [7] and are indicative of the significant association between RLS-6 and IRLS, the scale most commonly used to evaluate the RLS. Such a degree of closeness was expected, as both scales are self-completed or informed by the patients and were designed for the same objective, although their different structures (in components and scoring method) could have given rise to noticeable differences in their performance. However, CGIS data have a different origin, which explains their correlation with the RLS-6 at a lower level than the IRLS. The ESS was unrelated to the RLS-6 in this study, as the RLS-6 did not assess daytime sleepiness in a single item or separate domain.

The distribution of the RLS-6 scores with respect to groups based on such concepts as age, gender, RLS duration and severity showed that only severity categories based on other measures in the study (IRLS and CGIS) generated significant differences among them, thus confirming the discriminative ability of the scale (Table 6). This performance indicates that, in addition to evaluative ability, RLS-6 is a potential discriminative instrument (able to distinguish, at a point in time, between groups determined by specific characteristics or an independent measure) [30]. In summary, the scale scores are consistent with theoretically derived hypotheses regarding the underlying construct it intends to measure.

The relative change in the responsiveness of the RLS-6 was similar to that observed for the IRLS. However, the effect size and standardized response mean were moderately higher for the IRLS. For both parameters, values of 0.50–0.79 are indicative of a moderate effect and ≥0.80 of a large effect [28,31–33]; some values were "large" for the IRLS and "moderate" for RLS-6, revealing a lower sensitivity to change for the RLS-6. This discrepancy can be attributed to the more complex structure of the IRLS (10 items, two factors) [2], which can capture variation in aspects not included into the RLS-6. This also explains the difference in the coefficient of responsiveness with both scales distinguishing the effect of the treatments (placebo vs. lisuride). Overall, the effect size and standardized response mean for the placebo arm were higher for the IRLS total score than for the RLS-6 domains, whereas the relative change was similar. These findings are in line with the meta-analysis of the placebo effect conducted by Fulda et al. [8]. Nevertheless, the magnitude of the placebo effect with different measures is remarkable and may be related more with RLS as a disorder assessed through purely subjective inferences than with scale properties [5]. In the early validation study, the maximum effect size of improvement was observed for the RLS-6 item "severity during the night," [7] which is in line with the present study (domain 2, RLS at nighttime) (Table 7).

A strong association ($r_S > 0.60$) was found between the change captured by the IRLS and the RLS-6 for both groups of treatment. Previous studies, with a diversity of interventions, have unanimously found an evident sensitivity to a change in the RLS-6; overall, these findings are in line with the outcomes in the present study [10,34–36]. Therefore, the intrinsic responsiveness of the RLS-6 can be deemed satisfactory.

The main limitations of the study were related to the net prevalence of women in the sample and the lack of the scale reproducibility testing. Furthermore, there were no independent interviews comparing the scale with the usual gold standard of validation, as done for the IRLS validation.

In conclusion, the RLS-6 seems to be an acceptable, reliable, precise, valid, and responsive instrument for the assessment of RLS severity in a specific and pragmatic manner. The RLS-6 is comparable to the IRLS in this regard, and the two scales can be considered compatible and not contradictory. Each scale provides information not captured by the other scale. Indeed, many therapeutic trials where the IRLS has been used as the primary outcome have applied both scales because RLS-6 provides detailed additional information on RLS symptom severity at different times and under different circumstances. In addition, the findings of other studies support the compatibility of the scales. In a comparative study of the IRLS with other measures of RLS severity, s good correlation was noted between the IRLS and the RLS-6 [37]. In this study, both scales showed a placebo effect around 25%. Future studies with the RLS-6 will confirm the stability of this performance.

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Intellectual property and contact information

The RLS-6 is the result of a joint work undertaken by EURLSSG members. The EURLSSG owns intellectual property over the RLS-6 including but not limited to all and any translations and other derivatives (eg, electronic versions). The EURLSSG has assigned Mapi Research Trust for the management of the instrument licenses and permission to use. Please consult the Mapi Research Trust website http://www.proqolid.org.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.10.014.

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